NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP Technical Report on the Photococarcinogenesis Study of

Retinoic Acid and Retinyl Palmitate [CAS Nos. 302-79-4 (All-*trans*-retinoic acid) and 79-81-2 (All-*trans*-retinyl palmitate)] in SKH-1 Mice (Simulated Solar Light and Topical Application Study)

NTP TR 568

AUGUST 2012

NTP TECHNICAL REPORT

ON THE

PHOTOCOCARCINOGENESIS

STUDY OF

RETINOIC ACID AND RETINYL PALMITATE

**[CAS Nos. 302-79-4 (All-*trans*-retinoic acid)
and 79-81-2 (All-*trans*-retinyl palmitate)]**

IN SKH-1 MICE

**(SIMULATED SOLAR LIGHT
AND TOPICAL APPLICATION STUDY)**

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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August 2012

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FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Technical Report series began in 1976 with carcinogenesis studies conducted by the National Cancer Institute. In 1981, this bioassay program was transferred to the NTP. The studies described in the Technical Report series are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected substances in laboratory animals (usually two species, rats and mice). Substances selected for NTP toxicity and carcinogenicity studies are chosen primarily on the basis of human exposure, level of production, and chemical structure. The interpretive conclusions presented in NTP Technical Reports are based only on the results of these NTP studies. Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports. Selection *per se* is not an indicator of a substance's carcinogenic potential.

The NTP conducts its studies in compliance with its laboratory health and safety guidelines and FDA Good Laboratory Practice Regulations and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use are in accordance with the Public Health Service Policy on Humane Care and Use of Animals. Studies are subjected to retrospective quality assurance audits before being presented for public review.

NTP Technical Reports are indexed in the NIH/NLM PubMed database and are available free of charge electronically on the NTP website (*http://ntp.niehs.nih.gov*) or in hardcopy upon request from the NTP Central Data Management group at *cdm@niehs.nih.gov* or (919) 541-3419.

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The photococarcinogenesis study of retinoic acid and retinyl palmitate was conducted at the Food and Drug Administration's (FDA) National Center for Toxicological Research (NCTR) under an interagency agreement between the FDA and the National Institute of Environmental Health Sciences (NIEHS). The study was monitored by a Toxicology Study Selection and Review Committee composed of representatives from the NCTR and other FDA centers, NIEHS, and other *ad hoc* members from other governmental agencies and academia. The interagency agreement was designed to use the staff and facilities of the NCTR in the testing of FDA priority chemicals and to provide FDA scientists and regulatory policymakers with information for hazard identification and risk assessment.

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CONTENTS

SUMMARY

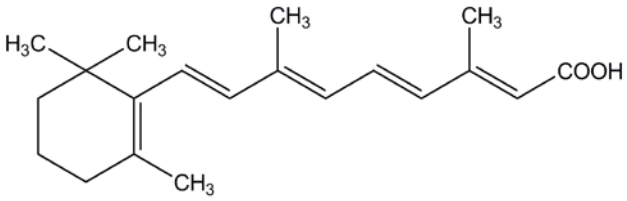
Background
Retinoic acid is the most active biological form of vitamin A, and retinyl palmitate is the major storage form of vitamin A in the skin. People cannot produce vitamin A themselves but must obtain it through the diet. Skin care products containing vitamin A are becoming popular as treatments for aging and wrinkles resulting from sun exposure.

Methods
In the mornings, groups of 36 male and female hairless mice were exposed to synthetic solar light for four hours. Other groups were not exposed to light and were control groups. In the afternoon, we applied creams containing retinyl palmitate or retinoic acid to some of the animals; other groups received the carrier creams alone or no treatment at all. The treatment and exposures were performed five days per week for 40 weeks, followed by 12 weeks of no treatment. Throughout the study the animals were monitored for development of skin cancers.

Results
As expected, exposure to synthetic solar light resulted in a variety of skin cancers in the mice. Mice given the carrier creams in addition to light exposure developed more tumors per animal, with a shorter time before the appearance of tumors. Mice given creams containing retinyl palmitate or retinoic acid had even more tumors and earlier onset of tumors than animals given the carrier cream, both with and without exposure to the synthetic solar light.

Conclusions
We conclude that treatment with the carrier cream increased the incidence of skin tumors in hairless mice, both in the presence and absence of synthetic solar light. Inclusion of retinoic acid or retinyl palmitate in the cream increased the number of tumors and decreased the time to appearance of tumors compared to animals given just the carrier cream.

ABSTRACT

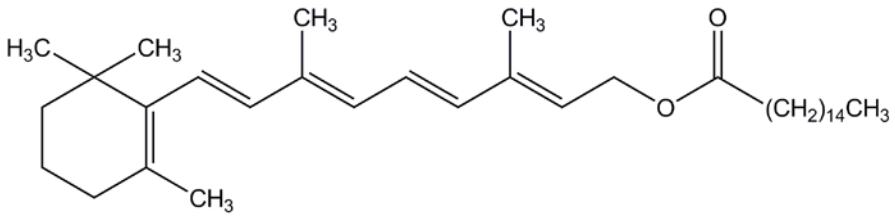


ALL-*trans*-RETINOIC ACID

CAS No. 302-79-4

Chemical Formula: $C_{20}H_{28}O_2$ Molecular Weight: 300.45

Synonyms: All-(*E*)-retinoic acid; all-*trans*-β-A; all-*trans*-tretinoin; all-*trans*-vitamin A_1 acid; beta RA; nonatetranoic acid; tretin M; tretinoin; vitamin A acid; vitamin A_1 acid
Trade names: Renova®, Retin-A®, Retinova®, Vesanoid®



ALL-*trans*-RETINYL PALMITATE

CAS No. 79-81-2

Chemical Formula: $C_{36}H_{60}O_2$ Molecular Weight: 524.88

Synonyms: All-*trans*-retinyl palmitate; retinol palmitate; retinol hexadecanoate; retinyl palmitate; vitamin A palmitate
Trade names: Aquasol A®, Arovit®, Optovit-A®, Palmitate A®

Topical retinoids, compounds that are metabolites, analogues, or derivatives of retinol and possess biological vitamin A activity, are among the most used adjunctive agents for the mitigation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of photodamaged and chronically aged skin. Retinoic acid (RA) is the most active biological form of vitamin A and remains the medical treatment of choice for photoaged skin. Retinyl palmitate (RP) is the major storage form of vitamin A in the skin and, because RP is also the most stable of available vitamin A esters, it is readily incorporated into the oil phase of cosmetic creams or lotions. Therefore, the topical application of RP is a practical strategy for increasing the levels of vitamin A in the skin. Usual cosmetic product concentrations of RA range from 0.025% to 0.1% and those of RP range from 0.1% to 5%.

With a maximum absorbance around 325 nm, RA and RP absorb both ultraviolet A and B radiation (UVA and UVB) in incident sunlight. A 1-year study was conducted in mice to determine whether RA and RP would alter the photocarcinogenicity of broad-UV spectrum light generated by xenon arc lamps, termed simulated solar light (SSL), or narrow spectrum UV light generated by UVA and UVB lamps.

1-YEAR STUDY

Groups of 36 male and 36 female Crl:SKH-1 *(hr⁻/hr⁻)* hairless mice were irradiated 5 days per week (Monday through Friday) in the morning for 40 weeks with SSL at levels of 0.00, 6.85, or 13.70 mJ•CIE/cm^2 that were emitted from glass-filtered 6.5 kW xenon arc lamps. The mice received topical applications of control cream or creams containing 0.001% (w/w) RA or 0.1%, 0.5%, 1.0%, or 2.0% RP to the dorsal skin region in the afternoon of the same days of irradiance exposures. Separate groups of 36 female Crl:SKH-1 *(hr⁻/hr⁻)* hairless mice were irradiated with UV light emitted from fluorescent UVA or UVB lamps at a single level that was equivalent to the amount of UVA or UVB generated by SSL at a level of 13.70 mJ•CIE/cm^2 SSL and received topical application of control cream or creams containing 1.0% RP or 0.001% RA. A 12-week observation period followed the 40-week treatment/exposure period. Additional groups of 36 male and 36 female mice received no cream and were exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL or to a single level of either UVA or UVB light (females only), equivalent to the amount of UVA or UVB generated by SSL at a level of 13.70 mJ•CIE/cm^2.

Mice that received no cream treatment and were exposed to increasing levels of SSL showed significant SSL exposure-dependent decreases in survival, earlier in-life onset of skin lesions, and significant SSL exposure-dependent increases in the incidences and multiplicities of in-life skin lesions, as well as in the incidences and multiplicities of histopathology determined squamous cell nonneoplastic skin lesions (hyperplasia and focal atypical hyperplasia) and neoplastic skin lesions (papilloma, carcinoma *in situ*, and/or carcinoma). Female mice that received no cream treatment and were exposed to UVA showed significant increases in survival, later onset of in-life skin lesions, and significantly decreased incidences and multiplicities of in-life skin lesions when compared to female mice that received SSL at a level of 13.70 mJ•CIE/cm^2. Female mice that received no cream treatment and were exposed to UVB demonstrated significant decreases in survival and significant increases in the multiplicities of in-life skin lesions when compared to female mice that received SSL at a level of 13.70 mJ•CIE/cm^2.

The control cream was composed of a base cream (85%, w/w) and diisopropyl adipate (15%, w/w). The control cream was formulated specifically to blend with the RA and RP test articles; although the ingredients listed as components of the control cream were found as common ingredients in many, if not most, cosmetic creams or lotions. Diisopropyl adipate, another ingredient common to a variety cosmetic and skin care products, was used as a carrier for the RA and RP in order to incorporate them into the control cream. The topical treatment of mice with the control cream imparted significant effects when compared with comparable measurements in mice that received no cream treatment and were exposed to the same level of SSL. Specifically, the exposure of mice to control cream resulted in decreased survival rates, earlier times to the onset of skin lesions, and increased incidences and multiplicities of in-life skin lesions and squamous cell neoplasms in both the absence and presence of SSL exposure and increased incidences and multiplicities of in-life skin lesions in female mice exposed to UVA.

The application of RA (0.001%, w/w) creams to mice significantly decreased survival, even in the absence of SSL exposure in male mice, when compared to mice that received the control cream and the same level of SSL. Significantly earlier in-life skin lesion onset and significantly increased multiplicities of skin lesions were observed at each SSL level, including 0.00 mJ•CIE/cm^2, in male mice and in female mice exposed to 6.85 mJ•CIE/cm^2 SSL, UVA, or UVB. No histopathology was conducted on the RA cream treated mice.

Significant dose trend effects and earlier in-life skin lesion onsets were observed in mice that received the RP cream treatments in the presence of SSL, UVA, or UVB compared with mice that received control cream treatment and the same level of irradiation. In mice exposed to SSL, there were significantly increased multiplicities of in-life skin lesions at RP doses of 0.1% to 1.0%. Significant dose-related trends were observed in the incidences of squamous cell carcinoma and/or squamous cell carcinoma *in situ* in female mice exposed to 6.85 mJ•CIE/cm^2 SSL. Significant RP dose-related increases were also observed in the multiplicities of squamous cell papilloma and in the combination of all squamous cell neoplasms.

CONCLUSIONS

These experiments investigated the effect of topical applications of creams containing RA or RP on the photocarcinogenic activity of SSL in male and female SKH-1 hairless mice. Skin lesions were assessed during the in-life phase and/or by histopathologic evaluation at necropsy.

Control Cream

Under the conditions of these studies, the topical treatment of SKH-1 mice with the control cream resulted in earlier onsets of in-life skin lesions and higher incidences and multiplicities of in-life skin lesions, when compared to untreated controls, in the absence and presence of SSL.

The topical treatment of SKH-1 mice with control cream resulted in higher incidences and multiplicities of squamous cell neoplasms of the skin when compared to untreated controls in the absence and presence of SSL.

Retinoic Acid

Compared to the control cream, RA further enhanced the effects of SSL in SKH-1 mice based upon earlier onsets and increased multiplicities of in-life skin lesions.

Retinyl Palmitate

Compared to the control cream, RP further enhanced the effects of SSL in SKH-1 mice based upon earlier onsets and increased multiplicities of in-life skin lesions.

Compared to the control cream, RP further enhanced the photocarcinogenic activity of SSL in SKH-1 mice based upon increased incidences and multiplicities of squamous cell neoplasms of the skin.

Summary of the 1-Year Photococarcinogenesis Study of Retinoic Acid and Retinyl Palmitate and 0.00 mJ•CIE/cm^2 SSL in SKH-1 Mice

	Male			Female		
	Control Cream[a]	**Retinoic Acid**	**Retinyl Palmitate**	**Control Cream**	**Retinoic Acid**	**Retinyl Palmitate**
Concentrations in cream	NA	0.001%	1.0% or 2.0%	NA	0.001%	1.0% or 2.0%
Kaplan-Meier estimates for mean survival time	No effect	Decreased	Decreased	No effect	No effect	Decreased
Body weights	No effect	No effect	Decreased	No effect	No effect	Decreased
In-life median skin lesion onset	Earlier	No effect	Earlier or No effect	Earlier	No effect	Earlier or No effect
In-life skin lesion incidence rates	Increased	No effect[b]	No effect[b]	Increased	No effect	Increased
Multiplicity of in-life skin lesions	Increased	Increased	Increased or No effect	Increased	No effect	Increased or No effect
Incidence rates of histopathology determined focal atypical squamous hyperplasia	No effect	—[c]	—	No effect	—	—
Multiplicity of histopathology determined focal atypical squamous hyperplasia	No effect	—	—	No effect	—	—
Incidence rates of histopathology determined squamous neoplasms (papilloma, carcinoma *in situ*, and/or carcinoma)	Increased	—	—	Increased	—	—
Multiplicity of histopathology determined squamous neoplasms (papilloma, carcinoma *in situ*, and/or carcinoma)	Increased	—	—	No effect	—	—

NA = Not Applicable

[a] Comparisons for control cream are relative to no cream group; all other comparisons are relative to control cream groups.

[b] A very high incidence in the control cream group precluded detection of an increase.

[c] No histopathology performed on this group

Summary of the 1-Year Photococarcinogenesis Study of Retinoic Acid and Retinyl Palmitate and 6.85 mJ•CIE/cm^2 SSL in SKH-1 Mice

	Male			Female		
	Control Cream[a]	**Retinoic Acid**	**Retinyl Palmitate**	**Control Cream**	**Retinoic Acid**	**Retinyl Palmitate**
Concentrations in cream	NA	0.001%	0.1%, 0.5%, 1.0%, or 2.0%	NA	0.001%	0.1%, 0.5%, 1.0%, or 2.0%
Kaplan-Meier estimates for mean survival time	Decreased	Decreased	Decreased	No effect	Decreased	Decreased
Body weights	No effect	No effect	No effect	No effect	No effect	No effect
In-life median skin lesion onset	Earlier	Earlier	Earlier	Earlier	Earlier	Earlier
In-life skin lesion incidence rates	Increased	No effect[b]	No effect[b]	Increased	No effect[b]	No effect[b]
Multiplicity of in-life skin lesions	Increased	Increased	Increased or No effect	Increased	Increased	Increased
Incidence rates of histopathology determined focal atypical squamous hyperplasia	Increased	—[c]	No effect[b]	Increased	—	Increased
Multiplicity of histopathology determined focal atypical squamous hyperplasia	Increased	—	Increased	Increased	—	Increased
Incidence rates of histopathology determined squamous neoplasms (papilloma, carcinoma *in situ*, and/or carcinoma)	Increased	—	No effect[b]	Increased	—	No effect
Multiplicity of histopathology determined squamous neoplasms (papilloma, carcinoma *in situ*, and/or carcinoma)	Increased	—	Increased	Increased	—	Increased

NA = Not Applicable

[a] Comparisons for control cream are relative to no cream group; all other comparisons are relative to control cream groups.

[b] A very high incidence in the control cream group precluded detection of an increase.

[c] No histopathology performed on this group

Summary of the 1-Year Photococarcinogenesis Study of Retinoic Acid and Retinyl Palmitate and 13.70 mJ•CIE/cm^2 SSL in SKH-1 Mice

	Male			Female		
	Control Cream[a]	**Retinoic Acid**	**Retinyl Palmitate**	**Control Cream**	**Retinoic Acid**	**Retinyl Palmitate**
Concentrations in cream	NA	0.001%	0.1%, 0.5%, 1.0%, or 2.0%	NA	0.001%	0.1%, 0.5%, 1.0%, or 2.0%
Kaplan-Meier estimates for mean survival time	Decreased	Decreased	Decreased	No effect	Decreased	Decreased
Body weights	No effect	No effect	No effect	No effect	No effect	Decreased
In-life median skin lesion onset	Earlier	Earlier	Earlier	Earlier	Earlier	Earlier
In-life skin lesion incidence rates	No effect[b]	No effect[b]	No effect[b]	No effect	No effect[b]	No effect[b]
Multiplicity of in-life skin lesions	Increased	Increased	Increased	Increased	No effect	Increased
Incidence rates of histopathology determined focal atypical squamous hyperplasia	No effect[b]	—[c]	No effect[b]	No effect	—	No effect[b]
Multiplicity of histopathology determined focal atypical squamous hyperplasia	Increased	—	Increased	Increased	—	Increased or No effect
Incidence rates of histopathology determined squamous neoplasms (papilloma, carcinoma *in situ*, and/or carcinoma)	No effect[b]	—	No effect[b]	No effect	—	No effect[b]
Multiplicity of histopathology determined squamous neoplasms (papilloma, carcinoma *in situ*, and/or carcinoma)	Increased	—	Increased	Increased	—	Increased

NA = Not Applicable

[a] Comparisons for control cream are relative to no cream group; all other comparisons are relative to control cream groups.

[b] Very high incidences in the control groups precluded detection of an increase.

[c] No histopathology performed on this group

Summary of the 1-Year Photococarcinogenesis Study of Retinoic Acid and Retinyl Palmitate and UVA, UVB, or 13.70 mJ•CIE/cm^2 SSL in SKH-1 Female Mice

	No Cream[a]		Control Cream[a]		0.001% Retinoic Acid Cream[a]		1.0% Retinyl Palmitate Cream[a]	
	UVA	**UVB**	**UVA**	**UVB**	**UVA**	**UVB**	**UVA**	**UVB**
Kaplan Meier estimates for mean survival time	Increased	Decreased	Increased	Decreased	Increased	Decreased	Increased	Decreased
Body weights	No effect	No effect	No effect	No effect	No effect	No effect	No effect	No effect
In-life median skin lesion onset	Later	Earlier	Later	No effect	Later	No effect	Later	No effect
In-life skin lesion incidence rates	Decreased	No effect[b]	Decreased	No effect[b]	Decreased	No effect[b]	Decreased	No effect[b]
Multiplicity of in-life skin lesions	Decreased	Increased	Decreased	No effect	Decreased	Increased	Decreased	Increased

[a] Comparisons are relative to 13.70 mJ•CIE/cm^2 group within each treatment group.
[b] A very high incidence in the 13.70 mJ•CIE/cm^2 group precluded detection of an increase.

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft NTP Technical Report on retinoic acid and retinyl palmitate on January 26, 2011, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF PEER REVIEW PANEL COMMENTS

On January 26, 2011, the draft Technical Report on the photococarcinogenicity study of retinoic acid and retinyl palmitate received public review by the National Toxicology Program's Technical Reports Peer Review Panel. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. M.D. Boudreau, NCTR, briefed the panel on the photococarcinogenicity study of retinoic acid (RA) and retinyl palmitate (RP). RP was nominated to the NTP for phototoxicity and photococarcinogenicity testing by the Center for Food Safety and Applied Nutrition within the FDA, based upon widespread use of the compound in cosmetic retail products applied to sun-exposed skin and an association between topical application of retinoids and enhanced photococarcinogenesis. The objective of the 1-year photococarcinogenesis study was to determine whether the topical application of creams containing RA or RP would alter the process of photocarcinogenesis in SKH-1 hairless mice exposed to simulated solar light (SSL), UVA, or UVB. The proposed conclusions were:

Control Cream
Under the conditions of these studies, the topical treatment of SKH-1 mice with the control cream resulted in earlier onsets of in-life skin lesions and higher incidences and multiplicities of in-life skin lesions in the absence and presence of SSL or UVA, and higher incidences and multiplicities of squamous cell neoplasms when compared to untreated controls in the absence and presence of SSL.

Retinoic Acid
Compared to the control cream, retinoic acid enhanced the photocarcinogenic activity of SSL and UVB in SKH-1 mice based upon earlier onsets and increased multiplicities of in-life skin lesions.

Retinyl Palmitate
Compared to the control cream, retinyl palmitate enhanced the photocarcinogenicity activity of SSL and UVB in SKH-1 mice based upon earlier onsets and increased multiplicities of in-life skin lesions and increased incidences and multiplicities of squamous cell neoplasms.

Oral public comments were provided from the Environmental Working Group (EWG) and the Personal Care Products Council (PCPC).

Dr. O.V. Naidenko, Senior Scientist at EWG, said the EWG strongly supported the study, which represents the culmination of a 10-year research program on RP begun at NCTR. Her comments covered three major points: the experimental protocol for the study was appropriately chosen, the lines of evidence all point to the photocarcinogenic effect of RP in combination with sunlight, and the findings of the NTP study are in agreement with the research database on the phototoxicity and photococarcinogenicity of retinoid compounds. Dr. Naidenko concluded by stating that EWG considered the study, despite its limitations, "clean and very informative for public health."

Dr. J.E. Bailey, Executive Vice President for Science at PCPC, said PCPC was concerned about the use of this NTP study for risk management and risk assessment. Dr. M.E. Ginevan, an independent consultant hired by PCPC to analyze the study and its results, said the group was pleased by the well-defined charge to the NTP panel. He noted the interval between the nomination and the report (11 years) and questioned the reasons listed for removing animals from the study, suggesting they may have skewed the results, leading to incorrect statistical analysis of outcomes. He said the effects of RP independent from those of the control cream could not be estimated, and the control cream itself was "a potent carcinogen" and that this was an "inadequate study of carcinogenic activity."

Dr. Rice, first primary reviewer, noted that this study was obviously different from the classic NTP bioassays. He felt that the control cream should have had no effect on the latency, incidence, or multiplicity of skin lesions. He was concerned that the animals scratching themselves as a result of irritation from high doses of retinoids could be a cocarcinogenic stimulus. He thought that the conclusion of photocarcinogenicity for RA was not sufficiently supported by the data. The other primary reviewers, Drs. Cattley, Klaunig, and Smart, all concurred with Dr. Rice's statements.

Responding to the reviewers' comments, Dr. Boudreau noted that in studies such as these, the control cream must be customized to the compound being tested. Each control cream is formulated specifically to blend with the test article. She said the ingredients of the control cream are quite generic. Diisopropyl adipate, a common ingredient in cosmetics, was used as a carrier for the RA and RP in order to incorporate them into the control cream. She added that in most

photococarcinogenesis protocols, there are three experimental groups: an untreated control group exposed to SSL only, a group exposed to the control cream and SSL, and the treated group. The control cream is compared to the untreated group at the same level of SSL to determine the effect of the control cream relative to SSL alone, and the treatment groups are compared to the control cream at the same level of SSL to determine the effect of treatment above that of the control cream. This protocol design allows for parsing out the specific effects of the test articles. She said that the control cream was not irritating, and that no episodes of scratching were seen in the control cream-only group; scratching was seen only with the higher doses of RA and RP. Animals were removed according to specific guidelines regarding skin lesions and skin condition. Similar photococarcinogenesis protocols are used by industry; however histopathology is not typically conducted. That was the practice used to determine the effects of RA, because it would not be possible to discern whether the lesions were due to effects of radiation or because the skin was compromised.

Dr. Birt stated that the report should be clearer that the cream being used is relevant to skin care products and enhances skin cancer, perhaps by adding language addressing that issue to the title of the report. Dr. N.J. Walker, NIEHS pointed out that such language was in the conclusions. Dr. Miller agreed with Dr. Birt that the effects of the control cream should be more prominently featured, perhaps in the report's introduction. He asked if there had been any similar previous studies in which a control cream had been used that had no effect. Dr. Boudreau said that a study of aloe vera used a control cream with no independent effect, and that there were plans to conduct follow-up studies with that type of cream and the retinoids. Dr. P.C. Howard, NCTR, said the FDA had reviewed the report and asked NCTR to conduct follow-up studies to clarify the role of the vehicle in order to clarify some of the issues that had also been raised by the panel.

The panel reviewed the draft conclusions and Dr. Novak suggested that the conclusions be rewritten to address the concerns raised in the discussion. The NTP rewrote the conclusions for consideration by the panel. The revised conclusions were:

These experiments investigated the effect of topical applications of creams containing RA or RP on the photocarcinogenic activity of SSL in male and female SKH-1 hairless mice. Skin lesions were assessed during the in-life phase and/or by histopathologic evaluation at necropsy.

Control Cream
Under the conditions of these studies, the topical treatment of SKH-1 mice with the control cream resulted in earlier onsets of in-life skin lesions and higher incidences and multiplicities of in-life skin lesions, when compared to untreated controls, in the absence and presence of SSL.

The topical treatment of SKH-1 mice with control cream resulted in higher incidences and multiplicities of squamous cell neoplasms of the skin when compared to untreated controls in the absence and presence of SSL.

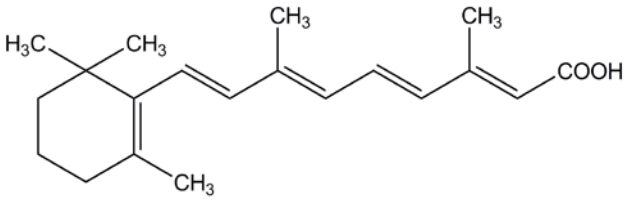
Retinoic Acid
Compared to the control cream, RA further enhanced the effects of SSL in SKH-1 mice based upon earlier onsets and increased multiplicities of in-life skin lesions.

Retinyl Palmitate
Compared to the control cream, RP further enhanced the effects of SSL in SKH-1 mice based upon earlier onsets and increased multiplicities of in-life skin lesions.

Compared to the control cream, RP further enhanced the photocarcinogenic activity of SSL in SKH-1 mice based upon increased incidences and multiplicities of squamous cell neoplasms of the skin.

Dr. Rice moved that the conclusions be accepted as modified. Dr. Klaunig seconded the motion, which passed unanimously with 10 votes.

INTRODUCTION

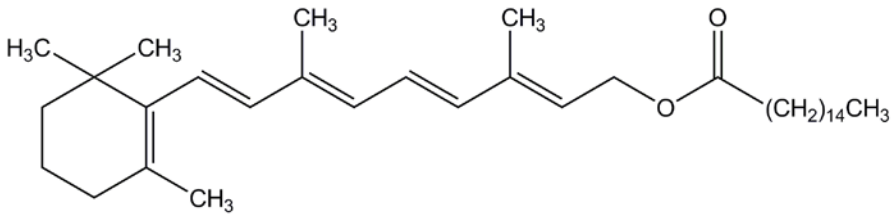


ALL-*trans*-RETINOIC ACID

CAS No. 302-79-4

Chemical Formula: $C_{20}H_{28}O_2$ Molecular Weight: 300.45

Synonyms: All-(*E*)-retinoic acid; all-*trans*-β-A; all-*trans*-tretinoin; all-*trans*-vitamin A_1 acid; beta RA; nonatetranoic acid; tretin M; tretinoin; vitamin A acid; vitamin A_1 acid
Trade names: Renova®, Retin-A®, Retinova®, Vesanoid®



ALL-*trans*-RETINYL PALMITATE

CAS No. 79-81-2

Chemical Formula: $C_{36}H_{60}O_2$ Molecular Weight: 524.88

Synonyms: All-*trans*-retinyl palmitate; retinol palmitate; retinol hexadecanoate; retinyl palmitate; vitamin A palmitate
Trade names: Aquasol A®, Arovit®, Optovit-A®, Palmitate A®

CHEMICAL AND PHYSICAL PROPERTIES

Vitamin A is a generic term for retinoids, lipid soluble compounds that are metabolites, analogues, and derivatives of retinol, that possess biological vitamin A activity (Figure 1). Retinol is also referred to as preformed vitamin A, and vitamin A activity is defined in terms of retinol equivalents (RE) or international units (IU), where 1 µg of retinol equals 1 RE or 3.33 IU of vitamin A activity. The basic structure of the retinoid molecules consists of a cyclic end group, a polyene side chain, and a polar end group. The conjugated system formed by alternating carbon:carbon double bonds in the polyene side chain is responsible for the color of retinoids, which are typically yellow, orange, or red. Variations in side chains and end groups create the different classes of retinoids, which also exhibit substantial variations in pharmacokinetic and metabolic behavior, as well as receptor binding properties. Irrespective of the classifications, the biological activity of retinol serves as the prototype for all retinoids.

Vitamin A readily undergoes many chemical and metabolic modifications, and some of its metabolites are highly reactive. An often undesirable characteristic of many retinoids is that they exert detergent-like properties in cellular membranes and are extremely sensitive to destruction by ultraviolet (UV) radiation. Both UVA and UVB radiation reduce the vitamin A content in human epidermis (Andersson *et al.*, 1999; Fu *et al.*, 2007). Sun-exposed epidermis contains less retinyl esters than adjacent unexposed skin (Carlotti *et al.*, 2004). Furthermore, UV radiation decreases the content of vitamin A in the epidermis as a function of time and UV dose (Sorg *et al.*, 1999).

All-*trans*-Retinoic Acid

All-*trans*-retinoic acid (RA) is a naturally occurring oxidized derivative of retinol that exerts a wide range of biological effects. RA appears as a yellow to light-orange crystalline powder that, in solution, is extremely sensitive to UV light, heat, oxygen, and oxidizing agents (NTP, 1992). The absorption maximum of RA (λ_{max}) is 349.6 nm and the absorption maxima and molar extinction coefficients of RA solutions are 351 nm and 45,000 in methanol (*Merck*, 2006a) and 350 nm and 44,300 in ethanol (Robeson *et al.*, 1955). RA is practically insoluble in water (<1 mg/mL at 25° C), slightly soluble in alcohol and chloroform, sparingly soluble in ether, and soluble in methylene chloride (Meyskens and Fuller, 1980; Ponzoni and Lanciotti, 1990; *Martindale*, 1993). RA is soluble at approximately 40 mg/mL in dimethylsulfoxide and at about 2.7 mg/mL in 95% ethanol (Sigma-Aldrich, 1996a).

Degradation and isomerization of RA are minimized by storage under an inert gas (argon for example), in the dark, at –70° C preferably, or at a maximum temperature of –20° C (Meyskens and Fuller, 1980; Ponzoni and Lanciotti, 1990; Baura and Furr, 1998). Solutions of RA in pure organic solvents are reasonably stable when prepared in subdued light and stored in the dark, whereas aqueous solutions deteriorate quickly (NRC, 1972). Several methods for the synthesis of RA have been published (Robeson *et al.*, 1955; *Merck*, 2006a; Dawson and Hobbs, 1994).

All-*trans*-Retinyl Palmitate

All-*trans*-retinyl palmitate (RP) is a naturally occurring retinoid formed by the enzymatic esterification of retinol and palmitic acid. RP appears as a light yellow to yellow-red semisolid or a clear to hazy golden viscous, oily liquid with a faint odor. The activity of 1 IU of vitamin A is contained in 0.55 µg of RP (*Martindale*, 1993). RP is soluble in most organic solvents such as chloroform, ether, and vegetable oil, is slightly soluble in alcohol, and is insoluble in water (CIR, 1987). A clear yellow solution is obtained at approximately 100 mg/mL in chloroform (Sigma-Aldrich, 1996b). RP in the semisolid state and in solutions is sensitive to air and light. In peroxide- and acid-free organic solutions, RP is reasonably stable when stored in the dark at –20° C (*Merck*, 2006b). The absorption maximum and molar extinction coefficient of RP in ethanol are 325 to 328 nm and 52,490, respectively (*Merck*, 2006b). The product can be synthetically prepared, and methods for the synthesis and purification of RP have been described (Baxter and Roberson, 1942; Furr *et al.*, 1986; Dawson and Hobbs, 1994).

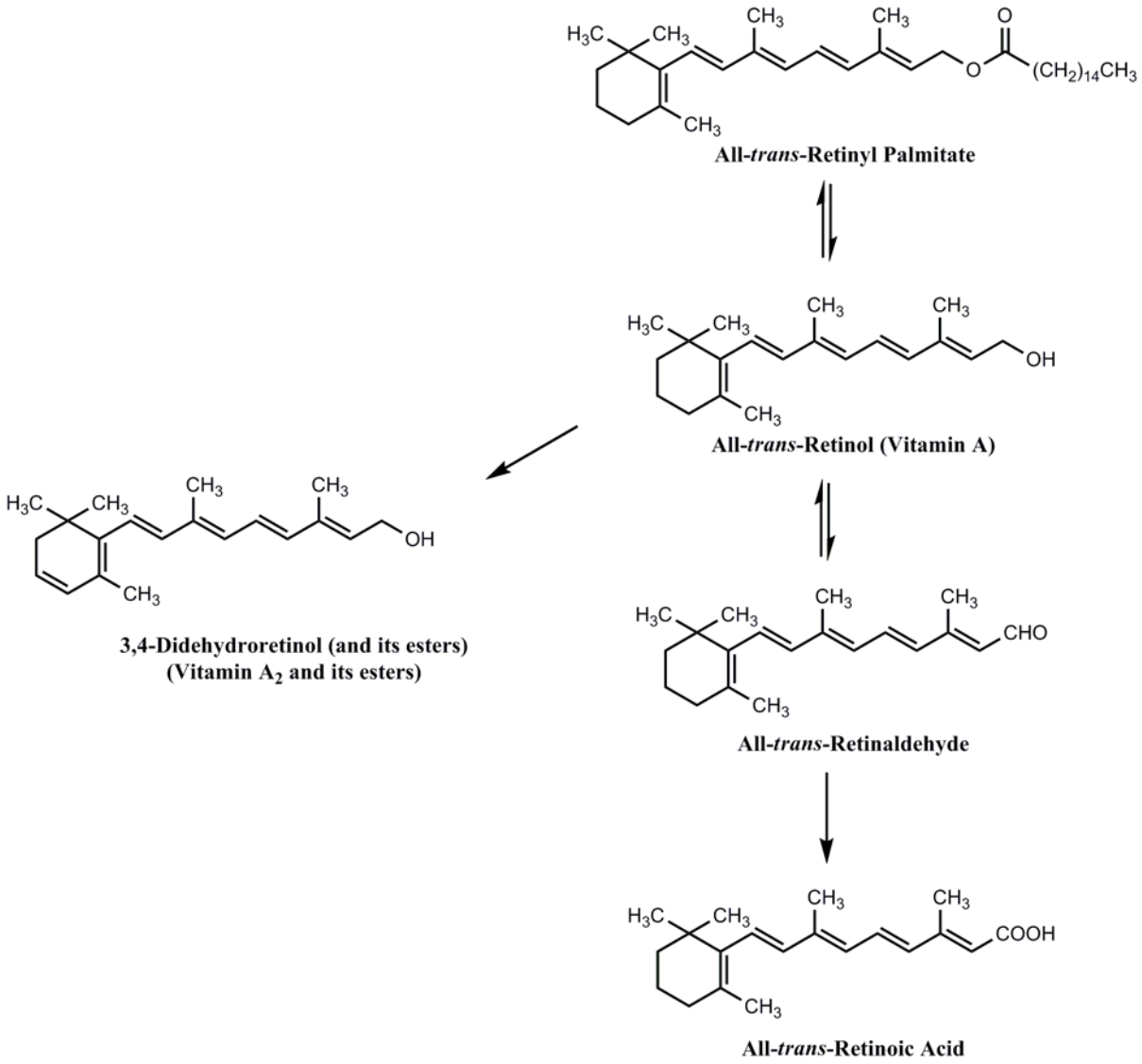


FIGURE 1
Structures of Selected Retinoids

PRODUCTION, USE, AND HUMAN EXPOSURE

While vitamin A is required for the development and maintenance of healthy skin, higher animals are incapable of *de novo* synthesis of compounds with vitamin A activity; therefore, these compounds must be obtained from exogenous sources. Vitamin A in the skin is predominately derived from the diet. Increasingly, however, skin care products containing various retinoids are becoming an important source of cutaneous vitamin A.

All-*trans*-Retinoic Acid

RA is currently used in a number of dermal drug products such as Retin-A® cream [containing 0.1%, 0.05%, or 0.025% RA (tretinoin)] for treating psoriasis and acne vulgaris and Renova® or Retinova® [containing 0.05% RA (tretinoin)], which are used as adjunctive agents for the mitigation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin (PDR, 2001). RA was the first retinoid developed for this type of topical use and is a component of many commercial products that are advertised as being able to slow skin aging or remove wrinkles and stretch marks by increasing collagen production in the dermis. RA is also used by some to treat hair loss, and under the tradename Vesanoid® it is used to treat at least one form of cancer (acute promyelocytic leukemia, also called acute myeloid leukemia subtype M3). RA, usually together with other drugs, induces the differentiation and terminal cell division of immature leukemic blood cells (Huang *et al.,* 1988; Castaigne *et al.,* 1990). The pathology of the leukemia is due to highly proliferative immature cells, and RA drives these cells to develop into functional cells that help to alleviate the disease.

All-*trans*-Retinyl Palmitate

RP is a naturally occurring retinoid formed by the enzymatic esterification of retinol and palmitic acid. RP is the major ester of retinol found in the retina, liver, skin, and intestine of most vertebrates and is the form most abundant in the diet of mammals (Biesalski and Nohr, 2004). In mammals, RP is metabolically inert, which enables cells to store high concentrations of vitamin A without affecting regulatory steps and vitamin A activity (Vahlquist, 1999).

RP is a widely used ingredient in facial makeup and skin and hair care preparations and is promoted for its beneficial effects on the appearance of skin. Concentrations of RP in cosmetic preparations are usually less than or equal to 1% (CIR, 1987). Since retinyl esters are more chemically and thermally stable than retinol, retinyl esters are the preferred retinoid for use in skin care products (Idson, 1990). RP is the most stable of available vitamin A esters and can be readily incorporated into an anhydrous base or the oil phase of a cosmetic cream or lotion (Idson, 1990). Therefore, topical application of RP is a practical strategy for increasing levels of vitamin A in the skin. Studies suggest that enzymes are available in skin to metabolize RP to retinol during skin absorption (Boehnlein *et al.,* 1994).

Data available from the Food and Drug Administration's (FDA) Voluntary Cosmetics Registration Program on cosmetic products indicate that 102 cosmetic formulations in the United States market contained RP in 1981, and this increased to 355 in 1992, 667 in 2000, and more than 700 in 2004 (FDA, 2004).

RP is commercially produced by the esterification of retinol with palmitic acid, and several processes have been developed for its synthesis. Two major synthetic procedures for retinol are those of Hoffmann-La Roche and of Badische Anilin- und Soda-Fabrik (BASF) (CFSAN, 2000). The Hoffmann-La Roche procedure involves a 14-carbon aldehyde as a key intermediate and the efficient reduction of acetylenic to olefinic bonds near the end of the synthetic process. The BASF procedure depends on the Wittig reaction, by which a phosphonium ylide reacts with an aldehyde or ketone to yield an olefin and phosphine oxide (Olsen, 1991). Retinol may be esterified by any one of several procedures. An imidazolide method is widely used because the nonacidic reaction conditions used in this procedure stabilize retinol (Frickel, 1984). RP is insoluble in water but soluble in diethyl ether. While all retinoids have limited chemical and photochemical stability, RP has been shown to be more stable chemically than retinol (Carlotti *et al.,* 2002). Gradual decomposition of RP occurs in the presence of light and air, and RP is reactive with oxidizing agents. The Cosmetic Ingredient Review (CIR) Expert Panel found that retinol and RP were safe as cosmetic ingredients in the practices and concentration ranges of use (CIR, 1987). In the CIR report, RP was reportedly used in a total of 102 formulations, most of which were makeup and skin care preparations. Of these 102 products, 86% incorporated RP at concentrations in the range of less than or equal to 0.1% to 1%; only 1% of productions or formulations incorporated RP at concentrations greater than 5%. In 2006, the CIR revised the "as used" concentrations for cosmetic ingredients found safe as used; RP was listed as safe as used in concentrations up to 5% (CIR, 2006).

THE STRUCTURE AND PHYSIOLOGY OF SKIN

The skin is the largest organ of the body, with a surface area in humans of approximately 2 m^2 and a thickness that varies between 0.5 and 4 mm (Kerr, 1999). Many of the specialized physiological functions of the skin are made possible by its unique structure, which is anatomically divided into an outer layer, the epidermis, and the underlying dermis (Figure 2). The primary architecture of the epidermis is formed through the division of keratinocytes in the basal layer of the epidermis followed by a process of differentiation and upward migration to the skin's surface forming the upper layers of the viable epidermis. Through processes not fully understood, the epidermis can also form specialized skin appendages, such as hair, feathers, horns, nails, claws, hooves, and glandular structures (Monteiro-Riviere, 2004).

Human epidermis consists of four or five cell layers depending on the location. The first layer, the stratum basale, is a single layer of keratinocytes that is able to divide and proliferate and is attached to adjacent cells and to the basement membrane, a thin extracellular matrix that separates the epidermis from the dermis (Lavker and Sun, 1982). The most superficial layer of the skin, the stratum corneum, is composed of lipids and several layers of completely keratinized dead cells, corneocytes, that are devoid of nuclei and are constantly being shed (Madison, 2003). The estimated minimum time for the upward migration of a keratinocyte in the stratum basale and the appearance of this newly formed cell as a corneocyte in the stratum corneum is approximately 14 days, with complete replacement of the epidermis occurring every 52 to 75 days (Hoath and Leahy, 2003).

The dermis interfaces with the epidermis through a layer of upward protrusions of dermal papillae (Figure 2), which provide a firm anchor to physically sustain and support the epidermis. The dermal papillae contain a network of capillaries. Since the epidermis contains no blood vessels, the metabolic needs of the epidermis are met through diffusion of nutrients and waste products between the epidermis and capillaries in the dermis.

Compared to other terrestrial mammals, hair development in humans is rudimentary; whereas, the human epidermis is thicker and well-formed, and the thickness persists throughout adulthood (Hoath and Leahy, 2003). Rodents, for example, and other terrestrial mammals typically have a thick epidermis at the time of birth, but the epidermis thins subsequently as the animal matures and develops a coat of fur (Figure 3). The epidermis of male and female SKH-1 mice is similar in thickness, but the male dermis is thicker and the hypodermis of the male is thinner than that of the female. In general, SKH-1 hairless mouse skin is more permeable than human skin and is highly susceptible to chemically induced skin cancer (Benavides *et al.*, 2009). SKH-1 mice are highly susceptible to UV radiation-induced skin cancer and develop lesions that resemble UV radiation-induced tumors in humans; the SKH-1 mouse is widely considered to be the most suitable mouse model for studies of UV radiation carcinogenesis (de Gruijl and Forbes 1995).

Vitamin A has long been known to play a critical role in epithelial homeostasis (Wolbach and Howe, 1925; Randolph and Siegenthaler, 1999). Clinical observations made by Bloch (1921) and experimental studies by Mori (1922) and Wolbach and Howe (1925) first established a link between a diet deficient in vitamin A and abnormal keratinization of epithelia. These early observations served as the foundation for the hypothesis that all epithelial tissues, including epidermis, require adequate vitamin A to sustain normal growth and differentiation.

ABSORPTION OF ALL-*trans*-RETINOIC ACID AND ALL-*trans*-RETINYL PALMITATE

Absorption of All-*trans*-Retinoic Acid in Animals

The transport and metabolism of orally administered radioactive RA were examined by Smith *et al.* (1973). Groups of vitamin A-deficient rats received daily oral doses of RA for 52 days in amounts that either sustained inadequate growth or in amounts sufficient to maintain normal growth. The groups were then administered a final radioactive dose of RA. In both groups of rats, circulating RA (approximately 87%) was found bound to serum albumin and not to retinol binding protein (RBP). Additionally, the total recovery of the radioactive compound in the intact carcasses represented less than 5% to 10% of the administered dose, suggesting that RA was not stored to any significant extent in rat tissues and was excreted rapidly.

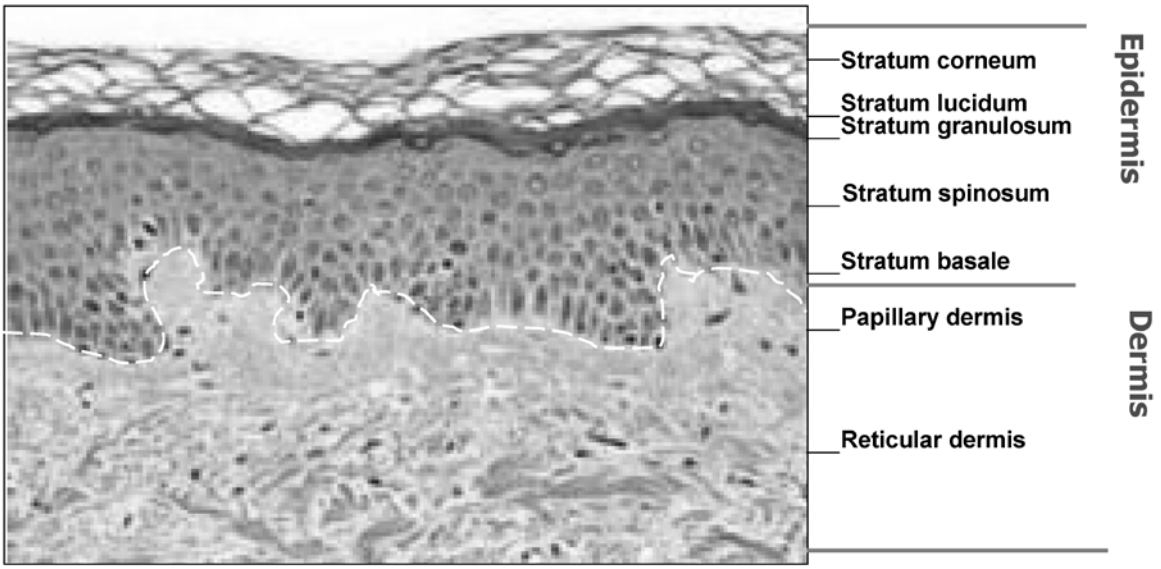


FIGURE 2
Schematic of the Structure of Human Skin
The skin of all mammals consists of three layers of tissue: the epidermis, an outermost layer that contains the primary protective structure, the stratum corneum; the dermis, a fibrous layer that supports and strengthens the epidermis; and the hypodermis, a subcutaneous layer of fat beneath the dermis that supplies nutrients to the other two layers and cushions and insulates the body. The transition from the dermis to hypodermis is irregular and poorly defined.

The epithelial layer of human skin, the epidermis, is primarily protective and consists of five layers that reflect visible changes or stages along the process of keratinocyte maturation. Cells of the stratum corneum layer are dead, protective keratinized "squames" that are eventually sloughed off. The stratum lucidium layer is found beneath the stratum corneum of thick skin and is only found on the palms of the hands and the soles of the feet. The cells of the stratum lucidum are flattened and contain an oily substance that is the result of exocytosis of lamellar bodies accumulated while the keratinocytes are moving through the stratum spinosum and stratum granulosum. It is this substance that gives the stratum lucidum its waterproof properties, and it is also called the barrier layer of the skin. Cells in the stratum granulosum layer accumulate *keratohyalin*, visible as darkly stained granules. The presence of this layer is diagnostic for keratinized stratified squamous epithelium. Cells of the stratum spinosum layer are attached to one another by desmosomes ("spines") and reinforced by tonofilaments. These cells gradually move outward as new cells are formed from the basal layer. Cells of the basal layer are attached to the basement membrane (dashed line) by hemidesmosomes. When a basal cell divides, one of the daughters migrates upward to replenish outer layers of cells.

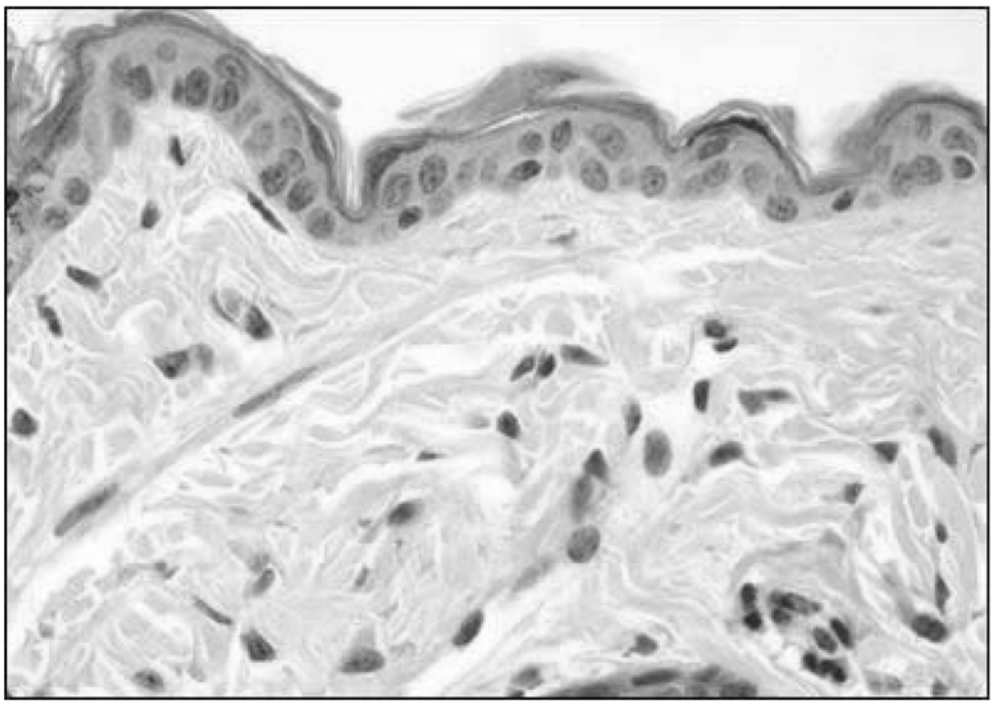


FIGURE 3
Schematic of the Structure of the SKH-1 (hr^-/hr^-) Mouse Skin
There are several structural differences between human skin and that of the SKH-1 (hr^-/hr^-) mouse. For example, human skin exhibits greater topographic differences than the SKH-1 mouse, and the epterestidermis of human skin is thicker. The epidermis of human skin is five to six cell layers thick at its minimum. In contrast, the epidermis of the SKH-1 mouse is one to two cell layers thick. Pigment from melanocytes and hair follicles are also present in human skin but not in the albino SKH-1 (hr^-/hr^-) mouse skin.

There are many similarities between human and SKH-1 mouse skin in the development of nonmelanoma skin carcinogenesis, including the development of malignant squamous cell carcinoma from preexisting benign lesions. The hairless SKH-1 mouse is sensitive to the immunosuppressive effects of UV radiation, and produces an immune protection factor and an erythema protection factor that is equivalent to the human sun protection factor (SPF) in the presence of sunscreen. However, there are significant differences between the mouse model and humans as well. For example, ras^{Ha} mutations are much less frequent in human skin cancers. Additionally, basal cell carcinomas and actinic keratoses are much more common in humans, while hairless SKH-1 mice usually develop benign squamous papillomas. Additionally, the stages of skin carcinogenesis are much more discrete in the SKH-1 mouse.
(Image modified from on-line version; Conti *et al.*, 2004).

Absorption of All-*trans*-Retinoic Acid in Humans

The amount of RA in the diet is small, probably in the range of 10 to 100 μg/day (IARC, 1999). The amount of RA ingested in the diet thus presents neither a benefit nor a risk, especially upon consideration that RA is rapidly metabolized, not stored to any extent in tissues, and does not accumulate over time (Blaner and Olson, 1994). Due to its association with significant systemic side effects, such as hypertriglyceridemia, muco-cutaneous toxicity, corneal opacities, skeletal hyperostosis, and teratogenesis, oral use of RA is generally not recommended except for treatment of medical disorders (Lehman *et al.,* 1988).

Typical fasting plasma levels of RA are in the range of 4 to 14 nM/L in humans and 7.3 to 9 nM/L in rats (Cullum and Zile, 1985; Eckhoff and Nau, 1990). Plasma RA can be derived from dietary sources and from endogenous metabolism of retinol in tissues. Dietary RA is variably absorbed, and its bioavailability is enhanced with concomitant food intake (Cunningham and Bryce, 2004). Shapiro and Latriano (1998) reviewed the pharmacokinetic and pharmacodynamic properties of oral administration of RA. In humans treated with RA (45 to 80 mg/m^2 per day) for acute myeloid leukemia, studies showed that the time to maximal plasma concentration was 1 to 2 hours, the area under the concentration time curve (AUC) ranged from 387 to 682 μg/L, and elimination was rapid with a $T_{½}$ of 40 to 60 minutes (Shapiro and Latriano, 1998). Repeated oral dosing with RA for 2 to 6 weeks, on the other hand, was associated with a significant decrease in both plasma peak levels and AUC, suggesting that accelerated clearance from plasma was associated with increased RA catabolism (Muindi *et al.,* 1992).

Absorption of All-*trans*-Retinyl Palmitate

Vitamin A is ingested by mammals either as retinyl esters (primarily RP) from animal products or as provitamin A carotenoids from plants (Biesalski and Nohr, 2004). After digestion, RP is hydrolyzed in the intestinal lumen and absorbed via a carrier-mediated process into the intestinal cells as retinol (Erlanson and Borgström, 1968; Rigtrup *et al.,* 1994a,b; van Bennekum *et al.,* 2000). Cellular retinol binding protein (CRBP) type II is a cellular protein within the brush border of the enterocyte that binds retinol with high affinity and facilitates its absorption (Cunningham and Bryce, 2004).

Intestinal Uptake and Delivery by Circulation

Retinoids are dispersed and emulsified in the stomach; however, the stomach does not play a role in the hydrolysis of retinoids (Borel *et al.,* 2001). Rather, digestion and hydrolysis occur in the lumen of the duodenum, where pancreatic and biliary enzymes are secreted (Harrison and Gad, 1989). In the intestinal mucosa cell, retinol, regardless of dietary origin, is re-esterified with long-chain fatty acids, primarily palmitic acid, to retinyl esters by lecithin:retinol acyltransferase (LRAT), acyl-coenzyme A:retinol acyltransferase (ARAT), or both (Helgerud *et al.,* 1982; Ong *et al.,* 1987; Harrison, 1998). Subsequently, retinyl esters along with other dietary lipids are incorporated into chylomicrons and transported to the lymphatic system (Huang and Goodman, 1965; Nayak *et al.,* 2001). Smaller amounts of retinyl esters may be found in very low density lipoproteins (Lemieux *et al.,* 1998).

In general, dietary retinoid uptake and clearance from the postprandial circulation are very similar for mice, rats, rabbits, and humans (Vogel *et al.,* 1999). In the vascular compartment, much of the chylomicron triacylglycerol is hydrolyzed by lipoprotein lipase, which yields chylomicron remnants that contain most of the newly absorbed retinyl esters (Hazzard and Bierman, 1976; Goodman and Blaner, 1984). The chylomicron remnants acquire apolipoprotein E (apoE) either in the plasma or in the space of Disse (Hamilton *et al.,* 1990). ApoE is required for uptake of chylomicron remnants by the liver; however, the exact mechanisms involved in this process are uncertain. A receptor-mediated internalization of chylomicron remnants occurs in liver hepatocytes, where most retinyl esters in chylomicron remnants are efficiently removed from circulation (Hussain *et al.,* 1991; Cunningham and Bryce, 2004). Approximately 30% of chylomicron retinyl esters are cleared from the circulation by extrahepatic tissues (Vogel *et al.,* 1999). The entire process of intestinal absorption to hepatic storage is apparently more regulated for RP than for the synthetic retinoids (Cunningham and Bryce, 2004).

Under conditions of adequate vitamin A nutrition, the main site of vitamin A storage is the liver, where over 95% of the total neutral retinoids are stored as retinyl esters, predominately as RP (Futterman and Andrews, 1964; Linder *et al.,* 1971). Hepatic parenchymal cells are directly involved in the uptake of chylomicron remnants, in the synthesis and secretion of RBP, and in the release of retinol from stellate cells, which are the major storage cells for retinyl esters in the liver (Blomhoff *et al.,* 1990, 1992). In hepatic parenchymal cells, dietary retinyl esters are hydrolyzed to retinol soon after their uptake and prior to transfer of retinol to the stellate cells for re-esterification and storage as retinyl esters in lipid droplets (Blomhoff *et al.,* 1990, 1991, 1992; Blaner and Olson, 1994; Blaner *et al.,* 1994; Hinds *et al.,* 1997).

Depending on the need and physiologic conditions, retinyl esters stored in the liver are hydrolyzed and free retinol is secreted bound to a carrier protein. The transport of retinol from stores in the liver to potential sites of action is accomplished exclusively by means of its specific plasma transport protein, RBP (Soprano and Blaner, 1994). RBP has one binding site for one molecule of all-*trans*-retinol, and RBP circulates in the plasma as a 1:1 molar complex with another plasma protein, transthyretin (TTR; formerly called prealbumin) (Wei *et al.,* 1995). The RBP-TTR complex reduces glomerular filtration and renal catabolism of the low molecular weight (~ 21,000) RBP. Other retinoids, such as RA, are carried less specifically by albumin and other serum proteins (Arnhold *et al.,* 1996; Harrison, 2005). Normal levels of plasma retinol-RBP remain constant between 2 and 3 μM in well-nourished humans and slightly lower in well-nourished rats, mice, and rabbits (Goodman and Blaner, 1984; Soprano and Blaner, 1994). Retinol bound to RBP-TTR in the plasma is effectively taken up by tissue cells, and particularly by vitamin A-dependent target tissues such as the eye, skin, and other epithelia.

Percutaneous Uptake and Deposition of Systemic Retinol

Despite the fact that the epidermis is avascular, with the nearest blood supply residing in the dermis, it contains significant quantities of vitamin A (Randolph and Siegenthaler, 1999). Total retinol content in normal human epidermis averages 335 ng/g on a wet tissue weight basis (Randolph and Siegenthaler, 1999). The total vitamin A content of the epidermis clearly indicates that plasma retinol has access to and is taken up by epidermal cells, though the mode of uptake of retinol into human skin is a matter of controversy (Vahlquist and Törmä, 1992; Creek *et al.,* 1993). Some investigators have presented data supporting the hypothesis of receptor-independent uptake of retinol into keratinocytes (Hodam and Creek, 1998); other studies imply involvement of a receptor protein to which the RBP of the RBP-retinol complex is bound (Båvik *et al.,* 1995; Smeland *et al.,* 1995). More recently, expression of the RPE65 gene and protein was demonstrated in cultured human keratinocytes, providing evidence for the involvement of receptor-mediated endocytosis in retinoid-RBP uptake (Hinterhuber *et al.,* 2004). Subsequent studies demonstrated that the gene for RPE65 was expressed in histological sections of normal human epidermis and that expression was down regulated in squamous cell carcinomas (Hinterhuber *et al.,* 2005). While these studies suggest that specific receptors for retinoid-RBP are involved in the cellular uptake of retinol in skin, other investigators have provided evidence that retinol uptake from RBP occurs passively via diffusion across the membrane following its disassociation from RBP (Creek *et al.,* 1993). Randolph and Simon (1993) observed that epidermal keratinocytes maintained in culture medium that contained a physiologic concentration of retinol have an intracellular level of retinol similar to that in intact epidermis. Consistent with this observation, *in vitro* studies by Hodam and Creek (1998) showed that uptake and subsequent esterification of retinol by human keratinocytes was not facilitated by complexing retinol with RBP. These *in vitro* studies suggest that cellular uptake of retinol could be independent of a specific receptor and could involve free retinol in equilibrium with RBP. In general, the delivery of retinol to tissues through the circulation may involve a variety of overlapping pathways that provide compensatory mechanisms under different physiologic conditions (Soprano and Blaner, 1994; Paik *et al.,* 2004). It was suggested that changes in physiologic conditions, such as levels of vitamin A intake and storage, may influence the relative importance of receptor-mediated and receptor-independent cellular uptake of retinol (Paik *et al.,* 2004).

Under normal physiologic conditions, retinol taken up from the plasma by keratinocytes in the skin is found bound to CRBP type I, a specific binding protein for retinol that resides in the cytoplasm (Ong, 1994). Keratinocytes also contain cellular retinoic acid binding protein (CRABP) types I and II, which are specific cytosolic binding proteins for RA. Both CRBP and CRABP are known to function as modulators of retinol metabolism. CRBP and CRABP have the ability to direct the metabolism of bound retinol by sequestering retinoids so that they are unavailable for reaction with some enzymes but are still accessible to other enzymes. For example, Ong *et al.* (1994) showed that CRBP-retinol is restricted from esterification by ARAT, but is available for esterification by LRAT. Additionally, Napoli (1999, 2000) showed that the interaction of CRBP-retinol with a specific retinol dehydrogenase may initiate the synthesis of RA. CRABP is involved in the metabolism of RA to more polar metabolites (Ong, 1994). For example, at low physiologic concentrations of RA, rat testicular microsomes were found to metabolize RA more rapidly when bound to CRABP than when in the free state (Fiorella and Napoli, 1991; Fiorella *et al.,* 1993).

CRBP and CRABP are expressed in the cytoplasm of keratinocytes in all strata of the epidermis. Using immunohistochemical methods, Busch *et al.* (1992) showed that CRBP and CRABP levels are lowest in epidermal basal cells and increase in suprabasal layers of the skin. The highest levels of CRBP and CRABP were found in the stratum granulosum. The incremental

abundance of the retinoid binding proteins in keratinocytes in progressively later stages of differentiation suggests that they play an important role in the differentiation process. In general, the concentration of CRBP in a tissue is thought to be a good indicator of the concentration of retinol in that tissue; however, Randolph and Siegenthaler (1999) found that the epidermal concentrations of CRBP (~80 nM) and RBP (~50 nM) are only about one-fourth of the unesterified retinol concentration in the epidermis (~600 nM). This excess of retinol over total binding protein suggests that epidermal CRBP is likely saturated with retinol, which favors retinol esterification by LRAT over RA synthesis (Randolph and Simon, 1993; Kurlandsky *et al.,* 1994). Consistent with a role for CRBP in modulating the production of RA from retinol, the expression of CRBP in the epidermis appears to be regulated by retinoid concentration. The topical application of retinol to the skin increases the content of retinol in the epidermis and results in increases in CRBP mRNA levels throughout the epidermis along with a concomitant increase in the epidermal content of retinyl esters (Kang *et al.,* 1995; Duell *et al.,* 1996). Similarly, topical treatment of skin with RA increases the expression of CRBP mRNA in a manner similar to retinol (Fisher *et al.,* 1995), suggesting that keratinocytes throughout the epidermis are able to control their supply of retinol and the synthesis of RA by regulating the expression of CRBP mRNA.

Esterification of cutaneous retinol appears to primarily involve two enzymes, LRAT and ARAT. LRAT is a microsomal enzyme that catalyzes the reversible transfer of the *sn-1* fatty acid from membrane-associated phosphatidylcholine to retinol bound to CRBP (Ruiz *et al.,* 1999). LRAT plays an important role in regulating retinol storage and diverting retinol from metabolism to more biologically active retinoids such as RA (Kurlandsky *et al.,* 1996). ARAT catalyzes the reversible transfer of the fatty acid from acyl-CoA to free retinol, in other words, retinol not bound to CRBP. While ARAT activity in the skin and other organs has been described, molecular identification and characterization of ARAT has remained elusive (O'Byrne *et al.,* 2005). Some evidence suggests that the ARAT activity responsible for the esterification of retinol may be attributed to acyl CoA:diacylglycerol acyltransferase (DGAT) (Orland *et al.,* 2005; Yen *et al.,* 2005). High levels of expression for genes in the DGAT family have been demonstrated in interfollicular human skin and in sebaceous glands (Turkish *et al.,* 2005; Yen *et al.,* 2005).

Kurlandsky *et al.* (1996) studied retinol esterification in keratinocytes derived from different layers of human skin and found that keratinocytes from the basal layer of the epidermis esterified retinol four times faster per cell than keratinocytes derived from suprabasal layers of the skin. Since holoCRBP was required for retinol esterification by cells derived from the basal layer, this activity was attributed to LRAT. Additional experiments by Kurlandsky *et al.* (1996) supported the view that ARAT was primarily responsible for retinol esterification by keratinocytes in the suprabasal layers of the skin. It has been observed that the pH in the upper layers of the epidermis may additionally favor retinol esterification through a pathway involving ARAT, since it was shown that CRBP-independent ARAT activity has a pH optimum between 5.5 and 6.0 (Törmä and Vahlquist, 1990) which is close to the pH at the skin's surface (Rothman, 1954).

Cutaneous Absorption and Deposition of Retinoids

It is widely acknowledged that the stratum corneum is the rate-limiting barrier in skin to the absorption of most topically applied chemicals. The stratum corneum is composed of approximately 40% lipids, 40% proteins, and 20% water and is generally permeable only to small lipophilic molecules (Elias and Feingold, 1988). Although factors such as the number of epidermal cell layers and the thickness of the stratum corneum may modulate absorption, the major barrier to topical absorption of chemicals is the intercellular lipid channels (Monteiro-Riviere, 2004). Studies have shown that strategies such as lipid extraction, inhibition of lipid synthesis, and penetration enhancers that biochemically alter epidermal lipid composition also affect epidermal barrier function (Monteiro-Riviere *et al.,* 2001).

Cutaneous Absorption and Deposition of Retinoic Acid – *In vitro* Studies

Lehman *et al.* (1988) used Franz diffusion cells to investigate the influence of vehicle, photodegradation, and dose on the *in vitro* percutaneous absorption of tritiated RA and several of its metabolites in monkey and human skin samples. They found that the penetration of retinoids through monkey and human skin was highly vehicle-dependent. Of the five vehicles examined, penetration followed the order propylene glycol = isopropyl alcohol > mineral oil > diisopropyl adipate > polyethylene glycol 400. Isopropanol consistently yielded the highest total penetration and offered the additional benefits of adequate solubility, rapid evaporation from the surface of the skin, and cosmetic acceptability. More than 60% of the applied RA dose remained on the skin surface, approximately 30% was found in the epidermis, approximately 10% was deposited in the dermis, and less than 1% penetrated the skin and was collected into the receptor. Furthermore, the amount of RA that penetrated the epidermis did not increase in proportion to dose administered over a 35-fold range in human skin.

Bailly *et al.* (1998) evaluated the metabolism of radiolabeled RA by human skin biopsies treated topically for 24 hours. The topical treatment with RA resulted in a 50% to 70% recovery of the applied radioactivity, with the greatest accumulation of radioactivity recovered in the epidermis and 5- and 30-fold lower accumulations in the dermis and medium, respectively. Sixty-six percent of the radioactivity in the epidermis was recovered as RA and 17% as more polar metabolites. In the dermis, the proportion of polar metabolites increased to 24% of the radioactivity recovered, and in the medium, polar metabolites accounted for more than 90% of the recovered radioactivity.

Due to their availability, animal skin models are routinely used as surrogates for human skin in percutaneous absorption studies *in vitro*. Hairless animal skin has the added advantage of not requiring shaving prior to testing. Fresno Contreras *et al.* (2005) evaluated the permeation behavior of tritiated RA delivered to hairless rat skin in three systems: hydrogel with RA, hydrogel with the RA encapsulated in liposomes composed of stratum corneum lipids and the addition of hyaluronic acid, or hydrogel with RA not encapsulated but with the addition of hyaluronic acid. Accumulation of RA in the surface and skin layers was evaluated by tape-stripping and dissection techniques. Using Franz-type diffusion cells, these authors found that the *in vitro* diffusion and permeability of tritiated RA in rat skin was significantly lower in formulations that contained hyaluronic acid and specifically in the case of the RA encapsulated in stratum corneum lipid liposomes. Percutaneous absorption of RA was significantly lower by the treatment of rat skin with hyaluronic acid and encapsulation. Hyaluronic acid and encapsulation of RA prolonged the release of RA and promoted retention of RA in the stratum corneum, epidermis, and dermis layers of rat skin. RA levels remained significantly higher in the skin up to 8 hours after the application of the hyaluronic acid and encapsulated liposome cream application. Encapsulating systems were also shown to protect retinoids from degradation under UVB and UVA radiation over time (Carlotti *et al.*, 2004).

Cutaneous Absorption and Deposition of Retinoic Acid – Animal Studies

Results from *in vivo* and *in vitro* studies suggest that cutaneous drug deposition is related to the follicular density of the skin. Hisoire and Bucks (1997) examined the percutaneous delivery of tritiated RA in haired (Hartley strain) and hairless [Crl:IAF/HA(hr/hr)] guinea pig skin. Haired animal skin was clipped and shaved 1 day prior to sacrifice. Hairless skin was not shaved. Full thickness dorsal skin was mounted on flow-through diffusion cells, and the RA formulation was applied on the epidermal skin surface. Contrary to expectations, the penetration profile indicated that hairless guinea pig skin was much more permeable to RA than haired skin despite the lower follicular density in the hairless animal, suggesting that the absorption of RA through guinea pig skin was influenced more by the structural and compositional differences in the stratum corneum that exist between the animal strains than follicular density.

Cutaneous Absorption and Deposition of Retinoic Acid – Human Studies

Topical RA is generally used to treat acne, photodamage, and disorders of dyskeratinization. RA topically applied has poor cutaneous penetration (Latriano *et al.*, 1997; Shapiro and Latriano, 1998). Human percutaneous absorption studies of radiolabeled and non-radiolabled RA in various formulations administered to different surface areas have indicated that RA is minimally absorbed through the skin and, therefore, would be expected to add little to endogenous RA levels (Schaefer and Zesch, 1975; Thorne, 1992). In fact, no study has been found to document an increase of RA concentrations above endogenous levels in humans, regardless of the surface area of application (Sass *et al.*, 1996; Latriano *et al.*, 1997).

Buchan *et al.* (1994) applied 2 g of a gel containing 0.025% RA to the face, neck, and upper chest of four subjects overnight for a period of 14 days and found that plasma levels of RA and its metabolites did not increase above endogenous levels. Latriano *et al.* (1997) found that the absorption of RA (approximately 2%) was not altered by either a single application or by 28 days of daily applications. In patients who received long-term therapy (greater than 1 year), absorption of RA averaged 1.1%. Mean plasma concentrations of RA after 28 days of treatment with a 0.05% concentration of RA as Renova®, Retinova®, or Retin-A® were not significantly different from endogenous concentrations before treatment.

Cutaneous Absorption and Deposition of Retinyl Palmitate – *In vitro* Studies

The penetration and percutaneous absorption of RP have been studied by a number of investigators using both *in vitro* and *in vivo* approaches. *In vitro* methods have been used to assess both the penetration and metabolism of topically applied retinol and RP.

Boehnlein *et al.* (1994) investigated the percutaneous absorption of RP through excised human skin and hairless guinea pig skin. After mounting excised skin in a flow-through diffusion cell, RP was applied (20 µg/cm^2) in acetone. The amount of applied material, or its metabolites, that penetrated into the skin and the amount that passed through the skin into the receptor fluid were

assessed at different time points. After 24 hours, 17.8% and 30% of the topically applied material had penetrated and were deposited in human and guinea pig skin, respectively. In human skin, approximately 44% of the absorbed RP was hydrolyzed to retinol. A much smaller amount of the RP (0.2%) penetrated completely through the skin into the receptor fluid of the diffusion cell. Hairless guinea pig skin was found to be more permeable to RP than skin from humans; however, retinol was the only metabolite of RP detected in both hairless guinea pig and human skin, suggesting that topically applied RP may deliver significant retinol into the skin.

Jenning *et al.* (2000) evaluated the penetration of RP-loaded solid-lipid nanoparticles that were incorporated into a hydrogel or an oil-in-water cream in pig skin. RP was applied to full-thickness pig skin mounted in Franz diffusion cells for 6 or 24 hours. RP was incorporated into three different formulations: an oil-in-water cream with freely dispersed RP, an oil-in-water cream with freely dispersed RP and drug-free solid-lipid nanoparticles, and an oil-in-water cream with RP encapsulated in solid-lipid nanoparticles. Following the conventional cream application, RP accumulated in the upper skin layers over 24 hours, with a much smaller but increasing amount of RP found in the deeper skin layers. The addition of solid-lipid nanoparticles did not increase RP penetration. After 6 hours, the highest RP level in the deeper layers was obtained with the conventional cream (14.6 ng as compared with 7.9 ng for the drug-free solid-lipid nanoparticles and 5.5 ng for the RP-encapsulated solid-lipid nanoparticles). When drug-free solid-lipid nanoparticles were added to the conventional formulation, a reduction of the amount of RP in the upper skin layers resulted (75.5 ng compared with 150.4 ng at 6 hours). The recovered amount of RP in the deeper skin layers was greater than that recovered from the conventional cream treatment only after prolonged treatment for 24 hours, indicating that the barrier properties of the stratum corneum were altered by the presence of solid-lipid nanoparticles. The encapsulation of RP in solid-lipid nanoparticles resulted in RP localization in the upper skin layers, which decreased after 24 hours. RP levels in the deeper skin layers increased but remained lower than with the other formulations, indicating that drug targeting was obtained by RP encapsulation.

Antille *et al.* (2004) examined the penetration and subsequent metabolism of a number of retinoids after topical application to human skin explants mounted in Franz cells. Twenty-four hours following the application (2.5 mg/cm^2) of a cream containing 0.02% retinol, approximately 100-fold increases in retinol and 5-fold increases in retinyl esters (predominately RP) were observed in the skin. Application of RP under similar conditions resulted in a nearly 3-fold increase in the skin level of retinol and 33-fold increase the skin level of RP. No increases in the levels of retinaldehyde or RA were observed after topical application of either compound. The penetration of retinol and RP into the skin of hairless mice was also examined *in vitro* and *in vivo*, and both retinol and RP were found to penetrate mouse skin dramatically better than human skin (Antille *et al.*, 2004). Abdulmajed and Heard (2004) characterized the penetration and metabolism of topically applied RP in different layers of excised human skin. Approximately 60% of the applied RP was found in the skin or had penetrated through the skin. Taken together, these *in vitro* and *in vivo* results indicate that topically applied retinol and RP readily penetrate the skin, and that esterification of retinol and hydrolysis of RP are major routes of metabolism after topical application in these systems.

Cutaneous Absorption and Deposition of Retinyl Palmitate – Human Studies

Consistent with the results of *in vitro* studies, clinical studies and *in vivo* experimental studies demonstrate that both retinol and RP penetrate skin. Kang *et al.* (1995) reported that topically applied retinol not only penetrates human skin, but is metabolized and elicits biochemical changes in the skin. One day after a single application (100 µL/18 cm^2) of a cream containing 1.6% retinol, the levels of cutaneous retinol increased 70-fold, the levels of 13-*cis*-retinol increased 280-fold, and the levels of retinyl esters (predominately retinyl linoleate) increased 260-fold. No significant increases in RA or its metabolites were found. In addition, a single topical treatment that was covered with an occlusive bandage for 4 days resulted in significant increases in epidermal thickness with increased mitotic figures in the epidermis. Biochemical changes were also observed, including a 3-fold increase in levels of both CRBP and CRABP.

Duell *et al.* (1996) examined the metabolism of retinol (0.3%) for periods up to 4 days after topical application and bandage occlusion. Isomerization of the topically applied all-*trans*-retinol to 13-*cis*-retinol, presumably occurring at the skin surface prior to penetration, was the most prominent chemical change observed. In addition, increases in cutaneous levels of retinol (3.7-fold), retinyl esters (150-fold), and 3,4-didehydroretinol (15-fold) were observed. In a subsequent study, Duell *et al.* (1997) examined the effects of topically applied RP (0.6%) on cutaneous retinoid levels at 48 and 72 hours after application. Time-dependent increases in levels of 14-hydroxy-4,14-*retro*-retinol, 13-*cis*-retinol, all-*trans*-retinol, RP, and retinyl linoleate were observed. The most dramatic increases were observed in levels of 13-*cis*-retinol (approximately 15-fold), all-*trans*-retinol

(approximately 5-fold), and retinyl linoleate (approximately 35-fold). The large increase in the retinyl linoleate level was interpreted as an indication that topically applied RP is first hydrolyzed in the skin to retinol with subsequent re-esterification to retinyl linoleate.

Pudney *et al.* (2007) used confocal Raman spectroscopy to monitor the *in vivo* delivery of solutions of all-*trans*-retinol into human skin. Two all-*trans*-retinol (0.3%) solutions were prepared in different solvents: one with 30% propylene glycol/70% ethanol and the other with 99.7% MYRITOL®318 (caprylic/capric acid triglyceride) oil used in skin creams. Solutions were applied and then confocal Raman depth profiles were obtained of the stratum corneum and viable epidermis up to 10 hours after treatment. The all-*trans*-retinol in propylene glycol/ethanol penetrated through the stratum corneum and into the viable epidermis, and its penetration was highly correlated with the depth of penetration of the propylene glycol, an efficient penetration enhancer. In contrast, the all-*trans*-retinol in caprylic/capric acid triglyceride was found to only slightly penetrate the skin, suggesting that the different vehicles can greatly alter the penetration of chemicals into the skin.

PHYSIOLOGICAL AND ENVIRONMENTAL FACTORS THAT AFFECT CUTANEOUS LEVELS OF ALL-*trans*-RETINOIC ACID AND ALL-*trans*-RETINYL PALMITATE

Interactions with Micronutrients

Vitamin A has been known for some time to interact with other micronutrients including vitamin E, vitamin C, zinc, and iron.

Interactions with Micronutrients in Animals

A synergism between vitamins A and E has been demonstrated by a number of investigators, in particular Ames (1958, 1969), who showed that when rats were fed a vitamin E deficient diet, serum vitamin A levels decreased, regardless of the amount of vitamin A administered orally or intravenously. Serum vitamin A levels were restored to normal by supplementation with vitamin E.

It has been suggested that excesses of vitamins C or E could appreciably reduce an individual's vitamin A status (Bieri, 1973). The synthesis of vitamin C in the livers of rats was shown to be impaired by both a deficiency and an excess of vitamin A (Sastry *et al.,* 1962). Furthermore, feeding vitamin C to vitamin A-deficient rats prevented the decrease in hepatic synthesis of vitamin C; however, vitamin C intake had no effect in rats with excess vitamin A. As vitamin C is not endogenously synthesized in humans, vitamin C may act as an antioxidant for excess hepatic retinol.

Severe zinc deficiency often accompanies vitamin A deficiency. Zinc is required to synthesize RBP, which transports vitamin A; therefore, a deficiency in zinc limits the ability of the body to mobilize vitamin A stores from the liver and transport vitamin A to tissues (Vannucchi, 1991). Experiments in rats showed that lower serum retinol concentrations and significantly reduced (50%) cellular hepatic RBP concentrations were observed in zinc-deficient compared with pair-fed animals fed adequate zinc (Mobarhan *et al.,* 1992). In other studies, a zinc-deficient diet was shown to cause increases in both the concentration and the content of hepatic vitamin A but did not alter the ratio of retinol to retinyl esters in rats (Boron *et al.,* 1988). Activities of retinol (alcohol) dehydrogenase were decreased and of retinal oxidase were increased in zinc-deficient animals, indicating that zinc deficiency may cause decreased retinol degradation.

The effects of maternal zinc and vitamin A deficiencies on vitamin A status and pregnancy outcomes were examined in rats (Duncan and Hurley, 1978). Rats were depleted of vitamin A during growth and, at mating, were fed vitamin A depleted diets that contained 0.5, 9, or 100 µg zinc/g of diet, which represented deficient, marginally deficient, or adequate zinc levels, respectively. The rats were then administered retinyl palmitate at 0, 8, or 400 µg retinyl palmitate/kg body weight per day. The numbers of implantation sites affected and malformed fetuses increased with marginal and deficient intakes of either vitamin A or zinc, but the consequences were more severe with combined deficiencies.

Disorders in the metabolism of iron have been reported in vitamin A deficiency, and decreased hemoglobin and packed cell volume have been observed in humans (Hodges *et al.,* 1978). Studies have also shown that iron deficiency decreases liver vitamin A mobilization in rats (Jang *et al.,* 2000). Additionally, studies with heavy metals found an inverse relationship between copper and vitamin A plasma levels (Moore *et al.,* 1972; Sklan *et al.,* 1987).

Interactions with Micronutrients in Humans

In dermatologic applications involving a defect in keratinization, namely keratosis follicularis, pityriasis rubra pilaris, and acne vulgaris, a combination therapy of vitamin A and vitamin E has shown a high degree of

success where vitamin A therapy alone had previously failed to control such conditions (Ayres *et al.*, 1979). In contrast, large doses of vitamin E have been shown to reduce the amount of vitamin A formed in the liver (Swick and Baumann, 1952).

An interaction between zinc and vitamin A was found in patients suffering from various pathologic conditions that severely compromise hepatic function such as cirrhosis, cystic fibrosis, and idiopathic hemochromatosis (Christian and West, 1998). Zinc participates in the absorption, mobilization, transport, and metabolism of micronutrients, including vitamin A; there is also evidence that vitamin A affects zinc absorption and utilization (Smith, 1980).

Interactions with Alcohol and Drugs

Lower hepatic vitamin A levels have been well documented in alcoholics. Consumption of ethanol is commonly associated with deleterious effects, some of which are due to vitamin A deficiency, which aggravates alcohol-induced liver injury, fetal alcohol syndrome, and carcinogenesis (Leo and Lieber, 1999). Both acute and chronic ethanol ingestion have been shown to decrease dietary intake of retinoids and to accelerate the breakdown of retinol through cross-induction of degradative enzymes. There is also competition between ethanol and retinoic acid precursors involving alcohol dehydrogenases and acetaldehyde dehydrogenases (Wang, 2005). The net result of ethanol ingestion is reduced hepatic stores of vitamin A and altered distribution of vitamin A in other tissues (Mobarhan *et al.*, 1991).

Interactions with Alcohol and Drugs in Animals

The combined effects of maternal consumption of dietary ethanol and high doses of vitamin A by gavage on plasma, liver, and fetal vitamin A levels were examined in pregnant rats (Sundaresan *et al.*, 1994). Consumption of ethanol by pregnant rats was accompanied by increases in plasma retinol levels at high daily doses (80,000 IU vitamin A/kg) of vitamin A intake and caused differential effects on fetal levels of vitamin A: female fetuses had significantly higher levels of retinyl palmitate and total vitamin A than fetuses of pregnant rats that received the same dose of vitamin A in the absence of ethanol administration. Ethanol has also been shown to provoke acute exacerbations of psoriasis (Poikolainen *et al.*, 1990). Since retinoids have a beneficial effect in the treatment of psoriasis, an ethanol-induced decrease of intracellular retinol and retinoic acid might explain the worsening of psoriasis with ethanol intake. Ethanol ingestion in both young and older rats induced an altered tissue distribution of vitamin A. After receiving a liquid diet containing 36% of the total energy as ethanol for 3 weeks, older rats had lower serum retinol and higher vitamin A concentrations in the liver than younger animals; however, decreased levels of CRBP were observed in older ethanol-fed animals (Mobarhan *et al.*, 1991).

Interactions with Alcohol and Drugs in Humans

Studies have shown that serum levels of vitamin A in drug addicts are significantly lower than those in non-addict controls. Additionally, studies showed a negative correlation between the serum concentrations of vitamin A and drug habit; a higher number of illicit drugs used and a longer period of addiction resulted in decreased levels of vitamin A (Islam *et al.*, 2001).

Photochemical Interactions

Photochemical Interactions – *In vitro*

Pathways for the photochemical decomposition of retinoids include photoisomerization, photodimerization, and photooxidation (Mousseron-Canet, 1971; Dillon *et al.*, 1996). The light absorbed by retinoids is known to drive a number of photochemical transformations including isomerization, the generation of reactive/radical species, and the formation of degradation products such as lipid peroxides. The importance of retinoid photoisomerization for signal transduction in vision and in light-sensing by microorganisms is well established (Becker, 1988; Hellingwerf *et al.*, 1996). Less is known about the biological importance of retinoid-photosensitized formation of reactive species and light-induced degradation of retinoids.

Generally, the photosensitized formation of reactive species proceeds through two possible mechanisms, and in many cases leads to oxidative damage. In Type I photosensitized reactions, the photoexcited sensitizer reacts directly with the substrate or solvent resulting in either hydrogen-atom or electron transfer. The radicals so produced may initiate free radical chain reactions. Type II photosensitized oxidations involve exchange of energy from the excited photosensitizer to O_2 yielding $^1O_2$ (singlet O_2), which readily oxidizes a wide range of substrates (Foote, 1991).

Experimental studies have demonstrated that photoexcitation of retinol and retinyl esters results in the formation of reactive species via both Type I and Type II photosensitization reactions. Grady and Borg (1968) conducted *in vitro* studies to investigate the role of charge separation in photoreception. Retinals and retinol, frozen (-196° C) in acetone, were induced to form their characteristic free radicals by irradiation with visible light in the absence of added redox agents. After exposure to visible light, radicals were detected by electron spin resonance (ESR) spectroscopy. The data indicated strong localization of excitation energy and of unpaired electron distribution in retinol, with relative

delocalization in the retinaldehydes. Although the radicals could not be resolved and identified, free radicals were viewed as probable products of the light-induced triplet states and as possible participants in the first isomerization step in the photochemical conversion of retinoids to rhodopsin. More recently, Dillon *et al.* (1996) used the nitrone spin trap, 5,5-dimethylpyrroline-*N*-oxide (DMPO), to demonstrate the formation of carbon-centered radicals when retinal, retinol, or RP were irradiated with broadband UV light ($\lambda > 300$ nm). Irradiation of retinal or retinol, dissolved in methanol, resulted in spin-trapped hydroxymethyl radicals formed by hydrogen abstraction from the solvent by the photoexcited retinoid. Xia *et al.* (2006) showed that reactive oxygen species (ROS) were formed when solutions of RP in 70% ethanol/water were irradiated at 320 nm. Photoexcitation of RP in the presence of 2,2,6,6-tetramethylpiperidine, a specific probe for singlet O_2, resulted in the formation of the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical, providing evidence that singlet O_2 was generated. Additional nitrone spin traps, DMPO and 5-*tert*-butoxycarboxycarbonyl 5-methyl-1-pyrroline *N*-oxide (BMPO), were used to investigate the role of O_2^- (superoxide) (Xia *et al.,* 2006). When RP was irradiated in the presence of DMPO or BMPO, ESR signals characteristic for adducts with superoxide (i.e., DMPO-$^{\bullet}$OOH or BMPO-$^{\bullet}$OOH, respectively) were observed. Consistent with the involvement of superoxide, the ESR signal was quenched in the presence of superoxide dismutase. These results demonstrate that both singlet O_2 and superoxide are formed following photoexcitation of RP.

The described studies show that irradiation of retinol and its esters can result in formation of free radicals and ROS. Potential biological targets for these reactive species have also been studied. Polyunsaturated fatty acids are especially susceptible to oxidative damage elicited by reactive species (Buettner, 1993). Cherng *et al.* (2005) showed that the photosensitization of RP results in the formation of lipid hydroperoxides. Irradiation of a solution containing 1 mM RP and 100 mM methyl linoleate in ethanol was conducted with a broadband radiation source [98.9% UVA (315 to 400 nm), 1.1% UVB (280 to 315 nm), and < 0.0001% UVC (250 to 280 nm)] and the extent of lipid peroxidation was assessed by high performance liquid chromatography (HPLC) analysis, monitoring the eluate at 235 nm. A UV dose-dependent formation of lipid peroxides was observed. The lipid peroxidation resulting from the photosensitization of RP was inhibited by dithiothreitol, sodium azide, and superoxide dismutase, suggesting that superoxide plays a role in the formation of lipid peroxides by RP.

Isolated DNA has also been investigated as a target for damage elicited by reactive intermediates resulting from the photosensitization of RP (Yan *et al.,* 2005). Solutions containing supercoiled ΦX174 phage DNA and 0.1 or 1 mM RP were exposed to broadband radiation composed predominately of UVA light. Light-dependent DNA strand cleavage was observed, which was partially inhibited by sodium azide, indicating the involvement of radicals or ROS such as singlet O_2, superoxide, or both.

Photochemical Interactions in Animals

Gaspar and Campos (2007) evaluated the influence of two different UV-filter combinations on the photostability and the efficacy of a formulation containing vitamin A, C, and E derivatives. The vehicle consisted of a phosphate-based self-emulsifying wax and hydroxymethyl cellulose, and contained or not a vitamin formulation consisting of RP (1,700,000 IU/g), 2% vitamin E acetate, and 2% ascorbyl tetraisopalmitate. The vitamin/vehicle formulation was supplemented or not with a photo-unstable UV-filter combination that contained octyl methoxycinnamate, avobenzone, and 4-methylbenzilidene camphor or a photostable UV-filter combination that contained octyl methoxycinnamate, benzophenone-3, and octocrylene. Photostability studies were conducted by applying the vehicle, the vitamin formulation in vehicle, or the vitamin formulation in the presence of the photochemically stable or unstable UV-filter combinations in vehicle to glass plates and exposing the plates to UVA/UVB irradiation. The filter components and vitamins were then quantified by HPLC with detection at 325 and 235 nm and by spectrophotometry. To simulate the effects of daily use, the formulations were applied once daily to hairless mice for 5 days, and hydration, erythema, viscoelastic properties of the skin, skin irritation, and anti-aging effects were measured in skin samples by different noninvasive biophysics techniques. In addition, histopathology, epidermal thickness, and the number of epidermal cell layers were evaluated. Both UV-filter combinations enhanced the photostability of RP, with the photostable filter offering the greatest UV protection. *In vivo* efficacy studies showed that compared with the vehicle alone, the vitamin formulation, alone and when supplemented with the photostable or photo-unstable UV-filter combinations, enhanced the hydration of the skin, enhanced epidermal thickness, and increased the number of epidermal cell layers. However, the vitamin formulation without UV-filter supplementation, which was the least UV-stable formulation, provoked skin irritation on the hairless mouse skin, suggesting that the presence of both photostable and photo-unstable UV-filters reduced skin irritation and that the photostable UV-filter combination provided the greatest UV stability for RP.

Other Factors that Affect Cutaneous Levels of All-*trans*-Retinoic Acid and All-*trans*-Retinyl Palmitate in Animals

Although the cutaneous levels of retinol, retinyl esters, and metabolites of retinol are tightly controlled under normal conditions, several physiologic and environmental factors have been found to affect these levels.

While data are not available for humans, studies with mice suggest that age influences the levels of vitamin A in the skin. Törmä *et al.* (1987) determined that levels of both retinol and RP increased 8 to 10 times in the epidermis of hairless mice after birth and that adult values were attained by 3 weeks of age. The increases in epidermal retinol and RP levels were accompanied by a 2-fold increase in ARAT activity in the epidermis between 3 days and 6 weeks of age. Yan *et al.* (2006a) determined that levels of RP increased in the stratum corneum, epidermis, and dermis of hairless mice between 10 to 20 weeks of age, with smaller changes observed in the levels of retinol. Older mice (60 and 68 weeks old) had lower levels of retinol and RP in all strata of the skin. It is not known at this time whether analogous age-related effects on cutaneous levels of vitamin A occur in humans, and if so, whether these effects have biological significance.

Other Factors that Affect Cutaneous Levels of All-*trans*-Retinoic Acid and All-*trans*-Retinyl Palmitate in Humans

Diseases of the skin, particularly those characterized by abnormal differentiation and hyperproliferation, can result in alterations in the skin concentrations of vitamin A and its metabolites. Vahlquist *et al.* (1982) analyzed serum and skin biopsies from male patients with Darier's disease (keratosis follicularis), a genetically determined disorder of keratinization, and from healthy male controls for carotene, retinol, dehydroretinol, and RBP. The serum carotene levels of affected patients were lower than controls, but serum levels of retinol and RBP did not differ from controls, regardless of disease severity. In the epidermis of lesional skin, the concentration of didehydroretinol (vitamin A_2) was markedly higher than control levels, especially in the severe cases, and suggested that the abnormal distribution of retinoids might reflect localized disturbances of vitamin A metabolism rather than a defect in serum vitamin A transport. The concentrations of vitamin A and caroteneoids were also measured in serum and skin biopsies of 61 patients with acne vulgaris, atopic dermatitis, ichthyosis vulgaris, or lichen planus and compared with those in 37 healthy subjects (Rollman and Vahlquist, 1985). Low serum levels of retinol and high levels of dehydroretinol were previously reported in hyperproliferative forms of ichthyosis vulgaris. However in this study, the mean serum concentrations of retinol and RBP were significantly decreased in patients with acne, were slightly increased in those with ichthyosis vulgaris, and were otherwise normal. In skin biopsies, the mean dehydroretinol concentrations were markedly increased in lesions of atopic dermatitis and lichen planus. No consistent abnormalities were found in skin biopsies of patients with ichthyosis vulgaris.

BIOLOGICAL EFFECTS OF TOPICALLY APPLIED ALL-*trans*-RETINOIC ACID AND ALL-*trans*-RETINYL PALMITATE

Effects of Topical Applications on Cutaneous Levels of All-*trans*-Retinoic Acid and All-*trans*-Retinyl Palmitate

Most of the effects of vitamin A on the skin are thought to involve its principal bioactive metabolite, RA and its 9-*cis*-retinoic acid isomer (Roos *et al.*, 1998). The cutaneous biological effects are thought to result from the interactions of RA or 9-*cis*-retinoic acid with nuclear receptors that are known to be ligand-inducible transcription factors that activate or repress the transcription of downstream target genes. Two families of nuclear retinoid receptors, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs) that share only 29% homology in their ligand binding domain have been shown to mediate the actions of RA. The RARs, including RARα, RARβ, and RARγ, have a high affinity for directly binding RA and become transcriptionally activated by this binding. The RXRs, including RXRα, RXRβ, and RXRγ, differ from the RARs in that they are unable to bind RA, but they bind and are activated by 9-*cis*-retinoic acid (Allenby *et al.*, 1993). These receptors function to regulate transcription by binding to DNA sequences located within the promoter of target genes termed retinoic acid response elements (RARE) or retinoid X response elements (RXRE) (Soprano *et al.*, 2007).

Effects of Topical Applications on Cutaneous Levels of Retinoic Acid in Animals

RA has limited beneficial use; its retention by the skin after topical application is desired, but its systemic absorption is associated with several undesirable systemic side effects (Fresno Contreras *et al.*, 2005).

Connor and Smit (1987) compared the levels of RA detected in SKH-1 hairless mouse skin epidermis and dermis at 4 hours following topical application of retinol to those detected at 4 hours after topical [11-^{3}H]RA

treatment. Retinol (0, 50, 100, or 200 nmoles) or RA (2, 8, 60, or 100 nmoles) spiked with [11-^{3}H]RA were applied in 0.2 mL acetone to the dorsal skin surface of SKH-1 mice under reduced or dark-room lighting. The epidermis and dermis of treated skin areas were separately extracted and analyzed for retinoid content. Control epidermis and dermis samples showed that endogenous retinol concentration was 8-fold higher in the epidermis than in the dermis and levels of RA were below detection limits in the epidermis or dermis from control mice. The epidermal retinol levels increased with retinol dose but appeared to saturate after a retinol dose of 100 nmoles. The levels of RA detected after retinol treatment were two to three orders of magnitude lower than levels found after topical administration of equivalent doses of RA. The elimination half-lives of retinol following topical application of 100 nmoles were 3.0 ± 0.2 and 8.6 ± 1.5 hours from the epidermis and dermis, respectively, and were similar to the corresponding values for an equivalent dose of RA, 3.2 ± 0.1 and 5.43 ± 0.35 hours, respectively. However, the derived maximum tissue contents, calculated by extrapolating back to zero time, were lower after retinol administration (124.5 ± 24.4 nmoles/g epidermis and 1.81 ± 0.33 nmoles/g dermis) than after RA administration (547.0 ± 59 nmoles/g epidermis and 4.56 ± 0.43 nmoles/g dermis), indicating that retinol may have a lower tissue uptake than RA. Antille *et al.* (2003) found no elevation of RA in the skin of hairless mice after topical application of retinol. However, these investigators assessed levels of RA 24 hours after topical application of retinol, and the results of Connor and Smit (1987) suggest RA levels may have decreased below detectable limits 24 hours postapplication.

Effects of Topical Applications on Cutaneous Levels of Retinoic Acid in Humans

The topical application of RA has demonstrated efficacy in keratinization disorders and in the treatment of cutaneous lesions in humans; however, limited data are available on the percutaneous absorption of topically applied RA and its effects on retinoid levels. Latriano *et al.* (1997) assessed the absorption of RA (tretinoin) and plasma levels of RA and its metabolites after single and repeated topical applications. In the first study, 28 subjects received a single 0.05% dose of tritiated RA in an emollient cream formulation (Renova®, Retinova®), cream alone (Retin-A®), or 28 days of repeated nonradioactive doses of RA. In the second study, subjects received a single topical dose of tritiated RA cream (n=5) or 1 year of repeated nonradioactive applications (n=4). Percutaneous absorption of RA was approximately 2% after a single dose or 28 days of daily applications. In subjects who received long-term applications of RA, absorption averaged 1.1%. Neither single-dose nor long-term treatment with topical RA formulations appeared to affect the endogenous levels of RA or its metabolites.

Effects of Topical Applications on Cutaneous Levels of Retinyl Palmitate in Animals

A recent study provides additional information regarding the spatial distribution of retinoids in skin following topical application of RP. Yan *et al.* (2006b) studied the profiles of retinol and RP in strata of the skin of SKH-1 mice treated daily for 4 consecutive days with 0.5% (w/w) RP as an oil-in-water emulsion cream. The levels of RP and retinol in the stratum corneum, viable epidermis, and dermis, as well as whole skin, were determined at time points from 24 hours to 18 days following the final topical application. A rapid and sustained diffusion of RP into all three skin layers was observed, although the epidermis at each measured time point contained the highest level of RP and retinol on a unit weight basis. Levels of RP in the intact skin were approximately 15-fold higher 1 day after the final application of the 0.5% RP cream than 18 days after the last application; however, levels of RP 18 days after treatment were still significantly higher than the levels in control mice. In contrast, the levels of retinol returned to control values within 11 days after the last application of RP.

In a subsequent study, Yan *et al.* (2006a) examined the distribution of retinoids in the epidermis and dermis of female SKH-1 hairless mice that received single or repeated topical applications of creams containing RP (0.5% or 2.0%). RP was rapidly absorbed from the surface of the skin into the epidermis. Compared with untreated controls, the levels of RP and retinol 1 day after application were significantly higher in the epidermis of mice that received topical RP applications, with small, but significant, accumulation of RP in the dermis when compared with vehicle control mice. The levels of RP and retinol in intact skin and isolated epidermis and dermis skin layers of RP-treated mice showed steady decreases with time, but the levels remained higher than those of controls for a period up to 18 days after application.

Effects of Topical Applications on Cutaneous Levels of Retinyl Palmitate in Humans

Concerns have been raised about potential systemic toxicity resulting from the increased use of retinol and retinyl esters in topically applied products. The results of these clinical and experimental studies uniformly demonstrate that topical application is an effective strategy for loading the skin with substantial levels of vitamin A. In addition, these studies indicate that topically applied retinol and RP trigger biochemical changes in the skin that might be expected from the perturbation of retinoid homeostasis. These biochemical changes

include increased expression of retinol and RA binding proteins as well as increased levels of enzymes that metabolize RA. Duell *et al.* (1997) studied the effectiveness of RP in comparison with RA to induce RA 4-hydroxylase, epidermal erythema, and increased epidermal thickness. The topical application of RA to human skin was shown to induce erythema and hyperplasia. A single application of 0.3% RP produced a significant 38% (55 ± 5 µm) increase in epidermal thickness 4 days later in comparison to the epidermal thickness of vehicle-treated skin. Erythema was not observed following RP treatment. A linear dose-response increase in RA 4-hydroxylase activity was observed with RA (0.001% to 0.05%). The application of RP induced a similar linear dose-response; however, a 10-fold higher concentration was required to achieve the same magnitude of response induced with RA. Application of RP increased epidermal levels of retinol but not RP, suggesting that the hydrolysis of RP to retinol and subsequent conversion of retinol to RA occurred in the epidermis and resulted in the induction of RA 4-hydroxylase activity.

Sobeck *et al.* (2002) conducted a pilot study in 12 volunteers to determine the uptake of 0.1% RP from toothpaste into buccal mucosa cells. In this study, volunteers applied the toothpaste cream to the inside of their cheeks for 10 days followed by a wash out phase. An uptake of vitamin A (RP) was demonstrated in all volunteers, and significantly increased uptake was observed between day 0 and day 3, while a significant decrease was observed between day 3 and days 17 and 21 during growth and differentiation of the mucosal epithelium.

Effects of Topical Applications of Retinoids and Ultraviolet Light Exposure on Cutaneous Levels of All-*trans*-Retinoic Acid and All-*trans*-Retinyl Palmitate

Retinoids in sun-exposed skin, whether derived from the diet or from topical application, are irradiated with light having wavelengths expected to drive light-induced alterations. A characteristic feature of retinoids is their sensitivity to UV light. UVA light (320 nm to 400 nm) and UVB light (290 nm to 320 nm) have been shown to reduce the vitamin A content in human skin (Antille *et al.,* 2003). With a maximum absorbance around 325 nm, vitamin A absorbs both UVA and UVB radiation. This is the same region of the solar spectrum that is responsible for most of the skin-damaging effects of the sun (Sorg *et al.,* 2001). While both UVA and UVB radiation in incident sunlight penetrate into the skin, the effects of UVA on the photochemical alteration of retinoids may be quantitatively more important due to the relative abundance of UVA radiation in sunlight and the deeper penetration of UVA radiation into the skin compared to UVB radiation. For example, about one third of UVA radiation having a wavelength of 400 nm penetrates into the epidermis to a depth of 0.1 mm *in vivo*, whereas about 99% of UVB radiation having a wavelength of 300 nm penetrates into the epidermis to a depth of only 0.03 mm (Matsui and DeLeo, 1995). Insights into the effects of UV exposure on cutaneous retinyl esters are provided by studies of retinyl esters irradiated in various solvents and by studies in animal models. Retinyl esters dissolved in a range of solvents readily photodegrade and are more photolabile than retinol (Semenzato *et al.,* 1992; Ihara *et al.,* 1999).

Topical Applications of Retinoids and Ultraviolet Exposure *In vitro*

The photodegradation of cutaneous retinol and retinyl esters has been observed following a single exposure of excised human skin to sunlight, exposure of rabbit skin to narrow band radiation, or exposure of mice to UVA or UVB light (Berne *et al.,* 1984; Törmä *et al.,* 1988; Tang *et al.,* 1994; Sorg *et al.,* 2002). Berne *et al.* (1984) investigated the effect of UV radiation on the concentrations of retinol in rabbit skin *in vivo* and in human skin *in vitro*, and reported that the level of retinol was reduced at 334 nm and the photodecomposition at this wavelength was extensive in the epidermis. When cultured keratinocytes containing tritiated retinol that was partially converted to tritiated retinyl esters were exposed to sunlight, 80% of the retinyl esters disappeared; whereas, approximately 80% of the retinol remained, suggesting that sunlight-induced photodegradation of retinyl esters proceeds more rapidly than of retinol and that, as in solution, retinyl esters are more photolabile than retinol (Chen *et al.,* 1992). The biological consequences of photodegradation of cutaneous retinol and retinyl esters are not known.

Lehman *et al.* (1988) investigated the influence of photodegradation on the percutaneous absorption of tritiated RA and several of its metabolites in monkey and human skin *in vitro*. The investigators found that exposure to light caused a 60% degradation of RA on the surface of the skin, but did not change the amount of compound that penetrated the epidermis.

Carlotti *et al.* (2004) examined the penetration and the photostability of hydrogels or oil-in-water emulsions of RP in relation to UVA and UVB at pH of 4.0 to 8.0, alone and with the addition of sunscreens or antioxidants. In skin penetration studies, most of the RP remained on the surface of pig skin suspended in Franz cells. After 24 hours there was no RP in the receiving phase and approximately 0.015% of the applied dose was detected in the skin samples. Emulsions were found to be better vehicles than hydrogels at protecting the stability of RP in the presence of pH or temperature

changes. However, the presence of an antioxidant or high concentration of sunscreen was found to improve the chemical stability and photostability of RP over time; the percentage of RP decreased when stored in the absence of antioxidant at 25° C or 40° C, and after 15 days RP was not detected.

Topical Applications of Retinoids and Ultraviolet Exposure in Animals

Yan *et al.* (2007) examined the *in vivo* effects of repeated topical applications of RP (0.0% or 0.5%, w/w) and concomitant exposure to simulated solar light (SSL) to alter skin levels of RP and retinol in SKH-1 hairless mice. Groups of mice received either none or daily exposures to SSL (CIE weighted dose of 13.7 mJ/cm^2) and topical applications of cream 5 days per week for a period of 13 weeks. Mice were sacrificed and the skin at the site of application was tape-stripped to remove unabsorbed RP on the surface of the skin. The epidermis and dermis skin layers of mice treated with the control and 0.5% RP creams were isolated, and these along with the intact skin samples of all mice were analyzed by HPLC for RP and retinol content. Significant RP-induced dose-response increases in the levels of RP and retinol were observed in the intact skins of mice. In addition, analysis of epidermis and dermis skin layers of the mice that received 0.5% RP showed substantially higher amounts of RP and retinol when compared with the same skin layers of control mice. These results suggest that exogenously supplied RP may have an impact on vitamin A homeostasis in the skin.

Sunlight-induced degradation of retinyl esters proceeds much faster than that of retinol, and it has been suggested that CRBP protects retinol from photodegradation (Tang *et al.*, 1994). However, studies using hairless mice treated topically with retinol before and after UVB exposure showed that retinol was depleted to a similar extent after the UVB exposure of pretreated mice as compared to untreated mice, in spite of an induction of CRBP (Tran *et al.*, 2001).

Törmä *et al.* (1988) examined the regulation of retinol esterification in hairless mice exposed to UV radiation. Serum levels of retinol and retinyl esters were analyzed by HPLC at 0 and 12 days after a single irradiation with UVB (280 to 320 nm) at a dose of 0.34 J/cm^2 or UVA (320 to 400 nm) at a dose of 1.0 J/cm^2. The immediate retinol-reducing effects of UVB and UVA were similar; however, UVB elicited a more rapid reestablishment of epidermal retinol and a concomitant transient depletion of serum retinol after 2 to 3 days. The activity of retinyl-esterase synthetase was not affected by irradiation, but the ARAT activity increased to 167% on the second day after irradiation with UVB.

Berne *et al.* (1984) investigated the effect of UV irradiation on the concentration of cutaneous retinoids in rabbit skin *in vivo* and in human skin *in vitro*. The irradiation sources were Phillips SP500 W water-cooled high-pressure mercury lamps with water-cooled filters, and irradiation was performed by the application of the light aperture directly to the skin for various periods of time from 0.5 to 15 minutes. The ears of the rabbit and frozen human skin samples were irradiated with four different narrow-wavelength bands (313, 334, 365, or 405 nm) at a dose of 3 J/cm^2. In other experiments, the ears of rabbits were irradiated with a single band width at 334 nm and at a single dose of 0.5, 1.0, or 3 J/cm^2 or six repeated doses of 0.5 J/cm^2. Fresh human skin was irradiated *in vitro* with 334 nm at a single dose of 3 or 10 J/cm^2. The skins were then removed and separated into the dermis and epidermis. In rabbit skin, dose-dependent reductions of retinol were observed, with maximal effects obtained at 334 nm, a wavelength that coincides with the absorption maximum for retinol in organic solvents. Re-establishment of preirradiation levels of cutaneous retinol required more than a week in the rabbit. In human skin samples, the photodecomposition of retinol was most extensive in the epidermis and progressively less so in the dermis, likely reflecting the extent of radiation penetration in the skin.

Effects of Topical Applications of All-*trans*-Retinoic Acid and All-*trans*-Retinyl Palmitate on Systemic Retinoid Levels

Topical Retinoid Application and Systemic Levels in Humans

Ries and Hess (1999) reported that topical application of retinol at concentrations expected in some cosmetics (0.25%) caused no increase in plasma levels of retinol or its metabolites; however, details of the topical exposure and methods of analysis were not provided.

Nohynek *et al.* (2006) published results from a clinical study of female volunteers. Baseline plasma levels of retinol, retinyl esters and RAs were determined prior to initiating 3 weeks of topical applications of creams containing all-*trans*-retinol or RP. Thereafter, one group of 14 subjects received daily application (approximately 1 mg/cm^2 over 3,000 cm^2 of the back, hips and legs) of a cream containing 0.30% retinol, while another group of 14 subjects received daily application of a cream containing 0.55% RP. Plasma levels of retinoid were determined on the first and the last day of topical treatments. On each day designated for plasma sampling, multiple samples were drawn over a 24-hour period to compensate for any circadian variations in plasma retinoid levels. A 12-day wash out period was followed by a single oral administration of

10,000 IU retinol or 30,000 IU retinyl palmitate, which was followed by an additional 24-hour determination of plasma values. Neither the topical treatment with creams containing retinol nor creams containing RP caused significant increases in plasma levels of retinol, retinyl esters, or RA. In contrast, although plasma levels of retinol remained in the physiologic range, there was an increase in plasma values of retinyl esters and RA after oral administration, suggesting qualitatively different responses in humans to oral vitamin A compared with that following topical application.

In a randomized, parallel-designed, placebo-controlled, double-blind study, 40 volunteers cleaned their teeth either with a placebo toothpaste or toothpaste containing RP (1 mg/g) for 56 days (Sobeck *et al.*, 2003). Buccal mucosal cells and blood samples were taken. A significant uptake of RP in buccal mucosal cells occurred after 7 days and a significant increase in plasma retinol was observed after 17 days. The uptake of RP and the subsequent hydrolysis to retinol resulted in enhanced levels of vitamin A in buccal mucosal cells.

Toxicity of Topically Applied All-*trans*-Retinoic Acid and All-*trans*-Retinyl Palmitate

Dermal Irritation in Animals

Sabella *et al.* (1951) demonstrated that retinol dissolved in sesame oil, applied topically to the dorsal skin of ovariectomized mature female rats, resulted in a significant increase in thickness of the epidermis. In this study ovariectomized female rats were divided into groups that received no treatment, sesame oil, estradiol in sesame oil, retinol (5,000 IU/mL) in sesame oil, or estradiol and retinol in sesame oil. The treatments were administered twice daily for 10 days, and the total daily dose of retinol was 3,700 IU. Significant acanthosis was observed in the epidermis, including the stratum granulosum, in the retinol- and retinol/estradiol-treated rats, and the epidermis was approximately twice as thick when compared with the epidermis of rats in the other groups. The thickness was attributed to an increase in the number of cell layers in the epidermis and an apparent increase in cell size. The authors also suggested that an increase in the rate of keratin formation may have contributed to the increase in the stratum granulosum layer of the epidermis. The effects were entirely local in nature, and estradiol did not affect the epidermal response to retinol.

In a similar study, the influence of retinol on the epidermis of Long-Evans male rats was examined by Bern *et al.* (1955). Rats received either no treatment, topical applications of sesame oil or retinol (1,000 IU) in sesame oil, or subcutaneous injections of sesame oil or retinol (1,000 IU) in sesame oil. A 1-inch felt pad was attached with adhesive tape to the shaved dorsal area between the scapulae of all rats. Topical applications were accomplished by daily injection into the felt pad of 300 µL of sesame oil or 300 µL of sesame oil containing 1,000 IU retinol. Subcutaneous injections of similar amounts of materials were performed by insertion of a hypodermic needle directly under the center of the skin area covered by the pad. Treatments continued for 10, 20, 30, or 60 days, after which times subsets of the animals were killed and the skin at the test area was removed and examined, and epidermal thickness was measured. Topical applications of retinol induced acanthosis regardless of the length of treatment, and no signs of adaptation to the topical retinol treatments were evident in rats. The subcutaneous administration of retinol in sesame oil produced no significant reactions in the overlying epidermis, although deposits of the oil solutions were evident.

Dermal Irritation of Retinoic Acid in Humans

Redness, dryness, edema, and scaly crusts are common manifestations of chemical-induced skin irritation. RA has been shown to be a contact irritant, and daily application of RA has been shown to induce an erythematous scaling reaction in human skin and monolayer epidermal cell cultures (Varani *et al.*, 2007). Fisher *et al.* (1991) examined the specificity of the retinoid reaction compared with that of another known skin irritant, sodium lauryl sulfate, in human subjects. Adult volunteers were treated once topically with a commercial preparation of 0.1% RA (Retin-A®), which was applied to approximately 50 cm^2 of skin. A similar-sized area of skin on the contralateral side was treated with water-washable cream vehicle. Control and RA treated areas were biopsied and evaluated. Other subjects were treated with sodium lauryl sulfate (2% in the water-washable cream vehicle) or Retin-A®. Several cellular, histologic, immunologic, and biochemical parameters were examined. The investigators found that many of the observed changes did not appear to be specific to RA-treated skin and that the changes may, therefore, be more associated with epidermal hyperplasia and repair than with the specific direct response to RA *per se*. In addition, no significant differences were found in the histologic changes induced by sodium lauryl sulfate and RA.

Dermal Irritation of Retinyl Palmitate in Animals

Two lots of moisturizer that contained 0.1% RP were evaluated for dermal irritation in groups of three albino rabbits (CIR, 1987). Samples of 500 µL were applied to the shaved back of each test rabbit and a vehicle control sample was applied to the contralateral side for 4 days. The dermal response to the treatments was scored using an 8-point system, with a score of 0 indicating no

evidence of irritation to a score of 8 indicating severe irritation. Irritation indexes for the experimental and control lots were 3.5 and 3.4, respectively in one group, and 3.3 and 3.1, respectively in the other group. The two lots were considered mildly irritating, including the vehicle controls. A similar procedure was used to evaluate the dermal toxicity of a body lotion containing 0.1% RP in three albino rabbits (CIR, 1987). A 500 µL sample of the body lotion was applied daily for 4 days to the shaved back of each rabbit. Well-defined erythema and edema developed within 48 hours and persisted throughout the 7-day study, resulting in subsequent dehydration and desquamation. The body lotion had an irritation index of 3.1.

A dermal toxicity study was conducted on a body lotion containing 0.1% RP in New Zealand albino rabbits (CIR, 1987). The animals (five/sex) were shaved twice weekly and received daily applications of vehicle lotion or RP (6 mg/cm^2) in the vehicle lotion to the flank skin for 90 days. Individual body weight gains, group feed consumption, hematology and clinical chemistry values, urinalysis results, organ weight/body weight ratios, and microscopic evaluations showed no systemic toxicity. All animals developed slight to moderate erythema and edema during the first week of the study, and these symptoms, along with moderate desquamation, persisted throughout the study and were considered indicative of mild dermatitis.

Dermal Irritation of Retinyl Palmitate in Humans

One case report of contact allergy to RP was found (Blondeel, 1984). In this instance, a 55-year old woman had a melanoma on her back removed and replaced by a skin graft. She developed eczematous dermatitis after the use of several topical applications of RP on the donor graft site. Patch tests with a modification of the European Standard series were positive for nickel only. The individual ingredients of the applied cream gave a positive reaction. Further testing with pure RP (10^6 IU/gram) without additives as well as antioxidants used in the formulation resulted in a positive reaction for RP only. The pure RP was negative in 20 other patients, and the investigator noted that the RP may contain trace levels of nickel.

Jordan *et al.* (1975) reported that two male volunteers with positive test reactions to RA were negative when patch tested with 0.1% retinol or RP in petrolatum. A retest conducted 8 months after the initial testing produced the same results.

Phototoxicity

The photocytotoxicity of vitamin A, and concomitant damage to cellular components, has been studied by a number of investigators.

***In vitro* Phototoxicity**

Klamt *et al.* (2003) examined the photocytotoxic effects of retinol using Sertoli cells. Cells were treated with 7 µM retinol for up to 48 hours and then exposed to 1 J/cm^2 of UVC light (256 nm). A 20% to 25% reduction in viability was noted along with fragmentation of genomic DNA, generation of ROS, and peroxidation of mitochondrial lipids. When chelators were added to the cells prior to irradiation, mitigation of damage was observed, implying a metal-catalyzed enhancement of UV photodamaging effects. The investigators suggested that Fe^{+2}-catalyzed destruction of H_2O_2 to yield hydroxyl radicals contributed to the observed photocytotoxicity and cellular damage (Klamt *et al.*, 2000, 2003, 2008; Dal-Pizzol *et al.*, 2001). Yan *et al.* (2005) observed photocytotoxicity after irradiation of Jurkat T-cells that were preincubated with RP, anhydroretinol, or 5,6-epoxy-retinol. Cells exposed to 150 µM of each retinoid and a combination of 3.5 J/cm^2 UVA and 6.3 J/cm^2 visible light exhibited significant toxicity. A Comet assay was used to assess DNA damage in these cells, and the results indicated that significant fragmentation of cellular DNA had occurred.

Phototoxicity of Retinoic Acid in Animals

RA has been shown to stimulate collagen synthesis in UVB-exposed but not in nonirradiated hairless mouse skin (Chen *et al.*, 1992). Mice were irradiated with a total dose of 0.25, 0.77, or 1.43 J/cm^2 UVB for up to 10 weeks. Postirradiation treatment with 0.1% RA five times a week induced collagen synthesis in a time- and dose-dependent fashion in photodamaged skin. By contrast, no stimulation of collagen synthesis was detectable in the nonirradiated animals treated with RA for 10 weeks.

Phototoxicity of Retinoic Acid in Humans

Abnormal cutaneous photosensitivity has been associated as a side effect of treatment with RA. Although an increased susceptibility to sunburn reactions has been reported to occur in 5% to 12% of patients, other studies have failed to produce evidence of an abnormal response to sunlight in patients taking RA (Ferguson and Johnson, 1989).

Chronic Topical Toxicity

Chronic Topical Toxicity of Retinoic Acid in Animals

Kligman *et al.* (1992) examined the long-term effects of topical RA (tretinoin) in hairless mice. The dorsal skin of mice was treated three times weekly with 0.025% RA, vehicle cream, or sham treatment, and application was continued for up to 2 years. Biweekly examinations revealed no sign of RA toxicity, and growth and longevity were similar among all groups. The skin

of RA-treated mice had visual characteristics that resembled the skin of younger animals, while control animals had yellowed, irregularly thickened skin. Histologically, plump hyperplastic, but otherwise normal cells were observed in the epidermis of RA-treated mice, while control mouse skins displayed compressed cell layers. In addition, new foci of collagen surrounded by large and abundant fibroblasts and increased amounts of elastic fibers and glycosaminoglycans were present in RA-treated mice; these were all absent in control-treated mice. The results suggested that topical RA may reverse some of the effects of photo- and chronologically-aged skin.

Chronic Topical Toxicity of Retinyl Palmitate

No chronic studies were found that evaluated the toxicology of topically applied RP.

Reproductive Toxicity and Teratogenicity

Reproductive Toxicity and Teratogenicity of Retinoic Acid

RA is the biologically active form of vitamin A for all nonvisual functions of the vitamin and is essential for cell growth and differentiation, reproduction, and embryonic development (Meyskens and Fuller, 1980; Aneskievich and Fuchs, 1992; Maden, 1994; Underhill and Weston, 1998; Collins and Mao, 1999). RA combines with specific nuclear receptor proteins that bind to DNA and regulate the expression of various genes. RA is therefore classified as a hormone. RA is also teratogenic and induces differential patterns of malformations in mammalian embryos based on the different stages of embryonic development (Nau, 1993; Underhill and Weston, 1998; Collins and Mao, 1999; Arnhold *et al.*, 2002; Li and Sun, 2004; Bartholin *et al.*, 2006).

Time-mated Sprague-Dawley rats were administered RA topically to previously clipped intact dorsal skin on gestational days 11 through 14 at three dose levels (12, 100, or 250 mg/kg body weight) (Seegmiller *et al.*, 1990). Maternal weight gain, pup weight, number of resorptions, number of fetuses with gross malformations, and skeletal and organ anomalies were determined. Beginning at gestational day 15, dams treated dermally with RA exhibited skin lesions at the site of application; most dams showed vaginal bleeding by day 16, and approximately 20% did not survive to day 19. Relative to control animals, maternal weight gains in the treated groups were decreased by approximately 50% at the lowest dose, with essentially no weight gain at the intermediate- and high-dose levels. Decreases in fetal weights at the two higher dose levels were significant, but there were no differences from controls in the number of resorptions or malformation frequencies.

Reproductive Toxicity and Teratogenicity of Retinyl Palmitate

Hayes *et al.* (1981) administered Fischer 344 rats 0, 3.2, 32, or 128 mg RP/kg (approximately 1,000, 10,000, or 40,000 USP units per animal) daily by gavage on gestational days 6 to 15. Maternal toxicity, as evidenced by decreased body weight gain and decreased feed and water consumption, was observed at the 128 mg/kg dose level. Maternal toxicity was also observed at the 32 mg/kg dose, but the degree of toxicity was considered slight. Incidences of fetal resorption and embryolethality were significantly increased at the 128 mg/kg dose of RP; among fetuses surviving this dose, 52 of 60 had one or more major malformations, including cleft palate, exencephaly, microphthalmia, anophthalmia, hydronephrosis, brachygnathia, and pinna anomalies, and great vessel and heart anomalies. The lower doses were neither embryolethal nor teratogenic.

Mutagenicity and Antimutagenicity

Retinol and RP have been shown to be nonmutagenic and nongenotoxic and to exert antimutagenic properties in a number of test systems (Teelmann, 1989; Dufour *et al.*, 2009). Retinol at concentrations up to 16 µg/mL did not increase the frequency of sister chromatid exchanges in V79 cells with or without metabolic activation; however, retinol inhibited sister chromatid exchange formation induced by the mutagens cyclophosphamide and aflatoxin B_1 (Huang *et al.*, 1982). The inhibition was dose- and time-dependent and suggested that retinol may have no direct effect on the genetic material but may inhibit metabolic activation of an indirect mutagen or carcinogen.

Retinyl palmitate has been shown to inhibit the effects of 3-methylcholanthrene and benzo[*a*]pyrene binding to DNA (Rocchi *et al.*, 1983). Retinyl palmitate also had an inhibitory effect on the mutagenicity of *ortho*-aminoazotoluene, although its inhibition was approximately 50% that of retinol (Busk and Ahlborg, 1982).

Cherng *et al.* (2005) reported that RP and its photodecomposition products, anhydroretinol and 5,6-epoxy-RP, were neither mutagenic nor photomutagenic in Ames mutagenicity assays with *Salmonella typhimurium* TA102. In addition, when the retinoids were incubated with calf thymus DNA, no DNA adducts were detected using a ^{32}P postlabeling method. Mei *et al.* (2005) used L5178Y/*Tk*$^{+/-}$ mouse lymphoma cells to examine the photomutagenicity of RP. In the absence of UV radiation, RP did not exhibit mutagenicity; however, RP showed dose-dependent photomutagenicity in cells treated with 1 to 25 µg/mL RP and exposed to UVA light (82.8 mJ/cm^2 per minute

for 30 minutes). In an attempt to determine the underlying mechanism for the photomutagenicity, Mei *et al.* (2005) evaluated the loss of heterozygosity at four microsatellite loci in *Tk* mutants spanning the entire chromosome 11 on which the *Tk* gene is located. While the mutational spectrum was significantly different from the negative control for RP in the presence of UVA light, the mutational spectrum was not different from that elicited by UVA light only, which suggests that both UVA light alone and RP in combination with UVA light induced mutations through oxidative DNA damage. The difference in results of photomutagenicity tests of RP obtained with mouse lymphoma assays and those obtained with Ames tests in *S. typhimurium* TA102 indicates that RP and UVA light induce clastogenicity, since compounds that are clastogenic often induce detectable mutagenicity in the mouse lymphoma assay but are rarely mutagenic in microbial mutagenesis assays (Chen *et al.,* 2002).

A more recent study refuted the positive photogenotoxic results obtained by Mei *et al.* (2005). In a study by Dufour *et al.* (2009), the genotoxicity of RP was tested in Chinese hamster ovary cells in the dark, under preirradiation (UVA irradiation and subsequent treatment of cells with RP), or simultaneous irradiation conditions. The source of irradiation for this study was a solar-simulating light, and the ratio of UVB:UVA radiation delivered to the cells was 1:32. The results obtained in this study indicated that RP had no *in vitro* clastogenic or photoclastogenic potential and were inconsistent with the reported positive photogenotoxic/photoclastogenic effects observed in mouse lymphoma cells, although the RP concentration (40 μg/mL) was higher than the 25 μg/mL RP concentration used in the mouse lymphoma assays.

Carcinogenicity/Photococarcinogenicity

The effects of topical RA on ultraviolet radiation-induced photocarcinogenicity have been studied and the results remain controversial since RA has been reported to enhance, reduce, or have no effect on photoinduced carcinogenesis (Forbes *et al.,* 1979; Epstein and Grekin, 1981; Kligman and Kligman, 1981).

Forbes *et al.* (1979) found that the topical application of RA solutions greatly enhanced the response of hairless mouse skin to SSL. In this study SKH-1 hairless male and female mice received daily topical applications of RA [0.0%, 0.001%, or 0.01% RA (w/v) in reagent grade methanol] or croton oil [0.1% (w/v) in reagent grade methanol] for 30 weeks. Beginning on the first day of treatment with croton oil, and on the fifteenth day of treatment with RA, each application was preceded by a 2-hour exposure to SSL at a dose equivalent to 5 minutes of noon summer solstice at 40° N latitude. Unirradiated controls were treated with methanol only or 0.01% RA in methanol. Tumors were found to appear much earlier and in much greater numbers in animals treated daily with RA immediately after the SSL exposure. No dose response was observed, as the doses of RA were equally effective in producing carcinogenesis.

Epstein and Grekin (1981) found no evidence of cutaneous cancers in Uscd hairless mice that were exposed to UVB and topically treated with RA dissolved in a vehicle solution containing butylated hydroxytoluene (0.1%), 95% alcohol (59.6%), and polyethylene glycol (40.2%). In this study, the dorsal region of hairless mice was exposed to 1.25 mJ/cm^2 of UVB followed by the topical application to the same region of 100 μL of the vehicle or 0.05%, 0.025%, or 0.005% RA solutions three times a week over a 12-month period. The mice were regularly examined and tumors greater than 4, 50, or 100 mm^3 were tabulated. The results showed that the 0.025% and 0.005% RA solutions had no influence on UV-induced cutaneous cancer formation, and the 0.05% RA solution significantly inhibited the photocarcinogenesis.

Because divergent results were obtained with albino hairless mice, Kligman and Kligman (1981) examined the ability of RA to enhance photocarcinogenesis in lightly pigmented SKH-2 hairless mice. A two-arm study design was followed. In the first arm of the study, mice received UV exposure only, or UV exposure and concomitant topical application of RA (0.001%) or vehicle, or no UV exposure and topical application of RA (0.01%) or vehicle only for 30 weeks. The UV exposures ceased at 30 weeks, and the topical treatments continued from weeks 31 to 45. In the second arm of the study, tumors were induced by exposing mice to UV only for 30 weeks. During weeks 31 to 45, mice no longer received UV exposure but either received no topical treatment, or received topical applications of 0.001% RA in vehicle, 0.01% RA in vehicle, or vehicle alone. FS 20 sun lamps provided the source of irradiation, and the exposures were for 30 minutes daily, three times per week. Topical applications were administered five times per week, and the applications followed irradiation exposures. RA did not enhance photocarcinogenesis in either arm of the study with regard to onset, tumor yield, or tumor progression, suggesting that the different treatment schedules and different strains of mice may have produced the disparate results.

In a more recent study, Halliday *et al.* (2000) attempted to mimic as closely as possible the human use of RA. Two hairless mouse strains (Skh:HR-1, an albino mouse, and Skh-HR-2, a lightly pigmented mouse) were exposed 5 days/week to solar-simulated ultraviolet radiation, followed by treatment with 0.05% RA for 25 weeks. The pigmented mouse strain was selected to more closely resemble human skin. The mice were initially exposed to 102 mJ/cm^2 UVB, or approximately 33% of the minimal erythemal dose (MED) of UVB, and exposures were increased by 20% per week for the first 4 weeks and remained at this level for the remainder of the study. The results of the study showed that topical application of 0.05% RA followed by exposure to one-third MED of solar-simulated UV radiation on the following day enhanced the formation of squamous cell carcinoma in both the albino and pigmented mice. RA increased the multiplicity of UV-induced squamous cell tumors compared with mice that received the solvent and the same UV exposure at every time point from week 16 for the albino mouse strain and from week 21 for the pigmented mouse strain. Comparison between strains showed that the development of a tan provided only modest protection from UV-induced carcinogenesis.

STUDY RATIONALE

RP was nominated by the Center for Food Safety and Applied Nutrition (CFSAN) within the FDA for phototoxicity and photocarcinogenicity testing based on the increasingly widespread use of this compound in cosmetic retail products for use on sun-exposed skin, the biochemical and histological cutaneous alterations elicited by RP, and the association between topical application of retinoids and enhancement of photocarcinogenesis. Experimental studies indicated that topically applied RA can, under some conditions of testing, enhance photocarcinogenesis. The effects of topically applied RP have not yet been evaluated.

DOSE SELECTION

In preliminary range-finding studies, groups of SKH-1 hairless albino mice (12 males and 12 females/group) were exposed to SSL at an irradiance level of 13.75 mJ•CIE/cm^2 in the morning, 5 days a week for 13 weeks (Appendix I). In the afternoon of the same days of SSL exposure, mice were administered topical applications of creams that contained RP (0.1%, 0.5%, 1.0%, 5.0%, 10.0%, or 13.0%; wt RP/wt of cream) or RA (0%, 0.01%, or 0.1%; wt RA/wt of cream). After the 13 weeks of treatment, the animals were euthanized, and mouse skin from dorsal and ventral sites were processed and examined by histopathology.

RP at concentrations of 5.0%, 10.0%, and 13.0% (wt/wt) and RA at concentrations of 0.01% or 0.1% (wt/wt) in creams were not well tolerated by SKH-1 mice with or without exposure to SSL. Epidermal acanthosis, dermal inflammation, and epidermal necrosis were evident in the 5.0% and greater RP groups and in both RA groups (0.01% and 0.1%). At a meeting of the Toxicology Study Selection and Review Committee in May 2003, Committee members recommended that the doses of RP for the photococarcinogenesis studies be 0%, 0.1%, 0.5%, 1.0%, and 2.0%. Recommendations were to set the dose of RA at 0.001%.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Test Articles

All-*trans*-retinoic acid (RA) (lot 072K1606) and all-*trans*-retinyl palmitate (RP) (lot 092K0637) were obtained from Sigma Chemical Company (St. Louis, MO). Identity and purity analyses were conducted by the Chemistry Support Unit of the National Center for Toxicological Research (NCTR, Jefferson, AR) (Appendix D). Reports on analyses performed in support of the study on the effect of retinoic acid and retinyl palmitate on the photocarcinogenicity of simulated solar light are on file at the NCTR.

Structural characterization analyses of RA (a yellow to light-orange crystalline powder) and RP (a light yellow to yellow-red semisolid or a clear hazy to hazy golden viscous, oily liquid with a faint odor) were performed using direct exposure probe electron impact-mass spectrometry (DEP/EI-MS) and proton nuclear magnetic resonance (NMR) spectroscopy. The DEP/EI-MS revealed one major component with a base peak ion of *m/z* 300 as retinoic acid and one major component with a base peak ion of *m/z* 268 for retinyl palmitate. The RA and RP samples were tentatively identified by electronic comparison to a reference mass spectra. Proton NMR results for both test articles were consistent with the structures of the chemicals.

The purity of lot 072K1606 of RA was determined using reverse phase high-performance liquid chromatography (HPLC) and the purity of lot 092K0637 of RP was determined using reverse phase HPLC and normal phase HPLC. Reverse phase purity estimates of approximately 99% and 97% were obtained for RA and RP, respectively. Normal phase analysis of RP determined an average content of approximately 88% all-*trans*, 9% 13-*cis*, and 1% 9-*cis* isomers.

To ensure stability, bulk RA was stored at –80° C in sealed amber glass vials in the original cardboard shipping container. Bulk RP was stored at 4° ± 2° C in sealed clear or amber glass vials in the original cardboard shipping container. At the end of the study, HPLC analyses of the bulk chemicals were performed by the Chemistry Support Unit at the NCTR, and no degradation of either test chemical was detected.

Diisopropyl adipate (lot 01200070941), used as a solvent for the incorporation of RA and RP into the control cream, was obtained from International Specialty Products, Inc. (Texas City, TX). The diisopropyl adipate (a clear free-flowing liquid) was characterized using proton NMR spectroscopy, gas chromatography electron impact (GC/EI) analysis, and gas chromatography/mass spectrometry (GC/MS). Proton NMR results for the chemical were consistent with the structure of diisopropyl adipate. GC/EI analysis revealed one major component with a base peak ion of *m/z* 129 and the samples were tentatively identified by electron comparison to a mass spectrum of the *bis*(1-methylethyl) ester of hexanedioic acid. Lot 01200070941 was estimated to be 99.7% pure by GC/MS. To ensure stability, bulk diisopropyl adipate was stored at room temperature in its original container (a 7-gallon plastic pail) in a locked cabinet.

Base Cream

The base cream used for the control cream and dose cream formulations in this 1-year study was purchased from Cosmetech Laboratories, Inc. (Fairfield, NJ), in one lot (formulation CLI 1392901). The base cream had a pH of approximately 6.8, a specific gravity of approximately 98%, and a mean viscosity of 2,250 centipoise. The base cream was formulated by the supplier to account for 85% (w/w) of the final cream formulations (Table 1), and it was stored in the original containers (high-density polypropylene pails) in a walk-in cold room at approximately 4° C.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

A contract support group (Bionetics Corporation, Jefferson, AR) located at the NCTR prepared the control cream, master batch creams, and dose creams used in this study. All creams were constituted on a weight:weight basis.

Control Cream

The control cream was prepared twice weekly and was composed of the base cream, which accounted for 85%

TABLE 1
Formulation of the Base Cream Used in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Item No.	Phase[a]	Ingredient	% (w/w)
1	A	Water, deionized	59.65
2	A	Disodium EDTA	0.10
3	A	Glycerin 96%	2.50
4	A	Carbopol 981 (2% Solution)	7.50
5	B	Mineral Oil 65/75	7.50
6	B	BRIJ 721	1.50
7	B	Stearic Acid XXX	2.00
8	B	Cetearyl Alcohol	0.25
9	B	Octyl Palmitate	2.50
10	C	NaOH (20% Solution), sufficient quantity to adjust pH to 7.0	0.50
11	D	Germaben II	1.00
		Total	85.00

[a] Manufacturing instructions: heat phase A to 75° C. Add phase B to phase A. Add phase C. Cool to 40° C and add phase D. Homogenize mixture and package cream at 35° C.

of the final control cream formulation, and diisopropyl adipate, which accounted for the remaining 15% of the final control cream formulation.

Master Batch Creams

Twice weekly, the Chemistry Support Unit at the NCTR prepared a 0.6667 mg/g solution of RA dissolved in diisopropyl adipate. An RA (0.01%) master batch cream was subsequently prepared twice weekly and was composed of the base cream (85%) and the 0.6667 mg/g RA solution (15%), previously prepared by the Chemistry Support Unit.

An RP (2.0%) master batch cream was prepared twice weekly and was composed of the base cream (85%), with RP (2.0%) and diisopropyl adipate (13%) accounting for the remaining 15%. The 2.0% RP master batch cream served as the high dose RP dose cream in the study and as the source of RP for the 0.1%, 0.5%, and 1.0% RP dose creams.

Retinoic Acid and Retinyl Palmitate Dose Creams

Dose creams of RA (0.001%) and RP (0.1%, 0.5%, and 1.0%) were prepared twice weekly by mixing the appropriate amount of control cream with the master batch cream of either RA or RP. Aliquots of the 2.0% RP master batch cream were used for the 2.0% RP dose cream.

In order to protect the test chemicals from degradation, the cream formulations were shielded from ultraviolet light and mixed with Teflon®-coated impellers and spatulas. The dose formulations were dispensed under an argon stream into 20 mL amber-colored glass vials with Teflon®-lined screw-caps and stored at approximately 4° C for up to 3 days. Each vial contained sufficient control or dose cream for a single day of topical applications. The glass vials of the prepared creams were delivered to the NTP-FDA Center for Phototoxicology at the NCTR and stored at approximately 4° C until application to the mice.

Homogeneity and stability studies of the 0.001% RA dose cream and homogeneity studies of the 0.1% RP dose cream were performed by the Chemistry Support Unit at the NCTR using HPLC. Homogeneity was confirmed, and stability was confirmed for at least 7 days for dose creams stored under argon gas in amber glass vials sealed with Teflon®-lined screw caps at approximately 4° C.

Dose certification of the RA and RP dose creams were conducted approximately weekly by the Chemistry Support Unit at the NCTR using HPLC. The conditions of use of the test chemicals in this study dictated that dose creams be administered to the mice prior to completion of dose certification analyses. Therefore, while an acceptability range of ± 10% of target concentration was desirable, the goal of the dose certifications was to

enable calculation of the dose that was administered to an animal at a specific point in time. The mean (over the 1-year study) percent target ± standard deviation for RA in the 0.001% RA dose cream was 89.4 ± 11.8% (Table D3); the corresponding results for RP in the 0.1%, 0.5%, 1.0%, and 2.0% RP dose creams were 102.2 ± 7.3%, 107.5 ± 10.5%, 100.3 ± 11.5%, and 100.3 ± 10.4%, respectively (Table D4).

LIGHT SOURCE AND IRRADIANCE DOSIMETRY

This study was conducted in a similar manner as that of other photococarcinogenesis studies conducted in the NTP-FDA Center for Phototoxicology at the NCTR (NTP, 2007, 2010). The sources of irradiance were glass-filtered (WG320, 1 mm; SCHOTT North America, Inc., Elmsford, NY) 6.5 kW xenon arc lamps (Atlas Electric, Spokane, WA), portable 0.25 inch plate glass filtered fluorescent ultraviolet-A (UVA) lamps, or Kodacel-filtered fluorescent ultraviolet-B (UVB) lamps. The output spectra emitted from the irradiance sources were measured on a weekly basis using a calibrated spectroradiometer. Exposures were monitored with solar light PMA-1101 broad-band dosimeters (Solar Light Company, Inc., Glenside, PA) that were attached to the center-front of each animal rack.

The xenon arc lamp source of irradiance is commonly referred to as simulated solar light (SSL). In the present study, mice were exposed to filtered SSL at 0, 0.3, 0.6, or 0.9 minimal erythema doses (MED) of light (NTP, 2007, 2010). One MED is defined as the minimal amount of radiation that causes slight erythema within 24 hours after irradiation. The actual measured exposure to light in this study was based on the convention of the Commission Internationale de l'Eclairage (CIE, 1987, 1999). The light exposures were determined by measuring the irradiance from the SSL source in mW/cm^2 and multiplying the irradiance by the human erythema action spectrum to obtain a weighted irradiance in $mW•CIE/cm^2$. Since exposure to 1 $mW•CIE/cm^2$ equals 1 $mJ•CIE/cm^2$, the weighted irradiances from the SSL lamp source were multiplied by the duration of exposure to calculate the daily exposures received by the mice. Based on this convention, 0.0, 0.3, 0.6, and 0.9 MED doses of SSL were equivalent to 0.00, 6.85, 13.70, and 20.55 $mJ•CIE/cm^2$, respectively.

The weekly targeted doses of irradiance from the fluorescent UVA or UVB lamps that were administered to mice were based on the spectra distribution of the 6.5 kW xenon arc SSL lamp sources and were equivalent to the amount of UVA or UVB generated by the spectra of the SSL lamps at a dose equivalent to 13.70 $mJ•CIE/cm^2$. The targeted weekly dose of irradiance from the UVA lamps for this study was 7.36 mJ/cm^2, and the targeted daily irradiance dose from the UVA fluorescent lamps for this study was 1.47 mJ/m^2. The animal cage racks were positioned each day to receive a dose rate of 1.5 to 1.8 $\mu J/cm^2$ per second. Similarly, the targeted weekly dose of irradiance from the UVB lamps was 68.5 $mJ•CIE/cm^2$, and the targeted daily dose from the UVB fluorescent lamps for this study was 13.70 $mJ•CIE/cm^2$. The animal cage racks were positioned each day to receive a dose rate of 20 to 50 $\mu J/cm^2$ per second. Daily exposures of light in this Technical Report are given as $mJ•CIE/cm^2$. Appendixes E and F contain additional information on the spectral irradiance and the dosimetry of the lamp sources.

1-YEAR STUDY

Study Design

This study was designed to mimic human use of retinoids, in particular RA and RP, which are generally applied at night and, therefore, have a period of time between application and sun exposure. Groups of 36 male and 36 female SKH-1 mice were irradiated with light emitted from broad-spectrum simulated solar lamps in the morning, 5 days per week, including holidays, for 40 weeks. Additional groups of 36 female mice were irradiated with light emitted from narrow-spectrum UVA or UVB lamps. The mice were then treated in the afternoon, 5 days per week, with 75 µL (approximately 2 mg/cm^2) of control cream or cream containing 0.1%, 0.5%, 1.0%, or 2.0% RP, or 0.001% RA; additional groups of mice received no cream (Appendix J). A 12-week recovery/observation period followed the 40-week exposure/treatment period (Table 2).

Male and female mice that received no cream treatment in this study were exposed to 0.00, 6.85, 13.70, or 20.55 $mJ•CIE/cm^2$ each weekday. Male and female mice that received either the control or dosed creams were exposed to SSL at 0.00, 6.85, or 13.70 $mJ•CIE/cm^2$, except animals administered 0.1% or 0.5% RP cream were not exposed to $0.00•CIE/cm^2$. A single exposure level of either UVA or UVB light, equivalent to the wavelengths spectra of UVA or UVB generated by SSL at 13.70 $mJ•CIE/cm^2$, was administered to additional groups of female mice that received no cream, control cream, 1.0% RP cream, or 0.001% RA cream. The exposure levels of SSL, UVA, and UVB selected for this study were based on previous

TABLE 2
Treatment and Levels of Light Exposure for Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Cream Application	0.00 mJ·CIE/cm^2 per day SSL	6.85 mJ·CIE/cm^2 per day SSL	13.70 mJ·CIE/cm^2 per day SSL	20.55 mJ·CIE/cm^2 per day SSL	UVA	UVB
No cream	36 males 36 females	36 males 36 females	36 males 36 females	36 males 36 females	36 females	36 females
Control cream	36 males 36 females	36 males 36 females	36 males 36 females		36 females	36 females
0.1% Retinyl Palmitate		36 males 36 females	36 males 36 females			
0.5% Retinyl Palmitate		36 males 36 females	36 males 36 females			
1.0% Retinyl Palmitate	36 males 36 females	36 males 36 females	36 males 36 females		36 females	36 females
2.0% Retinyl Palmitate	36 males 36 females	36 males 36 females	36 males 36 females			
0.001% Retinoic Acid	36 males 36 females	36 males 36 females	36 males 36 females		36 females	36 females

NTP photococarcinogenesis studies conducted at this same test facility (NTP, 2007, 2010).

Creams were dispensed with a positive-displacement repeater pipette (Eppendorf Repeater® Plus; Fisher Scientific, Houston, TX) equipped with a 2.5 mL reservoir and distributed with a gloved finger to the dorsal skin region of the animal for 30 seconds. A single-channel, battery operated electronic timer (Fisher Scientific) was used to maintain consistency in the duration of the cream applications. The site of application extended from the nape of the neck to the base of the tail and midway along both sides of the animal. Animals receiving no cream treatment were not handled.

The mice were housed in stainless steel racks that allowed horizontal exposure to the SSL, UVA, or UVB light sources. The racks were placed at preset positions either around the SSL light source or in front of the UVA or UVB light sources with the front of the animal cage facing the light source. In the case of the SSL light source, racks were positioned approximately 2 meters from the light source. The duration of exposure to the light source was based on the dose of SSL, UVA, or UVB. Typical durations for SSL exposure levels of 6.85, 13.70, and 20.55 mJ•CIE/cm^2 were 30, 70, and 90 minutes, respectively.

Source and Specification of Animals

Male and female Crl:SKH-1 *(hr$^-$/hr$^-$)* BR hairless mice were obtained from Charles River Laboratories (Wilmington, MA). The SKH-1 mouse, which is immunocompetent and comparable to other mice in repairing DNA damage (Forbes *et al.*, 2003), was selected based on its historical use in photocarcinogenesis studies (Kligman, 1996; NTP, 2007, 2010). Mice were approximately 4 weeks old upon receipt, quarantined for 2 weeks, and acclimated for 1 week to the animal room environment prior to start of the study. Mice were approximately 8 weeks old at the beginning of the study. Forty-three mice were examined during the quarantine period for serological pathogens, parasites, and bacterial pathogens. Additional screenings of sentinel pairs of each sex were conducted at 3, 6, and 9 months according to the protocols of the NCTR Sentinel Animal Program (Appendix H).

Animal Maintenance

Mice were housed individually in a compartment, with six compartments per cage, six cages per column, and two columns per rack. Feed and water were available *ad libitum*, except during periods of SSL exposure. Due to the design of the racks, neither feed consumption nor water consumption was measured during the course of

the study. Cages were rotated daily, and racks were changed weekly. Further details of animal maintenance are given in Table 3. Information on feed composition and contaminants is provided in Appendix G.

Clinical Examinations and Pathology

Animals were observed twice daily. Body weights were recorded initially, weekly, and when an animal was removed from the study; clinical findings were recorded weekly and when an animal was removed from the study. Mice were examined weekly for the presence of skin lesions that were consistent with the development of UV light-induced skin tumors. The size of each lesion was measured with a digital vernier caliper (Digimatic 500, Mitutoyo America Corporation, Aurora, IL), and the size and location of the individual skin lesions were recorded in the NCTR Multi-Generation Support System database. Digital images of mice with skin lesions were captured each week and used to determine in-life skin lesion latency, incidence, and multiplicity. Mice were removed from the study when the diameter of a skin lesion was greater than or equal to 10 mm. Animals also were removed from the study when individual skin lesions could no longer be discerned due to the merging of the lesions, when the skin on the animal was compromised and breached, or when the health or welfare of an animal was inconsistent with continuance on the study.

Mice removed from the study due to morbidity, skin lesion size, significant skin lesion merging, or at study termination were euthanized by carbon dioxide inhalation. Complete necropsies were performed on all animals. Digital photographs of mice were taken after euthanasia but prior to necropsy. Gross skin lesions were mapped by the study pathologist and numerically labeled on the printed photographs to serve as a guide for the identification and trimming of trace gross lesions (TGLs) that were reported on the individual animal necropsy record (IANR) and to correlate the number of TGLs with the microscopic findings of the study pathologist.

At necropsy, gross lesions from all major organs and tissues were examined, removed, and placed in 10% neutral buffered formalin fixative, mounted in paraffin-plastic blocks, and stored. Descriptions of gross lesions were recorded on the IANR. Gross skin lesions were trimmed, processed, mounted in paraffin-plastic blocks, sectioned at 5 µm, and stained with hematoxylin and eosin. Additional samples of control (normal) skin from the right and left front, the rear dorsal region, and the abdominal ventral region were removed and similarly fixed and processed. For gross skin lesions that measured greater than 5 mm in diameter, samples of the lesions were frozen in liquid nitrogen. The photographdocumented gross skin lesions were correlated with the IANR entries for microscopic examination. Nonneoplastic skin lesions were graded for severity. Tissues other than skin were not microscopically evaluated. The skin of treatment/exposure groups examined by histopathology are listed in Table 3.

Microscopic evaluations were completed by the study pathologist, and the micropathology data were entered into the NCTR Laboratory Data Acquisition System. A microscopic finding was recorded with the corresponding gross observation for skin whenever possible. Microscopic findings were tabulated by the individual animal record in the pathology report and classified as either nonneoplastic or neoplastic. Neoplasms were further defined upon microscopic evaluation by type (squamous cell papilloma, keratoacanthoma, squamous cell carcinoma *in situ*, or squamous cell carcinoma) and were summarized by counts of each neoplasm type by treatment. As part of the pathology evaluation of skin lesions, the incidence (percentage of animals per treatment with neoplasms or nonneoplastic lesions) and multiplicity (average number of lesions per animal) were determined by lesion type. After completion of all microscopic evaluations, the tissue slides, paraffin blocks, and residual wet tissues were stored by Toxicology Pathology Associates in the NCTR pathology archives.

An internal review of the histopathology data was conducted by a quality control pathologist to assure the accuracy, standardization, and completeness of the histopathology examination and reporting process. The quality control pathologist reviewed the skin and skin lesions from 10% of the animals of each dose group. The quality control pathologist evaluated the gross IANR, the gross-to-microscopic correlation, and the histopathology of each case and concurrence or nonconcurrence was documented.

An independent quality assessment laboratory conducted an external pathology data review and quality assessment. The pathology quality assessment review consisted of a reexamination by quality assessment pathologists of all slides and diagnoses from 20% of the male and 20% of the female mice from each of the groups of mice that received no cream or received control cream and were not exposed to SSL; groups of mice that received no cream, control cream, 0.1% RP, or 0.5% RP and were exposed to SSL at 6.85 mJ•CIE/cm^2; and groups of mice that received no cream, control cream, 0.1% RP, or 0.5% RP and were exposed to SSL at 13.70 mJ/cm^2. No animals were included in the quality assessment review from the groups of mice exposed to SSL at 20.55 mJ•CIE/cm^2. Any cases of nonconcurrence between the quality assessment

pathologists and the study pathologist were forwarded to the Pathology Working Group (PWG) panel for resolution.

The quality assessment report, pathology tables, and the report of the study pathologist were reviewed by the PWG coordinator, who reviewed selected skin slides and addressed any inconsistencies in the diagnoses made by the study pathologist and quality assessment pathologists. Representative examples of treatment-related skin lesions and examples of inconsistent diagnoses between the study pathologist and the quality assessment pathologists were presented by the coordinator to the PWG for review. The PWG consisted of the quality assessment pathologist, the study pathologist, and other pathologists experienced in laboratory animal pathology. Each participant examined all slides and discussed his/her observations with the group. The final diagnoses for reviewed lesions represent a consensus among the study pathologist, quality assessment pathologists, and the PWG.

TABLE 3
Experimental Design and Materials and Methods in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Study Laboratory
National Center for Toxicological Research (Jefferson, AR)

Strain and Species
Crl:SKH-1 (hr^{-}/hr^{-}) hairless mice

Animal Source
Charles River Laboratories (Wilmington, MA)

Time Held Before Studies Began
2 weeks quarantine plus 1 week acclimation

Average Age When Studies Began
8 weeks

Date of First Dose and Exposure
June 23, 2003

Duration of Dosing and Exposure
40 weeks

Date of Last Dose and Exposure
May 14, 2004

Scheduled Necropsy Dates
June 23-August 11, 2004

Average Age at Scheduled Necropsy
61 weeks

Size of Study Groups
36 males and/or 36 females

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial body weights

Animals per Cage
One per compartment, six compartments per cage

Method of Animal Identification
Tail tattoo

Diet
Autoclaved NIH-31 open formula pelleted diet (Purina Mills, Richmond, IN) available *ad libitum*, except during light exposure

TABLE 3
Experimental Design and Materials and Methods in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Water
Millipore-filtered tap water (Jefferson, AR, municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*, except during light exposure

Cages
Lenderking model EXP355-72 stainless steel cage/racks (Lenderking Caging Products, Millersville, MD)

Animal Room Environment
Temperature: 25° ± 3° C
Relative humidity: 50% ± 20%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Dose Concentrations and Exposure Levels
No cream groups exposed to SSL at 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 (males and females) or UVA or UVB at equivalent amounts of UVA or UVB generated by SSL at 13.70 mJ•CIE/cm^2 (females only);

Control cream, 1.0% RP cream, 2.0% RP cream, and 0.001% RA cream groups exposed to SSL at 0.00, 6.85, or 13.70 mJ•CIE/cm^2 (males and females);

Control cream, 1.0% RP cream, and 0.001% RA cream groups exposed to UVA or UVB at equivalent amounts of UVA or UVB generated by SSL at 13.70 mJ•CIE/cm^2 (females only);

0.1% RP cream and 0.5% RP cream groups exposed to SSL at 6.85 or 13.70 mJ•CIE/cm^2 (males and females)

Type and Frequency of Observation
Observed twice daily; body weights recorded initially, weekly, and at removal from study; clinical findings recorded weekly and at removal from study; skin lesions digitally photographed weekly

Method of Kill
Carbon dioxide asphyxiation

Necropsy
Necropsies performed on all animals, except where noted. Skin lesions were digitally photographed, mapped, and labeled for correlation with microscopic findings.

Histopathology
Histopathology was limited to the examination of gross lesions and tissue masses on all animals including those that died early or were humanely killed. Histopathology on skin at the site of application and control skin samples was performed on no cream groups that received SSL at 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2, control cream groups that received SSL at 0.00, 6.85, or 13.70 mJ•CIE/cm^2, and 0.1% RP cream and 0.5% RP cream groups that received SSL at 6.85, or 13.70 mJ•CIE/cm^2

STATISTICAL METHODS

Several parameters (survival, body weight, lesion onset, incidence, and multiplicity) were evaluated statistically during the in-life phase of the study and following histopathology of mouse tissues to determine the effects of RA and RP on SSL-induced photocarcinogenesis. Separate statistical analyses were conducted for the following treatment groups:

1. Mice that did not receive cream treatment were compared as a function of the level of SSL exposure (Appendix J). Mice that received no cream treatment and were not exposed to SSL were the reference;
2. To determine the added effects of the control cream, mice that received the control cream were compared to mice that received no cream treatment and were exposed to the same source and level of irradiation;
3. Mice that received the RA or RP cream treatments were compared to mice that received the control cream treatment and exposed to the same source and level of irradiation; and

4. Among irradiation sources, mice exposed to either UVA or UVB were compared to mice that received the same cream treatment and were exposed to 13.70 mJ·CIE/cm^2 SSL.

Survival/Removal Analyses

Mice removed as incorrectly sexed were eliminated from the survival analyses; animals found dead, moribund, or harvested for a tumor-diameter threshold or for excessive tumor burden were considered uncensored; animals accidentally killed or terminally killed were censored at that point in the study. Because most of the uncensored animals were removed from the study for tumor-diameter threshold or excessive tumor burden, this analysis would more appropriately be termed a survival/removal rather than a survival analysis.

A Cox proportional hazards regression model was used to analyze the survival/removal data (Cox, 1972). The hazard function is the slope of the survival/removal regression line and indicates the probability of death/removal at a specified interval of time. In Cox regression modeling, the death/removal rates are expected to change over the course of a study, but at any particular time, the hazard function (slopes of the regression line) of any two groups are assumed to be proportional to each other. The ratio of the hazard functions estimates the relative risk. The hazard ratios and 95% confidence intervals were computed relative to the no cream/no irradiation treatment or to the control cream treatment, as appropriate, for each exposure level and source. All possible decreases in risk relative to the control group were expressed by a hazard ratio between 0 and 1, while all possible increases in risk relative to the baseline group were expressed by a hazard ratio between 1 and infinity. Two-sided P values less than or equal to 0.05 were considered statistically significant. Kaplan-Meier estimates of mean survival/removal times were calculated for each sex by treatment group and each level of SSL or UV light combination (Kaplan and Meier 1958). Kaplan-Meier estimate results were used to generate survival/removal curves and confidence intervals for the experimental groups of interest.

Body Weight Analyses

Body weight data were analyzed using a linear mixed effects model that assumed a heterogeneous first-order correlation structure to accommodate dependence among repeated measurements of body weights on the same animals across study weeks. In these analyses, treatment was a fixed effect with time as a random effect in a repeated measures ANOVA method. Body weight data from 0 to 52 weeks in 4-week intervals were included in the analyses. Orthogonal linear contrasts were used to test dose trends. Contrasts were used to compare treatment groups by weeks-on-study and were performed relative to the no light exposure or the control cream groups, as appropriate. Two-sided probability values were reported.

Analysis of In-Life Skin Lesion Onset, Incidence, and Multiplicity

A Cox proportional hazards regression model was used to compare in-life skin lesion onset among treatment groups for each exposure level of SSL or each type of UV exposure. Cox estimates of hazard functions were used to compute the relative hazard ratios, and probability values were determined using two-sided comparisons with the control cream or no light group, as appropriate. Kaplan-Meier estimates of the mean and median time to lesion onset for each treatment group within each SSL or UV exposure level were generated, along with Kaplan-Meier curves. The mean time of lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion.

In-life skin lesion incidence was compared among treatment groups, for each exposure level of SSL or for each type of UV exposure, using continuity-corrected Poly-3 tests. Two-sided comparisons were made with the control cream group or the group that received no light, as appropriate.

A Poisson regression model was used to compare in-life skin lesion multiplicity (number of skin lesions/animal for a given treatment group) among treatment groups for each SSL level of exposure or each type of UV exposure (Nelder and Wederburn, 1972). Statistical analyses were performed by carrying forward data to the end of the study (either week 52 or removal date) for each animal. The log-transformed "end of study week" was used as the offset to effectively convert the lesion count to a lesion rate. A skin lesion count of one half was added to each observation to ensure convergence of the Poisson regression algorithm. Two-sided comparisons were made using contrasts to the control cream or to the no cream no light groups, as appropriate.

Analysis of Histopathology Tumor Incidence and Tumor Multiplicity

Histopathology Tumor Incidence

The histopathology tumor incidences were presented as the number of mice bearing skin lesions at a specified anatomical site and the number of mice that were examined microscopically (Tables A1, A3, B1, and B3). Statistical analyses were conducted for any neoplastic or

nonneoplastic skin lesion morphology type with an incidence of three or more in any one group, along with the corresponding treatment group of the opposite sex (Tables A2 and B2).

The incidences of neoplastic and nonneoplastic skin lesions were analyzed using the continuity-corrected Poly-3 test (Bailer and Portier, 1988a,b; Portier and Bailer, 1989) with Bieler and Williams' (1993) modification. Tests of significance included dose-trend effects and pairwise comparisons of treatment groups with the control cream or to the no cream no light groups, as appropriate. Probability values are one-sided.

Analysis of Histopathology Tumor Multiplicity

The tumor counts represent the number of specific morphology type skin lesions evaluated and counted by histopathology subsequent to the necropsy of each animal. Poisson regression models for tumor counts by morphology type were used to analyze the data, with the log-transformed "end of study week" as an offset. A skin lesion count of one half was added to each observation to ensure convergence of the Poisson regression algorithm. Two-sided comparisons were made with contrasts to the control cream or no cream no light groups, as appropriate.

QUALITY ASSURANCE METHODS

This 1-year simulated solar light study on RA and RP was conducted in compliance with the Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). The Quality Assurance Unit of the NCTR performed audits and inspections of protocols, procedures, data, and reports throughout the course of this study. Independent and separate audits were conducted for the completeness and accuracy of the pathology data, pathology tables, pathology specimens, and the pathology report. The audit findings were reviewed and assessed by the NCTR staff, and all comments were resolved or otherwise addressed either before or during the preparation of the Technical Report.

Raw data sheets from the study are archived by the NCTR's record management unit. Histopathology samples collected during the course of the study are stored in the archives of Toxicologic Pathology Associates at the NCTR. Backup computer data are maintained by the computer staff at the NCTR. All records and samples are stored in accordance with Food and Drug Administration Good Laboratory Practice Regulations.

RESULTS

1-YEAR STUDY

The results on the groups of mice that received no cream treatment only and were used to assess baseline effects of simulated solar light (SSL) and ultraviolet (UV) radiation exposure can be found in Appendix J.

Animal Survival/Removal

The disposition of mice in the 1-year SSL study is shown in Tables 4 and 5 for male and female mice, respectively. Thirty-six male mice were initially allocated to each of 20 different treatment groups, and 36 female mice were initially allocated to each of 28 different treatment groups, including those treatment groups exposed to UVA or UVB light. With the exception of three incorrectly sexed mice and the autolysis of one mouse, all mice in the no cream, control cream, 0.1% RP cream, and 0.5% RP cream groups were examined microscopically by the study pathologist. Two accidental deaths occurred in groups that were not microscopically examined.

TABLE 4
Disposition of Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
No Cream				
Mice initially in study	36	36	36	36
Natural deaths	1	1[a]	1	1
Moribund	6	8	0	1
Skin lesion ≥ 10 mm	0	2	35	34
Terminal kill	27	25	0	0
Missexed	2[b]	0	0	0
Examined microscopically	34	35	36	36
Control Cream				
Mice initially in study	36	36	36	0
Natural deaths	2	1	0	
Moribund	3	7	3	
Skin lesion ≥ 10 mm	2	27	33	
Terminal kill	29	1	0	
Examined microscopically	36	36	36	
Retinyl Palmitate 0.1%				
Mice initially in study	0	36	36	0
Moribund		3	1	
Skin lesion ≥ 10 mm		33	35	
Terminal kill		0	0	
Examined microscopically		36	36	
Retinyl Palmitate 0.5%				
Mice initially in study	0	36	36	0
Natural death		0	1	
Moribund		3	0	
Skin lesion ≥ 10 mm		32	35	
Terminal kill		0	0	
Missexed		1[b]	0	
Examined microscopically		35	36	

TABLE 4
Disposition of Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Retinyl Palmitate 1.0%				
Mice initially in study	36	36	36	0
Natural deaths	1	0	1	
Moribund	7	1	2	
Skin lesion ≥ 10 mm	20	35	33	
Terminal kill	8	0	0	
Examined microscopically	0	0	0	
Retinyl Palmitate 2.0%				
Mice initially in study	36	36	36	0
Natural deaths	2	2	1	
Moribund	7	4	1	
Skin lesion ≥ 10 mm	24	30	34	
Terminal kill	3	0	0	
Examined microscopically	0	0	0	
Retinoic Acid 0.001%				
Mice initially in study	36	36	36	0
Moribund	3	1	0	
Skin lesion ≥ 10 mm	13	35	36	
Terminal kill	20	0	0	
Examined microscopically	0	0	0	

[a] Advanced autolysis precluded pathology examination.
[b] Incorrectly sexed and discarded from study.

TABLE 5
Disposition of Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2	UVA	UVB
No Cream						
Mice initially in study	36	36	36	36	36	36
Natural deaths	1	1	0	0	1	0
Moribund	1	2	3	0	8	1
Skin lesion ≥ 10 mm	0	3	32	36	0	35
Terminal kill	34	30	1	0	27	0
Examined microscopically	36	36	36	36	0	0
Control Cream						
Mice initially in study	36	36	36	0	36	36
Natural deaths	0	2	1		2	1
Moribund	6	0	3		5	1
Skin lesion ≥ 10 mm	2	10	32		3	34
Terminal kill	28	24	0		26	0
Examined microscopically	36	36	36		0	0

TABLE 5
Disposition of Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2	UVA	UVB
Retinyl Palmitate 0.1%						
Mice initially in study	0	36	36	0	0	0
Natural death		1	0			
Moribund		1	2			
Skin lesion ≥ 10 mm		30	34			
Terminal kill		4	0			
Examined microscopically		36	36			
Retinyl Palmitate 0.5%						
Mice initially in study	0	36	36	0	0	0
Natural deaths		0	2			
Moribund		1	2			
Skin lesion ≥ 10 mm		35	32			
Terminal kill		0	0			
Examined microscopically		36	36			
Retinyl Palmitate 1.0%						
Mice initially in study	36	36	36	0	36	36
Natural deaths	1	1	0		0	0
Moribund	6	1	0		4	1
Skin lesion ≥ 10 mm	20	34	36		15	35
Terminal kill	9	0	0		16	0
Accidental death	0	0	0		1	0
Examined microscopically	0	0	0		0	0
Retinyl Palmitate 2.0%						
Mice initially in study	36	36	36	0	0	0
Natural deaths	1	0	1			
Moribund	16	3	4			
Skin lesion ≥ 10 mm	19	33	30			
Terminal kill	0	0	0			
Accidental death	0	0	1			
Examined microscopically	0	0	0			
Retinoic Acid 0.001%						
Mice initially in study	36	36	36	0	36	36
Natural deaths	1	1	0		0	0
Moribund	1	1	1		3	3
Skin lesion ≥ 10 mm	5	32	35		6	33
Terminal kill	29	2	0		27	0
Examined microscopically	0	0	0		0	0

Control Cream Treatment

The analysis of the survival of male and female mice exposed to the same level of SSL and either no cream or control cream is shown in Table 6 and is graphically represented by Kaplan-Meier survival curves in Figures 4 and 5 for male and female mice, respectively. In the absence of SSL exposure, the application of control cream had no significant effect on the survival curves of male or female mice (Figures 4 and 5), and no significant differences were observed in comparison tests between the no cream and control cream groups (Table 6). The Kaplan-Meier curves for male mice exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL showed significant differences between no cream and control cream treatment groups, and significantly lower hazard ratios were observed for no cream male mice when compared to control cream groups that received the same level of SSL exposure (Table 6), suggesting that the topical application of control cream decreased the survival of male mice exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL. The survival of female mice exposed to SSL at levels of 6.85 or 13.70 mJ•CIE/cm^2 was unaffected by control cream treatment, and no significant differences were observed in comparison tests with the no cream groups.

TABLE 6
Cox Hazard Ratios for Mice Administered No Cream Compared to Those Administered Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ·CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit	P Value[a]
Male				
0.00 mJ•CIE/cm^2	1.05	0.37	2.99	0.929
6.85 mJ•CIE/cm^2	0.12	0.06	0.25	**<0.001**
13.70 mJ•CIE/cm^2	0.29	0.18	0.47	**<0.001**
Female				
0.00 mJ•CIE/cm^2	0.24	0.05	1.12	0.070
6.85 mJ•CIE/cm^2	0.46	0.17	1.22	0.117
13.70 mJ•CIE/cm^2	0.67	0.42	1.07	0.096

[a] Cox hazard ratio estimates relative risk of survival. Tests formed by suitable contrasts with the control cream group, which was assigned a Cox hazard ratio of 1.00. Increased survival relative to the control cream group is expressed by a hazard ratio < 1.00; decreased survival relative to the control cream group is expressed by a hazard ratio > 1.00. Significant P values appear in bold-faced type.

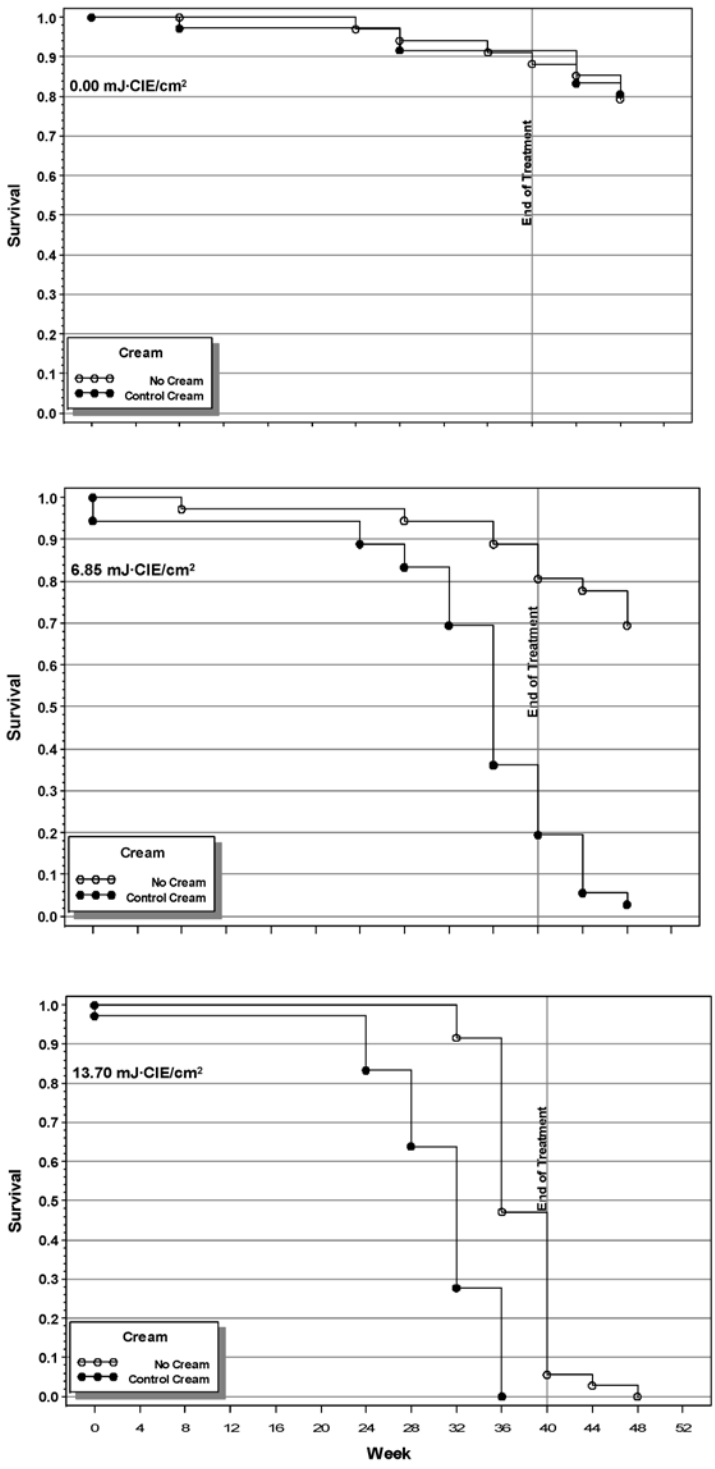


FIGURE 4
Kaplan-Meier Survival Curves for Male Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

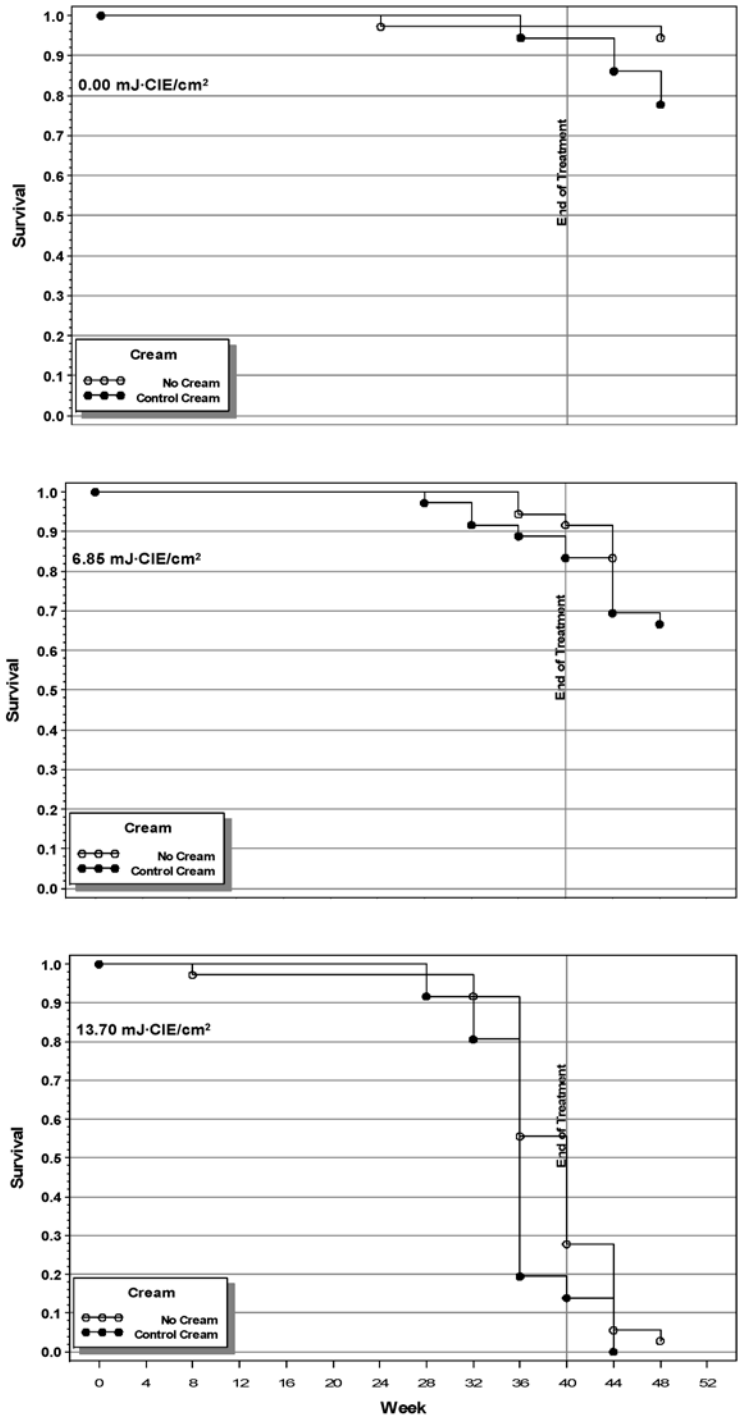


FIGURE 5
Kaplan-Meier Survival Curves for Female Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Retinoic Acid Treatment

The statistical analysis of the survival of male and female mice exposed to the same level of SSL and either retinoic acid (RA) cream or control cream is shown in Table 7 and is graphically represented by Kaplan-Meier survival curves for male mice in Figure 6 and female mice in Figure 7. In male mice, significantly greater Cox hazard ratios were observed for the RA cream groups when compared to the control cream groups that received the same level of SSL exposure, suggesting that the topical application of RA cream decreased the survival of male mice in both the presence and absence of SSL exposure. In the absence of exposure to SSL, the application of RA cream had no significant effect on the survival of female mice (Figure 7), and no significant differences were observed in comparison tests between the RA and control cream groups (Table 7). In contrast, significantly greater Cox hazard ratios were observed in female mice that were treated with RA cream and exposed to SSL when compared with control cream groups exposed to the same level of SSL (Table 7).

TABLE 7
Cox Hazard Ratios for Mice Administered Control Cream or Retinoic Acid Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit	P Value[a]
Male				
0.00 mJ•CIE/cm^2	2.85	1.17	6.92	**0.021**
6.85 mJ•CIE/cm^2	4.15	2.53	6.79	**<0.001**
13.70 mJ•CIE/cm^2	17.19	10.22	28.91	**<0.001**
Female				
0.00 mJ•CIE/cm^2	0.94	0.34	2.59	0.906
6.85 mJ•CIE/cm^2	8.65	4.44	16.83	**<0.001**
13.70 mJ•CIE/cm^2	10.76	6.50	17.81	**<0.001**

[a] Cox hazard ratio estimates relative risk of survival. Tests formed by suitable contrasts with the control cream group, which was assigned a Cox hazard ratio of 1.00. Increased survival relative to the control cream group is expressed by a hazard ratio < 1.00; decreased survival relative to the control cream group is expressed by a hazard ratio > 1.00. Significant P values appear in bold-faced type.

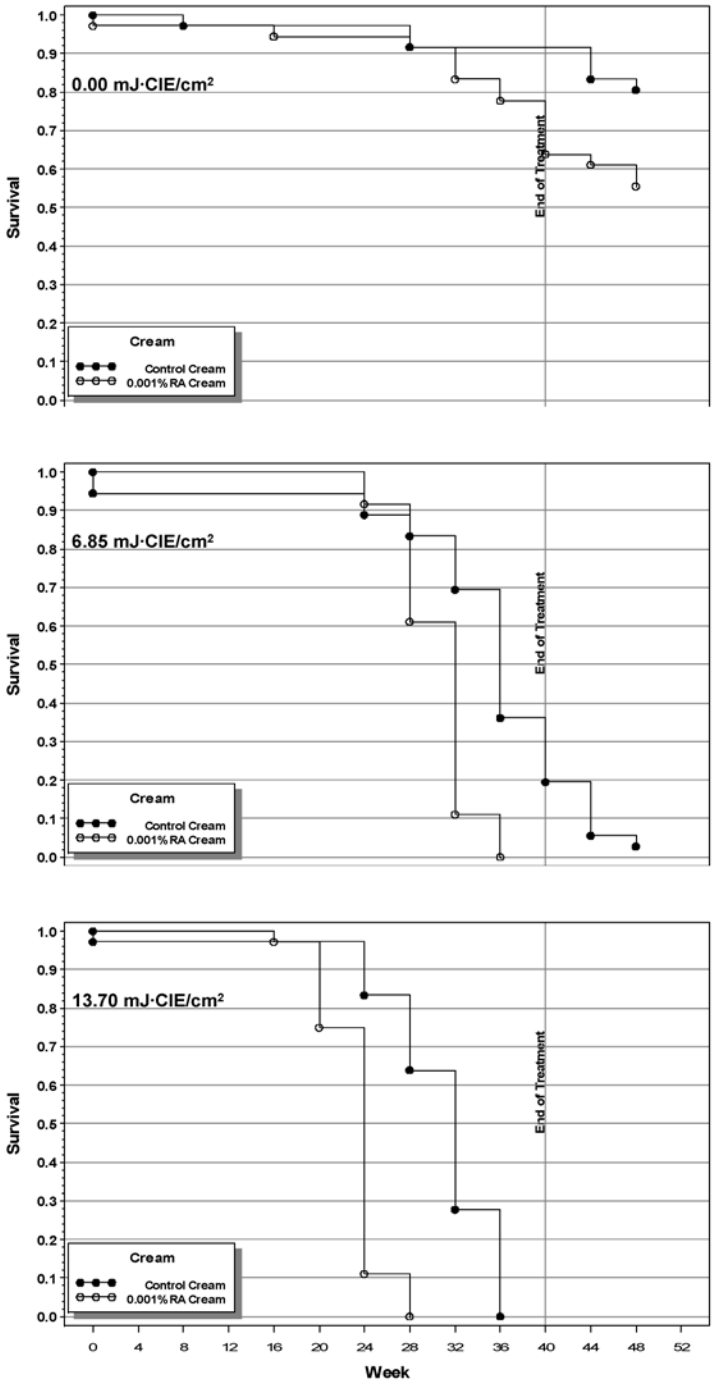


FIGURE 6
Kaplan-Meier Survival Curves for Male Mice Administered Control Cream or Retinoic Acid Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

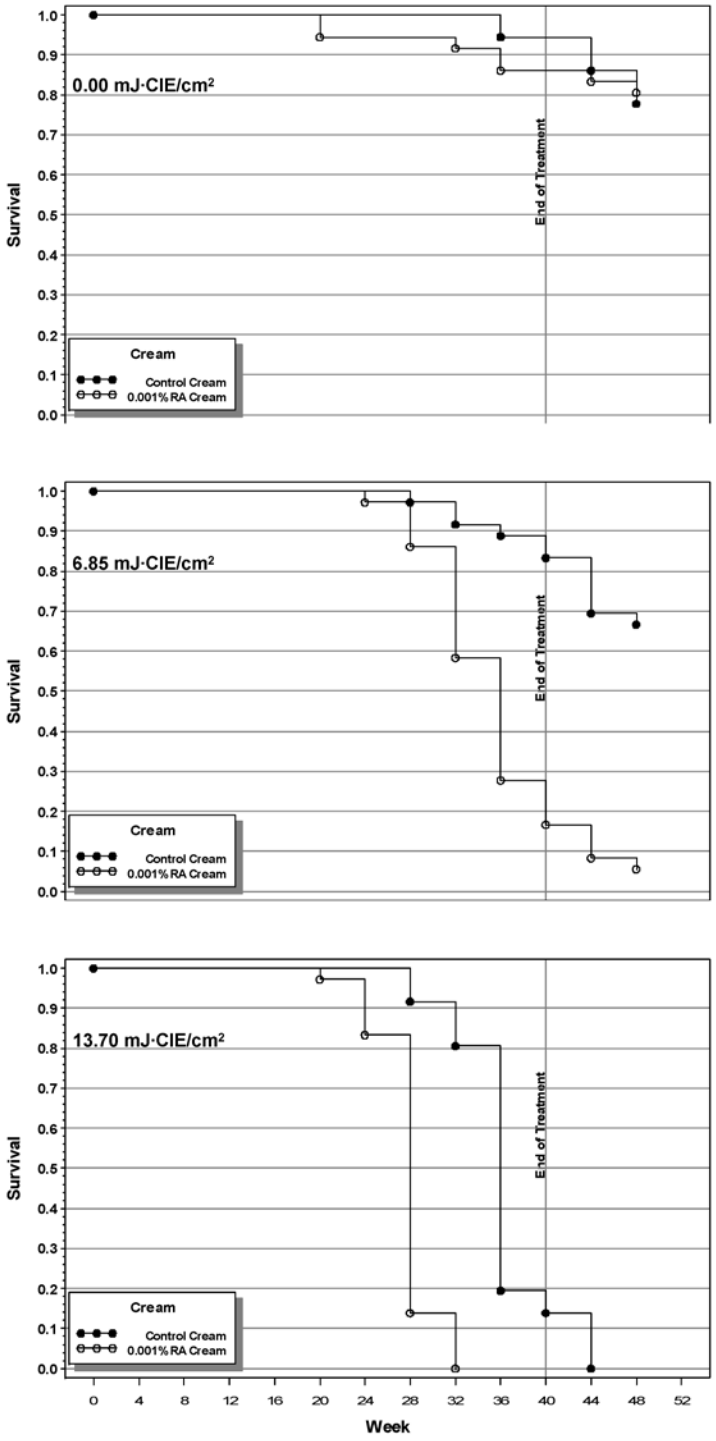


FIGURE 7
Kaplan-Meier Survival Curves for Female Mice Administered Control Cream or Retinoic Acid Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Retinyl Palmitate Treatment

The Cox hazard ratios for male and female mice that were administered retinyl palmitate (RP) cream and statistically compared to the control cream groups that were exposed to the same level of SSL are presented in Table 8, and Kaplan-Meier survival curves for these same treatment groups are graphically depicted in Figures 8 and 9. The daily application of creams containing RP significantly decreased the survival time of mice and significant RP dose trend decreases in survival were observed in male and female mice at each level of SSL exposure when compared to the survival time of control cream counterparts. Significantly decreased survival times were observed at each dose level of RP, as indicated by Cox hazard ratios greater than 1.00, in both male and female mice at each level of SSL exposure (Table 8). The Kaplan Meier curves of male and female mice similarly illustrated the decrease in survival (leftward shift) among mice administered RP cream when compared to the survival curves of same sex mice administered control cream and at the same level of SSL exposure. The differences in survival curves among RP cream and control cream mice were particularly noteworthy in the absence of SSL. As indicated in Table 8, male mice administered 1.0% or 2.0% RP cream and not exposed to SSL had approximately 8- and 17-fold increases (decreased survival) in their Cox hazard ratios and female mice treated similarly had approximately 8- and 50-fold increases in their Cox hazard ratios when compared with same sex mice administered control cream.

TABLE 8
Cox Hazard Ratios for Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit	P Value[a]
Male				
0.00 mJ•CIE/cm^2				
Control cream				**<0.001**
1.0% Retinyl palmitate	8.29	3.61	19.01	**<0.001**
2.0% Retinyl palmitate	16.93	7.46	38.42	**<0.001**
6.85 mJ•CIE/cm^2				
Control cream				**<0.001**
0.1% Retinyl palmitate	1.79	1.12	2.87	**0.015**
0.5% Retinyl palmitate	3.52	2.16	5.74	**<0.001**
1.0% Retinyl palmitate	5.71	3.45	9.44	**<0.001**
2.0% Retinyl palmitate	6.67	4.04	10.98	**<0.001**
13.70 mJ•CIE/cm^2				
Control cream				**<0.001**
0.1% Retinyl palmitate	5.10	3.13	8.33	**<0.001**
0.5% Retinyl palmitate	9.60	5.81	15.84	**<0.001**
1.0% Retinyl palmitate	8.61	5.22	14.22	**<0.001**
2.0% Retinyl palmitate	2.18	1.32	3.60	**<0.001**

TABLE 8
Cox Hazard Ratios for Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit	P Value[a]
Female				
0.00 mJ•CIE/cm^2				
Control cream				**<0.001**
1.0% Retinyl palmitate	7.87	3.57	17.34	**<0.001**
2.0% Retinyl palmitate	49.85	22.89	108.53	**<0.001**
6.85 mJ•CIE/cm^2				
Control cream				**<0.001**
0.1% Retinyl palmitate	4.78	2.45	9.31	**<0.001**
0.5% Retinyl palmitate	14.12	7.18	27.77	**<0.001**
1.0% Retinyl palmitate	14.04	7.15	27.57	**<0.001**
2.0% Retinyl palmitate	22.67	11.56	44.46	**<0.001**
13.70 mJ•CIE/cm^2				
Control cream				**<0.001**
0.1% Retinyl palmitate	3.35	2.08	5.39	**<0.001**
0.5% Retinyl palmitate	8.93	5.46	14.61	**<0.001**
1.0% Retinyl palmitate	11.82	7.12	19.61	**<0.001**
2.0% Retinyl palmitate	2.46	1.47	4.10	**<0.001**

[a] Cox hazard ratio estimates relative risk of survival. Tests formed by suitable contrasts with the control cream group, which was assigned a Cox hazard ratio of 1.00. Increased survival relative to the control cream group is expressed by a hazard ratio < 1.00; decreased survival relative to the control cream group is expressed by a hazard ratio > 1.00. Significant P values appear in bold-faced type.

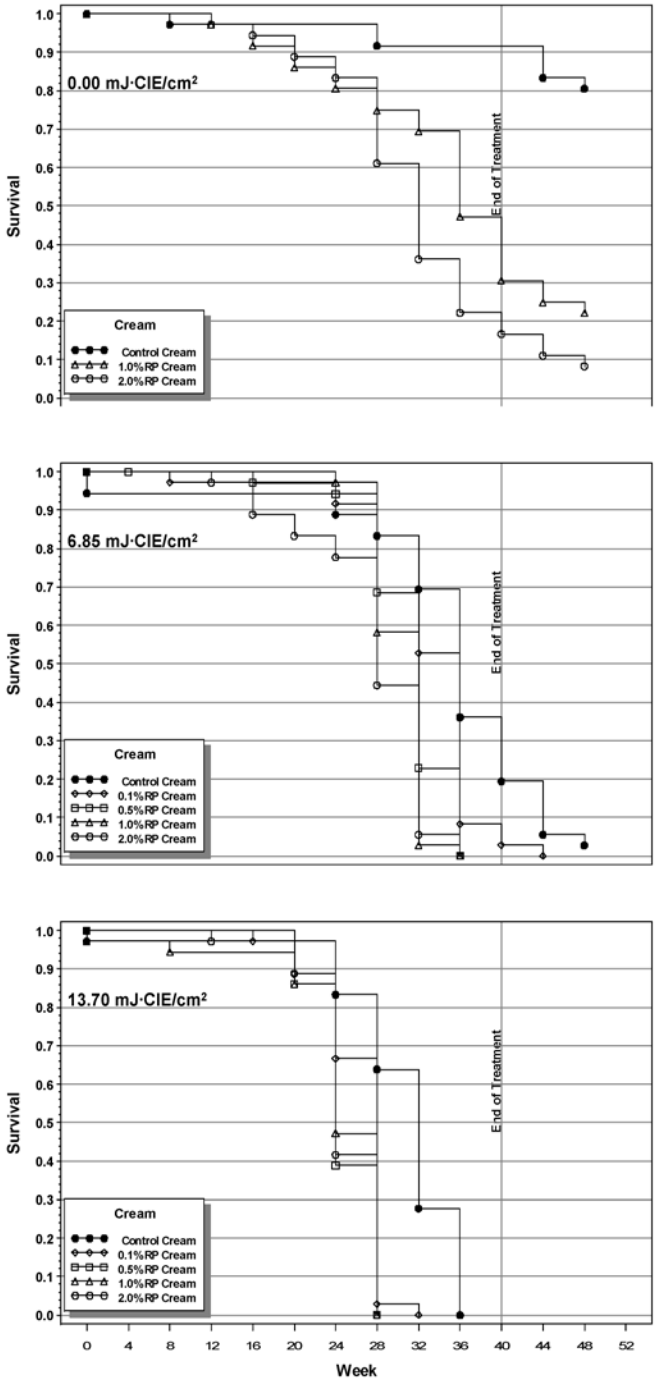


FIGURE 8
Kaplan-Meier Survival Curves for Male Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

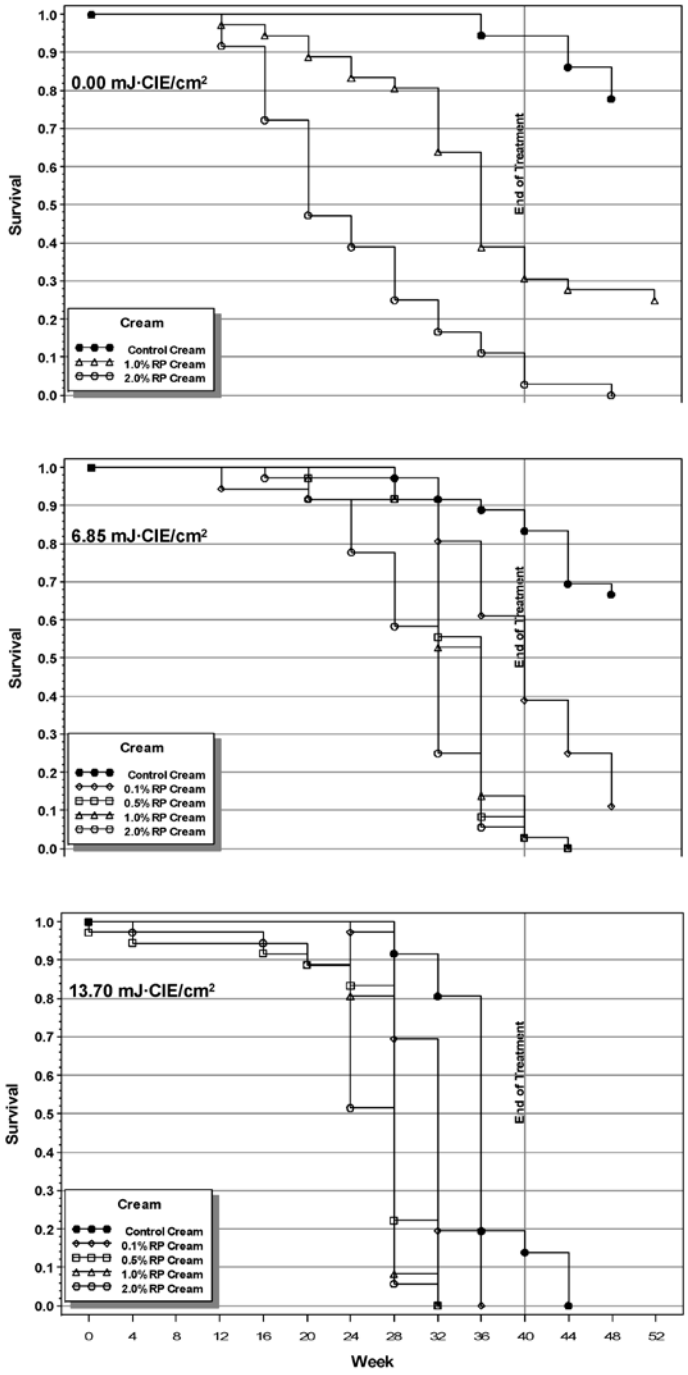


FIGURE 9
Kaplan-Meier Survival Curves for Female Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

UVA and UVB Treatment

The targeted doses of UVA or UVB irradiance that were administered to female mice were equivalent to the amount of UVA or UVB generated by the spectra of the SSL lamp source at an equivalent level of 13.70 mJ•CIE/cm^2 SSL. The statistical results of the Cox proportional method analysis of irradiation source on the survival of female mice treated with no cream, control cream, 1.0% RP cream, or 0.001% RA cream are shown in Table 9 and are graphically represented as Kaplan-Meier survival curves in Figures 10 and 11. In this analysis, comparisons are made to the corresponding no cream or cream group that was exposed to 13.70 mJ•CIE/cm^2 SSL.

As shown in Figures 10 and 11, mice exposed to UVA had significantly longer survival times when compared with the survival times of mice that received the same cream treatment and were exposed to SSL at 13.70 mJ•CIE/cm^2 (Table 9). Significant P values and lower Cox hazard ratios were observed for the groups of female mice exposed to UVA, irrespective of cream treatment.

In contrast, exposure of female mice to UVB significantly decreased survival times when compared with the survival times of female mouse groups that received the same cream treatment and were exposed to SSL at 13.70 mJ•CIE/cm^2. Higher Cox hazard ratios were also observed, suggesting that the survival of mice treated with retinoids was diminished to a greater extent in the presence of the narrow band spectra of UVB than in the presence of the broad band spectra of SSL.

TABLE 9
Cox Hazard Ratios for Female Mice Administered No Cream, Control Cream, Retinyl Palmitate Cream, or Retinoic Acid Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit	P Value[a]
UVA				
No cream	0.10	0.05	0.22	**<0.001**
Control cream	0.07	0.03	0.17	**<0.001**
1.0% Retinyl palmitate	0.04	0.01	0.12	**<0.001**
0.001% Retinoic acid	0.04	0.01	0.11	**<0.001**
UVB				
No cream	1.76	1.09	2.84	**0.020**
Control cream	1.60	1.00	2.56	**0.049**
1.0% Retinyl palmitate	2.64	1.62	4.30	**<0.001**
0.001% Retinoic acid	4.13	2.38	7.17	**<0.001**

[a] Cox hazard ratio estimates relative risk of survival. Tests formed by suitable contrasts with the same treatment group exposed to 13.70 mJ•CIE/cm^2 SSL, which was assigned a Cox hazard ratio of 1.00. Increased survival relative to the 13.70 mJ•CIE/cm^2 SSL group is expressed by a hazard ratio < 1.00; decreased survival relative to the 13.70 mJ•CIE/cm^2 SSL group is expressed by a hazard ratio > 1.00. Significant P values appear in bold-faced type.

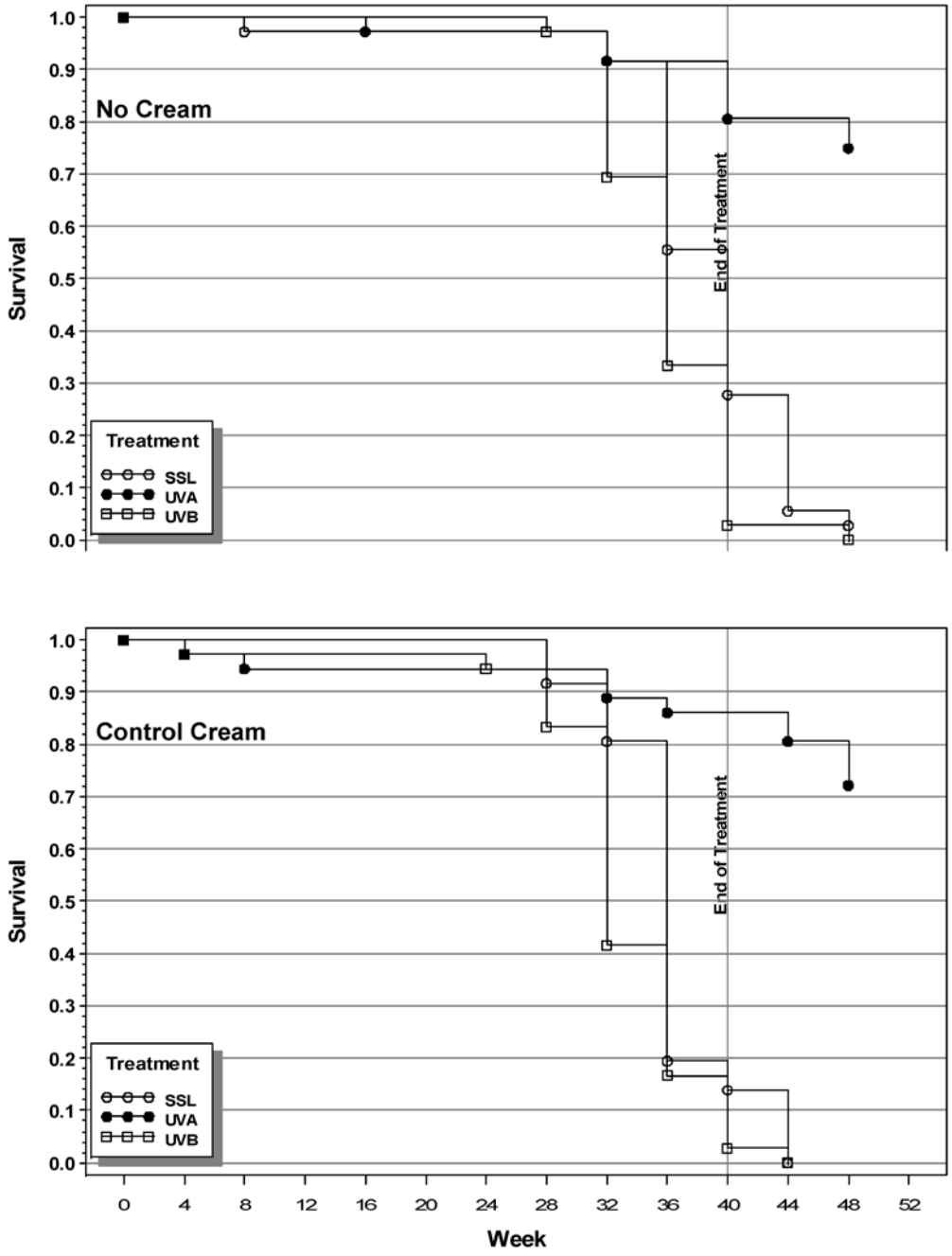


FIGURE 10
Kaplan-Meier Survival Curves for Female Mice Administered No Cream or Control Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

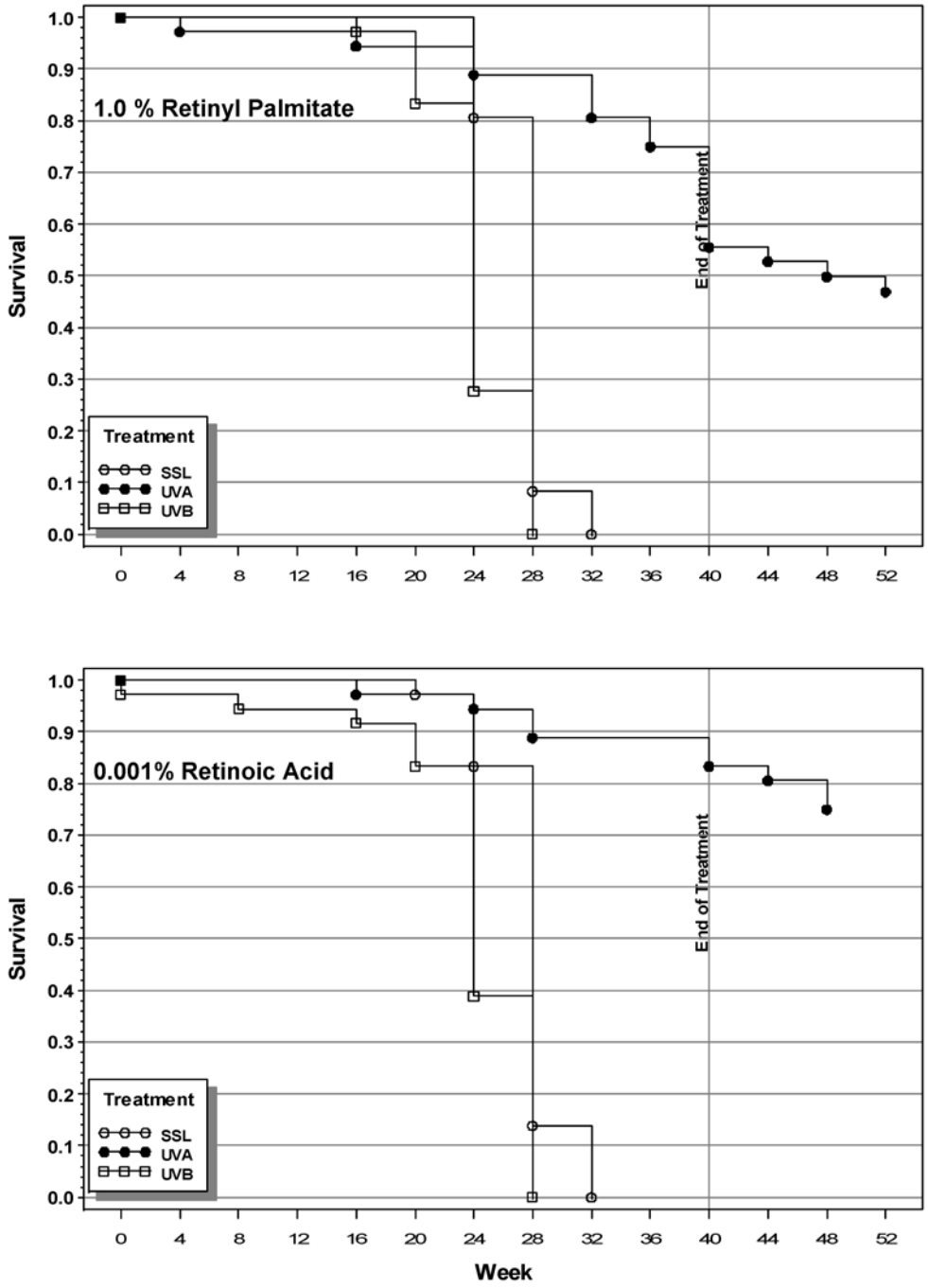


FIGURE 11
Kaplan-Meier Survival Curves for Female Mice Administered Retinyl Palmitate Cream or Retinoic Acid Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Body Weights

Summary tables of mean body weights, percentage of mean body weights relative to control weights, survival of mice over the 52 weeks of study, and statistical tests of dose trends and control comparisons for male and female mice in the 1-year study are shown in Appendix C.

Control Cream Treatment

There were no significant differences in pairwise comparison tests of mean body weights between no cream and control cream male mice, with the exception of a significantly greater body weight in the no cream group of males exposed to 6.85 mJ•CIE/cm^2 SSL at week 52 of the study (Tables C4 and C5).

Retinoic Acid Treatment

With few exceptions, the topical administration of RA creams to male and female mice had no significant effect on mean body weights when compared with the mean body weights of mice at the same point in time that were administered the control cream and the same level of SSL or UV source (Tables C6 and C7).

Retinyl Palmitate Treatment

The results of the mean body weight analysis for mice that received RP cream treatments and pairwise comparisons with mice that received control cream treatments are shown for male mice in Table C8 and for female mice in Table C9. In male and female mice that received daily applications of RP creams, sporadic significant dose trends in mean body weights and significant pairwise comparisons to control cream groups were observed in both the absence and presence of SSL; however, with only three exceptions among females, mean body weights for all groups remained 90% or above control cream values throughout the study.

In-Life Skin Lesion Onset

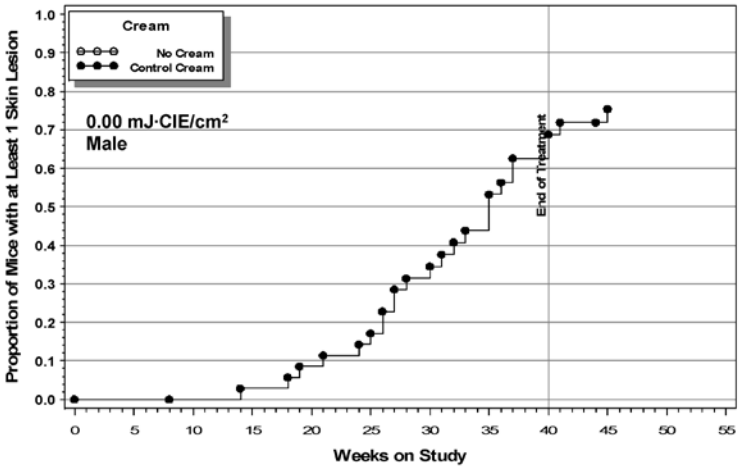
The time-to-skin-lesion onset was computed for each animal based on digital photographs captured during the in-life phase of the 1-year study, and the data were used to generate Kaplan-Meier curves. The mean and median times for skin lesion onset were calculated, and probability values were determined based on Cox contrasts for skin lesion onset. The reference group for contrasts was the same sex, same exposure control cream group.

Control Cream Treatment

The in-life Kaplan-Meier curves and Cox contrasts for skin lesion onset in male and female mice that received either no cream or control cream treatments are shown for SSL exposure levels of 0.00, 6.85, and 13.70 mJ•CIE/cm^2 in Figures 12, 13, and 14, respectively. In the absence of SSL exposure, the topical application of control cream induced skin lesions at an earlier time and with greater incidence than was observed in mice that received no cream treatment. In male mice that received control cream and were not exposed to SSL, the mean time for skin lesion onset was 34.3 weeks; whereas, there was no incidence of skin lesions in male mice that received no cream treatment and 0.00 mJ•CIE/cm^2 SSL. In female mice that received control cream and 0.00 mJ•CIE/cm^2 SSL, the mean week of skin lesion onset for the control cream (41.7) and no cream (46.0) groups were significantly different (Figure 12).

In male mice exposed to SSL at 6.85 mJ•CIE/cm^2, the mean week to skin lesion onset was 26.5 for the control cream group and 45.3 for the no cream group, a difference of 18.8 weeks. In female mice exposed to SSL at a level of 6.85 mJ•CIE/cm^2, the mean week of skin lesion onset was 33.9 for the control cream group and 45.2 for the no cream group, a difference of 11.3 weeks (Figure 13). Similar effects were observed, but to a lesser degree, when mice were exposed to 13.70 mJ•CIE/cm^2 SSL (Figure 14). These results suggest that the topical applications of control cream enhanced the development of skin lesions in male and female mice both in the absence and presence of SSL exposure.

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
No Cream	-	Q_{50} = -	< 0.001
Control Cream	34.3	Q_{50} = 35.0	



Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
No Cream	46.0	Q_{50} = -	0.003
Control Cream	41.7	Q_{50} = -	

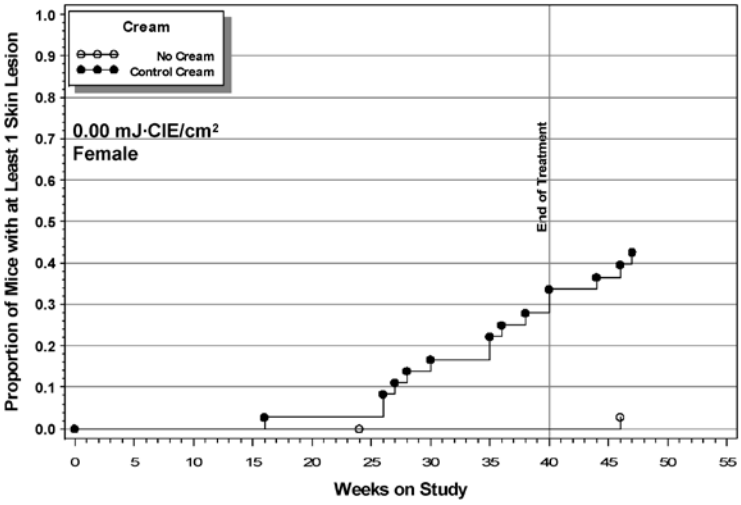
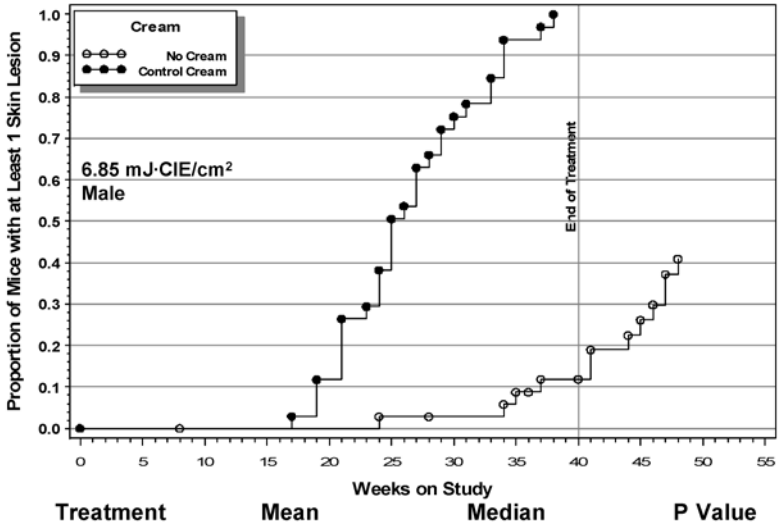


FIGURE 12
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Mice Administered No Cream or Control Cream and Exposed to 0.00 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. Dashed entries were not estimable. P values are based on the Cox proportional hazards model and represent pairwise comparisons to the control cream group.)

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
No Cream	45.3	Q_{50} = -	**< 0.001**
Control Cream	26.5	Q_{50} = 25.0	



Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
No Cream	45.2	Q_{50} = 49.0	< **0.001**
Control Cream	33.9	Q_{50} = 34.0	

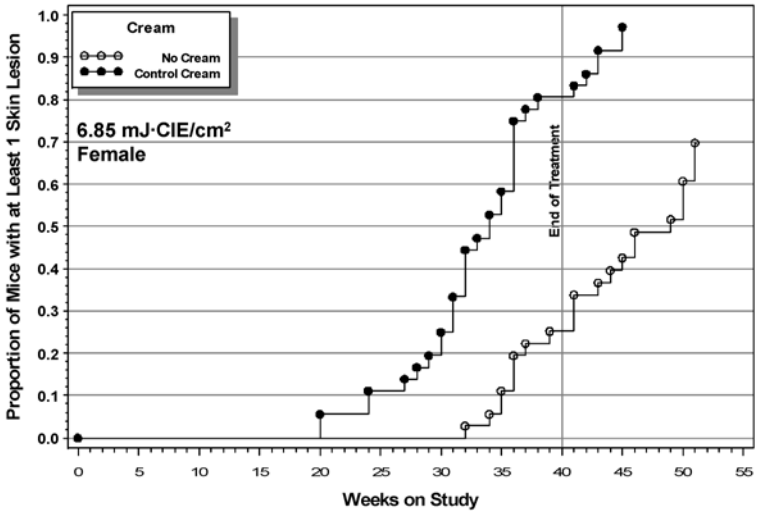
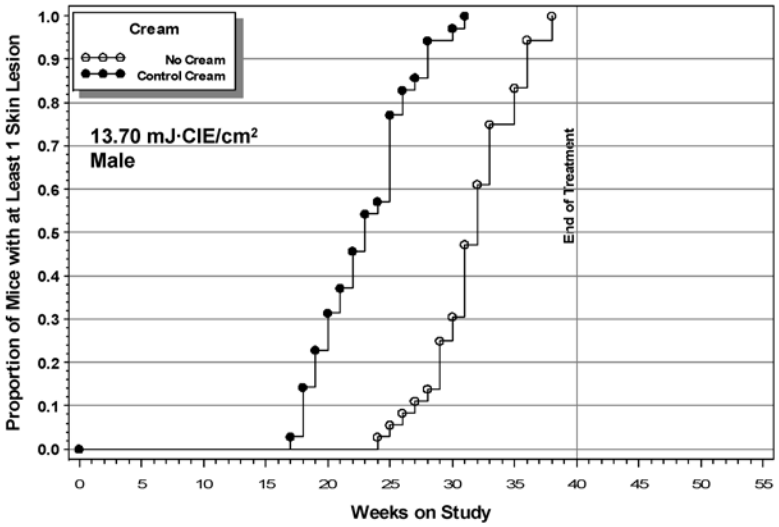


FIGURE 13
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Mice Administered No Cream or Control Cream and Exposed to 6.85 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. Dashed entries were not estimable. P values are based on the Cox proportional hazards model and represent pairwise comparisons to the control cream group.)

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
No Cream	31.7	Q_{50} = 32.0	**< 0.001**
Control Cream	23.0	Q_{50} = 23.0	



Treatment	Mean	Median	P Value
No Cream	33.1	Q_{50} = 33.0	**0.008**
Control Cream	27.8	Q_{50} = 29.0	

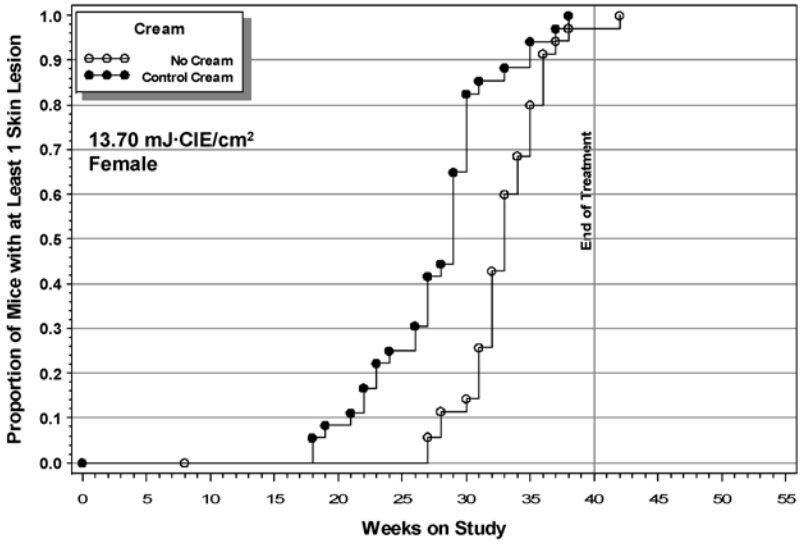


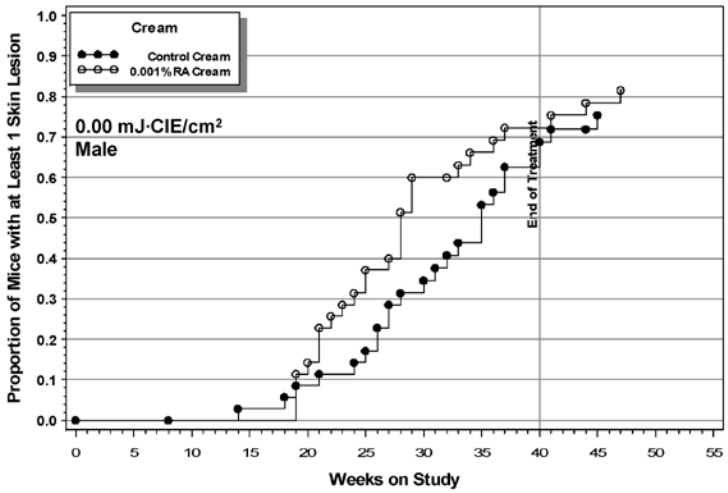
FIGURE 14
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Mice Administered No Cream or Control Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. P values are based on the Cox proportional hazards model and represent pairwise comparisons to the control cream group.)

Retinoic Acid Treatment

The Kaplan-Meier curves and Cox contrasts for skin lesion onset of male and female mice that received topical applications of either 0.001% RA cream or control cream are shown by SSL level in Figures 15 through 17. In the absence of SSL exposure, the topical application of 0.001% RA had no effect on skin lesion onset when compared with the same sex control cream group (Figure 15). In the presence of SSL exposure (6.85 and 13.70 mJ•CIE/cm^2), the weeks to skin lesion onset were significantly earlier in male and female mice that received 0.001% RA cream, and the Kaplan-Meier curves for the RA cream groups were shifted to the left of those for the control cream groups (Figures 16 and 17).

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	34.3	Q_{50} = 35.0	
0.001% Retinoic Acid	31.4	Q_{50} = 28.0	0.199



Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	41.7	Q_{50} = -	
0.001% Retinoic Acid	41.0	Q_{50} = -	0.253

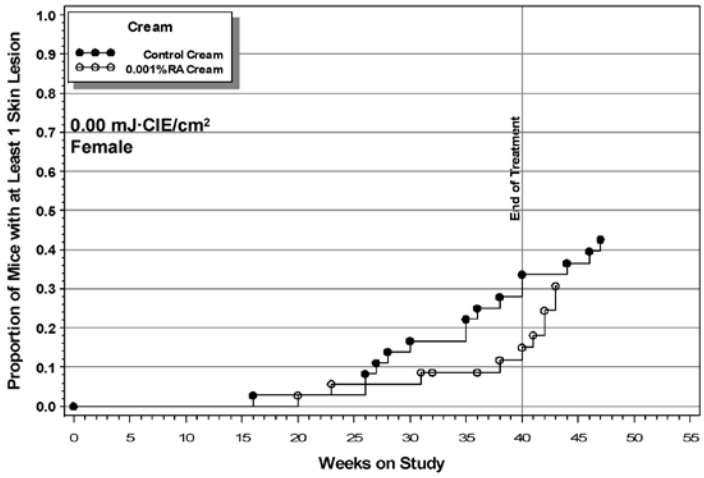
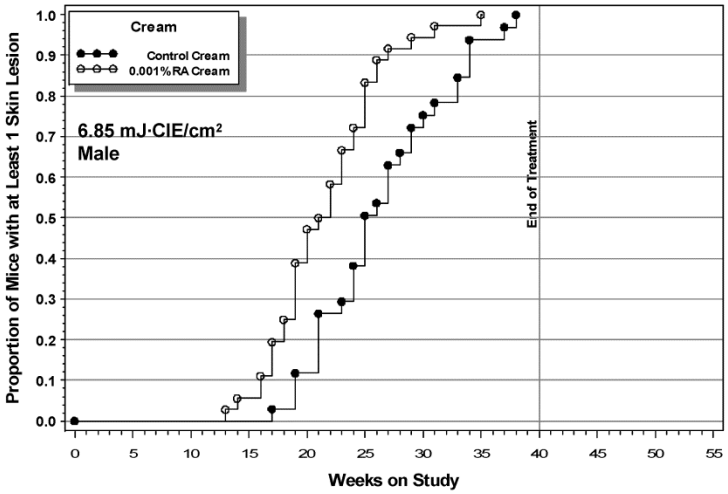


FIGURE 15
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Mice Administered Control Cream or Retinoic Acid Cream and Exposed to 0.00 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. Dashed entries were not estimable. P values are based on the Cox proportional hazards model and represent pairwise comparisons to the control cream group.)

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	26.5	Q_{50} = 25.0	
0.001% Retinoic Acid	21.6	Q_{50} = 21.5	**< 0.001**



Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	33.9	Q_{50} = 34.0	
0.001% Retinoic Acid	25.4	Q_{50} = 26.0	**< 0.001**

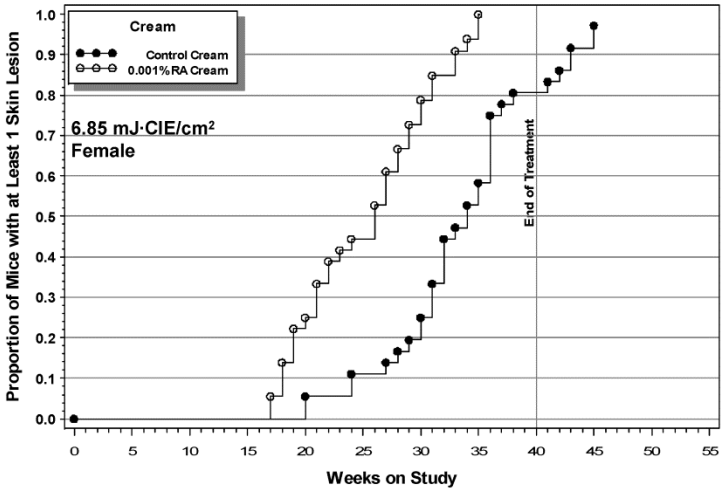
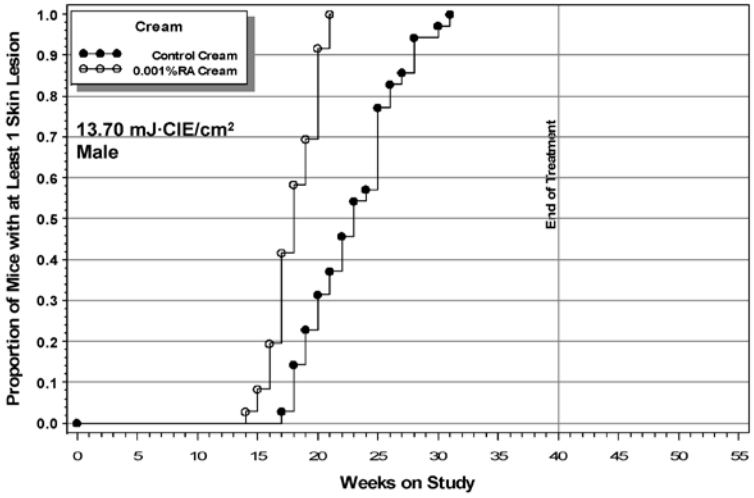


FIGURE 16
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Mice Administered Control Cream or Retinoic Acid Cream and Exposed to 6.85 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. P values are based on the Cox proportional hazards model and represent pairwise comparisons to the control cream group.)

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	23.0	Q_{50} = 23.0	
0.001% Retinoic Acid	18.1	Q_{50} = 18.0	**< 0.001**



Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	27.8	Q_{50} = 29.0	
0.001% Retinoic Acid	21.4	Q_{50} = 21.5	**< 0.001**

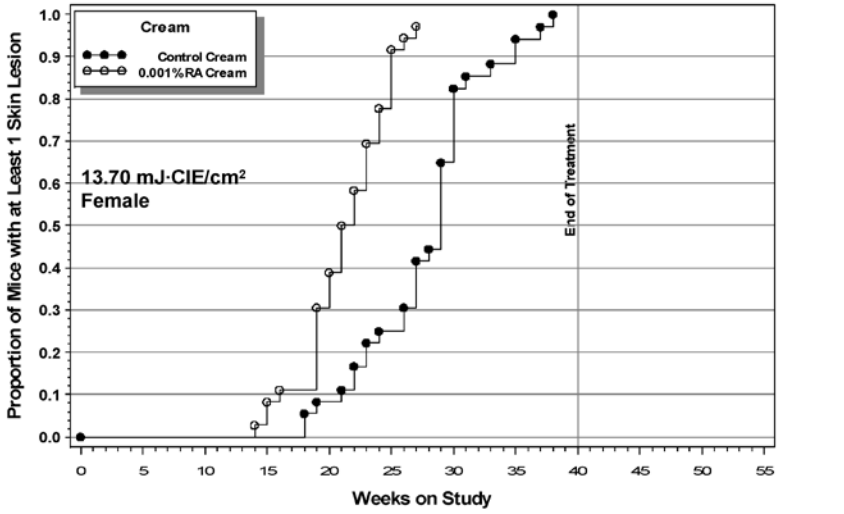


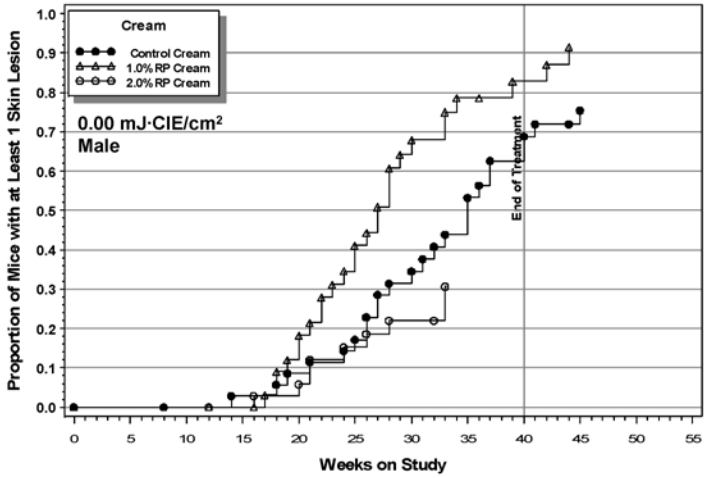
FIGURE 17
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Mice Administered Control Cream or Retinoic Acid Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. P values are based on the Cox proportional hazards model and represent pairwise comparisons to the control cream group.)

Retinyl Palmitate Treatment

The Kaplan-Meier curves and Cox contrasts for skin lesion onset in male and female mice that received topical applications of either RP creams (0.1%, 0.5%, 1.0%, or 2.0% RP, wt/wt) or control cream are shown for each level of SSL (0.00, 6.85, and 13.70 mJ•CIE/cm^2) in Figures 18 through 20, respectively. In the absence of SSL (0.00 mJ•CIE/cm^2), the onset of skin lesions occurred significantly earlier for male and female mice that received the 1% RP cream treatments (Figure 18). Skin irritation (erythema, scaling, pruitus, granulomas, and scabbing) was prevalent in the 2% RP cream treated mice and, in the absence of SSL, likely interfered with the detection of skin lesions that were consistent with the development of skin tumors. In the presence of SSL, significant dose-related trend test results were observed in RP-treated male and female mice exposed to 6.85 mJ•CIE/cm^2 or 13.70 mJ•CIE/cm^2 SSL (Figures 19 and 20, respectively). In pairwise comparison tests to the control cream groups, the mean week of skin lesion onset time in the presence of SSL exposure occurred in male and female mice at a significantly earlier time point in the study for each dose of RP.

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	34.3	Q_{50} = 35.0	**0.043**
1.0% Retinyl Palmitate	28.9	Q_{50} = 27.0	**0.007**
2.0% Retinyl Palmitate	30.7	Q_{50} = -	**0.043**



Treatment	Mean	Median	P Value
Control Cream	41.7	Q_{50} = -	0.727
1.0% Retinyl Palmitate	25.7	Q_{50} = 24.0	**< 0.001**
2.0% Retinyl Palmitate	22.8	Q_{50} = -	0.727

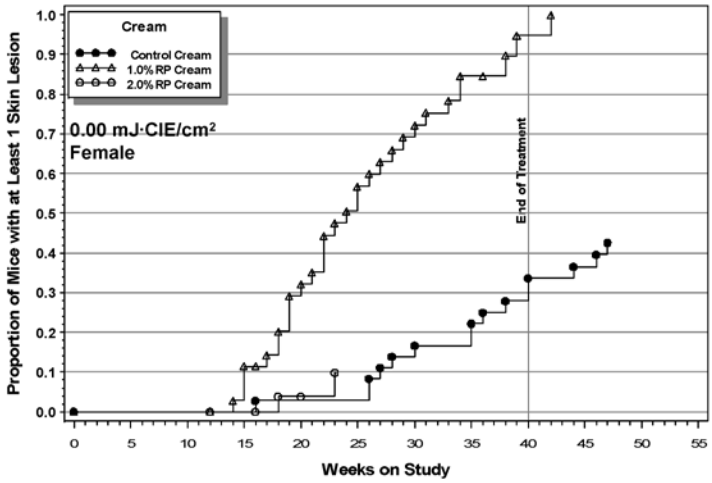
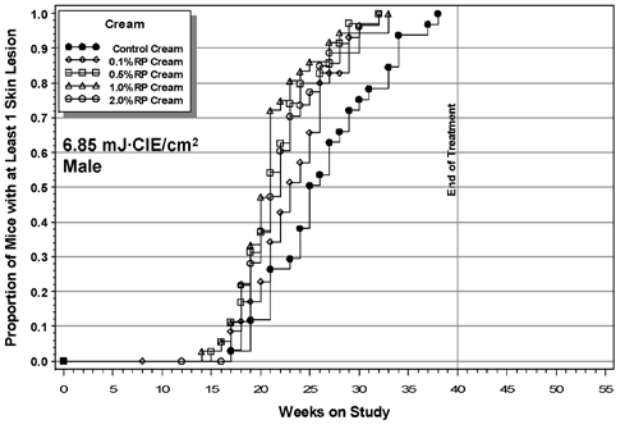


Figure 18
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 0.00 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. Dashed entries were not estimable. P values are based on the Cox proportional hazards model. P values for the control cream group represent linear trend results; P values for the RP cream groups represent pairwise comparisons to the control cream group.)

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	26.5	Q_{50} = 25.0	**0.018**
0.1% Retinyl Palmitate	23.6	Q_{50} = 23.0	**0.019**
0.5% Retinyl Palmitate	21.9	Q_{50} = 21.0	**< 0.001**
1.0% Retinyl Palmitate	21.3	Q_{50} = 21.0	**< 0.001**
2.0% Retinyl Palmitate	22.3	Q_{50} = 22.0	**0.003**



Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	33.9	Q_{50} = 34.0	**< 0.001**
0.1% Retinyl Palmitate	28.3	Q_{50} = 27.0	**0.004**
0.5% Retinyl Palmitate	24.8	Q_{50} = 26.5	**< 0.001**
1.0% Retinyl Palmitate	27.3	Q_{50} = 28.0	**< 0.001**
2.0% Retinyl Palmitate	23.9	Q_{50} = 23.0	**< 0.001**

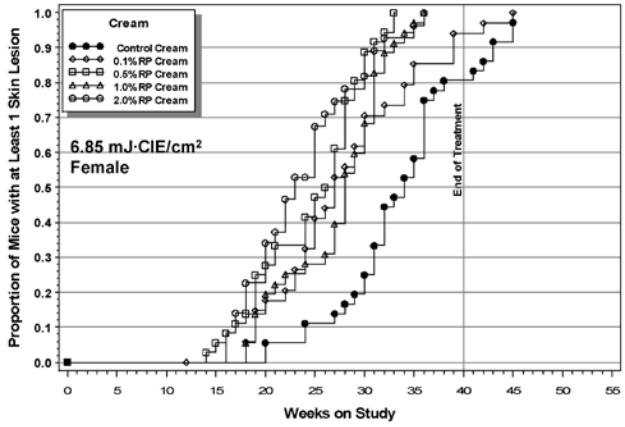
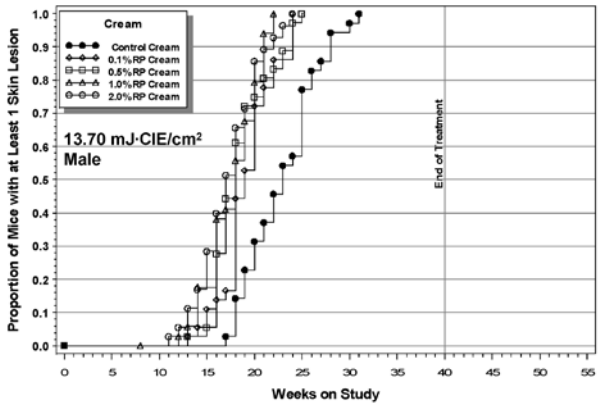


Figure 19
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. P values are based on the Cox proportional hazards model. P values for the control cream group represent linear trend results; P values for the RP cream groups represent pairwise comparisons to the control cream group.)

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	23.0	Q_{50} = 23.0	**< 0.001**
0.1% Retinyl Palmitate	19.3	Q_{50} = 19.0	**< 0.001**
0.5% Retinyl Palmitate	18.6	Q_{50} = 18.0	**< 0.001**
1.0% Retinyl Palmitate	17.8	Q_{50} = 18.0	**< 0.001**
2.0% Retinyl Palmitate	17.4	Q_{50} = 17.0	**< 0.001**



Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
Control Cream	27.8	Q_{50} = 29.0	**< 0.001**
0.1% Retinyl Palmitate	22.8	Q_{50} = 22.0	**< 0.001**
0.5% Retinyl Palmitate	20.9	Q_{50} = 20.0	**< 0.001**
1.0% Retinyl Palmitate	19.8	Q_{50} = 19.0	**< 0.001**
2.0% Retinyl Palmitate	20.5	Q_{50} = 20.0	**< 0.001**

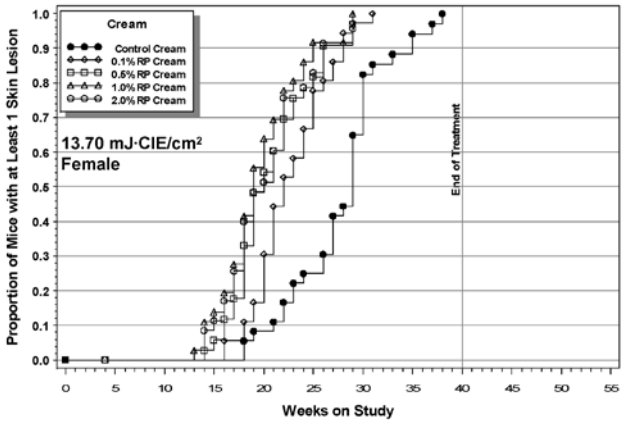


Figure 20
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. P values are based on the Cox proportional hazards model. P values for the control cream group represent linear trend results; P values for the RP cream groups represent pairwise comparisons to the control cream group.)

UVA and UVB Treatment

The Kaplan-Meier in-life skin lesion onset curves and Cox contrasts are compared across treatments within irradiation sources in Figure 21 and by treatment and across irradiation sources in Figures 22 and 23.

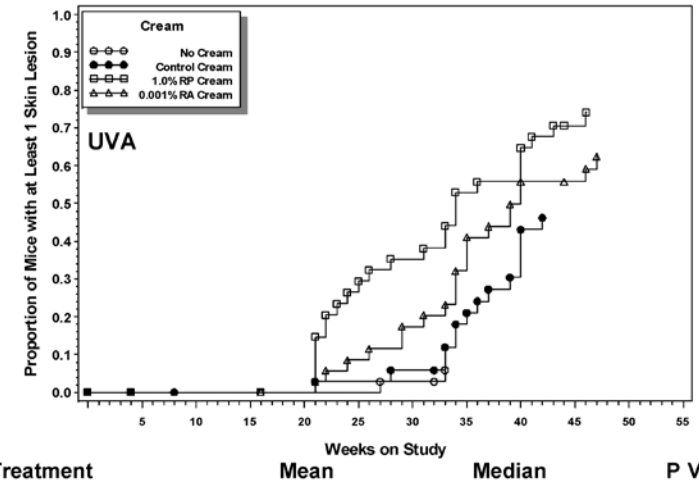
In pairwise comparison tests to the control cream group, the topical application of 0.001% RA cream had no effect on the week to skin lesion onset in female mice exposed to UVA (Figure 21). In contrast, significant differences were observed in the pairwise comparison tests between the weeks to skin lesion onset for the no cream and control cream groups and for the 1% RP and control cream groups (Figure 21, upper panel).

The treatment of female mice with 0.001% RA cream or 1.0% RP cream and exposure to UVB resulted in significantly earlier weeks to the onset of skin lesions than that of the control cream treated mice (Figure 21, lower panel). There was no significant difference between weeks to the onset of skin lesions of the no cream group and the control cream group.

Kaplan-Meier curves and Cox contrasts for in-life skin lesion onset are shown for the no cream and control cream groups among exposure types in Figure 22. Significant differences in Cox contrasts results for skin lesion onset were observed for no cream and control cream treated female mice exposed to UVA, when compared to the same treatment in female mice exposed to SSL at a level of 13.70 mJ•CIE/cm^2.

Kaplan-Meier curves of skin lesion onset and Cox contrast results are shown in Figure 23 for female mice that received topical applications of 0.001% RA cream or 1.0% RP cream and were exposed to UVA or UVB and compared with similarly treated mice that were exposed to SSL at 13.70 mJ•CIE/cm^2. Significantly later weeks to skin lesion onset were observed for UVA-exposed RA and RP cream groups when compared to the same treatment groups exposed to SSL at a level of 13.70 mJ•CIE/cm^2. There were no significant differences in the weeks to the onset of skin lesions for female mice treated with either the 0.001% RA or 1.0% RP creams and exposed to UVB and compared to skin lesion onset of SSL-exposed mice that were treated similarly.

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
No Cream	32.8	Q_{50} = -	**0.003**
Control Cream	39.0	Q_{50} = -	
1.0% Retinyl Palmitate	34.5	Q_{50} = 34.0	**0.004**
0.001% Retinoic Acid	38.9	Q_{50} = 40.0	0.145



Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
No Cream	30.1	Q_{50} = 30.0	0.064
Control Cream	26.8	Q_{50} = 26.0	
1.0% Retinyl Palmitate	21.8	Q_{50} = 22.0	**< 0.001**
0.001% Retinoic Acid	21.9	Q_{50} = 22.0	**< 0.001**

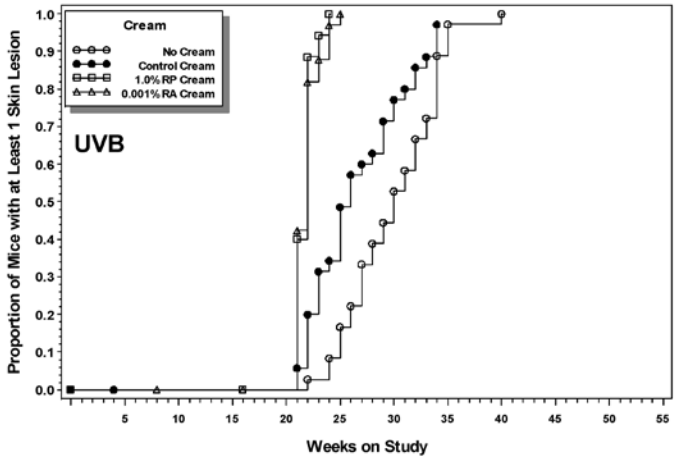
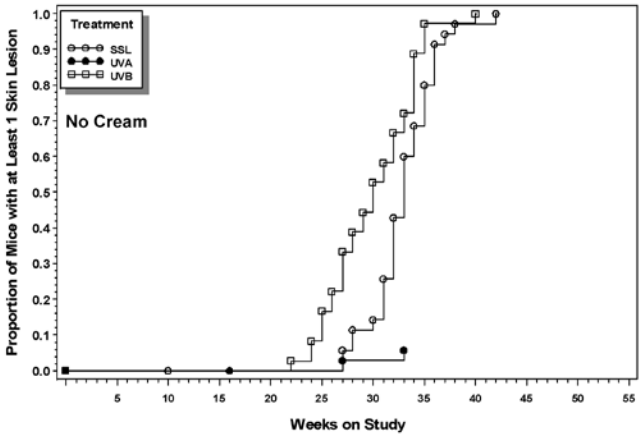


Figure 21
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Female Mice Administered No Cream, Control Cream, Retinyl Palmitate Cream, or Retinoic Acid Cream and Exposed to UVA or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. Dashed entries were not estimable. P values are based on the Cox proportional hazards model and represent pairwise comparisons to the control cream group.)

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
SSL	33.1	Q_{50} = 33.0	
UVA	32.8	Q_{50} = -	**< 0.001**
UVB	30.1	Q_{50} = 30.0	**0.004**



Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
SSL	27.9	Q_{50} = 29.0	
UVA	39.0	Q_{50} = -	**< 0.001**
UVB	26.8	Q_{50} = 26.0	0.386

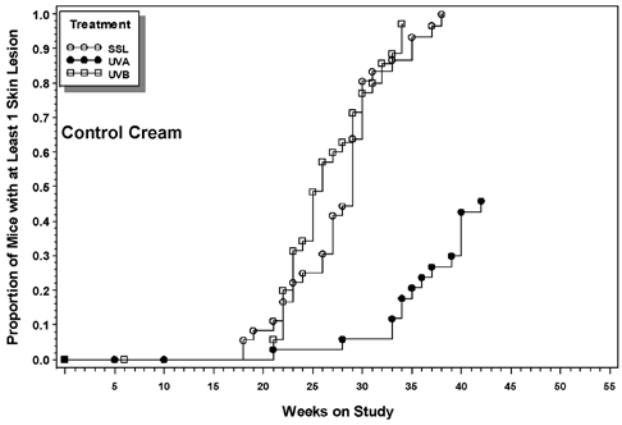
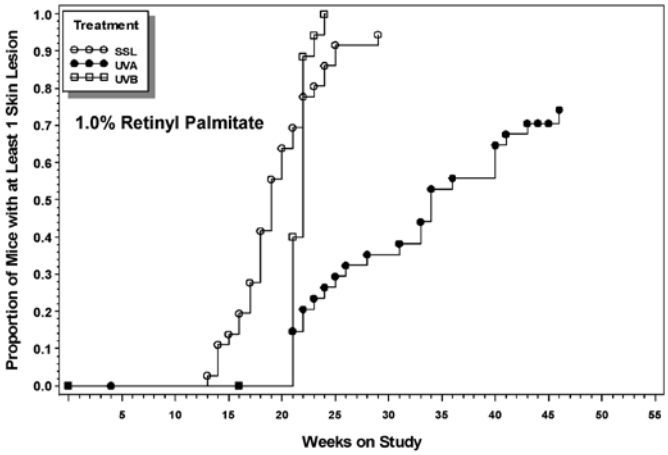


Figure 22
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Female Mice Administered Control Cream or No Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. Dashed entries were not estimable. P values are based on the Cox proportional hazards model and represent pairwise comparisons to the 13.70 mJ•CIE/cm^2 SSL group.)

Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
SSL	19.8	Q_{50} = 19.0	
UVA	34.5	Q_{50} = 34.0	**< 0.001**
UVB	21.8	Q_{50} = 22.0	0.602



Treatment	Mean Wk. of Onset	Median Wk. of Onset	P Value
SSL	21.4	Q_{50} = 21.5	
UVA	38.9	Q_{50} = 40.0	**< 0.001**
UVB	21.9	Q_{50} = 22.0	0.137

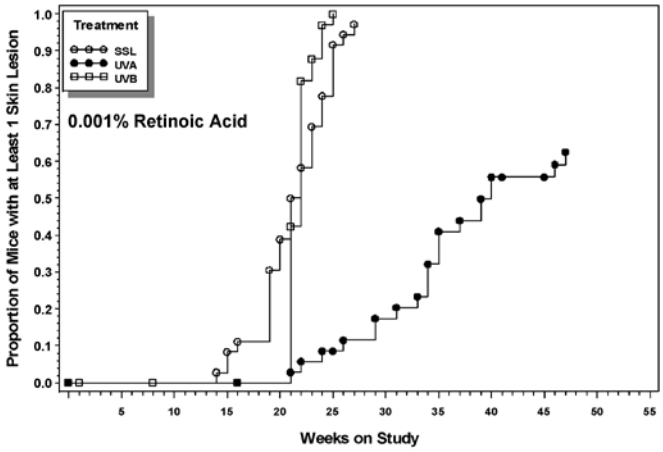


Figure 23
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Female Mice Administered Retinyl Palmitate Cream or Retinoic Acid Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
(The mean time to lesion onset represents the average time for the appearance of at least one measurable skin lesion in affected mice within a treatment group; median time to skin lesion onset represents the week in the study where 50% of the population of mice within a treatment group had at least one measurable skin lesion. Mean and median values are Cox estimates. P values are based on the Cox proportional hazards model and represent pairwise comparisons to the 13.70 mJ•CIE/cm^2 SSL group.)

In-Life Skin Lesion Incidence and Multiplicity

Control Cream Treatment

The results of the Poly-3 pairwise comparison tests of incidence rates and the Poisson regression tests for multiplicities of in-life determined skin lesions are shown for no cream and control cream treatment groups by SSL exposure level in Table 10. The incidence rates were significantly higher in control cream treated male and female mice exposed to 0.00 or 6.85 mJ•CIE/cm^2 SSL, compared to males and females administered no cream. The observed incidence rates of in-life skin lesions in no cream and control cream treated male and female mice that were exposed to 13.70 mJ•CIE/cm^2 SSL approached 100% for both treatment groups and sexes. The Poisson determined multiplicities of in-life skin lesions were significantly higher in male and female mice that received control cream treatments compared to those that received no cream treatments, both in the absence and presence of SSL exposure.

In female mice exposed to UVA, the Poly-3 pairwise contrasts for incidence of in-life skin lesions showed a significantly higher incidence in the control cream group compared to the no cream group (Table 10). There were no significant differences in the Poly-3 incidence rates of in-life skin lesions in mice that were exposed to UVB and received either the control cream or no cream treatment, as the incidences were approximately 100% for both groups. The Poisson regression tests of in-life skin lesion multiplicities were significantly higher in control cream treated mice compared to the no cream treated mice in the presence of UVA. There were no differences in the multiplicities of in-life skin lesions in female mice that were exposed to UVB and received either the control cream or no cream treatments.

TABLE 10
Incidences and Multiplicities of Skin Lesions Detected In-life in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	No Cream	Control Cream
0.00 mJ•CIE/cm^2		
Male		
Observed rate[a]	0/36 (0.0%)	20/36 (56.0%)
Adjusted rate[b]	0/30.8 (0.0%)	25/33.1 (75.6%)
First incidence (weeks)	—[d]	14
Incidence test results[c]		**P<0.001**
Observed mean lesion multiplicity ± SEM[e]	0.0 ± 0.0	1.1 ± 1.3
Overall LS mean[f] lesion multiplicity ± SEM	0.0 ± 0.1	1.2 ± 0.2
Multiplicity test results[g]		**P<0.001**
Female		
Observed rate	1/36 (3.0%)	15/36 (42.0%)
Adjusted rate	1/35.0 (2.9%)	15/34.8 (43.1%)
First incidence (weeks)	46	16
Incidence test results		**P<0.001**
Observed mean lesion multiplicity ± SEM	0.0 ± 0.2	0.5 ± 0.6
Overall LS mean lesion multiplicity ± SEM	0.0 ± 0.1	0.5 ± 0.2
Multiplicity test results		**P=0.028**

TABLE 10
Incidences and Multiplicities of Skin Lesions Detected In-life in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	No Cream	Control Cream
6.85 mJ•CIE/cm^2		
Male		
Observed rate	12/36 (33.0%)	33/36 (92.0%)
Adjusted rate	12/31.0 (38.6%)	33/33.1 (99.7%)
First incidence (weeks)	24	17
Incidence test results		**P<0.001**
Observed mean lesion multiplicity ± SEM	1.0 ± 2.0	6.5 ± 4.9
Overall LS mean lesion multiplicity ± SEM	1.2 ± 0.2	9.6 ± 0.6
Multiplicity test results		**P<0.001**
Female		
Observed rate	24/36 (67.0%)	35/36 (97.0%)
Adjusted rate	24/35.0 (68.5%)	35/36.0 (97.2%)
First incidence (weeks)	32	20
Incidence test results		**P=0.002**
Observed mean lesion multiplicity ± SEM	1.3 ± 1.5	5.0 ± 3.6
Overall LS mean lesion multiplicity ± SEM	1.4 ± 0.2	5.4 ± 0.4
Multiplicity test results		**P<0.001**
13.70 mJ•CIE/cm^2		
Male		
Observed rate	36/36 (100.0%)	35/36 (97.0%)
Adjusted rate	36/36.0 (100.0%)	35/35.0 (100.0%)
First incidence (weeks)	24	17
Incidence test results		P=1.000
Observed mean lesion multiplicity ± SEM	5.2 ± 2.1	8.5 ± 5.0
Overall LS mean lesion multiplicity ± SEM	7.0 ± 0.5	14.1 ± 0.8
Multiplicity test results		**P<0.001**
Female		
Observed rate	35/36 (97.0%)	35/36 (97.0%)
Adjusted rate	35/35.0 (100.0%)	35/35.2 (99.4%)
First incidence (weeks)	27	18
Incidence test results		P=1.000
Observed mean lesion multiplicity ± SEM	5.8 ± 2.9	8.0 ± 3.8
Overall LS mean lesion multiplicity ± SEM	7.7 ± 0.5	11.2 ± 0.7
Multiplicity test results		**P<0.001**

TABLE 10
Incidences and Multiplicities of Skin Lesions Detected In-life in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	No Cream	Control Cream
UVA		
Female		
Observed rate	2/36 (6.0%)	15/36 (42.0%)
Adjusted rate	2/31.7 (6.3%)	15/32.4 (46.3%)
First incidence (weeks)	27	21
Incidence test results		**P<0.001**
Observed mean lesion multiplicity ± SEM	0.1 ± 0.2	0.4 ± 0.6
Overall LS mean lesion multiplicity ± SEM	0.0 ± 0.1	0.5 ± 0.2
Multiplicity test results		**P=0.028**
UVB		
Female		
Observed rate	36/36 (100.0%)	34/36 (94.0%)
Adjusted rate	36/36.0 (100.0%)	34/34.5 (98.6%)
First incidence (weeks)	22	21
Incidence test results		P=1.000
Observed mean lesion multiplicity ± SEM	8.7 ± 4.2	7.5 ± 4.6
Overall LS mean lesion multiplicity ± SEM	12.1 ± 0.7	11.2 ± 0.7
Multiplicity test results		P=0.363

[a] Number of lesion-bearing animals/number of animals with skin observed
[b] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[c] P values are based on a two-sided continuity-corrected Poly-3 test and represent pairwise comparisons to the no cream group. Significant P values appear in bold-faced type.
[d] Not applicable; no lesions observed
[e] Standard error of the mean (SEM) is approximated based on an additive error structure.
[f] Least square (LS) means are estimated as lesions per animal per year.
[g] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal) and represent pairwise comparisons to no cream group. Significant P values appear in bold-faced type.

The effects of control cream treatment in female mice are compared across light exposure types in Table 11. The control group in these analyses was the female control cream group exposed to 13.70 mJ•CIE/cm^2 SSL. Control cream treated mice exposed to UVA had significantly lower incidences and multiplicities of in-life skin lesions than female mice exposed to SSL at 13.70 mJ•CIE/cm^2, while control cream treated mice exposed to UVB had similar incidences and multiplicities of in-life skin lesions as the control cream mice exposed to SSL.

TABLE 11
Incidences and Multiplicities of Skin Lesions Detected In-life in Female Mice Administered Control Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	13.70 mJ•CIE/cm^2	UVA	UVB
Observed rate[a]	35/36 (97.0%)	15/36 (42.0%)	34/36 (94.0%)
Adjusted rate[b]	35/35.2 (98.6%)	15/32.4 (46.3%)	34/34.5 (99.9%)
First incidence (weeks)	18	21	21
Incidence test results[c]		**P<0.001**	P=1.000
Observed mean lesion multiplicity ± SEM[d]	8.0 ± 3.8	0.4 ± 0.6	7.5 ± 4.6
Overall LS mean[e] lesion multiplicity ± SEM	11.2 ± 0.7	0.5 ± 0.2	11.6 ± 0.7
Multiplicity test results[f]		**P<0.001**	P=0.728

[a] Number of lesion-bearing animals/number of animals with skin observed
[b] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[c] P values are based on a two-sided continuity-corrected Poly-3 test and represent pairwise comparisons to the 13.70 mJ•CIE/cm^2 SSL group. Significant P values appear in bold-faced type.
[d] Standard error of the mean (SEM) is approximated based on an additive error structure.
[e] Least square (LS) means are estimated as lesions per animal per year.
[f] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal) and represent pairwise comparisons to 13.70 mJ•CIE/cm^2 SSL group. Significant P values appear in bold-faced type.

Retinoic Acid Treatment

The incidence rates and multiplicities of in-life skin lesions in mice treated with 0.001% RA cream or control cream are compared and the results are shown in Table 12. The incidence rates did not differ in the absence or presence of SSL exposure between mice that received the 0.001% RA cream treatment and those that received the control cream treatment. Incidence rates for these groups approached 100% in the presence of SSL, even at the lowest exposure level of 6.85 mJ•CIE/cm^2 SSL.

In male mice, the multiplicities of in-life skin lesions were significantly higher in groups that received the 0.001% RA cream when compared to the control cream groups, both in the absence and presence of SSL exposure (Table 12). With the exception of mice exposed to 6.85 mJ•CIE/cm^2, the multiplicities of in-life detected skin lesions were not significantly different in female mice that were exposed to SSL and treated with the 0.001% RA cream when compared with female mice that received control cream.

TABLE 12
Incidences and Multiplicities of Skin Lesions Detected In-life in Mice Administered Retinoic Acid Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream	0.001% Retinoic Acid Cream
0.00 mJ•CIE/cm^2		
Male		
Observed rate[a]	20/36 (56.0%)	25/36 (69.0%)
Adjusted rate[b]	25/33.1 (75.6%)	28/34.3 (81.7%)
First incidence (weeks)	14	19
Incidence test results[c]		P=0.750
Observed mean lesion multiplicity ± SEM[d]	1.1 ± 1.3	1.6 ± 1.6
Overall LS mean[e] lesion multiplicity ± SEM	1.2 ± 0.2	2.0 ± 0.3
Multiplicity test results[f]		**P=0.024**
Female		
Observed rate	15/36 (42.0%)	10/36 (28.0%)
Adjusted rate	15/34.8 (43.1%)	10/32.4 (30.9%)
First incidence (weeks)	16	20
Incidence test results		P=0.434
Observed mean lesion multiplicity ± SEM	0.5 ± 0.6	0.3 ± 0.6
Overall LS mean lesion multiplicity ± SEM	0.5 ± 0.2	0.4 ± 0.2
Multiplicity test results		P=0.631
6.85 mJ•CIE/cm^2		
Male		
Observed rate	33/36 (92.0%)	36/36 (100.0%)
Adjusted rate	33/33.1 (99.7%)	36/36.0 (100.0%)
First incidence (weeks)	17	13
Incidence test results		P=1.000
Observed mean lesion multiplicity ± SEM	6.5 ± 4.9	7.5 ± 4.8
Overall LS mean lesion multiplicity ± SEM	9.6 ± 0.6	12.5 ± 0.8
Multiplicity test results		**P=0.003**
Female		
Observed rate	35/36 (97.0%)	35/36 (97.0%)
Adjusted rate	35/36.0 (97.2%)	35/35.2 (99.5%)
First incidence (weeks)	20	17
Incidence test results		P=1.000
Observed mean lesion multiplicity ± SEM	5.0 ± 3.6	7.3 ± 3.8
Overall LS mean lesion multiplicity ± SEM	5.4 ± 0.4	10.3 ± 0.6
Multiplicity test results		**P<0.001**

TABLE 12
Incidences and Multiplicities of Skin Lesions Detected In-life in Mice Administered Retinoic Acid Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream	0.001% Retinoic Acid Cream
13.70 mJ•CIE/cm^2		
Male		
Observed rate	35/36 (97.0%)	36/36 (100.0%)
Adjusted rate	35/35.0 (100.0%)	36/36.0 (100.0%)
First incidence (weeks)	17	14
Incidence test results		P=1.000
Observed mean lesion multiplicity ± SEM	8.5 ± 5.0	7.9 ± 4.8
Overall LS mean lesion multiplicity ± SEM	14.1 ± 0.8	17.0 ± 1.0
Multiplicity test results		**P=0.023**
Female		
Observed rate	35/36 (97.0%)	35/36 (97.0%)
Adjusted rate	35/35.2 (99.4%)	35/35.2 (99.3%)
First incidence (weeks)	18	14
Incidence test results		P=1.000
Observed mean lesion multiplicity ± SEM	8.0 ± 3.8	5.8 ± 3.8
Overall LS mean lesion multiplicity ± SEM	11.2 ± 0.7	10.7 ± 0.7
Multiplicity test results		P=0.589
UVA		
Female		
Observed rate	15/36 (42.0%)	21/36 (58.0%)
Adjusted rate	15/32.4 (46.3%)	21/33.3 (63.1%)
First incidence (weeks)	21	21
Incidence test results		P=0.259
Observed mean lesion multiplicity ± SEM	0.4 ± 0.6	1.0 ± 1.1
Overall LS mean lesion multiplicity ± SEM	0.5 ± 0.2	1.1 ± 0.2
Multiplicity test results		**P=0.005**

TABLE 12
Incidences and Multiplicities of Skin Lesions Detected In-life in Mice Administered Retinoic Acid Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream	0.001% Retinoic Acid Cream
UVB		
Female		
Observed rate	34/36 (94.0%)	33/36 (92.0%)
Adjusted rate	34/34.5 (98.6%)	33/33.0 (100.0%)
First incidence (weeks)	21	17
Incidence test results		P=1.000
Observed mean lesion multiplicity ± SEM	7.5 ± 4.6	7.4 ± 4.1
Overall LS mean lesion multiplicity ± SEM	11.2 ± 0.7	15.8 ± 1.0
Multiplicity test results		**P<0.001**

[a] Number of lesion-bearing animals/number of animals with skin observed
[b] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[c] P values are based on a two-sided continuity-corrected Poly-3 test and represent pairwise comparisons to the control cream group. Significant P values appear in bold-faced type.
[d] Standard error of the mean (SEM) is approximated based on an additive error structure.
[e] Least square (LS) means are estimated as lesions per animal per year.
[f] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal) and represent pairwise comparisons to control cream group. Significant P values appear in bold-faced type.

In female mice exposed to UVA or UVB, there were no differences in the Poly-3 adjusted incidence rates between groups that received topical applications of control cream or cream that contained 0.001% RA (Table 12). Significantly higher multiplicities of in-life skin lesions were found for female mice exposed to UVA or UVB that received the 0.001% RA cream when compared with those that received control cream and either UVA or UVB exposures.

The effects of different exposure sources are compared in female mice treated with the 0.001% RA cream in Table 13. The reference group in these analyses was the female, 0.001% RA cream group that was exposed to 13.70 mJ•CIE/cm^2 SSL. Lower incidences of in-life skin lesions were observed in female mice exposed to UVA when compared with mice that were exposed to SSL. Significantly fewer numbers of skin lesions were also observed in female mice exposed to UVA, while significantly greater numbers of in-life skin lesions were observed in female mice exposed to UVB, in comparison tests with female mice that received the same treatment but were exposed to SSL.

TABLE 13
Incidences and Multiplicities of Skin Lesions Detected In-life in Female Mice Administered 0.001% Retinoic Acid Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	13.70 mJ•CIE/cm^2	UVA	UVB
Observed rate[a]	35/36 (97.0%)	21/36.0 (58.0%)	33/36.0 (92.0%)
Adjusted rate[b]	35/35.2 (99.9%)	21/33.3 (63.0%)	33/33.0 (100.0%)
First incidence (weeks)	14	21	21
Incidence test results[c]		**P<0.001**	P=1.000
Observed mean lesion multiplicity ± SEM[d]	5.8 ± 3.8	1.0 ± 1.1	7.4 ± 4.1
Overall LS mean[e] lesion multiplicity ± SEM	10.7 ± 0.7	1.2 ± 0.2	15.8 ± 1.0
Multiplicity test results[f]		**P<0.001**	**P<0.001**

[a] Number of lesion-bearing animals/number of animals with skin observed
[b] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[c] P values are based on a two-sided continuity-corrected Poly-3 test and represent pairwise comparisons to the 13.70 mJ•CIE/cm^2 SSL group. Significant P values appear in bold-faced type.
[d] Standard error of the mean (SEM) is approximated based on an additive error structure.
[e] Least square (LS) means are estimated as lesions per animal per year.
[f] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal) and represent pairwise comparisons to 13.70 mJ•CIE/cm^2 SSL group. Significant P values appear in bold-faced type.

Retinyl Palmitate Treatment

The incidence rates and multiplicities of in-life skin lesions in mice that were exposed to SSL at levels of 0.00, 6.85, or 13.70 mJ•CIE/cm^2 and treated with the control cream or creams containing RP at 0.1%, 0.5%, 1.0%, or 2.0% are compared in Table 14. In male mice, there were no significant dose trend effects and no significant differences in pairwise comparison tests of in-life skin lesion incidence rates in groups of mice that received RP creams or control creams and were then exposed to the SSL levels used in this study (0.00, 6.85, or 13.70 mJ•CIE/cm^2). In the absence of SSL exposure, a significant RP dose-related trend was observed in the incidence rates of in-life skin lesions in female mice, and a significant pairwise comparison was observed for the 1.0% RP cream group at this same level of SSL. In male and female groups treated with control cream or RP creams alike, incidence rates approached 100% in the presence of SSL and differences were not observed.

Female mice that received the 1.0% RP cream and were exposed to UVA had significantly higher in-life skin lesion incidence rates compared to mice that were exposed to UVA and treated with the control cream (Table 14). There was no difference between in-life skin lesion incidence rates in female mice exposed to UVB, as incidences approached 100% for both groups. Significantly higher multiplicities of in-life skin lesions were observed in the Poisson regression tests for female mice that received the 1.0% RP cream and exposure to either UVA or UVB when compared with female mice that received control cream and the same radiation exposure regimen.

Female mice that received 1.0% RP creams and were exposed to UVA or UVB are compared in Table 15 with female mice that received the same 1.0% RP cream treatment and were exposed to SSL at 13.70 mJ•CIE/cm^2. A significantly lower incidence and a significantly lower multiplicity of in-life skin lesions were observed in the 1.0% RP cream females that were exposed to UVA when compared to those that received the same RP cream treatment and were exposed to SSL. In contrast, significantly higher multiplicity of in-life skin lesions was observed in female mice exposed to UVB compared to the 1.0% RP cream treated females that were exposed to SSL.

TABLE 14
Incidences and Multiplicities of Skin Lesions Detected In-life in Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream	1.0% Retinyl Palmitate Cream	2.0% Retinyl Palmitate Cream
0.00 mJ•CIE/cm^2					
Male					
Observed rate[a]	20/36 (56.0%)			27/36 (75.0%)	8/36 (22.0%)
Adjusted rate[b]	25/33.1 (75.6%)			27/29.8 (90.6%)	8/16.5 (48.5%)
First incidence (weeks)	14			17	16
Incidence test results[c]	P=1.000			P=0.195	P=0.112
Observed mean lesion multiplicity ± SEM[d]	1.1 ± 1.3			2.0 ± 1.5	0.5 ± 1.0
Overall LS mean[e] lesion multiplicity ± SEM	1.2 ± 0.2			3.0 ± 0.4	1.0 ± 0.3
Multiplicity test results[f]	P=0.595			**P<0.001**	P=0.595
Female					
Observed rate	15/36 (42.0%)			31/36 (86.0%)	2/36 (6.0%)
Adjusted rate	15/34.8 (43.1%)			31/31.8 (97.3%)	2/7.7 (25.8%)
First incidence (weeks)	16			14	18
Incidence test results	**P<0.001**			**P<0.001**	P=0.749
Observed mean lesion multiplicity ± SEM	0.5 ± 0.6			2.4 ± 1.6	0.1 ± 0.5
Overall LS mean lesion multiplicity ± SEM	0.5 ± 0.2			3.5 ± 0.4	0.7 ± 0.3
Multiplicity test results	P=0.448			**P<0.001**	P=0.448
6.85 mJ•CIE/cm^2					
Male					
Observed rate	33/36 (92.0%)	34/36 (94.0%)	35/36 (97.0%)	35/36 (97.0%)	29/36 (81.0%)
Adjusted rate	33/33.1 (99.7%)	34/34.2 (99.5%)	35/35.0 (99.9%)	35/35.2 (99.4%)	29/29.6 (97.9%)
First incidence (weeks)	17	17	15	14	17
Incidence test results	P=0.441	P=1.000	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	6.5 ± 4.9	7.0 ± 4.6	7.3 ± 4.1	6.4 ± 4.4	4.1 ± 3.0
Overall LS mean lesion multiplicity ± SEM	9.6 ± 0.6	10.8 ± 0.7	12.2 ± 0.8	10.8 ± 0.7	7.6 ± 0.6
Multiplicity test results	**P=0.001**	P=0.185	**P=0.008**	P=0.217	**P=0.026**
Female					
Observed rate	35/36 (97.0%)	34/36 (94.0%)	36/36 (100.0%)	35/36 (97.0%)	30/36 (83.0%)
Adjusted rate	35/36.0 (97.2%)	34/34.0 (99.9%)	36/36.0 (100.0%)	35/35.1 (99.8%)	31/31.4 (98.7%)
First incidence (weeks)	20	18	14	18	16
Incidence test results	P=0.642	P=1.000	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	5.0 ± 3.6	6.3 ± 3.8	6.9 ± 3.2	5.4 ± 2.6	3.5 ± 2.8
Overall LS mean lesion multiplicity ± SEM	5.4 ± 0.4	8.3 ± 0.6	10.4 ± 0.7	8.2 ± 0.6	5.9 ± 0.5
Multiplicity test results	P=0.193	**P<0.001**	**P<0.001**	**P<0.001**	P=0.447

TABLE 14
Incidences and Multiplicities of Skin Lesions Detected In-life in Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream	1.0% Retinyl Palmitate Cream	2.0% Retinyl Palmitate Cream
13.70 mJ•CIE/cm^2					
Male					
Observed rate	35/36 (97.0%)	36/36 (100.0%)	36/36 (100.0%)	34/36 (94.0%)	34/36 (94.0%)
Adjusted rate	35/35.0 (100.0%)	36/36.0 (100.0%)	36/36.0 (100.0%)	34/34.0 (100.0%)	34/34.1 (99.8%)
First incidence (weeks)	17	13	13	12	11
Incidence test results	P=1.000	P=1.000	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	8.5 ± 5.0	8.9 ± 4.1	9.3 ± 4.9	8.8 ± 5.9	7.5 ± 4.1
Overall LS mean lesion multiplicity ± SEM	14.1 ± 0.8	17.0 ± 1.0	18.5 ± 1.0	18.1 ± 1.0	15.3 ± 0.9
Multiplicity test results	P=0.961	**P=0.019**	**P=0.001**	**P=0.002**	P=0.338
Female					
Observed rate	35/36 (97.0%)	36/36 (100.0%)	32/36 (89.0%)	34/36 (94.0%)	31/36 (86.0%)
Adjusted rate	35/35.2 (99.4%)	36/36.0 (100.0%)	32/32.3 (99.0%)	34/34.4 (98.8%)	31/31.6 (98.2%)
First incidence (weeks)	18	16	14	13	14
Incidence test results	P=0.399	P=1.000	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	8.0 ± 3.8	9.1 ± 4.4	6.3 ± 4.0	5.8 ± 3.4	3.3 ± 2.9
Overall LS mean lesion multiplicity ± SEM	11.2 ± 0.7	14.7 ± 0.8	12.0 ± 0.8	10.8 ± 0.8	7.0 ± 0.6
Multiplicity test results	**P<0.001**	**P=0.001**	P=0.450	P=0.675	**P<0.001N**
UVA					
Female					
Observed rate	15/36 (42.0%)			25/36 (69.0%)	
Adjusted rate	15/32.4 (46.3%)			25/33.3 (75.1%)	
First incidence (weeks)	21			21	
Incidence test results				**P=0.026**	
Observed mean lesion multiplicity ± SEM	0.4 ± 0.6			1.6 ± 1.4	
Overall LS mean lesion multiplicity ± SEM	0.5 ± 0.2			2.0 ± 0.3	
Multiplicity test results				**P<0.001**	

TABLE 14
Incidences and Multiplicities of Skin Lesions Detected In-life in Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream	1.0% Retinyl Palmitate Cream	2.0% Retinyl Palmitate Cream
UVB					
Female					
Observed rate	34/36 (94.0%)			35/36 (97.0%)	
Adjusted rate	34/34.5 (98.6%)			35/35.0 (99.9%)	
First incidence (weeks)	21			21	
Incidence test results				P=1.000	
Observed mean lesion multiplicity ± SEM	7.5 ± 4.6			8.9 ± 5.4	
Overall LS mean lesion multiplicity ± SEM	11.2 ± 0.7			18.1 ± 1.0	
Multiplicity test results				**P<0.001**	

[a] Number of lesion-bearing animals/number of animals with skin observed
[b] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[c] P values are based on a two-sided continuity-corrected Poly-3 test. P values in the control cream column (except UVA and UVB groups) are for the linear trend test; otherwise, P values represent pairwise comparisons to the control cream group from the same light exposure group. Significant P values appear in bold-faced type.
[d] Standard error of the mean (SEM) is approximated based on an additive error structure.
[e] Least square (LS) means are estimated as lesions per animal per year.
[f] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal). P values in the control cream column (except UVA and UVB groups) are for the linear trend test; otherwise, P values represent pairwise comparisons to the control cream group from the same light exposure group. Significant P values appear in bold-faced type.

TABLE 15
Incidences and Multiplicities of Skin Lesions Detected In-life in Female Mice Administered 1.0% Retinyl Palmitate Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	13.70 mJ•CIE/cm^2 SSL	UVA	UVB
Observed rate[a]	34/36 (94.0%)	25/36 (69.0%)	35/36 (97.0%)
Adjusted rate[b]	34/34.4 (99.7%)	25/33.3 (75.1%)	35/35.0 (100.0%)
First incidence (weeks)	13	21	21
Incidence test results[c]		**P=0.005**	P=1.000
Observed mean lesion multiplicity ± SEM[d]	5.8 ± 3.4	1.6 ± 1.4	8.9 ± 5.4
Overall LS mean[e] lesion multiplicity ± SEM	10.8 ± 0.8	2.0 ± 0.3	18.1 ± 1.0
Multiplicity test results[f]		**P<0.001**	**P<0.001**

[a] Number of lesion-bearing animals/number of animals with skin observed
[b] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[c] P values are based on a two-sided continuity-corrected Poly-3 test and represent pairwise comparisons to the 13.70 mJ•CIE/cm^2 SSL group. Significant P values appear in bold-faced type.
[d] Standard error of the mean (SEM) is approximated based on an additive error structure.
[e] Least square (LS) means are estimated as lesions per animal per year.
[f] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal) and represent pairwise comparisons to 13.70 mJ•CIE/cm^2 SSL group. Significant P values appear in bold-faced type.

Skin Neoplasms

This section describes the statistically significant changes in incidences of neoplasms that occurred in the study. The skin at the site of application of the creams (coincident with SSL exposure) was the target tissue of the study. Summaries of the incidences of neoplasms and statistical analysis of primary neoplasms are presented in Appendix A for male mice and Appendix B for female mice.

The proliferative skin lesions induced by exposure of the SKH-1 mouse epidermis to SSL were characterized in this study by a progression of morphological alterations beginning with focal atypical squamous hyperplasia and continuing to squamous cell papilloma, keratoacanthoma, squamous cell carcinoma *in situ*, and eventually to squamous cell carcinoma. A clear differentiation among these changes was often difficult. Squamous cell papillomas were characterized as solitary foci, usually sessile, with arborized projections elevated above the surface of the skin and consist of a core of fibrovascular tissue contiguous with the dermis and covered by orderly arrangement of multiple layers of well-differentiated, often hyperkeratotic, stratified squamous epithelia (Plates 1A and 1B). A few of the more classic pedunculated papillomas (Plate 1A) with arborized projections arising from a single stalk did occur, but the incidence of this classic morphology was much lower than sessile-based papillomas (Plate 1B). Keratoacanthomas were characterized as dermal or subcutaneous, keratin-filled, cystic masses that opened onto the surface of the skin. The wall of this crateriform cyst had a buttress appearance and was composed of thick, folded layers of well-differentiated squamous epithelium enclosed by a prominent basal cell layer. Squamous cell carcinomas *in situ* were characterized as small nodules that at times rose above the surface of the skin and ranged in size from one to several millimeters in diameter (Plate 2A). By microscopic examination, squamous cell carcinomas *in situ* were discrete nodules that lacked the orderly arrangement of squamous epithelia, consisted of masses of sheets of cells that lacked cohesion and orientation, had borders that were sharply demarcated from and often compressed the underlying dermis, and were frequently observed in multiples and in proximity to other tumor types. In some instances, the epithelium was elevated; other lesions were depressed below the adjacent epidermis compressing the dermis and resulting in a cup-shaped lesion. Superficial ulceration was common. Atypical nuclei, numerous mitotic figures, and abundant keratin were often present. An inflammatory reaction, which consisted of lymphocytes, plasma cells, and polymorphonuclear leukocytes, variably infiltrated the underlying dermis. Squamous cell carcinomas were characterized by microscopy as downward projecting sheets, nests, and anastomosing cords of neoplastic squamous cells that extend into the

dermis and, in some instances, penetrated the skeletal muscle and invaded subcutaneous tissue (Plate 2B). Grossly, squamous cell carcinomas often appeared as nodular masses with irregular surfaces that were often ulcerated and crater-formed with large masses of keratin that occupied the central crater-formed depression of the mass.

In addition to the three morphologically distinct types of squamous cell neoplasia in the epidermis, combinations of these neoplasms were analyzed. These included the sum of squamous cell carcinomas *in situ* and squamous cell carcinomas and the sum of squamous cell papillomas, squamous cell carcinomas *in situ*, and squamous cell carcinomas.

Control Cream Treatment

The statistical comparisons of the incidence rates of skin neoplasia at the site of application between groups of mice that received no cream treatment and groups of mice that received control cream treatment at the same level of SSL are shown for males and females in Table 16. In the absence of SSL and in the presence of 6.85 mJ•CIE/cm^2 SSL, significantly increased incidences of squamous cell papilloma and of the combination of squamous cell papilloma, squamous cell carcinoma *in situ*, and/or squamous cell carcinoma were observed in male and female mice that received control cream treatments compared to same sex mice that received no cream treatment. Significantly increased incidences of squamous cell carcinoma *in situ* in male mice and significantly increased incidences of squamous cell carcinoma and the combination of squamous cell carcinoma *in situ* and/or squamous cell carcinoma were observed in male and female mice that received control cream treatment and were exposed to SSL at the level of 6.85 mJ•CIE/cm^2 as compared to their no cream counterparts. Significant differences in neoplasm incidences were not observed between the groups of mice that received control cream and those that received no cream when the level of SSL exposure was increased to 13.70 mJ•CIE/cm^2 with the exception of squamous cell carcinoma *in situ*, which was significantly increased in male mice that received the control cream treatment.

The results of the Poisson regression tests of multiplicities of squamous cell neoplasms are also shown for no cream and control cream treatment groups of male and female mice in Table 16, and are graphically represented at each SSL exposure level in Figures 24 through 26. At each and every level of SSL exposure, the multiplicities of squamous cell papillomas and of the combination of all squamous cell neoplasms (papilloma, carcinoma *in situ*, and/or carcinoma) were significantly higher in male mice that received the control cream treatment when compared to male mice that received no cream treatment. Higher multiplicities of squamous cell carcinoma *in situ* and the combination of squamous cell carcinoma *in situ* and/or squamous cell carcinoma were also observed in control cream treated male mice that were exposed to SSL at levels of 6.85 or 13.70 mJ•CIE/cm^2 (Figures 25 and 26). Significantly higher multiplicities of squamous cell papillomas and the combination of squamous cell papilloma, squamous cell carcinoma *in situ*, and/or squamous cell carcinoma were observed at both the 6.85 and 13.70 mJ•CIE/cm^2 levels of SSL in female mice that received control cream treatment when compared to their no cream counterparts.

TABLE 16
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Male						
Squamous Cell Papilloma						
Overall rate[a]	1/34 (2.9%)	17/36 (47.2%)	6/35 (17.1%)	31/36 (86.1%)	23/36 (63.9%)	28/36 (77.8%)
Adjusted rate[b]	1/30.8 (3.2%)	17/32.4 (52.4%)	6/30.7 (19.6%)	31/32.2 (96.2%)	23/28.5 (80.7%)	28/29.6 (94.6%)
Terminal rate[c]	1/27 (3.7%)	16/29 (55.2%)	5/25 (20.0%)	1/1 (100.0%)	0/0	0/0
First incidence (days)	368	347	354	192	246	173
Incidence test results[d]		**P<0.001**		**P<0.001**		P=0.069
Observed mean lesion multiplicity ± SEM[e]	0.03 ± 0.03	0.67 ± 0.15	0.34 ± 0.17	4.61 ± 0.70	1.22 ± 0.24	4.03 ± 0.72
LS adjusted mean[f] lesion multiplicity ± SEM	0.05 ± 0.13	0.73 ± 0.19	0.39 ± 0.17	6.76 ± 0.54	1.76 ± 0.29	6.80 ± 0.57
Multiplicity test results[g]		**P=0.004**		**P<0.001**		**P<0.001**
Keratoacanthoma						
Overall rate	0/34 (0.0%)	3/36 (8.3%)	0/35 (0.0%)	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)
Adjusted rate	0/30.8 (0.0%)	3/32.6 (9.2%)	0/30.5 (0.0%)	0/14.6 (0.0%)	0/15.8 (0.0%)	1/10.2 (9.8%)
Terminal rate	0/27 (0.0%)	2/29 (6.9%)	0/25 (0.0%)	0/1 (0.0%)	0/0	0/0
First incidence (days)	—[h]	320	—	—	—	192
Incidence test results		P=0.254		—[i]		P=0.828
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.08 ± 0.05	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.03
LS adjusted mean lesion multiplicity ± SEM	0.02 ± 0.13	0.11 ± 0.14	0.03 ± 0.13	0.21 ± 0.17	0.16 ± 0.16	0.35 ± 0.20
Multiplicity test results		P=0.607		P=0.386		P=0.431
Squamous Cell Carcinoma *in situ*						
Overall rate	0/34 (0.0%)	0/36 (0.0%)	1/35 (2.9%)	8/36 (22.2%)	14/36 (38.9%)	22/36 (61.1%)
Adjusted rate	0/30.8 (0.0%)	0/32.3 (0.0%)	1/30.7 (3.3%)	8/18.6 (43.0%)	14/23.8 (58.8%)	22/25.4 (86.7%)
Terminal rate	0/27 (0.0%)	0/29 (0.0%)	0/25 (0.0%)	1/1 (100.0%)	0/0	0/0
First incidence (days)	—	—	347	235	262	173
Incidence test results		—		**P<0.001**		**P=0.010**
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.03	0.33 ± 0.13	0.64 ± 0.17	1.31 ± 0.28
LS adjusted mean lesion multiplicity ± SEM	0.02 ± 0.13	0.03 ± 0.13	0.06 ± 0.13	0.68 ± 0.22	1.00 ± 0.23	2.41 ± 0.36
Multiplicity test results		P=0.968		**P=0.012**		**P=0.001**

TABLE 16
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Male (continued)						
Squamous Cell Carcinoma						
Overall rate	0/34 (0.0%)	1/36 (2.8%)	2/35 (5.7%)	9/36 (25.0%)	27/36 (75.0%)	19/36 (52.8%)
Adjusted rate	0/30.8 (0.0%)	1/32.3 (3.1%)	2/30.7 (6.5%)	9/18.2 (49.4%)	27/31.0 (87.1%)	19/22.6 (83.9%)
Terminal rate	0/27 (0.0%)	1/29 (3.4%)	1/25 (4.0%)	0/1 (0.0%)	0/0	0/0
First incidence (days)	—	368	354	276	243	192
Incidence test results		P=1.000		**P<0.001**		P=1.000
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.03 ± 0.03	0.06 ± 0.04	0.31 ± 0.10	1.33 ± 0.20	0.94 ± 0.20
LS adjusted mean lesion multiplicity ± SEM	0.02 ± 0.13	0.06 ± 0.13	0.09 ± 0.14	0.64 ± 0.21	1.91 ± 0.30	1.83 ± 0.32
Multiplicity test results		P=0.839		**P=0.024**		P=0.857
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma						
Overall rate	0/34 (0.0%)	1/36 (2.8%)	3/35 (8.6%)	16/36 (44.4%)	30/36 (83.3%)	27/36 (75.0%)
Adjusted rate	0/30.8 (0.0%)	1/32.3 (3.1%)	3/30.8 (9.7%)	16/22.0 (72.8)	30/32.8 (91.5%)	27/28.8 (93.8)
Terminal rate	0/27 (0.0%)	1/29 (3.4%)	1/25 (4.0%)	1/1 (100.0%)	0/0	0/0
First incidence (days)	—	368	347	235	243	173
Incidence test results		P=1.000		**P<0.001**		P=1.000
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.03 ± 0.03	0.09 ± 0.05	0.64 ± 0.15	1.97 ± 0.29	2.25 ± 0.41
LS adjusted mean lesion multiplicity ± SEM	0.02 ± 0.13	0.06 ± 0.13	0.12 ± 0.14	1.12 ± 0.25	2.75 ± 0.34	3.93 ± 0.45
Multiplicity test results		P=0.839		**P<0.001**		**P=0.033**
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma						
Overall rate	1/34 (2.9%)	17/36 (47.2%)	7/35 (20.0%)	32/36 (88.9%)	36/36 (100.0%)	33/36 (91.7%)
Adjusted rate	1/30.8 (3.2%)	17/32.4 (52.4%)	7/30.8 (22.7%)	32/32.8 (97.7%)	36/36.0 (100.0%)	33/33.4 (98.9%)
Terminal rate	1/27 (3.7%)	16/29 (55.2%)	5/25 (20.0%)	1/1 (100.0%)	0/0	0/0
First incidence (days)	368	347	347	192	243	173
Incidence test results		**P<0.001**		**P<0.001**		P=1.000
Observed mean lesion multiplicity ± SEM	0.03 ± 0.03	0.69 ± 0.15	0.43 ± 0.19	5.25 ± 0.72	3.19 ± 0.34	6.28 ± 0.84
LS adjusted mean lesion multiplicity ± SEM	0.05 ± 0.13	0.76 ± 0.19	0.49 ± 0.17	7.66 ± 0.57	4.35 ± 0.42	10.42 ± 0.70
Multiplicity test results		**P=0.003**		**P<0.001**		**P<0.001**

TABLE 16
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Female						
Squamous Cell Papilloma						
Overall rate	1/36 (2.8%)	7/36 (19.4%)	13/36 (36.1%)	31/36 (86.1%)	29/36 (80.6%)	31/36 (86.1%)
Adjusted rate	1/35.0 (2.9%)	7/33.9 (20.7%)	13/34.6 (37.6%)	31/34.9 (88.7%)	29/31.8 (91.2%)	31/32.8 (94.6%)
Terminal rate	1/34 (2.9%)	5/28 (17.9%)	10/30 (33.3%)	21/24 (87.5%)	1/1 (100.0%)	0/0
First incidence (days)	367	327	260	228	256	201
Incidence test results		**P=0.048**		**P<0.001**		P=0.944
Observed mean lesion multiplicity ± SEM	0.03 ± 0.03	0.25 ± 0.09	0.47 ± 0.13	2.64 ± 0.40	2.14 ± 0.34	3.64 ± 0.62
LS adjusted mean lesion multiplicity ± SEM	0.03 ± 0.12	0.27 ± 0.15	0.50 ± 0.17	2.83 ± 0.31	2.90 ± 0.35	5.13 ± 0.46
Multiplicity test results		P=0.224		**P<0.001**		**P<0.001**
Keratoacanthoma						
Overall rate	0/36 (0.0%)	1/36 (2.8%)	0/36 (0.0%)	1/36 (2.8%)	0/36 (0.0%)	1/36 (2.8%)
Adjusted rate	0/35.0 (0.0%)	1/33.8 (3.0%)	0/33.3 (0.0%)	1/30.7 (3.3%)	0/17.6 (0.0%)	1/15.1 (6.6%)
Terminal rate	1/34 (0.0%)	0/28 (0.0%)	0/30 (0.0%)	1/24 (4.2%)	0/1 (0.0%)	0/0
First incidence (days)	—	320	—	367	—	262
Incidence test results		P=0.986		P=0.968		P=0.939
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.03 ± 0.03	0.00 ± 0.00	0.03 ± 0.03	0.00 ± 0.00	0.03 ± 0.03
LS adjusted mean lesion multiplicity ± SEM	0.01 ± 0.12	0.04 ± 0.12	0.01 ± 0.12	0.06 ± 0.13	0.14 ± 0.15	0.22 ± 0.17
Multiplicity test results		P=0.839		P=0.787		P=0.743
Squamous Cell Carcinoma *in situ*						
Overall rate	0/36 (0.0%)	0/36 (0.0%)	2/36 (5.6%)	7/36 (19.4%)	18/36 (50.0%)	19/36 (52.8%)
Adjusted rate	0/35.0 (0.0%)	0/33.4 (0.0%)	2/33.3 (6.0%)	7/31.6 (22.1%)	18/26.5 (68.0%)	19/25.8 (73.6%)
Terminal rate	0/34 (0.0%)	0/28 (0.0%)	2/30 (6.7%)	4/24 (16.7%)	1/1 (100.0%)	0/0
First incidence (days)	—	—	367	306	256	219
Incidence test results		—		P=0.123		P=0.865
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.00 ± 0.00	0.08 ± 0.06	0.33 ± 0.13	0.97 ± 0.22	0.72 ± 0.14
LS adjusted mean lesion multiplicity ± SEM	0.01 ± 0.12	0.01 ± 0.12	0.10 ± 0.13	0.39 ± 0.16	1.40 ± 0.26	1.16 ± 0.25
Multiplicity test results		P=0.969		P=0.169		P=0.517

TABLE 16
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Female (continued)						
Squamous Cell Carcinoma						
Overall rate	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)	9/36 (25.0%)	24/36 (66.7%)	25/36 (69.4%)
Adjusted rate	0/35.0 (0.0%)	0/33.4 (0.0%)	1/33.8 (3.0%)	9/32.1 (28.0%)	24/29.0 (82.7%)	25/29.1 (86.0%)
Terminal rate	0/34 (0.0%)	0/28 (0.0%)	0/30 (0.0%)	4/24 (16.7%)	1/1 (100.0%)	0/0
First incidence (days)	—	—	299	306	235	219
Incidence test results		—		**P=0.009**		P=1.000
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.03	0.36 ± 0.11	0.94 ± 0.16	1.00 ± 0.18
LS adjusted mean lesion multiplicity ± SEM	0.01 ± 0.12	0.01 ± 0.12	0.04 ± 0.13	0.41 ± 0.17	1.36 ± 0.26	1.54 ± 0.28
Multiplicity test results		P=0.969		P=0.072		P=0.637
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma						
Overall rate	0/36 (0.0%)	0/36 (0.0%)	3/36 (8.3%)	11/36 (30.6%)	31/36 (86.1%)	32/36 (88.9%)
Adjusted rate	0/35.0 (0.0%)	0/33.4 (0.0%)	3/33.8 (8.9%)	11/32.1 (34.2%)	31/33.2 (93.4%)	32/33.3 (96.8%)
Terminal rate	0/34 (0.0%)	0/28 (0.0%)	2/30 (6.7%)	6/24 (25.0%)	1/1 (100.0%)	0/0
First incidence (days)	—	—	299	306	235	219
Incidence test results		—		**P=0.022**		P=0.913
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.00 ± 0.00	0.11 ± 0.07	0.69 ± 0.22	1.92 ± 0.22	1.72 ± 0.21
LS adjusted mean lesion multiplicity ± SEM	0.01 ± 0.12	0.01 ± 0.12	0.13 ± 0.13	0.77 ± 0.19	2.62 ± 0.33	2.53 ± 0.34
Multiplicity test results		P=0.969		**P=0.007**		P=0.846

TABLE 16
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Female (continued)						
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma						
Overall rate	1/36 (2.8%)	7/36 (19.4%)	16/36 (44.4%)	33/36 (91.7%)	34/36 (94.4%)	35/36 (97.2%)
Adjusted rate	1/35.0 (2.9%)	7/33.9 (20.7%)	16/35.0 (45.7%)	33/35.2 (93.8%)	34/34.7 (98.1%)	35/35.2 (99.4%)
Terminal rate	1/34 (2.9%)	5/28 (17.9%)	12/30 (40.0%)	22/24 (91.7%)	1/1 (100.0%)	0/0
First incidence (days)	367	327	260	228	235	201
Incidence test results		**P=0.048**		**P<0.001**		P=1.000
Observed mean lesion multiplicity ± SEM	0.03 ± 0.03	0.25 ± 0.09	0.58 ± 0.13	3.33 ± 0.49	4.06 ± 0.49	5.36 ± 0.70
LS adjusted mean lesion multiplicity ± SEM	0.03 ± 0.12	0.27 ± 0.15	0.61 ± 0.18	3.57 ± 0.35	5.38 ± 0.46	7.48 ± 0.55
Multiplicity test results		P=0.224		**P<0.001**		**P=0.003**

[a] Number of neoplasm-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are based on a two-sided, continuity-corrected Poly-3 test and represent pairwise comparisons to the no cream group. A lower incidence than that in the no cream group is indicated by **N**. Significant P values appear in bold-faced type.
[e] Standard error of the mean (SEM) is approximated based on an additive error structure.
[f] Least square (LS) means are estimated as lesions per animal per year.
[g] P values are based on the two-sided Poisson regression test of multiplicity (neoplasms per animal) and represent pairwise comparisons to the no cream group. Significant P values appear in bold-faced type.
[h] Not applicable; no neoplasms in animal group
[i] Value of statistic cannot be computed.

Male	P-Value	Female	P-Value
Carcinoma	0.839	Carcinoma	0.969
Carcinoma *in Situ*	0.968	Carcinoma *in Situ*	0.969
Papilloma	**0.004**	Papilloma	0.224
Carcinoma or Carcinoma *in Situ*	0.839	Carcinoma or Carcinoma *in Situ*	0.969
All Squamous Neoplasms	**0.003**	All Squamous Neoplasms	0.224

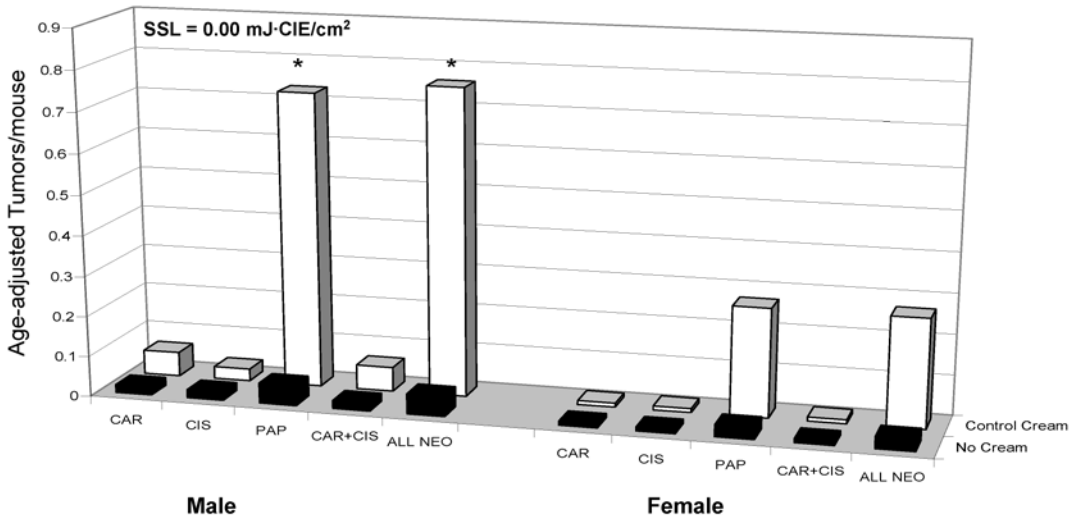


FIGURE 24
Comparisons of the Effects of No Cream and Control Cream on the Multiplicity of Squamous Cell Neoplasms in Male and Female Mice Exposed to SSL at 0.00 mJ•CIE/cm^2 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
Asterisks above chart bars denote significant pairwise comparisons with the no cream group (*, P≤0.05). Significant pairwise P values are bolded.
PAP = papilloma; CIS = carcinoma *in situ*; CAR = carcinoma; ALL NEO = PAP + CIS + CAR

Male	P-Value	Female	P-Value
Carcinoma	**0.024**	Carcinoma	0.072
Carcinoma *in Situ*	**0.012**	Carcinoma *in Situ*	0.169
Papilloma	**< 0.001**	Papilloma	**< 0.001**
Carcinoma or Carcinoma *in Situ*	**< 0.001**	Carcinoma or Carcinoma *in Situ*	**0.007**
All Squamous Neoplasms	**< 0.001**	All Squamous Neoplasms	**< 0.001**

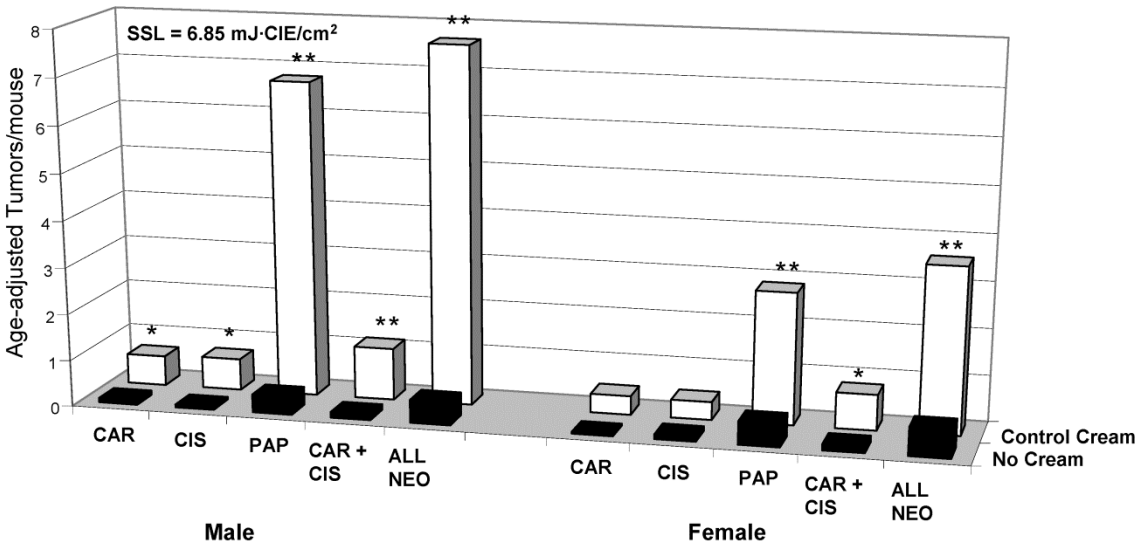


FIGURE 25
Comparisons of the Effects of No Cream and Control Cream on the Multiplicity of Squamous Cell Neoplasms in Male and Female Mice Exposed to SSL at 6.85 mJ•CIE/cm^2 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
Asterisks above chart bars denote significant pairwise comparisons with the no cream group (*, P≤0.05; **, P<0.001). Significant pairwise P values are bolded.
PAP = papilloma; CIS = carcinoma *in situ*; CAR = carcinoma; ALL NEO = PAP + CIS + CAR

Male	P-Value	Female	P-Value
Carcinoma	0.857	Carcinoma	0.637
Carcinoma *in Situ*	**0.001**	Carcinoma *in Situ*	0.517
Papilloma	**< 0.001**	Papilloma	**< 0.001**
Carcinoma or Carcinoma *in Situ*	**0.033**	Carcinoma or Carcinoma *in Situ*	0.846
All Squamous Neoplasms	**< 0.001**	All Squamous Neoplasms	**0.003**

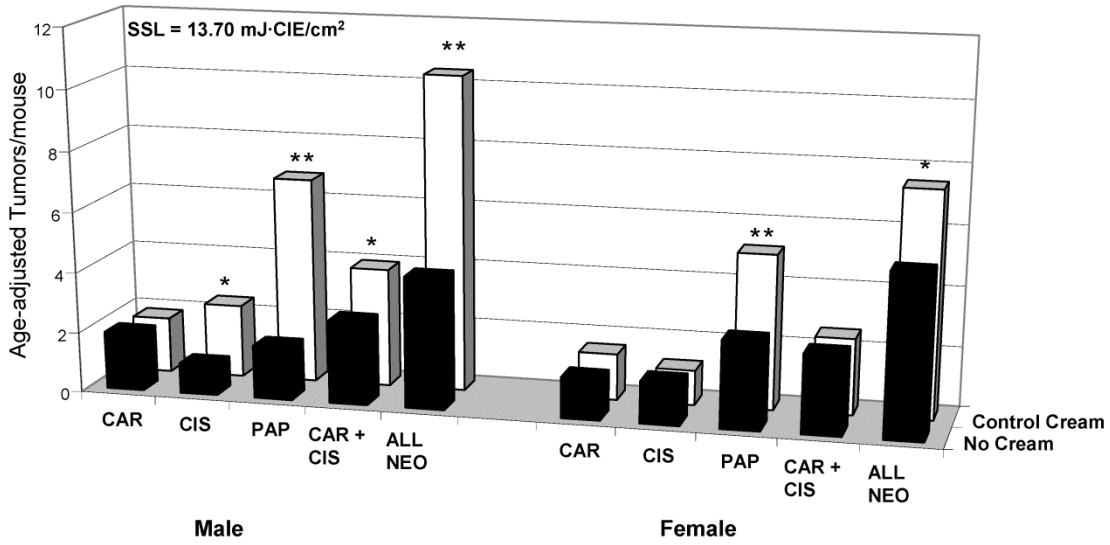


FIGURE 26
Comparisons of the Effects of No Cream and Control Cream on the Multiplicity of Squamous Cell Neoplasms in Male and Female Mice Exposed to SSL at 13.70 mJ•CIE/cm^2 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
Asterisks above chart bars denote significant pairwise comparisons with the no cream group (*, P≤0.05; **, P<0.001). Significant pairwise P values are bolded.
PAP = papilloma; CIS = carcinoma *in situ*; CAR = carcinoma; ALL NEO = PAP + CIS + CAR

Retinyl Palmitate Treatment

The incidences and multiplicities of skin neoplasia in male and female mice administered control cream or 0.1% or 0.5% RP cream are summarized in Table 17. Significant dose-related trend increases in the incidences of squamous cell carcinoma were observed in males and females that were exposed to the 6.85 mJ•CIE/cm^2 level of SSL, and in pairwise comparisons with same sex control cream groups significantly higher incidences of squamous cell carcinomas were observed in mice that were treated with the 0.5% RP cream. In female mice, significant dose-related trend increases were also observed in the incidences of squamous cell carcinoma *in situ* and in the combination of squamous cell carcinoma *in situ* and/or squamous cell carcinoma at the 6.85 mJ•CIE/cm^2 level of SSL.

As shown in Table 17 and Figure 27, significant dose-related increases in the multiplicities of squamous cell papilloma and in the multiplicities of the combination of all squamous cell neoplasms (papilloma, carcinoma *in situ*, and/or carcinoma) were observed in male and female mice exposed to SSL at levels of 6.85 and 13.70 mJ•CIE/cm^2. Significant pairwise comparison tests with same sex mice that received control cream and the same level of SSL were also observed at each dose level of RP creams. In female mice that were exposed to the 13.70 mJ•CIE/cm^2 level of SSL, significantly higher multiplicities of squamous cell carcinoma and of the combination of squamous cell carcinoma *in situ* and/or squamous cell carcinoma were observed when compared with female mice that received control cream and the same exposure level of SSL.

TABLE 17
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Male						
Squamous Cell Papilloma						
Overall rate[a]	31/36 (86.1%)	32/36 (88.9%)	34/35 (97.1%)	28/36 (77.8%)	34/36 (94.4%)	34/36 (94.4%)
Adjusted rate[b]	31/32.2 (96.2%)	32/32.8 (97.6%)	34/34.3 (99.6%)	28/29.6 (94.6%)	34/34.2 (99.4%)	34/34.3 (99.0%)
Terminal rate[c]	1/1 (100.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	192	192	131	173	128	156
Incidence test results[d]	P=0.596	P=1.000	P=1.000	P=0.175	P=0.427	P=0.560
Observed mean lesion multiplicity ± SEM[e]	4.61 ± 0.70	5.86 ± 0.75	7.23 ± 0.79	4.03 ± 0.72	6.08 ± 0.78	6.47 ± 0.70
LS adjusted mean[f] lesion multiplicity ± SEM	6.76 ± 0.54	8.97 ± 0.63	11.70 ± 0.74	6.80 ± 0.57	11.59 ± 0.79	12.97 ± 0.85
Multiplicity test results[g]	**P<0.001**	**P=0.007**	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**
Keratoacanthoma						
Overall rate	0/36 (0.0%)	1/36 (2.8%)	0/35 (0.0%)	1/36 (2.8%)	1/36 (2.8%)	1/36 (2.8%)
Adjusted rate	0/14.6 (0.0%)	1/12.2 (8.2%)	0/9.1 (0.0%)	1/10.2 (9.8%)	1/6.8 (14.7%)	1/5.9 (16.9%)
Terminal rate	0/1 (0.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	—[h]	255	—	192	192	178
Incidence test results	P=1.000	P=0.927	—[i]	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.06 ± 0.04	0.00 ± 0.00	0.03 ± 0.03	0.03 ± 0.03	0.03 ± 0.03
LS adjusted mean lesion multiplicity ± SEM	0.21 ± 0.17	0.33 ± 0.19	0.29 ± 0.19	0.35 ± 0.20	0.47 ± 0.22	0.52 ± 0.24
Multiplicity test results	P=0.851	P=0.639	P=0.752	P=0.630	P=0.687	P=0.576
Squamous Cell Carcinoma *in situ*						
Overall rate	8/36 (22.2%)	11/36 (30.6%)	9/35 (25.7%)	22/36 (61.1%)	17/36 (47.2%)	19/36 (52.8%)
Adjusted rate	8/18.6 (43.0%)	11/18.8 (58.6%)	9/15.5 (58.1%)	22/25.4 (86.7%)	17/20.0 (85.1%)	19/21.4 (88.9%)
Terminal rate	1/1 (100.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	235	226	214	173	150	156
Incidence test results	P=0.373	P=0.461	P=0.532	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	0.33 ± 0.13	0.42 ± 0.12	0.26 ± 0.07	1.31 ± 0.28	0.92 ± 0.22	0.78 ± 0.18
LS adjusted mean lesion multiplicity ± SEM	0.68 ± 0.22	0.86 ± 0.24	0.70 ± 0.23	2.41 ± 0.36	2.10 ± 0.37	1.97 ± 0.37
Multiplicity test results	P=0.875	P=0.572	P=0.969	P=0.468	P=0.550	P=0.393

TABLE 17
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Male (continued)						
Squamous Cell Carcinoma						
Overall rate	9/36 (25.0%)	8/36 (22.2%)	17/35 (48.6%)	19/36 (52.8%)	15/36 (41.7%)	12/36 (33.3%)
Adjusted rate	9/18.2 (49.4%)	8/16.7 (47.9%)	17/21.4 (79.3%)	19/22.6 (83.9%)	15/18.2 (82.5%)	12/15.1 (79.6%)
Terminal rate	0/1 (0.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	276	207	180	192	171	177
Incidence test results	**P=0.014**	P=1.000	**P=0.030**	P=0.907N	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	0.31 ± 0.10	0.28 ± 0.10	0.51 ± 0.10	0.94 ± 0.20	0.56 ± 0.13	0.56 ± 0.15
LS adjusted mean lesion multiplicity ± SEM	0.64 ± 0.21	0.66 ± 0.22	1.10 ± 0.27	1.83 ± 0.32	1.44 ± 0.32	1.54 ± 0.33
Multiplicity test results	P=0.127	P=0.964	P=0.179	P=0.713	P=0.392	P=0.535
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma						
Overall rate	16/36 (44.4%)	17/36 (47.2%)	21/35 (60.0%)	27/36 (75.0%)	27/36 (75.0%)	26/36 (72.2%)
Adjusted rate	16/22.0 (72.8%)	17/22.8 (74.7%)	21/24.3 (86.3%)	27/28.8 (93.8%)	27/28.3 (95.5%)	26/27.3 (95.2%)
Terminal rate	1/1 (100.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	235	207	180	173	150	156
Incidence test results	P=0.173	P=1.000	P=0.259	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	0.64 ± 0.15	0.69 ± 0.15	0.77 ± 0.13	2.25 ± 0.41	1.47 ± 0.24	1.33 ± 0.21
LS adjusted mean lesion multiplicity ± SEM	1.12 ± 0.25	1.28 ± 0.27	1.51 ± 0.30	3.93 ± 0.45	3.12 ± 0.43	3.04 ± 0.44
Multiplicity test results	P=0.329	P=0.664	P=0.318	P=0.281	P=0.195	P=0.158
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma						
Overall rate	32/36 (88.9%)	32/36 (88.9%)	35/35 (100.0%)	33/36 (91.7%)	35/36 (97.2%)	36/36 (100.0%)
Adjusted rate	32/32.8 (97.7%)	32/32.8 (97.6%)	35/35.0 (100.0%)	33/33.4 (98.9%)	35/35.1 (99.8%)	36/36.0 (100.0%)
Terminal rate	1/1 (100.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	192	192	131	173	128	156
Incidence test results	P=0.677	P=1.000	P=1.000	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	5.25 ± 0.72	6.56 ± 0.78	8.00 ± 0.82	6.28 ± 0.84	7.56 ± 0.84	7.81 ± 0.73
LS adjusted mean lesion multiplicity ± SEM	7.66 ± 0.57	10.0 ± 0.66	12.92 ± 0.78	10.42 ± 0.70	14.30 ± 0.87	15.55 ± 0.93
Multiplicity test results	**P<0.001**	**P=0.007**	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**

TABLE 17
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Female						
Squamous Cell Papilloma						
Overall rate	31/36 (86.1%)	31/36 (86.1%)	36/36 (100.0%)	31/36 (86.1%)	32/36 (88.9%)	28/36 (77.8%)
Adjusted rate	31/34.9 (88.7%)	31/33.2 (93.4%)	36/36.0 (100.0%)	31/32.8 (94.6%)	32/33.0 (97.0%)	28/29.0 (96.4%)
Terminal rate	21/24 (87.5%)	4/4 (100.0%)	0/0	0/0	0/0	0/0
First incidence (days)	228	167	167	201	191	187
Incidence test results	P=0.051	P=0.789	P=0.098	P=0.945	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	2.64 ± 0.40	3.44 ± 0.49	5.31 ± 0.61	3.64 ± 0.62	5.39 ± 0.78	5.39 ± 0.81
LS adjusted mean lesion multiplicity ± SEM	2.83 ± 0.31	4.51 ± 0.42	7.89 ± 0.58	5.13 ± 0.46	8.68 ± 0.63	10.28 ± 0.74
Multiplicity test results	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**
Keratoacanthoma						
Overall rate	1/36 (2.8%)	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)	0/36 (0.0%)	0/36 (0.0%)
Adjusted rate	1/30.7 (3.3%)	0/19.4 (0.0%)	0/12.0 (0.0%)	1/15.1 (6.6%)	0/9.5 (0.0%)	0/6.6 (0.0%)
Terminal rate	1/24 (4.2%)	0/4 (0.0%)	0/0	0/0	0/0	0/0
First incidence (days)	367	—	—	262	—	—
Incidence test results	P=0.909N	P=1.000	P=1.000	P=0.865N	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	0.03 ± 0.03	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.03	0.00 ± 0.00	0.00 ± 0.00
LS adjusted mean lesion multiplicity ± SEM	0.06 ± 0.13	0.14 ± 0.15	0.22 ± 0.17	0.22 ± 0.17	0.28 ± 0.19	0.42 ± 0.22
Multiplicity test results	P=0.468	P=0.704	P=0.441	P=0.462	P=0.804	P=0.462
Squamous Cell Carcinoma *in situ*						
Overall rate	7/36 (19.4%)	10/36 (27.8%)	9/36 (25.0%)	19/36 (52.8%)	25/36 (69.4%)	11/36 (30.6%)
Adjusted rate	7/31.6 (22.1%)	10/22.6 (44.2%)	9/18.1 (49.9%)	19/25.8 (73.6%)	25/27.8 (90.0%)	11/15.3 (71.9%)
Terminal rate	4/24 (16.7%)	2/4 (50.0%)	0/0	0/0	0/0	0/0
First incidence (days)	306	242	201	219	191	201
Incidence test results	**P=0.038**	P=0.149	P=0.097	P=0.686	P=0.083	P=1.000
Observed mean lesion multiplicity ± SEM	0.33 ± 0.13	0.47 ± 0.15	0.22 ± 0.07	0.72 ± 0.14	1.97 ± 0.42	0.64 ± 0.17
LS adjusted mean lesion multiplicity ± SEM	0.39 ± 0.16	0.74 ± 0.21	0.54 ± 0.21	1.16 ± 0.25	3.35 ± 0.41	1.58 ± 0.33
Multiplicity test results	P=0.822	P=0.180	P=0.539	P=0.772	**P<0.001**	P=0.299

TABLE 17
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

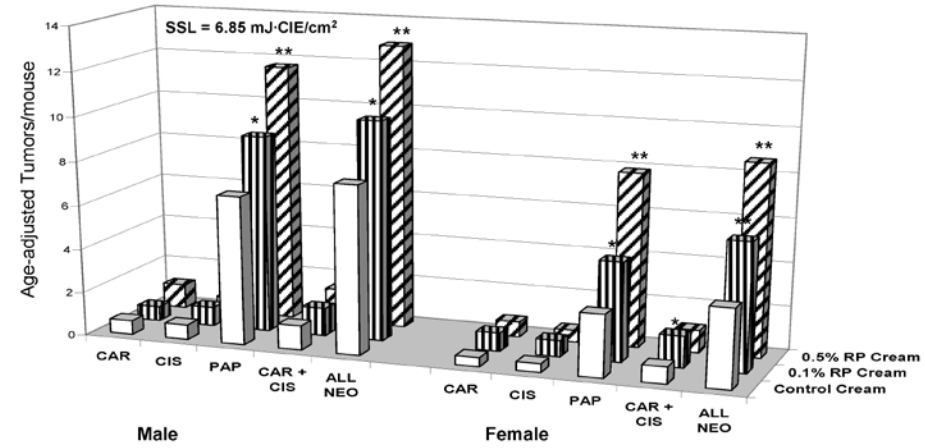
	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Female (continued)						
Squamous Cell Carcinoma						
Overall rate	9/36 (25.0%)	14/36 (38.9%)	16/36 (44.4%)	25/36 (69.4%)	29/36 (80.6%)	25/36 (69.4%)
Adjusted rate	9/32.1 (28.0%)	14/25.2 (55.6%)	16/22.6 (70.8%)	25/29.1 (86.0%)	29/30.8 (94.0%)	25/26.4 (94.6%)
Terminal rate	4/24 (16.7%)	0/4 (0.0%)	0/0	0/0	0/0	0/0
First incidence (days)	306	242	201	219	191	159
Incidence test results	**P<0.001**	P=0.057	**P=0.002**	P=0.140	P=0.352	P=0.332
Observed mean lesion multiplicity ± SEM	0.36 ± 0.11	0.56 ± 0.16	0.33 ± 0.09	1.00 ± 0.18	1.56 ± 0.20	1.22 ± 0.18
LS adjusted mean lesion multiplicity ± SEM	0.41 ± 0.17	0.84 ± 022	0.70 ± 0.22	1.54 ± 0.28	2.70 ± 0.37	2.65 ± 0.40
Multiplicity test results	P=0.512	P=0.114	P=0.283	P=0.078	**P=0.012**	**P=0.020**
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma						
Overall rate	11/36 (30.6%)	19/36 (52.8%)	21/36 (58.3%)	32/36 (88.9%)	34/36 (94.4%)	28/36 (77.8%)
Adjusted rate	11/32.1 (34.2%)	19/27.0 (70.4%)	21/25.9 (81.0%)	32/33.3 (96.8%)	34/34.5 (98.5%)	28/28.8 (97.1%)
Terminal rate	6/24 (25.0%)	2/4 (50.0%)	0/0	0/0	0/0	0/0
First incidence (days)	306	242	201	219	191	159
Incidence test results	**P<0.001**	**P=0.007**	**P<0.001**	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	0.69 ± 0.22	1.03 ± 0.21	0.56 ± 0.12	1.72 ± 0.21	3.53 ± 0.46	1.86 ± 0.26
LS adjusted mean lesion multiplicity ± SEM	0.77 ± 0.19	1.44 ± 0.26	1.03 ± 0.25	2.53 ± 0.34	5.78 ± 0.52	3.82 ± 0.47
Multiplicity test results	P=0.830	**P=0.037**	P=0.408	P=0.400	**P<0.001**	**P=0.022**

TABLE 17
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Female (continued)						
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, or Squamous Cell Carcinoma						
Overall rate	33/36 (91.7%)	34/36 (94.4%)	36/36 (100.0%)	35/36 (97.2%)	34/36 (94.4%)	32/36 (88.9%)
Adjusted rate	33/35.2 (93.8%)	34/34.1 (99.8%)	36/36.0 (100.0%)	35/35.2 (99.4%)	34/34.5 (98.5%)	32/32.2 (99.3%)
Terminal rate	22/24 (91.7%)	4/4 (100.0%)	0/0	0/0	0/0	0/0
First incidence (days)	228	167	167	201	191	159
Incidence test results	P=0.138	P=0.431	P=0.384	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM	3.33 ± 0.49	4.47 ± 0.56	5.86 ± 0.63	5.36 ± 0.70	8.92 ± 0.92	7.25 ± 0.90
LS adjusted mean lesion multiplicity ± SEM	3.57 ± 0.35	5.82 ± 0.47	8.69 ± 0.61	7.48 ± 0.55	14.18 ± 0.80	13.68 ± 0.85
Multiplicity test results	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**

[a] Number of neoplasm-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are based on a two-sided, continuity-corrected Poly-3 test. P values in the control cream columns are for the linear trend test; otherwise, P values represent pairwise comparisons to the respective control cream group. A negative trend or a lower incidence in a dose group is indicated by **N**. Significant P values appear in bold-faced type.
[e] Standard error of the mean (SEM) is approximated based on an additive error structure.
[f] Least square (LS) means are estimated as lesions per animal per year.
[g] P values are based on the two-sided Poisson regression test of multiplicity (neoplasms per animal). P values in the control cream columns are for the linear trend test; otherwise, P values represent pairwise comparisons to the respective control cream group. Significant P values appear in bold-faced type.
[h] Not applicable; no neoplasms in animal group
[i] Value of statistic cannot be computed.

Male	Trend	Female	Trend
Carcinoma	0.127	Carcinoma	0.512
Carcinoma *in Situ*	0.875	Carcinoma *in Situ*	0.822
Papilloma	**< 0.001**	Papilloma	**< 0.001**
Carcinoma or Carcinoma *in Situ*	0.329	Carcinoma or Carcinoma *in Situ*	0.830
All Squamous Neoplasms	**< 0.001**	All Squamous Neoplasma	**< 0.001**



Male	Trend	Female	Trend
Carcinoma	0.713	Carcinoma	0.078
Carcinoma *in Situ*	0.468	Carcinoma *in Situ*	0.722
Papilloma	**< 0.001**	Papilloma	**< 0.001**
Carcinoma or Carcinoma *in Situ*	0.281	Carcinoma or Carcinoma *in Situ*	0.400
All Squamous Neoplasms	**< 0.001**	All Squamous Neoplasma	**< 0.001**

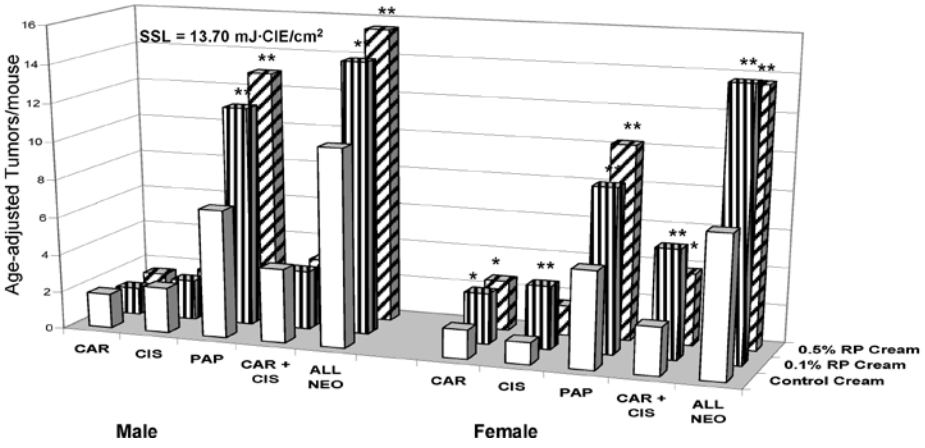


FIGURE 27
Comparisons of the Effects of Control Cream or Retinyl Palmitate Creams on the Multiplicity of Squamous Cell Neoplasms in Male and Female Mice Exposed to at 6.85 or 13.70 mJ·CIE/cm^2 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
Asterisks above chart bars denote significant pairwise comparisons with the control cream group (*, P≤0.05; **, P<0.001). Significant P values for dose-related trends are bolded.
PAP = papilloma; CIS = carcinoma *in situ*; CAR = Carcinoma; ALL NEO = PAP + CIS + CAR

Nonneoplastic Skin Lesions

This section describes biologically noteworthy histopathology changes in nonneoplastic lesions that occurred in the study. The skin at the site of application of the creams (coincident with the site of SSL exposure) was the target tissue of the study. Summaries of the incidences of nonneoplastic lesions are presented in Appendix A for male mice and Appendix B for female mice.

The skin of SKH-1 hairless mice examined in this study was characterized by an epidermis that usually consisted of one or two layers of squamous cells (Plate 3A). Hair shafts and adnexal structures, such as sebaceous glands, were either absent or were atypical in location and development. There were often prominent cystic structures in the dermis, which appeared to be remnants of hair follicles. The cysts were usually lined by squamous or low cuboidal epithelium and were either empty or contained small amounts of keratinized debris and, occasionally, fragmented hair shafts.

Exposure of SKH-1 mice to SSL and treatment with the control or RP cream formulations used in this study were not associated with diffuse thickening of the epidermis. This change was documented using the term "squamous hyperplasia" (Plate 3B).

The exposure of SKH-1 mice to SSL with or without the topical application of control or RP cream formulations was associated with focal nodular thickening of the epidermis; the term "focal atypical squamous hyperplasia" was used to describe this condition (Plate 3C). Focal atypical squamous hyperplasia was a circumscribed, moderate to severe, epidermal thickening; whereas, squamous hyperplasia was thinner and more diffuse. While focal atypical squamous hyperplasia was almost always detected grossly; squamous hyperplasia was usually visible only by microscopic examination. The squamous cells that comprise the nodule of focal atypical hyperplasia resembled normal epidermis; however, dysplastic changes, including the lack of cohesion or orientation, pleomorphism, nuclear atypia, and basal disorganization often accompanied this lesion. The incidence and multiplicity of focal atypical squamous hyperplasia was documented according to the number of nodules detected in the epidermis.

There were also a number of nonneoplastic skin lesions that were indirectly associated with exposure to SSL and/or the topical applications of control or RP cream formulations. These included abscesses, inflammation of the epidermis, dermis, or subcutaneous tissue, and necrosis and/or ulceration of the epidermis. These changes were likely the result of damage to the skin induced by exposure to SSL and/or the topical applications of the control or RP creams and were aggravated by self-mutilation and/or bacterial infections.

Control Cream Treatment

The incidences and multiplicities of nonneoplastic skin lesions are shown for control cream and no cream male and female mice in Table 18. In the absence of SSL exposure, significantly increased incidences of squamous cell hyperplasia were observed in male and female mice that received control cream treatments when compared with mice that received no cream treatment. When male and female mice were exposed to SSL at a level of 6.85 mJ•CIE/cm^2, the incidences of squamous cell hyperplasia, focal atypical squamous hyperplasia, and inflammation of the dermis were significantly increased in mice that were treated with control cream as compared with mice that received no cream treatment. There were no significant differences in the incidences of these same skin lesions in mice when the level of exposure to SSL was 13.70 mJ•CIE/cm^2. The multiplicities of focal atypical squamous hyperplasia were significantly increased in male and female mice that were treated with control cream as compared with the no cream treated same sex groups at both 6.85 and 13.70 mJ•CIE/cm^2 of SSL.

TABLE 18
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Male						
Cyst Epithelial Inclusion						
Overall rate[a]	3/34 (8.8%)	5/36 (13.9%)	4/35 (11.4%)	6/36 (16.7%)	3/36 (8.3%)	3/36 (8.3%)
Adjusted rate[b]	3/30.8 (9.7%)	5/32.3 (15.5%)	4/30.7 (13.0%)	6/17.9 (33.5%)	3/17.6 (17.1%)	3/11.6 (25.8%)
Terminal rate[c]	3/27 (11.1%)	5/29 (17.2%)	3/25 (12.0%)	0/1 (0.0%)	0/0	0/0
First incidence (days)	368	368	347	249	246	206
Incidence test results[d]		P=0.760		P=0.203		P=0.916
Squamous Cell Hyperplasia						
Overall rate	0/34 (0.0%)	6/36 (16.7%)	4/35 (11.4%)	23/36 (63.9%)	26/36 (72.2%)	27/36 (75.0%)
Adjusted rate	0/30.8 (0.0%)	6/34.9 (17.2%)	4/30.7 (13.0%)	23/29.4 (78.2%)	26/30.7 (84.7%)	27/29.3 (92.0%)
Terminal rate	0/27 (0.0%)	3/29 (10.3%)	3/25 (12.0%)	0/1 (0.0%)	0/0	0/0
First incidence (days)	—[e]	65	354	16	243	173
Incidence test results		**P=0.041**		**P<0.001**		P=0.500
Focal Atypical Squamous Hyperplasia						
Overall rate	0/34 (0.0%)	4/36 (11.1%)	9/35 (25.7%)	28/36 (77.8%)	32/36 (88.9%)	33/36 (91.7%)
Adjusted rate	0/30.8 (0.0%)	4/32.3 (12.4%)	9/30.7 (29.4%)	28/29.8 (94.0%)	32/33.5 (95.6%)	33/33.4 (98.8%)
Terminal rate	0/27 (0.0%)	4/29 (13.8%)	8/25 (32.0%)	1/1 (100.0%)	0/0	0/0
First incidence (days)	—	368	354	208	250	173
Incidence test results		P=0.127		**P<0.001**		P=0.928
Observed mean lesion multiplicity ± SEM[f]	0.00 ± 0.00	0.11 ± 0.05	0.60 ± 0.23	4.44 ± 0.67	4.22 ± 0.54	7.97 ± 0.85
LS adjusted mean[g] lesion multiplicity ± SEM	0.02 ± 0.13	0.14 ± 0.14	0.67 ± 0.19	6.52 ± 0.53	5.70 ± 0.48	13.15 ± 0.78
Multiplicity test results[h]		P=0.507		**P<0.001**		**P<0.001**
Inflammation of the Dermis						
Overall rate	0/34 (0.0%)	3/36 (8.3%)	3/35 (8.6%)	9/36 (25.0%)	5/36 (13.9%)	8/36 (22.2%)
Adjusted rate	0/30.8 (0.0%)	3/32.3 (9.3%)	3/30.5 (9.8%)	9/19.8 (45.5%)	5/18.3 (27.3%)	8/15.3 (52.4%)
Terminal rate	0/27 (0.0%)	3/29 (10.3%)	3/25 (12.0%)	0/1 (0.0%)	0/0	0/0
First incidence (days)	—	368	368	192	250	173
Incidence test results		P=0.249		**P=0.009**		P=0.196

TABLE 18
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Male (continued)						
Inflammation of the Epidermis						
Overall rate	0/34 (0.0%)	0/36 (0.0%)	1/35 (2.9%)	0/36 (0.0%)	1/36 (2.8%)	3/36 (8.3%)
Adjusted rate	0/30.8 (0.0%)	0/32.3 (0.0%)	1/30.5 (3.3%)	0/14.6 (0.0%)	1/16.0 (6.2%)	3/11.4 (26.3%)
Terminal rate	0/27 (0.0%)	0/29 (0.0%)	1/25 (4.0%)	0/1 (0.0%)	0/0	0/0
First incidence (days)	—	—	368	—	339	243
Incidence test results		—[i]		P=1.000		P=0.349
Necrosis of the Epidermis						
Overall rate	0/34 (0.0%)	0/36 (0.0%)	1/35 (2.9%)	3/36 (8.3%)	3/36 (8.3%)	5/36 (13.9%)
Adjusted rate	0/30.8 (0.0%)	0/32.3 (0.0%)	1/30.7 (3.3%)	3/16.3 (18.4%)	3/17.2 (17.4%)	5/13.2 (37.9%)
Terminal rate	0/27 (0.0%)	0/29 (0.0%)	0/25 (0.0%)	0/1 (0.0%)	0/0	0/0
First incidence (days)	—	—	354	235	264	173
Incidence test results		—		P=0.262		P=0.360
Ulceration of the Epidermis						
Overall rate	0/34 (0.0%)	1/36 (2.8%)	1/35 (2.9%)	0/36 (0.0%)	1/36 (2.8%)	3/36 (8.3%)
Adjusted rate	0/30.8 (0.0%)	1/32.3 (3.1%)	1/30.5 (3.3%)	0/14.6 (0.0%)	1/16.0 (6.2%)	3/11.4 (26.3%)
Terminal rate	0/27 (0.0%)	1/29 (3.4%)	1/25 (4.0%)	0/1 (0.0%)	0/0	0/0
First incidence (days)	—	368	368	—	339	241
Incidence test results		P=1.000		P=1.000		P=0.349

TABLE 18
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Female						
Cyst Epithelial Inclusion						
Overall rate	2/36 (5.6%)	0/36 (0.0%)	4/36 (11.1%)	5/36 (13.9%)	2/36 (5.6%)	9/36 (25.0%)
Adjusted rate	2/35.0 (5.7%)	0/33.4 (0.0%)	4/33.3 (12.0%)	5/31.7 (15.8%)	2/17.7 (11.3%)	9/19.8 (45.4%)
Terminal rate	2/34 (5.9%)	0/28 (0.0%)	4/30 (13.3%)	3/24 (12.5%)	1/1 (100.0%)	0/0
First incidence (days)	367	—	367	228	346	219
Incidence test results		P=0.493N		P=0.935		**P=0.031**
Squamous Cell Hyperplasia						
Overall rate	1/36 (2.8%)	7/36 (19.4%)	11/36 (30.6%)	24/36 (66.7%)	28/36 (77.8%)	33/36 (91.7%)
Adjusted rate	1/35.0 (2.9%)	7/34.2 (20.5%)	11/34.0 (32.4%)	24/35.3 (67.9%)	28/31.4 (89.3%)	33/34.4 (96.0%)
Terminal rate	1/34 (2.9%)	5/28 (17.9%)	9/30 (30.0%)	15/24 (62.5%)	1/1 (100.0%)	0/0
First incidence (days)	367	270	320	214	235	201
Incidence test results		**P=0.050**		**P=0.004**		P=0.436
Focal Atypical Squamous Hyperplasia						
Overall rate	0/36 (0.0%)	1/36 (2.8%)	16/36 (44.4%)	27/36 (75.0%)	33/36 (91.7%)	33/36 (91.7%)
Adjusted rate	0/35.0 (0.0%)	1/33.4 (3.0%)	16/33.9 (47.2%)	27/33.7 (80.1%)	33/33.8 (97.6%)	33/34.1 (96.8%)
Terminal rate	0/34 (0.0%)	1/28 (3.6%)	14/30 (46.7%)	19/24 (79.2%)	1/1 (100.0%)	0/0
First incidence (days)	—	367	320	235	235	219
Incidence test results		P=0.982		**P=0.006**		P=1.000
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.06 ± 0.06	0.78 ± 0.20	2.81 ± 0.49	4.75 ± 0.57	6.22 ± 0.76
LS adjusted mean lesion multiplicity ± SEM	0.01 ± 0.12	0.07 ± 0.13	0.81 ± 0.19	3.01 ± 032	6.27 ± 0.49	8.65 ± 0.59
Multiplicity test results		P=0.716		**P<0.001**		**P=0.002**
Inflammation of the Dermis						
Overall rate	2/36 (5.6%)	2/36 (5.6%)	1/36 (2.8%)	15/36 (41.7%)	12/36 (33.3%)	18/36 (50.0%)
Adjusted rate	2/35.0 (5.7%)	2/33.6 (6.0%)	1/33.3 (3.0%)	15/33.9 (44.3%)	12/23.5 (51.1%)	18/25.8 (69.7%)
Terminal rate	2/34 (5.9%)	1/28 (3.6%)	1/30 (3.3%)	9/24 (37.5%)	0/1 (0.0%)	0/0
First incidence (days)	367	349	367	214	256	201
Incidence test results		P=1.000		**P<0.001**		P=0.215

TABLE 18
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Female (continued)						
Inflammation of the Epidermis						
Overall rate	0/36 (0.0%)	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)	1/36 (2.8%)	3/36 (8.3%)
Adjusted rate	0/35.0 (0.0%)	0/33.4 (0.0%)	0/33.3 (0.0%)	1/31.5 (3.2%)	1/17.8 (5.6%)	3/16.2 (18.5%)
Terminal rate	0/34 (0.0%)	0/28 (0.0%)	0/30 (0.0%)	0/24 (0.0%)	0/1 (0.0%)	0/0
First incidence (days)	—	—	—	214	334	249
Incidence test results		—		P=0.978		P=0.516
Necrosis of the Epidermis						
Overall rate	0/36 (0.0%)	0/36 (0.0%)	0/36 (0.0%)	2/36 (5.6%)	2/36 (5.6%)	3/36 (8.3%)
Adjusted rate	0/35.0 (0.0%)	0/33.4 (0.0%)	0/33.3 (0.0%)	2/30.7 (6.5%)	2/18.2 (11.0%)	3/15.9 (8.9%)
Terminal rate	0/34 (0.0%)	0/28 (0.0%)	0/30 (0.0%)	2/24 (8.3%)	0/1 (0.0%)	0/0
First incidence (days)	—	—	—	367	320	249
Incidence test results		—		P=0.437		P=0.868
Ulceration of the Epidermis						
Overall rate	0/36 (0.0%)	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)	1/36 (2.8%)	2/36 (5.6%)
Adjusted rate	0/35.0 (0.0%)	0/33.4 (0.0%)	0/33.3 (0.0%)	1/31.5 (3.2%)	1/17.8 (5.6%)	2/15.8 (12.7%)
Terminal rate	0/34 (0.0%)	0/28 (0.0%)	0/30 (0.0%)	0/24 (0.0%)	0/1 (0.0%)	0/0
First incidence (days)	—	—	—	214	334	249
Incidence test results		—		P=0.978		P=0.911

[a] Number of lesion-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are based on a two-sided, continuity-corrected Poly-3 test and represent pairwise comparisons to the no cream group. A lower incidence than that in the no cream group is indicated by **N**. Significant P values appear in bold-faced type.
[e] Not applicable; no lesions in animal group
[f] Standard error of the mean (SEM) is approximated based on an additive error structure.
[g] Least square (LS) means are estimated as lesions per animal per year.
[h] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal) and represent pairwise comparisons to the no cream group. Significant P values appear in bold-faced type.
[i] Value of statistic cannot be computed.

Retinyl Palmitate Treatment

The incidences and multiplicities of nonneoplastic skin lesions in mice that were treated with creams containing 0.1% or 0.5% RP are compared in Table 19 with the incidences and multiplicities of nonneoplastic skin lesions in mice that were treated with the control cream. Significant dose-related trends for RP were observed in the incidences of inflammation of the dermis and epidermis, necrosis of the epidermis, and ulceration of the epidermis in male and female mice, and in the incidences of squamous cell hyperplasia in male mice at both 6.85 and 13.70 mJ•CIE/cm^2 SSL. A significant dose-related trend for RP was also observed in the incidences of squamous cell hyperplasia and focal atypical squamous hyperplasia in female mice at the SSL level of 6.85 mJ•CIE/cm^2. In male mice exposed to SSL at 6.85 mJ•CIE/cm^2, the incidence of focal atypical hyperplasia approached 100% in groups of mice treated with RP and control creams alike and significant trends were not observed. In pairwise comparisons with same sex mice that received control cream, significant differences were observed in the incidences of squamous cell hyperplasia in male and female mice, in the incidences of focal atypical squamous hyperplasia and inflammation of the dermis in female mice, and in the incidences of inflammation and ulceration of the epidermis in male mice that were treated with 0.1% or 0.5% RP and exposed to SSL at 6.85 mJ•CIE/cm^2. At the SSL level of 13.70 mJ•CIE/cm^2, significant differences in pairwise comparisons with mice that received control cream treatment were also observed. With the exception of inflammation of the dermis in male and female mice and necrosis of the epidermis in male mice, significant differences from the control cream groups occurred primarily in mice treated with the higher dose of RP cream.

The multiplicities of focal atypical squamous hyperplasia showed dose-related increases in both male and female mice at 6.85 mJ•CIE/cm^2 SSL and in males at 13.70 mJ•CIE/cm^2 SSL (Table 19). In pairwise comparison tests with groups of mice that were treated with the control cream, significant differences in the multiplicities of focal atypical squamous hyperplasia were observed for the 0.1% and 0.5% doses of RP in both male and female mice. When the level of SSL was increased to 13.70 mJ•CIE/cm^2, the dose effect of RP was inconsistent, and the level of SSL rather than the dose of RP was likely the major contributing effect.

TABLE 19
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Male						
Cyst Epithelial Inclusion						
Overall rate[a]	6/36 (16.7%)	0/36 (0.0%)	0/35 (0.0%)	3/36 (8.3%)	1/36 (2.8%)	1/36 (2.8%)
Adjusted rate[b]	6/17.9 (33.5%)	0/11.5 (0.0%)	0/9.1 (0.0%)	3/11.6 (25.8%)	1/6.8 (14.6%)	1/5.9 (16.8%)
Terminal rate[c]	0/1 (0.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	249	—[e]	—	206	164	156
Incidence test results[d]	**P=0.012N**	P=0.073N	P=0.146N	P=0.845N	P=1.000	P=1.000
Squamous Cell Hyperplasia						
Overall rate	23/36 (63.9%)	32/36 (88.9%)	34/35 (97.1%)	27/36 (75.0%)	34/36 (94.4%)	35/36 (97.2%)
Adjusted rate	23/29.4 (78.2%)	32/33.2 (96.2%)	34/34.4 (98.8%)	27/29.3 (92.0%)	34/34.4 (98.9%)	35/35.1 (99.6%)
Terminal rate	0/1 (0.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	16	83	131	173	128	156
Incidence test results	**P<0.001**	**P=0.016**	**P=0.002**	**P=0.014**	P=0.184	P=0.090
Focal Atypical Squamous Hyperplasia						
Overall rate	28/36 (77.8%)	33/36 (91.7%)	31/35 (88.6%)	33/36 (91.7%)	36/36 (100.0%)	35/36 (97.2%)
Adjusted rate	28/29.8 (94.0%)	33/33.3 (99.0%)	31/31.7 (97.8%)	33/33.4 (98.8%)	36/36.1 (100.0%)	35/35.1 (99.7%)
Terminal rate	1/1 (100.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	208	181	180	173	128	156
Incidence test results	P=0.423	P=0.488	P=0.840	P=1.000	P=1.000	P=1.000
Observed mean lesion multiplicity ± SEM[f]	4.44 ± 0.67	6.44 ± 0.69	8.09 ± 0.91	7.97 ± 0.85	7.92 ± 0.79	8.22 ± 0.77
LS adjusted mean[g] lesion multiplicity ± SEM	6.52 ± 0.53	9.84 ± 0065	13.06 ± 0.78	13.15 ± 0.78	14.96 ± 0.89	16.35 ± 0.95
Multiplicity test results[h]	**P<0.001**	**P<0.001**	**P<0.001**	**P=0.017**	P=0.126	**P=0.009**
Inflammation of the Dermis						
Overall rate	9/36 (25.0%)	12/36 (33.3%)	30/35 (85.7%)	8/36 (22.2%)	20/36 (55.6%)	32/36 (88.9%)
Adjusted rate	9/19.8 (45.5%)	12/19.4 (61.8%)	30/31.1 (96.4%)	8/15.3 (52.4%)	20/22.5 (89.0%)	32/32.6 (98.0%)
Terminal rate	0/1 (0.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	192	207	180	173	150	156
Incidence test results	**P<0.001**	P=0.406	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**

TABLE 19
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Male (continued)						
Inflammation of the Epidermis						
Overall rate	0/36 (0.0%)	7/36 (19.4%)	8/35 (22.9%)	3/36 (8.3%)	7/36 (19.4%)	14/36 (38.9%)
Adjusted rate	0/14.6 (0.0%)	7/16.2 (43.3%)	8/14.8 (54.1%)	3/11.4 (26.3%)	7/11.6 (60.1%)	14/17.1 (81.9%)
Terminal rate	0/1 (0.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	—	226	207	243	150	167
Incidence test results	**P<0.001**	**P=0.006**	**P<0.001**	**P<0.001**	P=0.134	**P<0.001**
Necrosis of the Epidermis						
Overall rate	3/36 (8.3%)	9/36 (25.0%)	14/35 (40.0%)	5/36 (13.9%)	11/36 (30.6%)	20/36 (55.6%)
Adjusted rate	3/16.3 (18.4%)	9/17.3 (52.1%)	14/19.1 (73.5%)	5/13.2 (37.9%)	11/15.1 (72.6%)	20/22.2 (90.2%)
Terminal rate	0/1 (0.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	235	228	207	173	150	163
Incidence test results	**P<0.001**	P=0.056	**P<0.001**	**P<0.001**	**P=0.047**	**P<0.001**
Ulceration of the Epidermis						
Overall rate	0/36 (0.0%)	7/36 (19.4%)	8/35 (22.9%)	3/36 (8.3%)	8/36 (22.2%)	10/36 (27.8%)
Adjusted rate	0/14.6 (0.0%)	7/16.0 (43.8%)	8/14.8 (54.1%)	3/11.4 (26.3%)	8/12.4 (64.6%)	10/13.6 (73.7%)
Terminal rate	0/1 (0.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	—	226	207	241	187	171
Incidence test results	**P<0.001**	**P=0.006**	**P<0.001**	**P=0.004**	P=0.065	**P=0.009**

TABLE 19
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

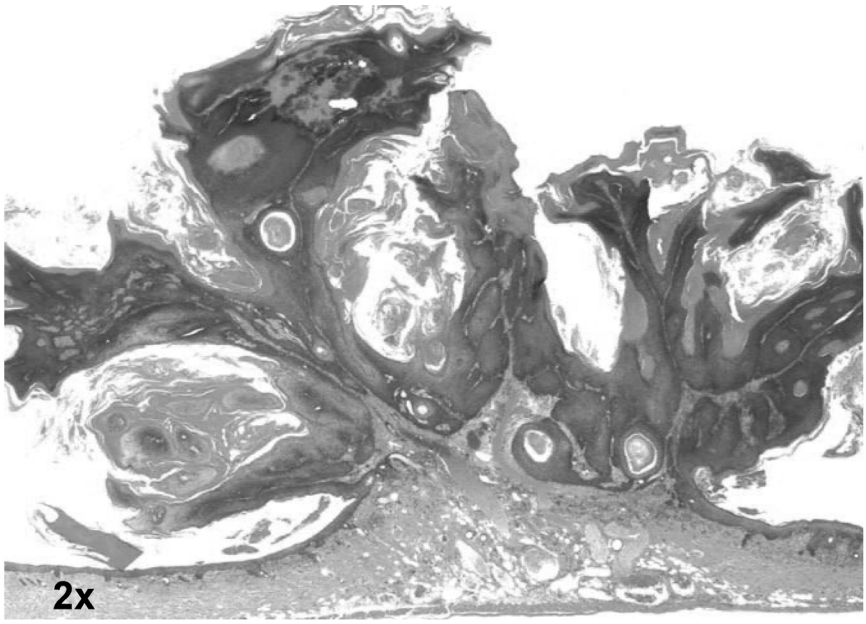
	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Female						
Cyst Epithelial Inclusion						
Overall rate	5/36 (13.9%)	4/36 (11.1%)	1/36 (2.8%)	9/36 (25.0%)	1/36 (2.8%)	0/36 (0.0%)
Adjusted rate	5/31.7 (15.8%)	4/20.5 (19.5%)	1/12.6 (7.9%)	9/19.8 (45.4%)	1/10.2 (9.8%)	0/6.6 (0.0%)
Terminal rate	3/24 (12.5%)	1/4 (25.0%)	0/0	0/0	0/0	0/0
First incidence (days)	228	277	270	219	248	—
Incidence test results	P=1.000	P=1.000	P=0.865N	**P=0.012N**	P=0.111N	P=0.139N
Squamous Cell Hyperplasia						
Overall rate	24/36 (66.7%)	32/36 (88.9%)	36/36 (100.0%)	33/36 (91.7%)	31/36 (86.1%)	35/36 (97.2%)
Adjusted rate	24/35.3 (67.9%)	32/35.0 (91.5%)	36/36.0 (100.0%)	33/34.4 (96.0%)	31/32.3 (95.9%)	35/35.2 (99.5%)
Terminal rate	15/24 (62.5%)	3/4 (75.0%)	0/0	0/0	0/0	0/0
First incidence (days)	214	107	167	201	191	3
Incidence test results	**P<0.001**	**P=0.021**	**P<0.001**	P=0.401	P=1.000	P=0.799
Focal Atypical Squamous Hyperplasia						
Overall rate	27/36 (75.0%)	31/36 (86.1%)	34/36 (94.4%)	33/36 (91.7%)	36/36 (100.0%)	30/36 (83.3%)
Adjusted rate	27/33.7 (80.1%)	31/31.8 (97.5%)	34/34.4 (98.9%)	33/34.1 (96.8%)	36/36.0 (100.0%)	30/30.6 (98.0%)
Terminal rate	19/24 (79.2%)	4/4 (100.0%)	0/0	0/0	0/0	0/0
First incidence (days)	235	235	201	219	191	159
Incidence test results	**P=0.002**	**P=0.041**	**P=0.016**	P=1.000	P=0.860	P=1.000
Observed mean lesion multiplicity ± SEM	2.81 ± 0.49	5.17 ± 0.69	5.08 ± 0.65	6.22 ± 0.76	6.97 ± 0.70	5.50 ± 0.75
LS adjusted mean lesion multiplicity ± SEM	3.01 ± 0.32	6.70 ± 0.50	7.57 ± 0.57	8.65 ± 0.59	11.15 ± 0.71	10.48 ± 0.75
Multiplicity test results	**P<0.001**	**P<0.001**	**P<0.001**	P=0.220	**P=0.006**	P=0.051
Inflammation of the Dermis						
Overall rate	15/36 (41.7%)	28/36 (77.8%)	36/36 (100.0%)	18/36 (50.0%)	31/36 (86.1%)	33/36 (91.7%)
Adjusted rate	15/33.9 (44.3%)	28/33.2 (84.3%)	36/36.0 (100.0%)	18/25.8 (69.7%)	31/32.3 (95.9%)	33/33.4 (98.8%)
Terminal rate	9/24 (37.5%)	2/4 (50.0%)	0/0	0/0	0/0	0/0
First incidence (days)	214	107	167	201	191	34
Incidence test results	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**

TABLE 19
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Female (continued)						
Inflammation of the Epidermis						
Overall rate	1/36 (2.8%)	2/36 (5.6%)	7/36 (19.4%)	3/36 (8.3%)	3/36 (8.3%)	9/36 (25.0%)
Adjusted rate	1/31.5 (3.2%)	2/20.9 (9.6%)	7/16.6 (42.2%)	3/16.2 (18.5%)	3/11.6 (25.8%)	9/13.8 (65.1%)
Terminal rate	0/24 (0.0%)	0/4 (0.0%)	0/0	0/0	0/0	0/0
First incidence (days)	214	111	227	249	208	187
Incidence test results	**P=0.002**	P=0.723	**P=0.003**	**P=0.003**	P=1.000	**P=0.007**
Necrosis of the Epidermis						
Overall rate	2/36 (5.6%)	4/36 (11.1%)	7/36 (19.4%)	3/36 (8.3%)	5/36 (13.9%)	14/36 (38.9%)
Adjusted rate	2/30.7 (6.5%)	4/20.5 (19.5%)	7/16.7 (42.0%)	3/15.9 (18.9%)	5/13.3 (37.7%)	14/17.9 (78.0%)
Terminal rate	2/24 (8.3%)	1/4 (25.0%)	0/0	0/0	0/0	0/0
First incidence (days)	367	277	227	249	191	159
Incidence test results	**P=0.007**	P=0.344	**P=0.011**	**P<0.001**	P=0.435	**P<0.001**
Ulceration of the Epidermis						
Overall rate	1/36 (2.8%)	3/36 (8.3%)	9/36 (25.0%)	2/36 (5.6%)	3/36 (8.3%)	6/36 (16.7%)
Adjusted rate	1/31.5 (3.2%)	3/20.6 (14.6%)	9/17.9 (50.3%)	2/15.8 (12.7%)	3/11.6 (25.8%)	6/11.3 (53.2%)
Terminal rate	0/24 (0.0%)	1/4 (25.0%)	0/0	0/0	0/0	0/0
First incidence (days)	214	111	227	249	208	208
Incidence test results	**P<0.001**	P=0.344	**P<0.001**	**P=0.024**	P=0.697	**P=0.040**

[a] Number of lesion-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are based on a two-sided, continuity-corrected Poly-3 test. P values in the control cream columns are for the linear trend test; otherwise, P values represent pairwise comparisons to the control cream group. A negative trend or a lower incidence in a dose group is indicated by **N**. Significant P values appear in bold-faced type.
[e] Not applicable; no lesions in animal group
[f] Standard error of the mean (SEM) is approximated based on an additive error structure.
[g] Least square (LS) means are estimated as lesions per animal per year.
[h] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal). P values in the control cream columns are for the linear trend test; otherwise, P values represent pairwise comparisons to the control cream group. Significant P values appear in bold-faced type.

A.



B.

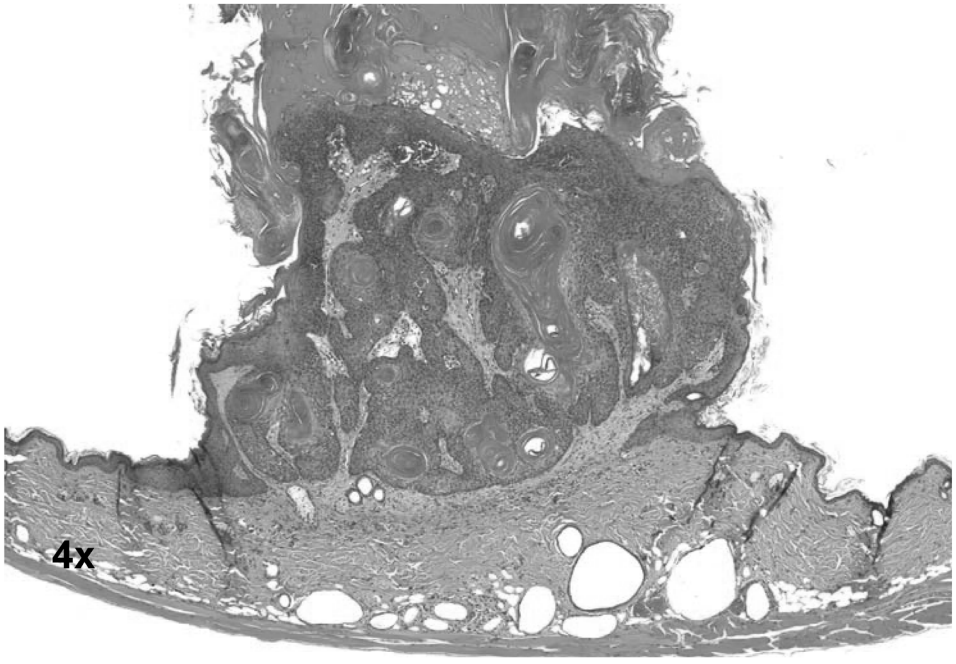


PLATE 1

Panel A: Squamous cell papilloma of the epidermis on a pedunculated base from a mouse that received retinyl palmitate (0.5%) and was exposed to SSL at 6.85 mJ•CIE/cm^2; H&E

Panel B: A sessile-based squamous cell papilloma of the epidermis from a male mouse that received control cream and was not exposed to UV radiation; H&E

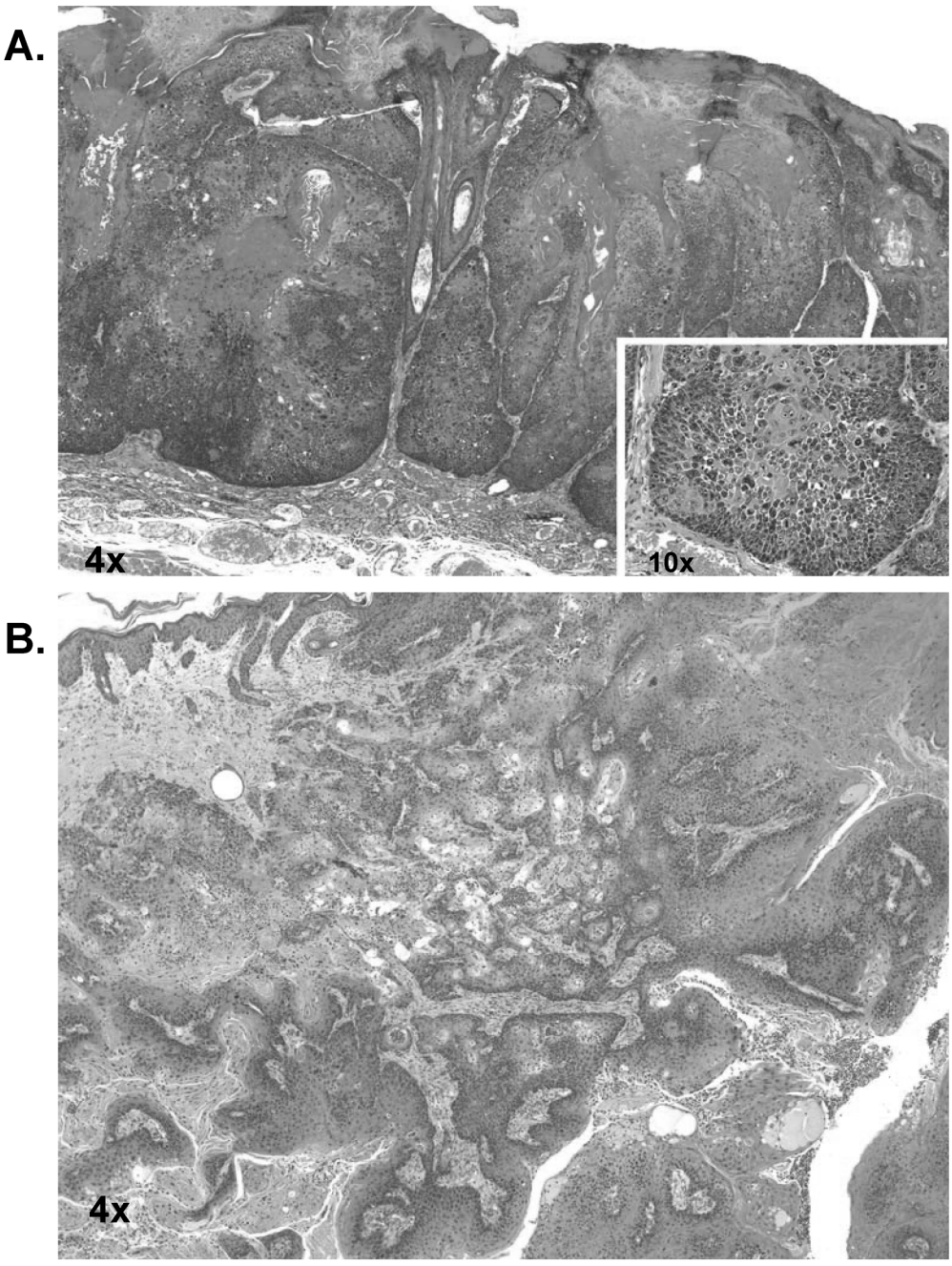


PLATE 2

Panel A: A squamous cell carcinoma *in situ* of the epidermis from a female mouse that received retinyl palmitate cream (0.5%) and was exposed to SSL at 6.85 mJ•CIE/cm^2 SSL; H&E

Panel B: A squamous cell carcinoma of the epidermis from a male mouse that received retinyl palmitate cream (0.5%) and was exposed to SSL at 6.85 mJ•CIE/cm^2; H&E

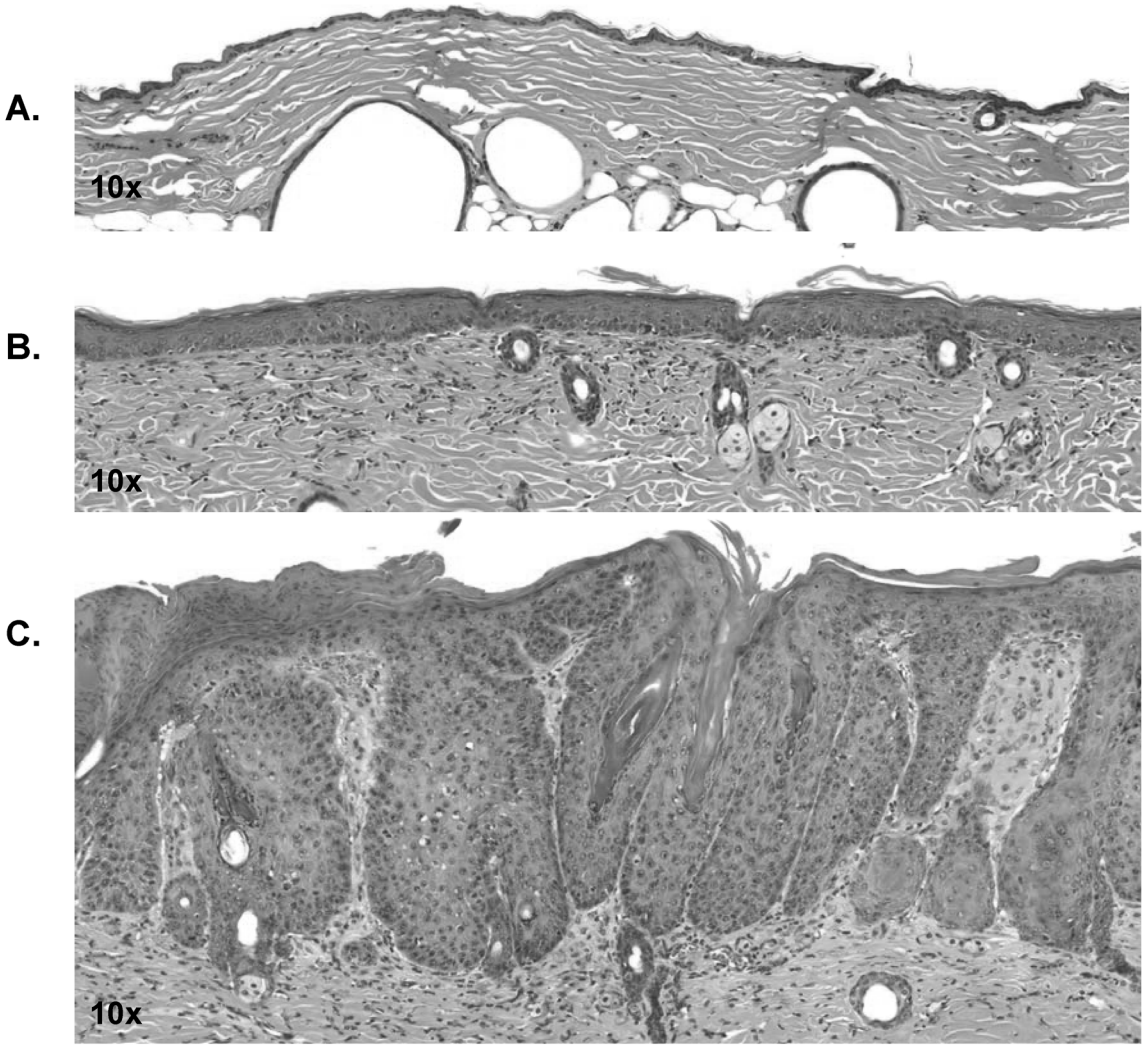


PLATE 3

Panel A: Normal squamous cell epithelium of a male mouse that received no cream treatment and was not exposed to UV radiation; H&E

Panel B: Mildly diffuse squamous cell hyperplasia of the epidermis of a male mouse that received the control cream and was exposed to SSL at 6.85 mJ•CIE/cm^2; H&E

Panel C**:** Marked focal atypical hyperplasia of the epidermis of a male mouse that received no cream treatment and was exposed to SSL at 6.85 mJ•CIE/cm^2; H&E

DISCUSSION AND CONCLUSIONS

Squamous cell neoplasia is one of the most common forms of human malignancy, representing one third of all new cancers diagnosed in the United States (Jemal *et al.,* 2007, 2008). The primary pathogenic factor for the development of squamous cell neoplasia in the general population is overexposure to sunlight-derived radiation (Mukhtar *et al.,* 1999; Armstrong and Kricker, 2001). The number of new cases of non-melanoma skin cancer diagnosed each year in the United States alone approaches one million and continues to rise (Jemal *et al.,* 2007, 2008).

Solar ultraviolet (UV) radiation is divided into three categories based on wavelength – UVC (200 to 280 nm), UVB (280 to 320 nm), and UVA (320 to 400 nm). UVC has the highest energy; however, it is filtered out by the stratospheric ozone layer and does not reach the surface of the Earth (F'guyer *et al.,* 2003). Currently, UVB and, to a much lesser extent, UVA are considered to be responsible for UV radiation-induced skin cancer (F'guyer *et al.,* 2003). At similar doses, UVB is generally regarded as more carcinogenic than UVA in mice (de Gruijl *et al.,* 1993). UVA constitutes the majority (98.7%) of solar UV radiation at the surface of the Earth but accounts for only 10% of the carcinogenic dose of sunlight; conversely, UVB constitutes a minor portion of solar UV radiation but has substantial direct and indirect adverse biological effects on skin. The impact of UVB radiation can be inferred from the characteristic point mutations in the p53 gene found in human squamous cell carcinoma and basal cell carcinoma (de Gruijl, 2002). In contrast to UVB, much of the mutagenic and carcinogenic action of UVA radiation appears to be mediated through reactive oxygen species (Bossi *et al.,* 2008). Both UVB and UVA radiation can give rise to reactive oxygen species-induced point mutations that may not be recognized as attributable to solar light exposure (de Gruijl, 1999, 2002). Furthermore, because solar radiation may act as both an initiator and a promoter of skin cancer, solar UV light is considered a complete carcinogen.

Over the last century, the general public has shown dramatic changes in its perception and attitude toward the sun, and lifelong sun exposure in individuals has increased exponentially (Singh and Griffiths, 2006). The impact of increased sun exposure has been increased incidences of photocarcinogenesis. Besides UV-induced skin cancers, chronic sun exposure is also responsible for the photoaging process in skin that is characterized by the formation of deep wrinkles, abnormal pigmentation, and a leathery appearance of the skin (Kligman, 1986; Gaspar and Campos, 2007). It has been estimated that photoaging or photodamage may account for 90% of age-associated cosmetic skin problems (Samuel *et al.,* 2005). Experimental studies with animal models confirm that both UVB and UVA contribute significantly to the photoaging process (Kligman, 1989). The accumulation of reactive oxygen species induced by sunlight exposure is thought to play an important role in the photoaging of human skin *in vivo* (Pillai *et al.,* 2005). Kligman *et al.* (1984) found repair of damaged skin was possible by simple avoidance of the insult (sun); however, despite public heath campaigns and sun awareness advertisements, the public still conforms to peer pressure that a suntan is desirable and tends to be more concerned about the cosmetic sequelae of chronic sun exposure such as wrinkles, rather than skin cancer.

There are numerous commercial daily-use products that for the most part target the undesirable cosmetic features of sun exposure by adopting one or both of two strategies (Watson *et al.,* 2008). Either the products offer protection of skin against photodamage or they offer correction of the visible signs of photodamage (Rai and Srinivas, 2007). Protection against photodamage by use of broad-spectrum sunscreens is well-documented as an effective means of reducing total lifetime UV dose and, thereby, preventing or ameliorating the effects of UV radiation on both the appearance and biomechanical properties of the skin (Smith *et al.,* 2002). However, it seems that the public would rather try to repair or treat wrinkles than prevent them by the use of sunscreens and sun avoidance measures (Singh and Griffiths, 2006). Therefore, there is increased interest in antiaging creams.

Photooxidative damage is known to play a role in the pathological processes of UV-induced skin damage and skin cancer and is also involved in the development of several disorders of the skin (F'guyer *et al.,* 2003; Pillai *et al.,* 2005). Skin is protected from UV radiation damage by endogenous antioxidants, such as superoxide dismutase, catalase, and vitamin A, found in its layers. However, the supply of antioxidants in skin is limited

and may not be sufficient to neutralize completely the free radicals generated by excessive sun exposure, which may enhance the development of skin photoaging and skin cancer (F'guyer *et al.,* 2003). The cutaneous antioxidant network is not only less than completely effective, but cutaneous antioxidants also tend to deteriorate with age (Yaar *et al.,* 2002; Yaar and Gilchrest, 2007).

Currently, topical application of retinoids, in particular tretinoin (a synonym for retinoic acid; RA), remains the medical treatment of choice for photoaged skin (Watson *et al.,* 2008). Studies have shown that the application of topical RA to photoaged skin of humans partially restores levels of collagens, reduces matrix metalloproteinase-1 expression, and ameliorates some of the clinical features such as wrinkles (Fisher *et al.,* 1999). Additionally, the topical application of RA has been found to accelerate greatly the formation of new connective tissue during the postirradiation period, and this effect is both time- and dose-dependent. A Cochrane review (Samuel *et al.,* 2005) concluded that the research literature is sufficient to support the use of topical tretinoin for mild to moderate photodamage on the face. However, dermatitis, erythema, scaling/dryness, burning/stinging, and irritation of the skin are common adverse events reported with RA use, and, in some cases, the severity is such as to preclude its use, even at low concentrations. RA also has been shown to increase the sensitivity of the skin to sun; therefore, unprotected skin may become more susceptible to sun damage and be at increased risk of skin cancer development (Eckhart *et al.,* 2008). In the United States and the European Union, RA is classified as a drug; whereas, retinol and retinyl esters are used worldwide in cosmetic preparations (Dufour *et al.,* 2009).

Commercial cosmetic antiaging products often incorporate vitamins or their congeners into their formulations, and vitamin A palmitate (RP) is among those that have gained notoriety due to its pharmacodynamic properties (Campos *et al.,* 1999). RP has been shown to act on epithelization in dry and rough skin, and since it absorbs UV radiation between 300 and 350 nm with a maximum at 325 nm, it may also serve as a biologically relevant UV filter (Campos *et al.,* 1999; Antille *et al.,* 2003). In 1987, a Cosmetic Ingredient Review Expert Panel conducted a safety assessment of RP and found, based on a review of animal and human data, that the use of RP was safe under the current practices and concentrations and that the RP concentrations (0.1% to 1%) in cosmetics were at most slightly irritating and did not result in skin sensitization (CIR, 1987). A subsequent 2006 review of existing data concurred and included a limit of up to 5% for RP (CIR, 2006). In cosmetic skin-care products, RP is typically used at concentrations of up to 0.3% retinol equivalents, corresponding to 0.55% RP; some products may contain higher percentages (Ries and Hess, 1999). Although the topical application of RP does not appear to pose a significant health risk at low concentrations, recent studies reported that RP in combination with UVA light produced genotoxic effects in mouse lymphoma or human Jurkat T-cells via a photoclastogenic mechanism (Mei *et al.,* 2005, 2006; Yan *et al.,* 2005). These results suggested a potential health hazard and raised the question whether there is a potential for photococarcinogenicity with RP topical applications.

The current 1-year photococarcinogenicity study of RA and RP was designed to test the hypothesis that the topical application of creams containing these chemicals would alter the process of UV radiation-induced photocarcinogenesis in SKH-1 hairless mice. In order to test this hypothesis, male and female SKH-1 mice were exposed to simulated solar light (SSL) in the morning of each weekday for 5 days per week. The mice then received either no cream treatment or were treated in the afternoons of the same weekdays for 5 days per week with either control creams or creams that contained either RA or RP.

With a maximum absorbance around 325 nm, retinoids such as RA and RP absorb both UVA and UVB radiation. While both UVA and UVB radiation in incident sunlight penetrate into the skin, the effects of UVA on the photochemical alteration of retinoids may be quantitatively more important due to the higher relative abundance of UVA radiation in sunlight and the deeper penetration of UVA radiation into the skin when compared to UVB radiation. To determine whether RA or RP would exert differential effects on UVA- or UVB-induced photocarcinogenesis, additional groups of female mice were exposed to narrow-band UVA or UVB in the morning of each weekday for 5 days per week at levels equivalent to the spectra of UVA or UVB produced by the broad-band spectrum of SSL at a level of 13.70 mJ•CIE/cm^2. The mice then received either no cream treatment or were treated in the afternoons of the same weekdays with either control cream or creams that contained either RA or RP. This treatment regime for all mice continued for a period of 40 weeks and was followed by a 12-week no-treatment observation period.

Several parameters (skin lesion onset, incidence, and multiplicity) were examined during the in-life phase of the study and after histopathology of mouse tissues to determine the effects of RA and RP on SSL-induced photocarcinogenesis. Skin lesion onset (the rate at which specified doses of UV radiation cause skin cancer under laboratory conditions) is the convention used by industry to determine whether a test

substance alters SSL-induced photocarcinogenesis. Histologic confirmation is not performed routinely for skin lesions observed during the in-life phase of photococarcinogenesis studies (Forbes *et al.,* 2003). Incidence is the percentage of animals within a particular treatment group that have at least one detectable in-life skin lesion or histopathology-detected squamous cell nonneoplastic lesion or neoplasm. Multiplicity is the total number of events (in-life skin lesions or histopathology-detected squamous cell nonneoplastic lesions or neoplasms) per animal within an at-risk treatment group.

The mice that did not receive cream and were exposed to SSL, UVA, or UVB served as the experimental calibration controls to confirm that the basic conditions of the experiment were able to produce a positive result: the development of squamous cell neoplasms, even in the event that none of the experimental mice that received the test chemicals produced a positive result. Because of the design of the animal rack/cage system used in this study and the direction of the incident light emitted from the UVA, UVB, and SSL lamp sources, the primary site of mouse skin exposure was coincident with the site of application for the control and dosed creams and extended from the nape of the neck to the base of the tail and midway along both sides of the animal.

As expected, the exposure of male and female mice that received no cream treatment to increasing levels of SSL resulted in exposure level-dependent decreases in survival and increases in the Cox relative hazard ratios. Concomitant with SSL exposure level-dependent decreases in survival, there were significant exposure level-dependent decreases in the time to onset of in-life detected skin lesions and significant exposure level-dependent increases in the incidences and multiplicities of these lesions.

The survival of female mice that received no cream treatment and were exposed to UVA was significantly longer and that of female mice exposed to UVB was significantly shorter when compared with female mice that received no cream treatment and were exposed to SSL at a level of 13.70 mJ•CIE/cm^2. Significant differences were also observed for incidences of skin lesions in mice that received UVA exposure compared to those that received SSL at a level of 13.70 mJ•CIE/cm^2. Less than 10% of the mice that received no cream treatment and were exposed to UVA developed a measurable skin lesion, whereas the incidence rate approached 100% among similarly treated mice exposed to SSL at 13.70 mJ•CIE/cm^2 or UVB. The multiplicities of in-life detected skin lesions reflected similar effects when compared across light sources. In mice exposed to UVA, a mean multiplicity of 0.1 was significantly lower than the mean multiplicity of 5.8 in mice exposed to SSL at a level of 13.70 mJ•CIE/cm^2. A significantly greater mean multiplicity of in-life skin lesions was observed in female mice exposed to UVB when compared to similarly treated mice exposed to SSL at 13.70 mJ•CIE/cm^2: 8.7 compared to 5.8, respectively. As the UVB content of the irradiation sources was matched, these results were somewhat surprising. The filtered xenon arc light source more closely simulates full-spectrum solar radiation than any other artificial light source (Atlas, 2009). In contrast, the emission of the fluorescent UVB lamp has very little resemblance to solar radiation. The irradiation of the UVB lamp peaks at approximately 313 nm and nearly all of its energy is concentrated between 280 nm and 360 nm (Atlas, 2009). A large fraction of its energy is at wavelengths shorter than those present in sunlight; shorter wavelengths are primarily responsible for sunburning and may increase the risk of skin cancer and may provide an explanation for the differences observed with lamp sources matched for UVB contribution.

Epidemiologic and experimental studies have demonstrated that increased incidences of skin cancer are the result of increased exposure to solar UV radiation (Bush *et al.,* 1999). Furthermore, since light sources that contain UVB are carcinogenic (IARC, 1992), significant positive exposure-related trends in incidences and multiplicities of in-life squamous cell neoplasms were anticipated for mice that received the no cream treatment and either SSL or UVB exposure. Nevertheless, confirmation of these results was necessary to establish an exposure trend with SSL as a comparison tool for the study designed to test the effects of topical applications of RA and RP on the photocarcinogenesis of SSL.

The efficiency, tolerability, and application properties of dermatologic products are directly related to the type of vehicle used in the formulation. Interactions between the vehicle, skin, and active ingredients influence the transport of the topical formulation and the release of the active ingredients into the skin (Daniels and Knie, 2007). Selection of the proper vehicle makes it possible to optimize both the cosmetic features and the properties of an incorporated active ingredient, and the site of application. Common vehicles used in dermatologic products are complex mixtures consisting of diverse ingredients that belong to six major groups including hydrophilic bases, lipophilic bases, emulsifiers, gel-forming agents, preservatives, and antioxidants (Daniels and Knie, 2007). Ideally, topically applied control vehicles should not elicit a response in subjects when compared with untreated controls.

Data collected from the hairless mouse model have indicated that the properties of a control cream may, at times, shorten the time to tumor formation and/or lower the minimum dose of radiation required to induce erythema, also known as the minimal erythema dose (MED) (Jacobs *et al.*, 2004).

In the current study, the topical application of the oil-in-water emulsion-type control cream had a significant effect on the survival of male mice in the presence of SSL. In addition, the weeks to in-life skin lesion onset in male and female mice that received control cream occurred at significantly earlier times in comparison tests with the weeks to onset of no cream treated animals in both the absence and presence of SSL. The incidences and multiplicities of in-life skin lesions were also significantly different between the no cream and control cream treated mice in the absence and presence of SSL exposure and when female mice were exposed to UVA. In every instance, the incidences and multiplicities of in-life skin lesions were significantly greater in control cream treated mice.

Similarly, the incidences of squamous cell neoplasms, especially those of papillomas and the combination (papilloma, carcinoma *in situ*, and/or carcinoma) of squamous cell neoplasms were significantly greater in male and female mice that received control cream when compared with mice that received no cream treatment, both in the absence and presence of SSL. The incidences of squamous cell papilloma were of particular noteworthiness due to the scale of differences between the groups. For example, in male mice treated with control cream and exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL observed incidences of squamous cell papilloma were 47.2%, 86.1%, and 77.8%, respectively, compared to 2.9%, 17.1%, and 63.9%, respectively, in no cream treatment groups exposed to the same levels of SSL. In general, the multiplicities of squamous cell neoplasms were also higher in groups of mice that received the control cream treatment when compared with same sex mice that received no cream treatment.

The effect of control cream has been noted by other investigators. For example, the application of a vehicle containing peanut oil and isopropyl myristate (7:3) enhanced the photocarcinogenesis of a xenon arc lamp source (Gibbs *et al.*, 1985). Isopropyl myristate is a fatty acid ester penetration enhancer that is used in cosmetic and topical preparations where good absorption through the skin is desired. More recently, the application of an oil-in-water emulsion-type acidic control cream (pH 3.5), but otherwise composed of very similar ingredients as those used in the control cream for the current study, was shown to enhance photocarcinogenesis in SKH-1 mice (NTP, 2007). In yet another study, a similar formulation of control cream, but with a pH of 6.0, had no effect on the photocarcinogenesis process (NTP, 2010), suggesting that the acidic control cream may have caused a disruption of the barrier function in skin.

Upon examination of the list of ingredients that were contained in the base cream used for the current study (Table 1), all of the contained ingredients are among common chemicals used in cosmetics, where they function as preservatives (EDTA and Germaben II), humectants (glycerin), thickeners (Carbopol 981), emollients (mineral oil), solvents (octyl palmitate), lubricants (BRIJ 721), emulsifiers (cetearyl alcohol), and fatty acids (stearic acid) (Kunin, 2009). The base cream used in the current study was formulated by the manufacturer to accommodate 15% filler ingredient(s). In the control cream, the filler was diisopropyl adipate.

Diisopropyl adipate [CAS No. 6938-94-9] is the ester of isopropyl alcohol and adipic acid, a six-carbon dicarboxylic acid. It is a viscous, colorless to light yellow liquid that is soluble in most organic solvents and insoluble in water. Diisopropyl adipate is used in the cosmetic industry as a non-oily emollient, solvent, and penetration enhancer with rapid absorbency and low residual touch perception (Goldemberg and De La Rosa, 1971).

Chemical penetration enhancers are present in a large number of transdermal, dermatological, and cosmetic products to aid dermal absorption of curatives and aesthetics (Rangarajan and Zatz, 2003; Karande *et al.*, 2005). Fatty acid diesters, such as diisopropyl adipate, are among such ingredients. It has been shown that fatty acid esters at concentrations up to 10 mg/g penetrate the skin of rats, independent of the number of carbon atoms (Catz and Friend, 1989; Fujii *et al.*, 2000). The fatty acid diesters have been found to act primarily on the stratum corneum layer of the skin and cause biophysical changes in stratum corneum lipids suggestive of lipid extraction (Sato *et al.*, 1988; Takahashi *et al.*, 2002). Lehman *et al*. (1988) found the percutaneous absorption of retinoids in monkey skin was highly vehicle dependent and followed the order: propylene glycol = isopropyl alcohol > mineral oil > diisopropyl adipate > polyethylene glycol.

Many chemical enhancers are toxic, skin irritating, or allergenic to some degree depending on their concentration and the frequency of their application (Ben-Shabat *et al.*, 2007). According to cosmetic industry submissions of product formulations to the FDA, the concentration of diisopropyl adipate in 112 cosmetic formulations ranged from less than 0.1% to 25% (CIR,

1984). In safety assessments, diisopropyl adipate produced no irritation in 24-hour patch tests and was moderately irritating in 21-day cumulative irritancy tests (CIR, 1984). In 2006, the Cosmetic Ingredient Expert Panel Review confirmed that among the 784 total cosmetic ingredients found safe as used, diisopropyl adipate was found safe in "as used" concentrations of up to 15%, which was the same concentration used in the control cream for the current study (CIR, 2006).

Among the most-used therapies for prevention and reversal of photodamage to the skin are topical retinoids (Fisher *et al.*, 1999). These include RA and its precursors (i.e., retinol, retinal, and retinyl esters with various fatty acids), which can be converted to RA within the skin under normal physiological conditions (Epstein, 1986; Pillai *et al.*, 2005). UV radiation has been shown to cause physical, chemical, and molecular changes in the skin (Giacomoni, 2008). UV radiation causes the depletion of cellular antioxidants, especially retinoids, and antioxidant enzymes, such as superoxide dismutase and catalase (Fisher *et al.*, 1999; Sorg *et al.*, 2005; Aitken *et al.*, 2007). The net result of these and other effects of UV-induced skin damage is the generation of free radicals and the development of skin cancer.

The pharmacologic efficacy of topically applied RA to enhance the repair of UV-induced skin damage and photoaging has been demonstrated in humans as well as in mice (Kligman, 1989; Nyirady *et al.*, 2001). RA has been shown to have chemopreventive actions in a variety of cellular, animal, and human studies (Epstein, 1986; Lotan, 1996; Harwood *et al.*, 2005; Cheepala *et al.*, 2007). However, skin tumor-induction, adverse effect reports of skin irritation, and even death have been associated with topical RA therapy (Fischer *et al.*, 1985; McCormick *et al.*, 1987; Samuel *et al.*, 2005; Weinstock *et al.*, 2009). RA is the most active form of vitamin A and is considered a drug. Usual concentrations of RA in cosmetics range from 0.025% up to 0.1%; higher concentrations of RA are available only by prescription (Bombei, 2009). Enhanced skin sensitization to UV radiation with use of RA has been demonstrated (Gilchrest, 1997).

In the current study, the RA cream was composed of the base cream (85%), RA (0.001%), and diisopropyl adipate (15%). In male and female mice exposed to SSL, there were statistically significant decreases in survival among groups treated with RA when compared with groups treated with control cream and exposed to the same level of SSL. The decrease in survival occurred in male mice even in the absence of SSL exposure, and survival decreased to a greater extent in male and female mice exposed to the higher levels of SSL. Concomitant with decreases in survival, significant decreases in the weeks to in-life skin lesion onset were observed in male and female mice treated with the 0.001% RA cream and exposed to SSL when compared to control cream treated mice that received the same level of SSL. The incidences of in-life detected skin lesions did not differ significantly between mice that received RA or control creams, either in the absence or presence of SSL. In comparison tests with control cream treated mice, however, the multiplicities of in-life skin lesions were significantly higher in male mice administered the 0.001% RA creams at each level of SSL, including 0.00 mJ•CIE/cm^2, and in female mice administered the 0.001% RA creams and exposed to SSL at 6.85 mJ•CIE/cm^2, or to UVA or UVB. When the effects of the 0.001% RA cream treatment were compared across irradiation source types, female mice exposed to UVA had significantly lower incidences and multiplicities compared to SSL-exposed female mice, while female mice exposed to UVB had similar incidences but significantly greater numbers of in-life skin lesions.

The relationship between chronic UV radiation and skin damage is well established in the literature. The eventual clinical manifestations of photodamage, especially on the human face, such as fine and coarse wrinkling, irregular pigmentation, and changes in the texture of the skin, have been associated with sun exposure and not as a consequence of aging alone. In addition to the undesirable visible effects, photodamage is also known to be associated with pathologic changes in the skin, including the development of skin cancer. Individuals increasingly seek treatment for the cosmetic and pathologic skin damage induced by sun exposure, and RA therapy has been shown to be effective in reducing many of the visible signs of skin photodamage (Gilchrest, 1997). Mild-to-moderate skin reactions such as erythema, peeling, and burning are among the most commonly reported side effects associated with the use of topical RA. Generally, these side effects subside with time and do not limit the use of topical RA. Usual concentrations of RA in cosmetics range from 0.025% to 0.1% (Bombei, 2009).

The RA creams used in this study were not well tolerated by mice, and significant skin irritation developed in the RA-treated animals, even though the concentration of RA was well below the 0.05% used by Halliday *et al.* (2000) and below the lower concentration of 0.025% found in most cosmetics. Mild to severe skin erythema, peeling, sores, and scratching were noted in the clinical observations of these mice. The animal skins became cracked and ruptured, either from self-mutilation or from the application of the creams, and this resulted in 60% or more of the animals being removed from the study due to skin conditions that were inconsistent with

the welfare of the animals. At a meeting of the Toxicology Study Selection and Review Committee in November 2004, a decision was made to exclude these animals from histopathology examination due to the fact that the condition of the skins of mice compromised the objectives of the study and because animals that received the 0.001% RA creams were removed at a time that was too early to develop skin neoplasms that were consistent with the development of SSL-induced skin tumors.

Topical applications of retinyl esters, in particular RP, have beneficial effects on the skin when applied at low concentrations (Campos *et al.,* 1999; Ries and Hess, 1999). In cosmetics, RP is used in skin care products at concentrations of up to 0.55%. Given that higher concentrations of RP tend to be irritating to the skin, they are considered unsuitable for cosmetic use (Fluhr *et al.*, 1999; Ries and Hess, 1999). High oral doses of RP may have teratogenic potential in humans (Rothman *et al.*, 1995). In contrast, the topical application of RP to human skin appears safe at the recommended cosmetic concentrations. Daily topical applications of RP-containing cosmetic creams for 3 weeks to female subjects of child-bearing age at the RP maximal cosmetic use concentration (0.55%) produced no effect on endogenous plasma levels of retinol, RP, or RA (Nohynek *et al.*, 2006).

In the current study, RP-containing creams were administered to male and female mice at RP concentrations of 0.1%, 0.5%, 1.0%, or 2.0% in an oil-in-water emulsion cream formulation. The base cream comprised 85% of the RP cream formulation and the RP in combination with diisopropyl adipate filled the remaining 15% of the topically applied creams. Significant dose trends and earlier weeks to in-life skin lesion onset were observed in mice that received RP cream treatments in the presence of SSL, UVA, or UVB when compared with mice that received control cream treatment and the same level or type of irradiation. In mice exposed to SSL, there also tended to be significantly greater multiplicities of in-life skin lesions for the 0.1%, 0.5%, and 1.0% RP groups compared to the control cream group, but not in every case, and not for mice that received the 2.0% RP creams, likely reflecting the shorter survival times of animals that received the 2.0% RP cream treatment and an insufficient time for skin lesion development.

Because recent studies reported that RP in combination with UVA light produced genotoxic effects in mouse lymphoma or human Jurkat T-cells via a photoclastogenic mechanism (Mei *et al.,* 2005, 2006; Yan *et al.,* 2005), enhanced or similar incidences and/or multiplicities of skin lesions were anticipated in mice exposed to UVA when compared with same-treatment counterparts that were exposed to SSL. This did not occur, and, in fact, significantly lower incidences and significantly lower multiplicities of skin lesions were observed in the UVA exposed mice when compared with SSL-exposed mice.

Histopathology evaluations conducted on mice that received the 0.1% and 0.5% RP creams indicated that significant dose-related trends were observed in the incidences of squamous cell carcinoma in male mice and in the incidences of squamous cell carcinoma *in situ*, squamous cell carcinoma, and the combination of these lesions in female mice exposed to SSL at the level of 6.85 mJ•CIE/cm^2. However, the incidences of other squamous cell neoplasms were similar among groups. Significant dose-related trend increases in the incidences of squamous cell neoplasia were not observed in male or female mice when the level of SSL was increased to 13.70 mJ•CIE/cm^2, suggesting that at the higher level of SSL the photocarcinogenesis effects of the light source overwhelmed the photocarcinogenesis effects of the RP dose levels. Significant linear RP dose trends were observed in the multiplicities of squamous cell papillomas, and in the combination of all squamous cell neoplasms.

The natural retinoids, retinol and its esters, have a good tolerance profile in contrast with the irritating potential of RA. In cosmetic products, the use of RP at concentrations up to 0.55% corresponds to 0.3% retinol equivalents (Ries and Hess, 1999). The 1.0% and 2.0% RP creams used in this study were not well tolerated by mice, and significant skin irritation of similar severity, like that observed in mice treated with 0.001% RA, also developed in the mice administered the 1.0% and 2.0% RP creams. Mild to severe skin erythema, peeling, and scratching were noted with increased incidences in the clinical observations of these animals. As with the RA cream treated mice, the animal skins became cracked and ruptured, either from self-mutilation or from the application of the creams, and resulted in 60% or more of the animals being removed from the study due to skin conditions that were inconsistent with the welfare of the animals. At a meeting of the Toxicology Study Selection and Review Committee in November 2004, a decision was made to exclude these animals from histopathology examination due to the fact that the condition of the skins of mice compromised the objectives of the study and because animals were removed at a time that was insufficient to develop skin lesions that were consistent with the development of SSL-induced skin tumors.

One can only speculate as to the nature of the skin irritation found in the groups of animals that received the

0.001% RA and the 1.0% and 2.0% RP creams. 1) The irritative potential of RA and other retinoids is well established, and skin irritancy may partially be explained by an overload of nonphysiological amounts of exogenous retinoids in the skin (Fluhr *et al.,* 1999). Others, however, have used higher concentrations of RA than those used in this study and in the same mouse model without an adverse effect (Kelly *et al.,* 1989; Kligman, 1989, 1996). 2) The mouse model may have demonstrated enhanced sensitivity to RA, RP, or to UV radiation exposure. The hairless mouse model has proved to be a useful model for human phototoxicity and photoaging studies. The ultraviolet-induced changes in this species, ranging from acute responses to those associated with chronic exposure, are comparable to those seen in humans (Kligman, 1989). 3) Exposure to UV radiation, in particular UVB, is also known to induce cutaneous changes, such as dryness and coarseness, and invokes a massive dermal inflammatory infiltration (Yaar and Gilchrest, 2007). Similar studies have been conducted using the identical levels of UV radiation and did not find skin irritation of the same mouse model (NTP, 2007, 2010). 4) The control cream, composed of the base cream and diisopropyl adipate, may have induced irritation of the mouse skin (Daniels and Knie, 2007). Cosmetic creams are well-known to influence the hydration of the stratum corneum; the hydrating effects of oil-in-water emulsion creams, as used in this study, depend upon the unbound water content of the formulation (Fluhr and Rigano, 2004). The addition of penetration enhancers such as diisopropyl adipate to skin creams may extract lipids from the stratum corneum and disrupt the barrier function of the skin (Mao-Qiang *et al.,* 1995). In their review of cosmetic ingredients found safe as used, the CIR found that diisopropyl adipate was safe as used at concentrations up to 15%, which is the same concentration of diisopropyl adipate used in the control cream for the current study (CIR, 2006). Diisopropyl adipate was reported in 112 cosmetic products in a voluntary cosmetic registration program; 101 of these product formulations were reported to contain less than 10% diisopropyl adipate. Only bath products and fragrance preparations were found to contain greater than 10% (CIR, 1984). The 15% concentration of diisopropyl adipate used in the control cream may have induced excessive skin dryness by extracting lipids and reducing the barrier function of the stratum corneum, resulting in enhanced penetration of the retinoids into the skin. As retinoids are known irritative agents, these factors along with the heightened immune response and skin dryness induced by exposure to SSL may have caused the severe skin irritation that was observed in these animals.

CONCLUSIONS

These experiments investigated the effect of topical applications of creams containing RA or RP on the photocarcinogenic activity of SSL in male and female SKH-1 hairless mice. Skin lesions were assessed during the in-life phase and/or by histopathologic evaluation at necropsy.

Control Cream

Under the conditions of these studies, the topical treatment of SKH-1 mice with the control cream resulted in earlier onsets of in-life skin lesions and higher incidences and multiplicities of in-life skin lesions, when compared to untreated controls, in the absence and presence of SSL.

The topical treatment of SKH-1 mice with control cream resulted in higher incidences and multiplicities of squamous cell neoplasms of the skin when compared to untreated controls in the absence and presence of SSL.

Retinoic Acid

Compared to the control cream, RA further enhanced the effects of SSL in SKH-1 mice based upon earlier onsets and increased multiplicities of in-life skin lesions.

Retinyl Palmitate

Compared to the control cream, RP further enhanced the effects of SSL in SKH-1 mice based upon earlier onsets and increased multiplicities of in-life skin lesions.

Compared to the control cream, RP further enhanced the photocarcinogenic activity of SSL in SKH-1 mice based upon increased incidences and multiplicities of squamous cell neoplasms of the skin.

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APPENDIX A
SUMMARY OF LESIONS IN MALE MICE IN THE 1-YEAR SIMULATED SOLAR LIGHT STUDY OF RETINOIC ACID AND RETINYL PALMITATE

TABLE A1a
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 0.00 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream
Disposition Summary		
Animals initially in study	36	36
Early deaths		
Moribund	5	3
Natural deaths	1	2
Skin lesion greater than 10 mm		2
Survivors		
Died last week of study	1	
Terminal kill	27	29
Missexed	2	
Animals examined microscopically	34	36
Integumentary System		
Skin, control	(34)	(36)
Skin, site of application	(34)	(36)
Keratoacanthoma, one		3 (8%)
Squamous cell carcinoma, one		1 (3%)
Squamous cell papilloma, one	1 (3%)	12 (33%)
Squamous cell papilloma, two		4 (11%)
Squamous cell papilloma, four		1 (3%)
Systems Examined with No Neoplasms Observed		
Alimentary System		
Cardiovascular System		
Endocrine System		
General Body System		
Genital System		
Hematopoietic System		
Musculoskeletal System		
Nervous System		
Respiratory System		
Special Senses System		
Urinary System		
Neoplasm Summary		
Total animals with primary neoplasms[b]	1	18
Total primary neoplasms	1	21
Total animals with benign neoplasms	1	18
Total benign neoplasms	1	20
Total animals with malignant neoplasms		1
Total malignant neoplasms		1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A1b
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 6.85 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Disposition Summary				
Animals initially in study	36	36	36	36
Early deaths				
Moribund	8	7	3	3
Natural deaths	1[b]	1		
Skin lesion greater than 10 mm	2	27	33	32
Survivors				
Terminal kill	25	1		
Missexed				1
Animals examined microscopically	35	36	36	35
Integumentary System				
Skin, control	(35)	(36)	(36)	(35)
Sarcoma	1 (3%)			
Squamous cell papilloma	1 (3%)			
Skin, site of application	(35)	(36)	(36)	(35)
Basal cell adenoma				1 (3%)
Keratoacanthoma, one			1 (3%)	
Squamous cell carcinoma, one	2 (6%)	7 (19%)	5 (14%)	15 (43%)
Squamous cell carcinoma, two		2 (6%)	3 (8%)	2 (6%)
Squamous cell carcinoma *in situ*, one	1 (3%)	5 (14%)	7 (19%)	8 (23%)
Squamous cell carcinoma *in situ*, two		2 (6%)	3 (8%)	1 (3%)
Squamous cell carcinoma *in situ*, three			1 (3%)	
Squamous cell carcinoma *in situ*, four		1 (3%)		
Squamous cell papilloma, one	4 (11%)	5 (14%)	4 (11%)	2 (6%)
Squamous cell papilloma, two		2 (6%)	3 (8%)	1 (3%)
Squamous cell papilloma, three	1 (3%)	5 (14%)	1 (3%)	3 (9%)
Squamous cell papilloma, four		4 (11%)	3 (8%)	6 (17%)
Squamous cell papilloma, five	1 (3%)	5 (14%)	3 (8%)	3 (9%)
Squamous cell papilloma, greater than five		10 (28%)	18 (50%)	19 (54%)

Systems Examined with No Neoplasms Observed
Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

TABLE A1b
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 6.85 mJ•CIE/cm^2 SSL

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Neoplasm Summary				
Total animals with primary neoplasms[c]	8	32	32	35
Total primary neoplasms	11	48	52	61
Total animals with benign neoplasms	6	31	32	34
Total benign neoplasms	7	31	33	35
Total animals with malignant neoplasms	4	16	17	21
Total malignant neoplasms	4	17	19	26

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Advanced autolysis precluded pathology examination.
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A1c
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 13.70 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Disposition Summary				
Animals initially in study	36	36	36	36
Early deaths				
Moribund		3	1	
Natural deaths	1			1
Skin lesion greater than 10 mm	35	33	35	35
Animals examined microscopically	36	36	36	36
Integumentary System				
Skin, control	(36)	(36)	(36)	(36)
Squamous cell papilloma		1 (3%)		
Skin, site of application	(36)	(36)	(36)	(36)
Keratoacanthoma, one		1 (3%)	1 (3%)	1 (3%)
Squamous cell carcinoma, one	13 (36%)	10 (28%)	7 (19%)	7 (19%)
Squamous cell carcinoma, two	7 (19%)	2 (6%)	7 (19%)	4 (11%)
Squamous cell carcinoma, three	6 (17%)	6 (17%)	1 (3%)	
Squamous cell carcinoma, four				1 (3%)
Squamous cell carcinoma, five	1 (3%)	1 (3%)		
Squamous cell carcinoma *in situ*, one	7 (19%)	12 (33%)	10 (28%)	13 (36%)
Squamous cell carcinoma *in situ*, two	3 (8%)	3 (8%)	3 (8%)	4 (11%)
Squamous cell carcinoma *in situ*, three	3 (8%)	2 (6%)	2 (6%)	1 (3%)
Squamous cell carcinoma *in situ*, four	1 (3%)	3 (8%)	1 (3%)	
Squamous cell carcinoma *in situ*, five		1 (3%)		1 (3%)
Squamous cell carcinoma *in situ*, greater than five		1 (3%)	1 (3%)	
Squamous cell papilloma, one	12 (33%)	3 (8%)	4 (11%)	3 (8%)
Squamous cell papilloma, two	6 (17%)	8 (22%)	1 (3%)	1 (3%)
Squamous cell papilloma, three	1 (3%)	3 (8%)	4 (11%)	3 (8%)
Squamous cell papilloma, four	3 (8%)	2 (6%)	6 (17%)	6 (17%)
Squamous cell papilloma, five		2 (6%)	4 (11%)	2 (6%)
Squamous cell papilloma, greater than five	1 (3%)	10 (28%)	15 (42%)	19 (53%)

Systems Examined with No Neoplasms Observed
Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

TABLE A1c
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 13.70 mJ•CIE/cm^2 SSL

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Neoplasm Summary				
Total animals with primary neoplasms[b]	36	33	35	36
Total primary neoplasms	64	71	67	66
Total animals with benign neoplasms	23	29	34	34
Total benign neoplasms	23	30	35	35
Total animals with malignant neoplasms	30	27	27	26
Total malignant neoplasms	41	41	32	31

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A1d
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 20.55 mJ•CIE/cm^2 SSL[a]

	No Cream
Disposition Summary	
Animals initially in study	36
Early deaths	
Moribund	1
Natural death	1
Skin lesion greater than 10 mm	34
Animals examined microscopically	36
Integumentary System	
Skin, control	(36)
Skin, site of application	(36)
Squamous cell carcinoma, one	6 (17%)
Squamous cell carcinoma, two	8 (22%)
Squamous cell carcinoma, three	4 (11%)
Squamous cell carcinoma, four	5 (14%)
Squamous cell carcinoma, five	3 (8%)
Squamous cell carcinoma, greater than five	2 (6%)
Squamous cell carcinoma *in situ*, one	9 (25%)
Squamous cell carcinoma *in situ*, two	3 (8%)
Squamous cell carcinoma *in situ*, three	5 (14%)
Squamous cell carcinoma *in situ*, four	1 (3%)
Squamous cell carcinoma *in situ*, five	4 (11%)
Squamous cell carcinoma *in situ*, greater than five	3 (8%)
Squamous cell papilloma, one	7 (19%)
Squamous cell papilloma, two	3 (8%)
Squamous cell papilloma, three	7 (19%)
Squamous cell papilloma, four	2 (6%)
Squamous cell papilloma, five	1 (3%)
Squamous cell papilloma, greater than five	2 (6%)
Systems Examined with No Neoplasms Observed	
Alimentary System	
Cardiovascular System	
Endocrine System	
General Body System	
Genital System	
Hematopoietic System	
Musculoskeletal System	
Nervous System	
Respiratory System	
Special Senses System	
Urinary System	
Neoplasm Summary	
Total animals with primary neoplasms[b]	34
Total primary neoplasms	75
Total animals with benign neoplasms	22
Total benign neoplasms	22
Total animals with malignant neoplasms	31
Total malignant neoplasms	53

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2a
Statistical Analysis of Primary Skin Neoplasms at the Site of Application in Male Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Squamous Cell Papilloma				
Overall rate[a]	1/34 (2.9%)	6/35 (17.1%)	23/36 (63.9%)	22/36 (61.1%)
Adjusted rate[b]	1/30.8 (3.2%)	6/30.7 (19.6%)	23/28.5 (80.7%)	22/24.7 (88.9%)
Terminal rate[c]	1/27 (3.7%)	5/25 (20.0%)	0/0	0/0
First incidence (days)	368	354	246	193
Poly-3 test[d]	P≤0.001	P=0.100	P≤0.001	P≤0.001
Squamous Cell Carcinoma *in situ*				
Overall rate	0/34 (0.0%)	1/35 (2.9%)	14/36 (38.9%)	25/36 (69.4%)
Adjusted rate	0/30.8 (0.0%)	1/30.7 (3.3%)	14/23.8 (58.8%)	25/27.4 (91.2%)
Terminal rate	0/27 (0.0%)	0/25 (0.0%)	0/0	0/0
First incidence (days)	—[e]	347	262	192
Poly-3 test	P≤0.001	P=0.999	P≤0.001	P≤0.001
Squamous Cell Carcinoma				
Overall rate	0/34 (0.0%)	2/35 (5.7%)	27/36 (75.0%)	28/36 (77.8%)
Adjusted rate	0/30.8 (0.0%)	2/30.7 (6.5%)	27/31.0 (87.1%)	28/29.6 (94.7%)
Terminal rate	0/27 (0.0%)	1/25 (4.0%)	0/0	0/0
First incidence (days)	—	354	243	192
Poly-3 test	P≤0.001	P=0.470	P≤0.001	P≤0.001
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma				
Overall rate	0/34 (0.0%)	3/35 (8.6%)	30/36 (83.3%)	31/36 (86.1%)
Adjusted rate	0/30.8 (0.0%)	3/30.8 (9.7%)	30/32.8 (91.5%)	31/32.0 (96.9%)
Terminal rate	0/27 (0.0%)	1/25 (4.0%)	0/0	0/0
First incidence (days)	—	347	243	192
Poly-3 test	P≤0.001	P=0.232	P≤0.001	P≤0.001

TABLE A2a
Statistical Analysis of Primary Skin Neoplasms at the Site of Application in Male Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma				
Overall rate	1/34 (2.9%)	7/35 (20.0%)	36/36 (100.0%)	34/36 (94.4%)
Adjusted rate	1/30.8 (3.2%)	7/30.8 (22.7%)	36/36.0 (100.0%)	34/34.2 (99.4%)
Terminal rate	1/27 (3.7%)	5/25 (20.0%)	0/0	0/0
First incidence (days)	368	347	243	192
Poly-3 test	P≤0.001	P=0.052	P≤0.001	P≤0.001

[a] Number of neoplasm-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are based on a two-sided, continuity-corrected Poly-3 test. P values in the control group (0.00 mJ•CIE/cm^2) column are for the linear trend test; otherwise, P values represent pairwise comparisons to the control group.
[e] Not applicable; no neoplasms in animal group

TABLE A2b
Statistical Analysis of Primary Skin Neoplasms at the Site of Application in Male Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Squamous Cell Papilloma						
Overall rate[a]	1/34 (2.9%)	17/36 (47.2%)	6/35 (17.1%)	31/36 (86.1%)	23/36 (63.9%)	28/36 (77.8%)
Adjusted rate[b]	1/30.8 (3.2%)	17/32.4 (52.4%)	6/30.7 (19.6%)	31/32.2 (96.2%)	23/28.5 (80.7%)	28/29.6 (94.6%)
Terminal rate[c]	1/27 (3.7%)	16/29 (55.2%)	5/25 (20.0%)	1/1 (100.0%)	0/0	0/0
First incidence (days)	368	347	354	192	246	173
Poly-3 test[d]		P≤0.001		P≤0.001		P=0.069
Keratoacanthoma						
Overall rate	0/34 (0.0%)	3/36 (8.3%)	0/35 (0.0%)	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)
Adjusted rate	0/30.8 (0.0%)	3/32.6 (9.2%)	0/30.5 (0.0%)	0/14.6 (0.0%)	0/15.8 (0.0%)	1/10.2 (9.8%)
Terminal rate	0/27 (0.0%)	2/29 (6.9%)	0/25 (0.0%)	0/1 (0.0%)	0/0	0/0
First incidence (days)	—[e]	320	—	—	—	192
Poly-3 test		P=0.254		—[f]		P=0.828
Squamous Cell Carcinoma *in situ*						
Overall rate	0/34 (0.0%)	0/36 (0.0%)	1/35 (2.9%)	8/36 (22.2%)	14/36 (38.9%)	22/36 (61.1%)
Adjusted rate	0/30.8 (0.0%)	0/32.3 (0.0%)	1/30.7 (3.3%)	8/18.6 (43.0%)	14/23.8 (58.8%)	22/25.4 (86.7%)
Terminal rate	0/27 (0.0%)	0/29 (0.0%)	0/25 (0.0%)	1/1 (100.0%)	0/0	0/0
First incidence (days)	—	—	347	235	262	173
Poly-3 test		—		P≤0.001	—	P=0.010
Squamous Cell Carcinoma						
Overall rate	0/34 (0.0%)	1/36 (2.8%)	2/35 (5.7%)	9/36 (25.0%)	27/36 (75.0%)	19/36 (52.8%)
Adjusted rate	0/30.8 (0.0%)	1/32.3 (3.1%)	2/30.7 (6.5%)	9/18.2 (49.4%)	27/31.0 (87.1%)	19/22.6 (83.9%)
Terminal rate	0/27 (0.0%)	1/29 (3.4%)	1/25 (4.0%)	0/1 (0.0%)	0/0	0/0
First incidence (days)	—	368	354	276	243	192
Poly-3 test		P=1.000		P≤0.001		P=1.000

TABLE A2b
Statistical Analysis of Primary Skin Neoplasms at the Site of Application in Male Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma						
Overall rate	0/34 (0.0%)	1/36 (2.8%)	3/35 (8.6%)	16/36 (44.4%)	30/36 (83.3%)	27/36 (75.0%)
Adjusted rate	0/30.8 (0.0%)	1/32.3 (3.1%)	3/30.8 (9.7%)	16/22.0 (72.8%)	30/32.8 (91.5%)	27/28.8 (93.8%)
Terminal rate	0/27 (0.0%)	1/29 (3.4%)	1/25 (4.0%)	1/1 (100.0%)	0/0	0/0
First incidence (days)	—	368	347	235	243	173
Poly-3 test		P=1.000		P≤0.001		P=1.000
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma						
Overall rate	1/34 (2.9%)	17/36 (47.2%)	7/35 (20.0%)	32/36 (88.9%)	36/36 (100.0%)	33/36 (91.7%)
Adjusted rate	1/30.8 (3.2%)	17/32.4 (52.4%)	7/30.8 (22.7%)	32/32.8 (97.7%)	36/36.0 (100.0%)	33/33.4 (98.9%)
Terminal rate	1/27 (3.7%)	16/29 (55.2%)	5/25 (20.0%)	1/1 (100.0%)	0/0	0/0
First incidence (days)	368	347	347	192	243	173
Poly-3 test		P≤0.001		P≤0.001		P=1.000
Squamous Cell Papilloma, Keratoacanthoma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma						
Overall rate	1/34 (2.9%)	18/36 (50.0%)	7/35 (20.0%)	32/36 (88.9%)	36/36 (100.0%)	33/36 (91.7%)
Adjusted rate	1/30.8 (3.2%)	18/32.8 (54.9%)	7/30.8 (22.7%)	32/32.8 (97.7%)	36/36.0 (100.0%)	33/33.4 (98.9%)
Terminal rate	1/27 (3.7%)	16/29 (55.2%)	5/25 (20.0%)	1/1 (100.0%)	0/0	0/0
First incidence (days)	368	320	347	192	243	173
Poly-3 test		P≤0.001		P≤ 0.001		P= 1.000

[a] Number of neoplasm-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values in the control cream columns represent pairwise comparisons to the respective no cream group and are based on a two-sided, continuity-corrected Poly-3 test. A lower incidence than that in the no cream group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A2c
Statistical Analysis of Primary Skin Neoplasms at the Site of Application in Male Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Squamous Cell Papilloma						
Overall rate[a]	31/36 (86.1%)	32/36 (88.9%)	34/35 (97.1%)	28/36 (77.8%)	34/36 (94.4%)	34/36 (94.4%)
Adjusted rate[b]	31/32.2 (96.2%)	32/32.8 (97.6%)	34/34.3 (99.1%)	28/29.6 (94.6%)	34/34.2 (99.4%)	34/34.3 (99.0%)
Terminal rate[c]	1/1 (100.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	192	192	131	173	128	156
Poly-3 test[d]	P=0.596	P=1.000	P=1.000	P=0.175	P=0.427	P=0.560
Keratoacanthoma						
Overall rate	0/36 (0.0%)	1/36 (2.8%)	0/35 (0.0%)	1/36 (2.8%)	1/36 (2.8%)	1/36 (2.8%)
Adjusted rate	0/14.6 (0.0%)	1/12.2 (8.2%)	0/9.1 (0.0%)	1/10.2 (9.8%)	1/6.8 (14.7%)	1/5.9 (16.9%)
Terminal rate	0/1 (0.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	—[e]	255	—	192	192	178
Poly-3 test	P=1.000	P=0.927	—[f]	P=1.000	P=1.000	P=1.000
Squamous Cell Carcinoma *in situ*						
Overall rate	8/36 (22.2%)	11/36 (30.6%)	9/35 (25.7%)	22/36 (61.1%)	17/36 (47.2%)	19/36 (52.8%)
Adjusted rate	8/18.6 (43.0%)	11/18.8 (58.6%)	9/15.5 (58.1%)	22/25.4 (86.7%)	17/20.0 (85.1%)	19/21.4 (88.9%)
Terminal rate	1/1 (100.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	235	226	214	173	150	156
Poly-3 test	P=0.373	P=0.461	P=0.532	P=1.000	P=1.000	P=1.000
Squamous Cell Carcinoma						
Overall rate	9/36 (25.0%)	8/36 (22.2%)	17/35 (48.6%)	19/36 (52.8%)	15/36 (41.7%)	12/36 (33.3%)
Adjusted rate	9/18.2 (49.4%)	8/16.7 (47.9%)	17/21.4 (79.3%)	19/22.6 (83.9%)	15/18.2 (82.5%)	12/15.1 (79.6%)
Terminal rate	0/1 (0.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	276	207	180	192	171	177
Poly-3 test	P=0.014	P=1.000	P=0.030	P=0.907N	P=1.000	P=1.000

TABLE A2c
Statistical Analysis of Primary Skin Neoplasms at the Site of Application in Male Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma						
Overall rate	16/36 (44.4%)	17/36 (47.2%)	21/35 (60.0%)	27/36 (75.0%)	27/36 (75.0%)	26/36 (72.2%)
Adjusted rate	16/22.0 (72.8%)	17/22.8 (74.7%)	21/24.3 (86.3%)	27/28.8 (93.8%)	27/28.3 (95.5%)	26/27.3 (95.2%)
Terminal rate	1/1 (100.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	235	207	180	173	150	156
Poly-3 test	P=0.173	P=1.000	P=0.259	P=1.000	P=1.000	P=1.000
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma						
Overall rate	32/36 (88.9%)	32/36 (88.9%)[g]	35/35 (100.0%)	33/36 (91.7%)[g]	35/36 (97.2%)[g]	36/36 (100.0%)[g]
Adjusted rate	32/32.8 (97.7%)	32/32.8 (97.6%)	35/35.0 (100.0%)	33/33.4 (98.9%)	35/35.1 (99.8%)	36/36.0 (100.0%)
Terminal rate	1/1 (100.0%)	0/0	0/0	0/0	0/0	0/0
First incidence (days)	192	192	131	173	128	156
Poly-3 test	P=0.677	P=1.000	P=1.000	P=1.000	P=1.000	P=1.000

[a] Number of neoplasm-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are based on a two-sided, continuity-corrected Poly-3 test. P values in the control cream columns are for the linear trend test; otherwise, P values represent pairwise comparisons to the respective control cream group. A negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.
[g] One of these animals also had keratoacanthoma; however, the overall incidence rate remains the same.

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 0.00 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream
Disposition Summary		
Animals initially in study	36	36
Early deaths		
Moribund	5	3
Natural deaths	1	2
Skin lesion greater than 10 mm		2
Survivors		
Died last week of study	1	
Terminal kill	27	29
Missexed	2	
Animals examined microscopically	34	36
Integumentary System		
Skin, control	(34)	(36)
Abscess		4 (11%)
Cyst epithelial inclusion	2 (6%)	2 (6%)
Hyperplasia, squamous	1 (3%)	
Dermis, inflammation, suppurative		1 (3%)
Dermis, inflammation, chronic active		1 (3%)
Epidermis, inflammation, suppurative	1 (3%)	
Epidermis, ulcer		1 (3%)
Skin, site of application	(34)	(36)
Cyst epithelial inclusion	3 (9%)	5 (14%)
Hyperplasia, squamous atypical, one, focal		4 (11%)
Hyperplasia, squamous		6 (17%)
Dermis, inflammation, chronic active		3 (8%)
Epidermis, ulcer		1 (3%)

Systems Examined with No Lesions Observed
Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 6.85 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Disposition Summary				
Animals initially in study	36	36	36	36
Early deaths				
Moribund	8	7	3	3
Natural deaths	1[b]	1		
Skin lesion greater than 10 mm	2	27	33	32
Survivors				
Terminal kill	25	1		
Missexed				1
Animals examined microscopically	35	36	36	35
Integumentary System				
Skin, control	(35)	(36)	(36)	(35)
Abscess	2 (6%)	1 (3%)	4 (11%)	
Cyst epithelial inclusion	6 (17%)	6 (17%)	1 (3%)	1 (3%)
Hyperplasia, squamous		1 (3%)		
Inflammation, suppurative	1 (3%)			
Necrosis	1 (3%)			
Dermis, inflammation, chronic active		2 (6%)	1 (3%)	
Epidermis, inflammation, suppurative		1 (3%)	1 (3%)	
Epidermis, necrosis		1 (3%)		
Epidermis, ulcer			1 (3%)	
Skin, site of application	(35)	(36)	(36)	(35)
Abscess		1 (3%)		
Cyst epithelial inclusion	4 (11%)	6 (17%)		
Hyperplasia, squamous atypical, one, focal	5 (14%)	2 (6%)	3 (8%)	1 (3%)
Hyperplasia, squamous atypical, two, focal	1 (3%)	2 (6%)	2 (6%)	
Hyperplasia, squamous atypical, three, focal		5 (14%)		2 (6%)
Hyperplasia, squamous atypical, four, focal	1 (3%)	3 (8%)	2 (6%)	2 (6%)
Hyperplasia, squamous atypical, five, focal	2 (6%)	2 (6%)	5 (14%)	3 (9%)
Hyperplasia, squamous atypical, greater than five, focal		14 (39%)	21 (58%)	23 (66%)
Hyperplasia, squamous	4 (11%)	23 (64%)	32 (89%)	34 (97%)
Dermis, inflammation, chronic active	3 (9%)	9 (25%)	12 (33%)	30 (86%)
Epidermis, inflammation, suppurative	1 (3%)		7 (19%)	8 (23%)
Epidermis, necrosis	1 (3%)	3 (8%)	9 (25%)	14 (40%)
Epidermis, ulcer	1 (3%)		7 (19%)	8 (23%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 6.85 mJ•CIE/cm^2 SSL

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Systems Examined with No Lesions Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 13.70 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Disposition Summary				
Animals initially in study	36	36	36	36
Early deaths				
Moribund		3	1	
Natural deaths	1			1
Skin lesion greater than 10 mm	35	33	35	35
Animals examined microscopically	36	36	36	36
Integumentary System				
Skin, control	(36)	(36)	(36)	(36)
Abscess	2 (6%)	2 (6%)	2 (6%)	
Cyst epithelial inclusion	3 (8%)	2 (6%)	2 (6%)	2 (6%)
Hyperplasia, squamous	3 (8%)		1 (3%)	2 (6%)
Inflammation, suppurative	1 (3%)		1 (3%)	1 (3%)
Ulcer			1 (3%)	
Dermis, inflammation, chronic active	4 (11%)	2 (6%)	3 (8%)	2 (6%)
Epidermis, inflammation, suppurative	1 (3%)	2 (6%)		
Epidermis, ulcer	1 (3%)	2 (6%)	2 (6%)	1 (3%)
Skin, site of application	(36)	(36)	(36)	(36)
Abscess				2 (6%)
Cyst epithelial inclusion	3 (8%)	3 (8%)	1 (3%)	1 (3%)
Hyperplasia, squamous atypical, one, focal	3 (8%)		1 (3%)	
Hyperplasia, squamous atypical, two, focal	6 (17%)		2 (6%)	2 (6%)
Hyperplasia, squamous atypical, three, focal	5 (14%)	7 (19%)	4 (11%)	2 (6%)
Hyperplasia, squamous atypical, four, focal	5 (14%)		3 (8%)	3 (8%)
Hyperplasia, squamous atypical, five, focal	3 (8%)	2 (6%)	2 (6%)	2 (6%)
Hyperplasia, squamous atypical, greater than five, focal	10 (28%)	24 (67%)	24 (67%)	26 (72%)
Hyperplasia, squamous	26 (72%)	27 (75%)	34 (94%)	35 (97%)
Keratin cyst		1 (3%)		
Dermis, inflammation, chronic active	5 (14%)	8 (22%)	20 (56%)	32 (89%)
Epidermis, inflammation, suppurative	1 (3%)	3 (8%)	7 (19%)	14 (39%)
Epidermis, necrosis	3 (8%)	5 (14%)	11 (31%)	20 (56%)
Epidermis, ulcer	1 (3%)	3 (8%)	8 (22%)	10 (28%)
Sebaceous gland, hyperplasia		1 (3%)	1 (3%)	

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 13.70 mJ•CIE/cm^2 SSL

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Systems Examined with No Lesions Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE A3d
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 20.55 mJ•CIE/cm^2 SSL[a]

	No Cream
Disposition Summary	
Animals initially in study	36
Early deaths	
Moribund	1
Natural death	1
Skin lesion greater than 10 mm	34
Animals examined microscopically	36
Integumentary System	
Skin, control	(36)
Abscess	1 (3%)
Cyst epithelial inclusion	2 (6%)
Hyperplasia, squamous	2 (6%)
Infiltration cellular, lymphocyte	1 (3%)
Dermis, inflammation, chronic active	4 (11%)
Epidermis, inflammation, suppurative	2 (6%)
Epidermis, necrosis	1 (3%)
Epidermis, ulcer	3 (8%)
Skin, site of application	(36)
Hyperplasia, squamous atypical, one, focal	2 (6%)
Hyperplasia, squamous atypical, two, focal	3 (8%)
Hyperplasia, squamous atypical, three, focal	8 (22%)
Hyperplasia, squamous atypical, four, focal	4 (11%)
Hyperplasia, squamous atypical, five, focal	4 (11%)
Hyperplasia, squamous atypical, greater than five, focal	9 (25%)
Hyperplasia, squamous	18 (50%)
Dermis, inflammation, chronic active	8 (22%)
Epidermis, inflammation, suppurative	1 (3%)
Epidermis, necrosis	2 (6%)
Epidermis, ulcer	1 (3%)
Sebaceous gland, hyperplasia	1 (3%)

Systems Examined with No Lesions Observed
Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

[a] Number of animals examined microscopically at the site and the number of animals with lesion

APPENDIX B
SUMMARY OF LESIONS IN FEMALE MICE IN THE 1-YEAR SIMULATED SOLAR LIGHT STUDY OF RETINOIC ACID AND RETINYL PALMITATE

TABLE B1a
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 0.00 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream
Disposition Summary		
Animals initially in study	36	36
Early deaths		
Moribund		3
Natural deaths	1	
Skin lesion greater than 10 mm		2
Survivors		
Died last week of study	1	3
Terminal kill	34	28
Animals examined microscopically	36	36
Integumentary System		
Skin, control	(36)	(36)
Squamous cell papilloma		1 (3%)
Skin, site of application	(36)	(36)
Keratoacanthoma, one		1 (3%)
Squamous cell papilloma, one	1 (3%)	5 (14%)
Squamous cell papilloma, two		2 (6%)
Systemic Lesions		
Multiple organs[b]	(36)	(36)
Lymphoma malignant		1 (3%)
Systems Examined with No Neoplasms Observed		
Alimentary System		
Cardiovascular System		
Endocrine System		
General Body System		
Genital System		
Hematopoietic System		
Musculoskeletal System		
Nervous System		
Respiratory System		
Special Senses System		
Urinary System		
Neoplasm Summary		
Total animals with primary neoplasms[c]	1	10
Total primary neoplasms	1	10
Total animals with benign neoplasms	1	9
Total benign neoplasms	1	9
Total animals with malignant neoplasms		1
Total malignant neoplasms		1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B1b
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 6.85 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Disposition Summary				
Animals initially in study	36	36	36	36
Early deaths				
Moribund	2		1	1
Natural deaths	1	2	1	
Skin lesions greater than 10 mm	3	10	30	35
Survivors				
Terminal kill	30	24	4	
Animals examined microscopically	36	36	36	36
Integumentary System				
Skin, control	(36)	(36)	(36)	(36)
Fibroma	1 (3%)			
Squamous cell papilloma	2 (6%)	1 (3%)	1 (3%)	1 (3%)
Skin, site of application	(36)	(36)	(36)	(36)
Basal cell carcinoma		1 (3%)		
Keratoacanthoma, one		1 (3%)		
Squamous cell carcinoma, one	1 (3%)	5 (14%)	10 (28%)	15 (42%)
Squamous cell carcinoma, two		3 (8%)	2 (6%)	1 (3%)
Squamous cell carcinoma, three		1 (3%)	1 (3%)	
Squamous cell carcinoma, four			1 (3%)	
Squamous cell carcinoma *in situ*, one	1 (3%)	3 (8%)	8 (22%)	9 (25%)
Squamous cell carcinoma *in situ*, two	1 (3%)	2 (6%)		
Squamous cell carcinoma *in situ*, three		1 (3%)	1 (3%)	
Squamous cell carcinoma *in situ*, four		1 (3%)	1 (3%)	
Squamous cell papilloma, one	11 (31%)	9 (25%)	6 (17%)	3 (8%)
Squamous cell papilloma, two		8 (22%)	5 (14%)	7 (19%)
Squamous cell papilloma, three	2 (6%)	6 (17%)	4 (11%)	2 (6%)
Squamous cell papilloma, four		1 (3%)	4 (11%)	10 (28%)
Squamous cell papilloma, five		3 (8%)	5 (14%)	1 (3%)
Squamous cell papilloma, greater than five		4 (11%)	7 (19%)	13 (36%)

Systems Examined with No Neoplasms Observed
Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

TABLE B1b
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 6.85 mJ•CIE/cm^2 SSL

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Neoplasm Summary				
Total animals with primary neoplasms[b]	17	33	34	36
Total primary neoplasms	19	50	56	62
Total animals with benign neoplasms	14	31	31	36
Total benign neoplasms	16	33	32	37
Total animals with malignant neoplasms	3	11	19	21
Total malignant neoplasms	3	17	24	25

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B1c
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 13.70 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Disposition Summary				
Animals initially in study	36	36	36	36
Early deaths				
Moribund	3	3	2	2
Natural death		1		2
Skin lesion greater than 10 mm	32	32	34	32
Survivors				
Terminal kill	1			
Animals examined microscopically	36	36	36	36
Integumentary System				
Skin, control	(36)	(36)	(36)	(36)
Squamous cell papilloma		1 (3%)	2 (6%)	
Sebaceous gland, adenoma	1 (3%)			
Skin, site of application	(36)	(36)	(36)	(36)
Basal cell carcinoma	1 (3%)			
Keratoacanthoma, one		1 (3%)		
Squamous cell carcinoma, one	12 (33%)	12 (33%)	12 (33%)	9 (25%)
Squamous cell carcinoma, two	8 (22%)	9 (25%)	9 (25%)	8 (22%)
Squamous cell carcinoma, three	3 (8%)	3 (8%)	3 (8%)	5 (14%)
Squamous cell carcinoma, four	1 (3%)	1 (3%)	5 (14%)	3 (8%)
Squamous cell carcinoma *in situ*, one	10 (28%)	15 (42%)	8 (22%)	4 (11%)
Squamous cell carcinoma *in situ*, two	3 (8%)	2 (6%)	10 (28%)	2 (6%)
Squamous cell carcinoma *in situ*, three	2 (6%)	2 (6%)	1 (3%)	5 (14%)
Squamous cell carcinoma *in situ*, four	2 (6%)		2 (6%)	
Squamous cell carcinoma *in situ*, five	1 (3%)		1 (3%)	
Squamous cell carcinoma *in situ*, greater than five			3 (8%)	
Squamous cell papilloma, one	13 (36%)	5 (14%)	3 (8%)	1 (3%)
Squamous cell papilloma, two	6 (17%)	12 (33%)	6 (17%)	3 (8%)
Squamous cell papilloma, three	2 (6%)	3 (8%)	3 (8%)	3 (8%)
Squamous cell papilloma, four	2 (6%)		4 (11%)	5 (14%)
Squamous cell papilloma, five	4 (11%)	4 (11%)	3 (8%)	1 (3%)
Squamous cell papilloma, greater than five	2 (6%)	7 (19%)	13 (36%)	15 (42%)

Systems Examined with No Neoplasms Observed
Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

TABLE B1c
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 13.70 mJ•CIE/cm^2 SSL

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Neoplasm Summary				
Total animals with primary neoplasms[b]	34	35	34	32
Total primary neoplasms	73	77	88	64
Total animals with benign neoplasms	29	31	32	28
Total benign neoplasms	30	33	34	28
Total animals with malignant neoplasms	31	32	34	28
Total malignant neoplasms	43	44	54	36

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B1d
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 20.55 mJ•CIE/cm^2 SSL[a]

	No Cream	
Disposition Summary		
Animals initially in study	36	
Early deaths		
Skin lesion greater than 10 mm	36	
Animals examined microscopically	36	
Integumentary System		
Skin, control	(36)	
Skin, site of application	(36)	
Squamous cell carcinoma, one	11	(31%)
Squamous cell carcinoma, two	8	(22%)
Squamous cell carcinoma, three	4	(11%)
Squamous cell carcinoma, four	3	(8%)
Squamous cell carcinoma *in situ*, one	9	(25%)
Squamous cell carcinoma *in situ*, two	6	(17%)
Squamous cell carcinoma *in situ*, three	4	(11%)
Squamous cell carcinoma *in situ*, four	2	(6%)
Squamous cell carcinoma *in situ*, five	1	(3%)
Squamous cell papilloma, one	9	(25%)
Squamous cell papilloma, two	4	(11%)
Squamous cell papilloma, three	4	(11%)
Squamous cell papilloma, four	1	(3%)
Squamous cell papilloma, five	1	(3%)
Squamous cell papilloma, greater than five	4	(11%)
Systems Examined with No Neoplasms Observed		
Alimentary System		
Cardiovascular System		
Endocrine System		
General Body System		
Genital System		
Hematopoietic System		
Musculoskeletal System		
Nervous System		
Respiratory System		
Special Senses System		
Urinary System		
Neoplasm Summary		
Total animals with primary neoplasms[b]	33	
Total primary neoplasms	71	
Total animals with benign neoplasms	23	
Total benign neoplasms	23	
Total animals with malignant neoplasms	30	
Total malignant neoplasms	48	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2a
Statistical Analysis of Primary Skin Neoplasms at the Site of Application in Female Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Squamous Cell Papilloma				
Overall rate[a]	1/36 (2.8%)	13/36 (36.1%)	29/36 (80.6%)	23/36 (63.9%)
Adjusted rate[b]	1/35.0 (2.9%)	13/34.6 (37.6%)	29/31.8 (91.2%)	23/26.1 (88.1%)
Terminal rate[c]	1/34 (2.9%)	10/30 (33.3%)	1/1 (100.0%)	0/0
First incidence (days)	367	260	256	187
Poly-3 test[d]	P≤0.001	P≤0.001	P≤0.001	P≤0.001
Squamous Cell Carcinoma *in situ*				
Overall rate	0/36 (0.0%)	2/36 (5.6%)	18/36 (50.0%)	22/36 (61.1%)
Adjusted rate	0/35.0 (0.0%)	2/33.3 (6.0%)	18/26.5 (68.0%)	22/25.4 (86.7%)
Terminal rate	0/34 (0.0%)	2/30 (6.7%)	1/1 (100.0%)	0/0
First incidence (days)	—[e]	367	256	187
Poly-3 test	P≤0.001	P=0.451	P≤0.001	P≤0.001
Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	1/36 (2.8%)	24/36 (66.7%)	26/36 (72.2%)
Adjusted rate	0/35.0 (0.0%)	1/33.8 (3.0%)	24/29.0 (82.7%)	26/28.4 (91.5%)
Terminal rate	0/34 (0.0%)	0/30 (0.0%)	1/1 (100.0%)	0/0
First incidence (days)	—	299	235	166
Poly-3 test	P≤0.001	P=0.986	P≤0.001	P≤0.001
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	3/36 (8.3%)	31/36 (86.1%)	30/36 (83.3%)
Adjusted rate	0/35.0 (0.0%)	3/33.8 (8.9%)	31/33.2 (93.4%)	30/31.5 (95.3%)
Terminal rate	0/34 (0.0%)	2/30 (6.7%)	1/1 (100.0%)	0/0
First incidence (days)	—	299	235	166
Poly-3 test	P≤0.001	P=0.221	P≤0.001	P≤0.001

TABLE B2a
Statistical Analysis of Primary Skin Neoplasms at the Site of Application in Female Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma				
Overall rate	1/36 (2.8%)	16/36 (44.4%)	34/36 (94.4%)	33/36 (91.7%)
Adjusted rate	1/35.0 (2.9%)	16/35.0 (45.7%)	34/34.7 (98.1%)	33/33.8 (97.7%)
Terminal rate	1/34 (2.9%)	12/30 (40.0%)	1/1 (100.0%)	0/0
First incidence (days)	367	260	235	166
Poly-3 test	P≤0.001	P≤0.001	P≤0.001	P≤0.001

[a] Number of neoplasm-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are based on a two-sided, continuity-corrected Poly-3 test. P values in the control group (0.00 mJ•CIE/cm^2) column are for the linear trend test; otherwise, P values represent pairwise comparisons to the control group.
[e] Not applicable; no neoplasms in animal group

TABLE B2b
Statistical Analysis of Primary Skin Neoplasms at the Site of Application in Female Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Squamous Cell Papilloma						
Overall rate[a]	1/36 (2.8%)	7/36 (19.4%)	13/36 (36.1%)	31/36 (86.1%)	29/36 (80.6%)	31/36 (86.1%)
Adjusted rate[b]	1/35.0 (2.9%)	7/33.9 (20.7%)	13/34.6 (37.6%)	31/34.9 (88.7%)	29/31.8 (91.2%)	31/32.8 (94.6%)
Terminal rate[c]	1/34 (2.9%)	5/28 (17.9%)	10/30 (33.3%)	21/24 (87.5%)	1/1 (100.0%)	0/0
First incidence (days)	367	327	260	228	256	201
Poly-3 test[d]		P=0.048		P≤0.001		P=0.944
Keratoacanthoma						
Overall rate	0/36 (0.0%)	1/36 (2.8%)	0/36 (0.0%)	1/36 (2.8%)	0/36 (0.0%)	1/36 (2.8%)
Adjusted rate	0/35.0 (0.0%)	1/33.8 (3.0%)	0/33.3 (0.0%)	1/30.7 (3.3%)	0/17.6 (0.0%)	1/15.1 (6.6%)
Terminal rate	0/34 (0.0%)	0/28 (0.0%)	0/30 (0.0%)	1/24 (4.2%)	0/1 (0.0%)	0/0
First incidence (days)	—[e]	320	—	367	—	262
Poly-3 test		P=0.986		P=0.968		P=0.939
Squamous Cell Carcinoma *in situ*						
Overall rate	0/36 (0.0%)	0/36 (0.0%)	2/36 (5.6%)	7/36 (19.4%)	18/36 (50.0%)	19/36 (52.8%)
Adjusted rate	0/35.0 (0.0%)	0/33.4 (0.0%)	2/33.3 (6.0%)	7/31.6 (22.1%)	18/26.5 (68.0%)	19/25.8 (73.6%)
Terminal rate	0/34 (0.0%)	0/28 (0.0%)	2/30 (6.7%)	4/24 (16.7%)	1/1 (100.0%)	0/0
First incidence (days)	—	—	367	306	256	219
Poly-3 test		—[f]		P=0.123		P=0.865
Squamous Cell Carcinoma						
Overall rate	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)	9/36 (25.0%)	24/36 (66.7%)	25/36 (69.4%)
Adjusted rate	0/35.0 (0.0%)	0/33.4 (0.0%)	1/33.8 (3.0%)	9/32.1 (28.0%)	24/29.0 (82.7%)	25/29.1 (86.0%)
Terminal rate	0/34 (0.0%)	0/28 (0.0%)	0/30 (0.0%)	4/24 (16.7%)	1/1 (100.0%)	0/0
First incidence (days)	—	—	299	306	235	219
Poly-3 test		—		P=0.009		P=1.000

TABLE B2b
Statistical Analysis of Primary Skin Neoplasms at the Site of Application in Female Mice Administered No Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2		6.85 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**	**No Cream**	**Control Cream**
Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma						
Overall rate	0/36 (0.0%)	0/36 (0.0%)	3/36 (8.3%)	11/36 (30.6%)	31/36 (86.1%)	32/36 (88.9%)
Adjusted rate	0/35.0 (0.0%)	0/33.4 (0.0%)	3/33.8 (8.9%)	11/32.1 (34.2%)	31/33.2 (93.4%)	32/33.0 (96.8%)
Terminal rate	0/34 (0.0%)	0/28 (0.0%)	2/30 (6.7%)	6/24 (25.0%)	1/1 (100.0%)	0/0
First incidence (days)	—	—	299	306	235	219
Poly-3 test		—		P=0.022		P=0.913
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma						
Overall rate	1/36 (2.8%)	7/36 (19.4%)	16/36 (44.4%)	33/36 (91.7%)	34/36 (94.4%)	35/36 (97.2%)
Adjusted rate	1/35.0 (2.9%)	7/33.9 (20.7%)	16/35.0 (45.7%)	33/35.2 (93.8%)	34/34.7 (98.1%)	35/35.2 (99.4%)
Terminal rate	1/34 (2.9%)	5/28 (17.9%)	12/30 (40.0%)	22/24 (91.7%)	1/1 (100.0%)	0/0
First incidence (days)	367	327	260	228	235	201
Poly-3 test		P=0.048		P≤0.001		P=1.000
Squamous Cell Papilloma, Keratoacanthoma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma						
Overall rate	1/36 (2.8%)	8/36 (22.2%)	16/36 (44.4%)	33/36 (91.7%)	34/36 (94.4%)	35/36 (97.2%)
Adjusted rate	1/35.0 (2.9%)	8/34.2 (23.4%)	16/35.0 (45.7%)	33/35.2 (93.8%)	34/34.7 (98.1%)	35/35.2 (99.4%)
Terminal rate	1/34 (2.9%)	5/28 (17.9%)	12/30 (40.0%)	22/24 (91.7%)	1/1 (100.0%)	0/0
First incidence (days)	367	320	260	228	235	201
Poly-3 test		P=0.024		P≤0.001		P=1.000

[a] Number of neoplasm-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values in the control cream columns represent pairwise comparisons to the respective no cream group and are based on a two-sided, continuity-corrected Poly-3 test.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B2c
Statistical Analysis of Primary Neoplasms at the Site of Application in Female Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Squamous Cell Papilloma						
Overall rate[a]	31/36 (86.1%)	31/36 (86.1%)	36/36 (100.0%)	31/36 (86.1%)	32/36 (88.9%)	28/36 (77.8%)
Adjusted rate[b]	31/34.9 (88.7%)	31/33.2 (93.4%)	36/36.0 (100.0%)	31/32.8 (94.6%)	32/33.0 (97.0%)	28/29.0 (96.4%)
Terminal rate[c]	21/24 (87.5%)	4/4 (100.0%)	0/0	0/0	0/0	0/0
First incidence (days)	228	167	167	201	191	187
Poly-3 test[d]	P=0.051	P=0.789	P=0.098	P=0.945	P=1.000	P=1.000
Keratoacanthoma						
Overall rate	1/36 (2.8%)	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)	0/36 (0.0%)	0/36 (0.0%)
Adjusted rate	1/30.7 (3.3%)	0/19.4 (0.0%)	0/12.0 (0.0%)	1/15.1 (6.6%)	0/9.5 (0.0%)	0/6.6 (0.0%)
Terminal rate	1/24 (4.2%)	0/4 (0.0%)	0/0	0/0	0/0	0/0
First incidence (days)	367	—[e]	—	262	—	—
Poly-3 test	P=0.909 N	P=1.000	P=1.000	P=0.865N	P=1.000	P=1.000
Squamous Cell Carcinoma *in situ*						
Overall rate	7/36 (19.4%)	10/36 (27.8%)	9/36 (25.0%)	19/36 (52.8%)	25/36 (69.4%)	11/36 (30.6%)
Adjusted rate	7/31.6 (22.1%)	10/22.6 (44.2%)	9/18.1 (49.9%)	19/25.8 (73.6%)	25/27.8 (90.0%)	11/15.3 (71.9%)
Terminal rate	4/24 (16.7%)	2/4 (50.0%)	0/0	0/0	0/0	0/0
First incidence (days)	306	242	201	219	191	201
Poly-3 test	P=0.038	P=0.149	P=0.097	P=0.686	P=0.083	P=1.000
Squamous Cell Carcinoma						
Overall rate	9/36 (25.0%)	14/36 (38.9%)	16/36 (44.4%)	25/36 (69.4%)	29/36 (80.6%)	25/36 (69.4%)
Adjusted rate	9/32.1 (28.0%)	14/25.2 (55.6%)	16/22.6 (70.8%)	25/29.1 (86.0%)	29/30.8 (94.0%)	25/26.4 (94.6%)
Terminal rate	4/24 (16.7%)	0/4 (0.0%)	0/0	0/0	0/0	0/0
First incidence (days)	306	242	201	219	191	159
Poly-3 test	P≤0.001	P=0.057	P=0.002	P=0.140	P=0.352	P=0.332

TABLE B2c
Statistical Analysis of Primary Neoplasms at the Site of Application in Female Mice Administered Control Cream or Retinyl Palmitate Creams and Exposed to 6.85 or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	6.85 mJ•CIE/cm^2			13.70 mJ•CIE/cm^2		
	Control Cream	**0.1% RP Cream**	**0.5% RP Cream**	**Control Cream**	**0.1% RP Cream**	**0.5% RP Cream**
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma						
Overall rate	11/36 (30.6%)	19/36 (52.8%)	21/36 (58.3%)	32/36 (88.9%)	34/36 (94.4%)	28/36 (77.8%)
Adjusted rate	11/32.1 (34.2%)	19/27.0 (70.4%)	21/25.9 (81.0%)	32/33.0 (96.8%)	34/34.5 (98.5%)	28/28.8 (97.1%)
Terminal rate	6/24 (25.0%)	2/4 (50.0%)	0/0	0/0	0/0	0/0
First incidence (days)	306	242	201	219	191	159
Poly-3 test	P≤0.001	P=0.007	P≤0.001	P=1.000	P=1.000	P=1.000
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma						
Overall rate	33/36 (91.7%)[f]	34/36 (94.4%)	36/36 (100.0%)	35/36 (97.2%) [f]	34/36 (94.4%)	32/36 (88.9%)
Adjusted rate	33/35.2 (93.8%)	34/34.1 (99.8%)	36/36.0 (100.0%)	35/35.2 (99.4%)	34/34.5 (98.5%)	32/32.2 (99.3%)
Terminal rate	22/24 (91.7%)	4/4 (100.0%)	0/0	0/0	0/0	0/0
First incidence (days)	228	167	167	201	191	159
Poly-3 test	P=0.138	P=0.431	P=0.384	P=1.000	P=1.000	P=1.000

[a] Number of neoplasm-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are based on a two-sided, continuity-corrected Poly-3 test. P values in the control cream columns are for the linear trend test; otherwise, P values represent pairwise comparisons to the respective control cream group. A negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] One of these animals also had a keratoacanthoma; however, the overall incidence rate remains the same.

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 0.00 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream
Disposition Summary		
Animals initially in study	36	36
Early deaths		
Moribund		3
Natural deaths	1	
Skin lesion greater than 10 mm		2
Survivors		
Died last week of study	1	3
Terminal kill	34	28
Animals examined microscopically	36	36
Integumentary System		
Skin, control	(36)	(36)
Abscess	1 (3%)	
Cyst epithelial inclusion	2 (6%)	4 (11%)
Hyperplasia, squamous	1 (3%)	
Ulcer		1 (3%)
Dermis, inflammation, chronic active	3 (8%)	1 (3%)
Epidermis, ulcer	1 (3%)	
Skin, site of application	(36)	(36)
Abscess	1 (3%)	1 (3%)
Cyst, multiple	1 (3%)	
Cyst epithelial inclusion	2 (6%)	
Hyperplasia, squamous atypical, two, focal		1 (3%)
Hyperplasia, squamous	1 (3%)	7 (19%)
Dermis, inflammation, chronic active	2 (6%)	2 (6%)

Systems Examined with No Lesions Observed
Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 6.85 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Disposition Summary				
Animals initially in study	36	36	36	36
Early deaths				
Moribund	2		1	1
Natural deaths	1	2	1	
Skin lesions greater than 10 mm	3	10	30	35
Survivors				
Terminal kill	30	24	4	
Animals examined microscopically	36	36	36	36
Integumentary System				
Skin, control	(36)	(36)	(36)	(36)
Abscess	1 (3%)			
Cyst epithelial inclusion	4 (11%)	6 (17%)	3 (8%)	1 (3%)
Hyperplasia, squamous atypical, focal			1 (3%)	
Hyperplasia, squamous		1 (3%)		4 (11%)
Dermis, inflammation, chronic active	1 (3%)	1 (3%)		
Skin, site of application	(36)	(36)	(36)	(36)
Abscess		1 (3%)		
Cyst epithelial inclusion	4 (11%)	5 (14%)	4 (11%)	1 (3%)
Hyperplasia, squamous atypical, one, focal	11 (31%)	6 (17%)	1 (3%)	8 (22%)
Hyperplasia, squamous atypical, two, focal	1 (3%)	5 (14%)	4 (11%)	3 (8%)
Hyperplasia, squamous atypical, three, focal	2 (6%)	6 (17%)	3 (8%)	2 (6%)
Hyperplasia, squamous atypical, four, focal	1 (3%)	3 (8%)	6 (17%)	2 (6%)
Hyperplasia, squamous atypical, five, focal	1 (3%)	2 (6%)	3 (8%)	3 (8%)
Hyperplasia, squamous atypical, greater than five, focal		5 (14%)	14 (39%)	16 (44%)
Hyperplasia, basal cell		1 (3%)	1 (3%)	
Hyperplasia, squamous	11 (31%)	24 (67%)	32 (89%)	36 (100%)
Dermis, inflammation, chronic active	1 (3%)	15 (42%)	28 (78%)	36 (100%)
Epidermis, inflammation, suppurative		1 (3%)	2 (6%)	7 (19%)
Epidermis, necrosis		2 (6%)	4 (11%)	7 (19%)
Epidermis, ulcer		1 (3%)	3 (8%)	9 (25%)
Sebaceous gland, hyperplasia			1 (3%)	

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 6.85 mJ•CIE/cm^2 SSL

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Systems Examined with No Lesions Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 13.70 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Disposition Summary				
Animals initially in study	36	36	36	36
Early deaths				
Moribund	3	3	2	2
Natural deaths		1		2
Skin lesion greater than 10 mm	32	32	34	32
Survivors				
Terminal kill	1			
Animals examined microscopically	36	36	36	36
Integumentary System				
Skin, control	(36)	(36)	(36)	(36)
Cyst epithelial inclusion	1 (3%)	4 (11%)	2 (6%)	
Edema				1 (3%)
Hyperplasia, squamous atypical, focal		1 (3%)		
Hyperplasia, squamous	1 (3%)	1 (3%)		6 (17%)
Dermis, inflammation, suppurative				1 (3%)
Dermis, inflammation, chronic active	1 (3%)		1 (3%)	2 (6%)
Epidermis, inflammation, suppurative	1 (3%)			
Epidermis, necrosis				1 (3%)
Epidermis, ulcer	2 (6%)			
Skin, site of application	(36)	(36)	(36)	(36)
Cyst epithelial inclusion	2 (6%)	9 (25%)	1 (3%)	
Hyperplasia, squamous atypical, one, focal	4 (11%)	5 (14%)	1 (3%)	3 (8%)
Hyperplasia, squamous atypical, two, focal	4 (11%)		1 (3%)	3 (8%)
Hyperplasia, squamous atypical, three, focal	4 (11%)	5 (14%)	6 (17%)	2 (6%)
Hyperplasia, squamous atypical, four, focal	5 (14%)	2 (6%)	4 (11%)	4 (11%)
Hyperplasia, squamous atypical, five, focal	3 (8%)	1 (3%)	5 (14%)	4 (11%)
Hyperplasia, squamous atypical, greater than five, focal	13 (36%)	20 (56%)	19 (53%)	14 (39%)
Hyperplasia, squamous	28 (78%)	33 (92%)	31 (86%)	35 (97%)
Dermis, inflammation, chronic active	12 (33%)	18 (50%)	31 (86%)	33 (92%)
Epidermis, inflammation, suppurative	1 (3%)	3 (8%)	3 (8%)	9 (25%)
Epidermis, necrosis	2 (6%)	3 (8%)	5 (14%)	14 (39%)
Epidermis, ulcer	1 (3%)	2 (6%)	3 (8%)	6 (17%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 13.70 mJ•CIE/cm^2 SSL[a]

	No Cream	Control Cream	0.1% Retinyl Palmitate Cream	0.5% Retinyl Palmitate Cream
Systems Examined with No Lesions Observed				
Alimentary System				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE B3d
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate: 20.55 mJ•CIE/cm^2 SSL[a]

	No Cream
Disposition Summary	
Animals initially in study	36
Early deaths	
Skin lesion greater than 10 mm	36
Animals examined microscopically	36
Integumentary System	
Skin, control	(36)
Abscess	1 (3%)
Cyst epithelial inclusion	4 (11%)
Hyperplasia, squamous	1 (3%)
Skin, site of application	(36)
Abscess	1 (3%)
Cyst epithelial inclusion	2 (6%)
Hyperplasia, squamous atypical, one, focal	4 (11%)
Hyperplasia, squamous atypical, two, focal	9 (25%)
Hyperplasia, squamous atypical, three, focal	7 (19%)
Hyperplasia, squamous atypical, four, focal	7 (19%)
Hyperplasia, squamous atypical, five, focal	4 (11%)
Hyperplasia, squamous atypical, greater than five, focal	4 (11%)
Hyperplasia, squamous	28 (78%)
Dermis, inflammation, chronic active	21 (58%)
Epidermis, inflammation, suppurative	3 (8%)
Epidermis, necrosis	1 (3%)
Epidermis, ulcer	4 (11%)

Systems Examined with No Lesions Observed
Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System
Urinary System

[a] Number of animals examined microscopically at the site and the number of animals with lesion

APPENDIX C
BODY WEIGHT DATA

TABLE C1
Mean Body Weights and Survival of Male Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Weeks on Study	0.00 mJ•CIE/cm^2 SSL			6.85 mJ•CIE/cm^2 SSL			
	No. of Survivors	Av. Wt. (g)[a]	P Value[b]	No. of Survivors	Av. Wt. (g)	P Value[c]	Wt. (% of controls)
0	36[d]	30.4 ± 0.6	0.471	36	29.6 ± 0.4	0.144	97.2
4	36[d]	33.8 ± 0.6	0.341	36	33.2 ± 0.4	0.343	98.2
8	36[d]	35.4 ± 0.6	0.195	36	34.7 ± 0.4	0.268	98.0
12	34	37.1 ± 0.5	0.008*	35	36.0 ± 0.4	0.274	97.2
16	34	37.2 ± 0.5	0.086	35	36.3 ± 0.4	0.407	97.7
20	34	37.5 ± 0.5	0.360	35	36.4 ± 0.4	0.194	97.1
24	34	37.8 ± 0.6	0.618	35	36.9 ± 0.5	0.323	97.6
28	33	37.9 ± 0.6	0.697	35	37.4 ± 0.5	0.638	98.8
32	32	38.4 ± 0.6	0.098	34	37.9 ± 0.5	0.703	98.8
36	32	38.3 ± 0.6		34	37.4 ± 0.7	0.385	97.7
40	31	37.7 ± 0.8		32	37.6 ± 0.7	0.694	99.6
44	30	38.7 ± 0.6		29	38.0 ± 0.6	0.314	98.1
48	28	38.7 ± 0.6		28	39.1 ± 0.5	0.730	101.0
52	27	39.0 ± 0.8		25	39.2 ± 0.7	0.725	100.5
Mean for Weeks							
0-52		36.3 ± 0.6			36.0 ± 0.5	0.287	99.1

Weeks on Study	13.70 mJ•CIE/cm^2 SSL				20.55 mJ•CIE/cm^2 SSL			
	No. of Survivors	Av. Wt. (g)	P Value[c]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[c]	Wt. (% of controls)
0	36	29.5 ± 0.3	0.098	96.8	36	30.0 ± 0.4	0.486	98.6
4	36	33.0 ± 0.4	0.254	97.9	36	33.2 ± 0.4	0.347	98.3
8	36	34.5 ± 0.4	0.165	97.5	36	34.6 ± 0.4	0.204	97.7
12	36	35.1 ± 0.4	0.011*	94.8	36	35.3 ± 0.4	0.020*	95.1
16	36	35.5 ± 0.5	0.046*	95.6	36	35.9 ± 0.4	0.155	96.6
20	36	36.7 ± 0.4	0.458	98.0	36	36.5 ± 0.4	0.249	97.3
24	36	36.9 ± 0.4	0.318	97.6	34	37.2 ± 0.5	0.601	98.4
28	36	37.0 ± 0.5	0.346	97.9	27	37.2 ± 0.5	0.797	98.2
32	36	37.4 ± 0.5	0.317	97.6	12	36.9 ± 0.8	0.122	96.2
36	32	37.6 ± 0.5	0.471	98.2	0			
40	17	37.7 ± 0.5	0.969	99.8	0			
44	2	37.9 ± 1.2	0.824	97.7	0			
48	1	39.5	0.284	102.1	0			
52	0				0			
Mean for Weeks								
0-52		35.4 ± 0.4		97.6		35.0 ± 0.4		96.3

* Significant at P≤0.05
[a] Mean ± standard error
[b] P value represents linear trend in body weight with increasing simulated solar light (SSL) level.
[c] P value represents pairwise comparison of body weight to 0.00 mJ•CIE/cm^2 SSL group.
[d] Includes two missexed animals

TABLE C2
Mean Body Weights and Survival of Female Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Weeks on Study	0.00 mJ•CIE/cm^2 SSL			6.85 mJ•CIE/cm^2 SSL			
	No. of Survivors	Av. Wt. (g)[a]	P Value[b]	No. of Survivors	Av. Wt. (g)	P Value[c]	Wt. (% of controls)
0	36	24.3 ± 0.3	0.620	36	23.2 ± 0.4	0.009*	95.5
4	36	26.9 ± 0.3	0.006*	36	26.4 ± 0.3	0.276	98.3
8	36	28.2 ± 0.3	0.053	36	27.5 ± 0.3	0.099	97.5
12	36	28.8 ± 0.3	0.036*	36	28.6 ± 0.3	0.629	99.3
16	36	29.2 ± 0.3	0.237	36	29.2 ± 0.4	0.975	100.0
20	36	30.0 ± 0.3	0.596	36	29.6 ± 0.4	0.356	98.6
24	36	30.3 ± 0.4	0.846	36	30.1 ± 0.3	0.657	99.3
28	35	30.6 ± 0.4	0.744	36	30.7 ± 0.4	0.792	100.3
32	35	30.8 ± 0.4	0.833	36	30.9 ± 0.4	0.873	100.2
36	35	30.9 ± 0.5	0.959	35	31.5 ± 0.4	0.263	102.0
40	35	31.8 ± 0.5		34	31.5 ± 0.4	0.583	99.1
44	35	31.7 ± 0.5		33	31.8 ± 0.4	0.929	100.4
48	35	32.2 ± 0.5		30	32.1 ± 0.5	0.845	99.6
52	34	32.3 ± 0.5		30	32.9 ± 0.6	0.529	101.9
Mean for Weeks							
0-52		29.8 ± 0.4			29.6 ± 0.3	0.693	99.3

Weeks on Study	13.70 mJ•CIE/cm^2 SSL				20.55 mJ•CIE/cm^2 SSL			
	No. of Survivors	Av. Wt. (g)	P Value[c]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[c]	Wt. (% of controls)
0	36	23.7 ± 0.2	0.194	97.7	36	23.8 ± 0.2	0.338	98.3
4	36	25.9 ± 0.3	0.020*	96.4	36	25.9 ± 0.3	0.014*	96.2
8	36	27.0 ± 0.3	0.008*	96.0	36	27.4 ± 0.3	0.088	97.4
12	35	28.0 ± 0.3	0.070	97.3	36	28.1 ± 0.2	0.077	97.4
16	35	29.4 ± 0.3	0.645	100.7	36	28.6 ± 0.3	0.158	97.8
20	35	30.2 ± 0.3	0.736	100.5	36	29.6 ± 0.3	0.327	98.5
24	35	30.5 ± 0.3	0.648	100.7	35	30.3 ± 0.3	0.923	100.0
28	35	30.9 ± 0.3	0.486	101.1	34	30.6 ± 0.3	0.842	100.2
32	35	31.3 ± 0.3	0.334	101.5	23	31.0 ± 0.4	0.969	100.5
36	30	31.5 ± 0.5	0.239	102.2	1	27.1 ± 0.2	0.967	87.8
40	20	31.9 ± 0.4	0.686	100.5	0			
44	10	31.3 ± 0.5	0.683	98.5	0			
48	2	30.4 ± 2.7	0.918	94.2	0			
52	1	33.4	0.833	103.5	0			
Mean for Weeks								
0-52		28.9 ± 0.35	0.976	97.1		28.2 ± 0.5		101.23

* Significant at P≤0.05
[a] Mean ± standard error
[b] P value represents linear trend in body weight with increasing simulated solar light (SSL) level.
[c] P value represents pairwise comparison of body weight to 0.00 mJ•CIE/cm^2 SSL group.

TABLE C3
Mean Body Weights and Survival of Female Mice Administered No Cream and Exposed to UVA or UVB Compared to SSL at 13.70 mJ•CIE/cm^2 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	13.70 mJ•CIE/cm^2 SSL		UVA			
Weeks on Study	No. of Survivors	Av. Wt. (g)[a]	No. of Survivors	Av. Wt. (g)	P Value[b]	Wt. (% of controls)
0	36	23.7 ± 0.2	36	24.2 ± 0.3	0.228	101.9
4	36	25.9 ± 0.3	36	26.4 ± 0.4	0.302	101.7
8	36	27.0 ± 0.3	36	28.2 ± 0.4	0.009*	104.2
12	35	28.0 ± 0.3	36	29.2 ± 0.4	0.014*	103.9
16	35	29.4 ± 0.3	35	30.0 ± 0.4	0.327	102.0
20	35	30.2 ± 0.3	35	30.4 ± 0.4	0.856	100.7
24	35	30.5 ± 0.3	35	30.1 ± 0.4	0.385	98.7
28	35	30.9 ± 0.3	35	31.0 ± 0.4	0.973	100.3
32	35	31.3 ± 0.3	35	30.9 ± 0.4	0.418	98.6
36	30	31.5 ± 0.5	33	31.8 ± 0.5	0.984	100.7
40	20	31.9 ± 0.4	33	32.3 ± 0.5	0.869	101.1
44	10	31.3 ± 0.5	29	32.0 ± 0.6	0.790	102.3
48	2	30.4 ± 2.7	29	32.6 ± 0.6	0.812	107.5
52	1	33.4	27	33.8 ± 0.7	0.748	101.3
Mean for Weeks						
0-52		28.9 ± 0.35		29.84 ± 0.4	0.543	103.1

	UVB			
Weeks on Study	No. of Survivors	Av. Wt. (g)	P Value[b]	Wt. (% of controls)
0	36	24.0 ± 0.3	0.483	101.1
4	36	25.9 ± 0.3	0.990	100.0
8	36	27.3 ± 0.3	0.490	101.1
12	36	29.3 ± 0.3	0.006*	104.4
16	36	29.4 ± 0.4	0.997	100.0
20	36	28.7 ± 0.5	0.007*	95.2
24	36	30.0 ± 0.4	0.329	98.3
28	36	31.6 ± 0.4	0.210	102.2
32	35	32.4 ± 0.5	0.064	103.5
36	20	32.0 ± 0.6	0.247	101.3
40	12	32.7 ± 0.8	0.154	102.5
44	1	32.7	0.313	104.6
48	1	34.3	0.266	113.0
52	0			
Mean for Weeks				
0-52		29.1 ± 0.3		100.4

* Significant at P≤0.05
[a] Mean ± standard error
[b] P values represent pairwise comparison to 13.70 mJ•CIE/cm^2 group.

TABLE C4
Mean Body Weights and Survival of Male Mice Administered Control Cream or No Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		No Cream			
Weeks on Study	No. of Survivors	Av. Wt. (g)[a]	No. of Survivors	Av. Wt. (g)	P Value[b]	Wt. (% of controls)
0.00 mJ•CIE/cm^2 SSL						
0	36	30.1 ± 0.5	36[c]	30.4 ± 0.6	0.659	101.1
4	36	32.7 ± 0.5	36[c]	33.8 ± 0.6	0.167	103.1
8	36	34.2 ± 0.6	36[c]	35.4 ± 0.6	0.171	103.4
12	35	35.5 ± 0.6	34	37.1 ± 0.5	0.086	104.4
16	35	36.1 ± 0.6	34	37.2 ± 0.5	0.213	103.1
20	35	36.8 ± 0.6	34	37.5 ± 0.5	0.510	101.9
24	35	36.9 ± 0.6	34	37.8 ± 0.6	0.357	102.3
28	35	37.0 ± 0.6	33	37.9 ± 0.6	0.296	102.4
32	33	37.4 ± 0.6	32	38.4 ± 0.6	0.385	102.6
36	33	37.2 ± 0.7	32	38.3 ± 0.6	0.284	103.0
40	33	37.4 ± 0.7	31	37.7 ± 0.8	0.759	100.8
44	33	37.5 ± 0.7	30	38.7 ± 0.6	0.388	103.2
48	30	38.5 ± 0.8	28	38.7 ± 0.6	0.847	100.5
52	29	37.4 ± 0.7	27	39.0 ± 0.8	0.058	104.3
Mean for Weeks						
0-52		35.8 ± 0.6		36.3 ± 0.6	0.180	101.5
6.85 mJ•CIE/cm^2 SSL						
0	36	29.0 ± 0.4	36	29.6 ± 0.4	0.334	101.9
4	34	32.8 ± 0.5	36	33.2 ± 0.4	0.402	101.0
8	34	34.7 ± 0.5	36	34.7 ± 0.4	0.837	99.9
12	34	36.1 ± 0.5	35	36.0 ± 0.4	0.945	99.8
16	34	36.7 ± 0.5	35	36.3 ± 0.4	0.679	99.0
20	34	36.5 ± 0.5	35	36.4 ± 0.4	0.925	99.6
24	34	37.5 ± 0.5	35	36.9 ± 0.5	0.464	98.3
28	32	38.3 ± 0.6	35	37.4 ± 0.5	0.293	97.7
32	30	38.8 ± 0.6	34	37.9 ± 0.5	0.404	97.7
36	23	38.1 ± 0.9	34	37.4 ± 0.7	0.701	98.3
40	11	38.3 ± 1.2	32	37.6 ± 0.7	0.584	98.2
44	7	36.7 ± 0.5	29	38.0 ± 0.6	0.730	103.4
48	2	37.1 ± 0.3	28	39.1 ± 0.5	0.655	105.5
52	1	31.9	25	39.2 ± 0.7	0.015*	122.8
Mean for Weeks						
0-52		35.2 ± 0.6		36.0 ± 0.5	0.677	102.2

TABLE C4
Mean Body Weights and Survival of Male Mice Administered Control Cream or No Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		No Cream			
Weeks on Study	**No. of Survivors**	**Av. Wt. (g)[a]**	**No. of Survivors**	**Av. Wt. (g)**	**P Value[b]**	**Wt. (% of controls)**
13.70 mJ•CIE/cm^2 SSL						
0	35	28.8 ± 0.4	36	29.5 ± 0.3	0.218	102.2
4	35	32.5 ± 0.5	36	33.0 ± 0.4	0.323	101.8
8	35	33.9 ± 0.5	36	34.5 ± 0.4	0.339	101.7
12	35	35.3 ± 0.5	36	35.1 ± 0.4	0.808	99.6
16	35	36.4 ± 0.6	36	35.5 ± 0.5	0.273	97.7
20	35	37.3 ± 0.5	36	36.7 ± 0.4	0.369	98.5
24	34	37.5 ± 0.5	36	36.9 ± 0.4	0.327	98.3
28	27	37.3 ± 0.6	36	37.0 ± 0.5	0.426	99.3
32	22	37.8 ± 0.7	36	37.4 ± 0.5	0.384	99.1
36	6	38.0 ± 1.2	32	37.6 ± 0.5	0.236	99.1
40	0		17	37.7 ± 0.5		
44	0		2	37.9 ± 1.2		
48	0		1	39.5		
52	0		0			
Mean for Weeks						
0-52		35.0 ± 0.4		35.4 ± 0.4		101.1

* Significant at P≤0.05
[a] Mean ± standard error
[b] P value represents pairwise comparison of body weights to control cream group at an equivalent dose of SSL.
[c] Includes two missexed animals

TABLE C5
Mean Body Weights and Survival of Female Mice Administered Control Cream or No Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		No Cream			
Weeks on Study	No. of Survivors	Av. Wt. (g)[a]	No. of Survivors	Av. Wt. (g)	P Value[b]	Wt. (% of controls)
0.00 mJ•CIE/cm^2 SSL						
0	36	24.0 ± 0.3	36	24.3 ± 0.3	0.580	101.1
4	36	26.5 ± 0.3	36	26.9 ± 0.3	0.407	101.4
8	36	27.7 ± 0.3	36	28.2 ± 0.3	0.292	101.7
12	36	28.2 ± 0.4	36	28.8 ± 0.3	0.227	102.1
16	36	28.6 ± 0.3	36	29.2 ± 0.3	0.231	102.0
20	36	29.5 ± 0.4	36	30.0 ± 0.3	0.260	101.9
24	36	29.8 ± 0.3	36	30.3 ± 0.4	0.328	101.6
28	36	30.2 ± 0.4	35	30.6 ± 0.4	0.528	101.2
32	36	30.6 ± 0.4	35	30.8 ± 0.4	0.755	100.6
36	36	30.6 ± 0.4	35	30.9 ± 0.5	0.693	100.8
40	34	31.3 ± 0.4	35	31.8 ± 0.5	0.437	101.6
44	34	31.3 ± 0.4	35	31.7 ± 0.5	0.466	101.5
48	31	31.2 ± 0.4	35	32.2 ± 0.5	0.119	103.2
52	28	31.8 ± 0.5	34	32.3 ± 0.5	0.420	101.5
Mean for Weeks						
0-52		29.3 ± 0.3		29.8 ± 0.4	0.285	101.8
6.85 mJ•CIE/cm^2 SSL						
0	36	23.6 ± 0.3	36	23.2 ± 0.4	0.373	98.3
4	36	26.0 ± 0.3	36	26.4 ± 0.3	0.339	101.5
8	36	26.9 ± 0.3	36	27.5 ± 0.3	0.258	101.9
12	36	28.0 ± 0.3	36	28.6 ± 0.3	0.188	102.1
16	36	29.0 ± 0.3	36	29.2 ± 0.4	0.664	100.7
20	36	29.5 ± 0.3	36	29.6 ± 0.4	0.848	100.3
24	36	30.3 ± 0.3	36	30.1 ± 0.3	0.743	99.5
28	36	30.8 ± 0.3	36	30.7 ± 0.4	0.777	99.5
32	34	30.6 ± 0.4	36	30.9 ± 0.4	0.560	101.0
36	33	31.6 ± 0.4	35	31.5 ± 0.4	0.962	99.7
40	32	31.6 ± 0.4	34	31.5 ± 0.4	0.908	99.7
44	30	31.8 ± 0.4	33	31.8 ± 0.4	0.775	100.3
48	25	32.2 ± 0.5	30	32.1 ± 0.5	0.912	99.5
52	24	32.7 ± 0.7	30	32.9 ± 0.6	0.683	100.5
Mean for Weeks						
0-52		29.3 ± 0.3		29.6 ± 0.3	0.736	100.9

TABLE C5
Mean Body Weights and Survival of Female Mice Administered Control Cream or No Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		No Cream			
Weeks on Study	**No. of Survivors**	**Av. Wt. (g)[a]**	**No. of Survivors**	**Av. Wt. (g)**	**P Value[b]**	**Wt. (% of controls)**
13.70 mJ•CIE/cm^2 SSL						
0	36	23.3 ± 0.3	36	23.7 ± 0.2	0.266	101.9
4	36	25.8 ± 0.3	36	25.9 ± 0.3	0.697	100.6
8	36	27.0 ± 0.3	36	27.0 ± 0.3	0.868	100.3
12	36	28.3 ± 0.4	35	28.0 ± 0.3	0.618	99.1
16	36	29.4 ± 0.4	35	29.4 ± 0.3	0.944	99.9
20	36	30.5 ± 0.4	35	30.2 ± 0.3	0.487	98.9
24	36	31.2 ± 0.5	35	30.5 ± 0.3	0.212	97.8
28	36	31.3 ± 0.5	35	30.9 ± 0.3	0.471	98.6
32	33	31.9 ± 0.5	35	31.3 ± 0.3	0.424	98.1
36	25	32.2 ± 0.6	30	31.5 ± 0.5	0.539	98.0
40	7	31.4 ± 0.9	20	31.9 ± 0.4	0.945	101.8
44	5	30.9 ± 1.5	10	31.3 ± 0.5	0.916	101.3
48	0		2	30.4 ± 2.7		
52	0		1	33.4		
Mean for Weeks						
0-52		29.0 ± 0.3		28.9 ± 0.3		99.6
UVA						
0	36	24.1 ± 0.3	36	24.2 ± 0.3	0.797	100.5
4	36	26.2 ± 0.4	36	26.4 ± 0.4	0.760	100.6
8	35	28.5 ± 0.4	36	28.2 ± 0.4	0.510	98.9
12	34	29.3 ± 0.4	36	29.2 ± 0.4	0.840	99.5
16	34	30.0 ± 0.3	35	30.0 ± 0.4	0.807	99.9
20	34	30.3 ± 0.3	35	30.4 ± 0.4	0.958	100.2
24	34	30.3 ± 0.4	35	30.1 ± 0.4	0.642	99.4
28	34	31.0 ± 0.4	35	31.0 ± 0.4	0.810	99.8
32	34	31.3 ± 0.4	35	30.8 ± 0.4	0.421	98.7
36	32	32.3 ± 0.4	33	31.8 ± 0.5	0.246	98.4
40	31	32.3 ± 0.4	33	32.3 ± 0.5	0.615	99.8
44	31	32.0 ± 0.5	29	32.0 ± 0.6	0.596	100.0
48	28	32.6 ± 0.6	29	32.6 ± 0.6	0.666	100.1
52	26	33.4 ± 0.7	27	33.8 ± 0.7	0.984	101.4
Mean for Weeks						
0-52		29.9 ± 0.4		29.8 ± 0.4	0.666	99.9

TABLE C5
Mean Body Weights and Survival of Female Mice Administered Control Cream or No Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		No Cream			
Weeks on Study	No. of Survivors	Av. Wt. (g)[a]	No. of Survivors	Av. Wt. (g)	P Value[b]	Wt. (% of controls)
UVB						
0	36	23.7 ± 0.3	36	24.0 ± 0.3	0.396	101.4
4	36	25.8 ± 0.3	36	25.9 ± 0.3	0.772	100.5
8	35	27.8 ± 0.3	36	27.3 ± 0.2	0.259	98.3
12	35	29.0 ± 0.3	36	29.3 ± 0.3	0.558	100.8
16	35	29.6 ± 0.3	36	29.4 ± 0.4	0.689	99.3
20	35	29.0 ± 0.5	36	28.7 ± 0.5	0.667	99.0
24	35	29.8 ± 0.4	36	30.0 ± 0.4	0.746	100.6
28	34	31.4 ± 0.3	36	31.6 ± 0.4	0.759	100.7
32	26	32.4 ± 0.4	35	32.4 ± 0.5	0.675	99.9
36	11	31.5 ± 0.7	20	32.0 ± 0.6	0.695	101.3
40	6	32.6 ± 0.7	12	32.7 ± 0.8	0.819	100.4
44	1	32.9	1	32.7	0.565	99.4
48	0		1	34.3		
52	0		0			
Mean for Weeks						
0-52		28.6 ± 0.3		29.0 ± 0.3		101.4

[a] Mean ± standard error
[b] P value represents pairwise comparison of body weights to control cream group at an equivalent dose of SSL or UV light.

TABLE C6
Mean Body Weights and Survival of Male Mice Administered Retinoic Acid Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		0.001% Retinoic Acid Cream			
Weeks on Study	No. of Survivors	Av. Wt. (g)[a]	No. of Survivors	Av. Wt. (g)	P Value[b]	Wt. (% of controls)
0.00 mJ•CIE/cm^2 SSL						
0	36	30.1 ± 0.5	36	29.5 ± 0.4	0.372	98.0
4	36	32.7 ± 0.5	35	33.1 ± 0.5	0.700	101.1
8	36	34.2 ± 0.6	35	34.5 ± 0.5	0.821	100.8
12	35	35.5 ± 0.6	35	35.6 ± 0.4	0.869	100.1
16	35	36.1 ± 0.6	35	35.8 ± 0.4	0.735	99.1
20	35	36.8 ± 0.6	34	36.3 ± 0.5	0.597	98.6
24	35	36.9 ± 0.6	34	36.6 ± 0.6	0.773	99.2
28	35	37.0 ± 0.6	34	37.1 ± 0.6	0.850	100.3
32	33	37.4 ± 0.6	31	36.6 ± 0.5	0.500	97.9
36	33	37.2 ± 0.7	29	36.4 ± 0.6	0.491	98.0
40	33	37.4 ± 0.7	27	36.1 ± 0.6	0.299	96.6
44	33	37.5 ± 0.7	23	35.1 ± 0.8	0.053	93.4
48	30	38.5 ± 0.8	22	35.3 ± 0.7	0.022*	91.7
52	29	37.4 ± 0.7	20	35.0 ± 0.9	0.069	93.7
Mean for Weeks						
0-52		35.8 ± 0.6		35.0 ± 0.5	0.279	97.7
6.85 mJ•CIE/cm^2 SSL						
0	36	29.0 ± 0.4	36	28.6 ± 0.5	0.471	98.3
4	34	32.8 ± 0.5	36	32.7 ± 0.4	0.979	99.5
8	34	34.7 ± 0.5	36	34.4 ± 0.4	0.806	99.2
12	34	36.1 ± 0.5	36	35.4 ± 0.4	0.344	98.0
16	34	36.7 ± 0.5	36	35.4 ± 0.4	0.048*	96.6
20	34	36.5 ± 0.5	36	36.3 ± 0.5	0.922	99.5
24	34	37.5 ± 0.5	34	37.5 ± 0.5	0.778	100.0
28	32	38.3 ± 0.6	29	37.3 ± 0.5	0.307	97.4
32	30	38.8 ± 0.6	19	37.5 ± 0.7	0.384	96.7
36	23	38.1 ± 0.9	1	37.0	0.326	97.2
40	11	38.3 ± 1.2	0			
44	7	36.7 ± 0.5	0			
48	2	37.1 ± 0.3	0			
52	1	31.9	0			
Mean for Weeks						
0-52		35.2 ± 0.6		34.8 ± 0.3		98.9

TABLE C6
Mean Body Weights and Survival of Male Mice Administered Retinoic Acid Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		0.001% Retinoic Acid Cream			
Weeks on Study	No. of Survivors	Av. Wt. (g)[a]	No. of Survivors	Av. Wt. (g)	P Value[b]	Wt. (% of controls)
13.70 mJ•CIE/cm^2 SSL						
0	35	28.8 ± 0.4	36	29.5 ± 0.4	0.262	102.3
4	35	32.5 ± 0.5	36	32.9 ± 0.4	0.511	101.3
8	35	33.9 ± 0.5	36	34.1 ± 0.5	0.855	100.3
12	35	35.3 ± 0.5	36	35.2 ± 0.4	0.912	99.8
16	35	36.4 ± 0.6	36	36.0 ± 0.5	0.576	98.9
20	35	37.3 ± 0.5	34	36.7 ± 0.6	0.520	98.5
24	34	37.5 ± 0.5	27	37.9 ± 0.6	0.186	101.1
28	27	37.3 ± 0.6	4	38.7 ± 2.3	0.508	103.6
32	22	37.8 ± 0.7	0			
36	6	38.0 ± 1.2	0			
40	0		0			
44	0		0			
48	0		0			
52	0		0			
Mean for Weeks						
0-52		35.0 ± 0.4		34.5 ± 0.4		98.5

* Significant at P≤0.05
[a] Mean ± standard error
[b] P value represents pairwise comparison of body weights to control cream group at an equivalent dose of SSL.

TABLE C7
Mean Body Weights and Survival of Female Mice Administered Retinoic Acid Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		0.001% Retinoic Acid Cream			
Weeks on Study	No. of Survivors	Av. Wt. (g)[a]	No. of Survivors	Av. Wt. (g)	P Value[b]	Wt. (% of controls)
0.00 mJ•CIE/cm^2 SSL						
0	36	24.0 ± 0.3	36	23.6 ± 0.4	0.400	98.2
4	36	26.5 ± 0.3	36	26.3 ± 0.3	0.603	99.1
8	36	27.7 ± 0.3	36	27.3 ± 0.4	0.499	98.8
12	36	28.2 ± 0.4	36	27.9 ± 0.4	0.474	98.7
16	36	28.6 ± 0.3	36	28.3 ± 0.4	0.604	99.0
20	36	29.5 ± 0.4	36	28.6 ± 0.4	0.128	97.0
24	36	29.8 ± 0.3	34	29.6 ± 0.4	0.349	99.2
28	36	30.2 ± 0.4	34	30.1 ± 0.4	0.560	99.7
32	36	30.6 ± 0.4	34	30.8 ± 0.3	0.959	100.6
36	36	30.6 ± 0.4	32	30.8 ± 0.4	0.902	100.7
40	34	31.3 ± 0.4	31	30.9 ± 0.4	0.308	98.8
44	34	31.3 ± 0.4	31	30.8 ± 0.4	0.240	98.5
48	31	31.2 ± 0.4	30	31.0 ± 0.4	0.549	99.3
52	28	31.8 ± 0.5	29	31.4 ± 0.4	0.347	98.7
Mean for Weeks						
0-52		29.3 ± 0.3		28.8 ± 0.4	0.332	98.4
6.85 mJ•CIE/cm^2 SSL						
0	36	23.6 ± 0.3	36	23.9 ± 0.2	0.386	101.3
4	36	26.0 ± 0.3	36	25.9 ± 0.3	0.750	99.5
8	36	26.9 ± 0.3	36	27.3 ± 0.3	0.442	101.2
12	36	28.0 ± 0.3	36	28.6 ± 0.4	0.220	102.1
16	36	29.0 ± 0.3	36	28.5 ± 0.3	0.260	98.3
20	36	29.5 ± 0.3	36	29.6 ± 0.3	0.877	100.2
24	36	30.3 ± 0.3	36	30.7 ± 0.3	0.322	101.4
28	36	30.8 ± 0.3	34	30.5 ± 0.4	0.586	99.2
32	34	30.6 ± 0.4	30	31.3 ± 0.4	0.129	102.3
36	33	31.6 ± 0.4	17	30.9 ± 0.4	0.811	97.8
40	32	31.6 ± 0.4	10	31.4 ± 0.5	0.724	99.4
44	30	31.8 ± 0.4	6	30.9 ± 0.7	0.849	97.3
48	25	32.2 ± 0.5	3	31.9 ± 0.4	0.686	98.9
52	24	32.7 ± 0.7	2	32.3 ± 1.0	0.738	98.6
Mean for Weeks						
0-52		29.3 ± 0.3		28.7 ± 0.3	0.911	97.7

TABLE C7
Mean Body Weights and Survival of Female Mice Administered Retinoic Acid Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		0.001% Retinoic Acid Cream			
Weeks on Study	No. of Survivors	Av. Wt. (g)[a]	No. of Survivors	Av. Wt. (g)	P Value[b]	Wt. (% of controls)
13.70 mJ•CIE/cm^2 SSL						
0	36	23.3 ± 0.3	36	23.6 ± 0.3	0.455	101.4
4	36	25.8 ± 0.3	36	26.0 ± 0.3	0.595	100.9
8	36	27.0 ± 0.3	36	27.1 ± 0.2	0.811	100.4
12	36	28.3 ± 0.4	36	28.1 ± 0.3	0.682	99.3
16	36	29.4 ± 0.4	36	28.5 ± 0.3	0.050*	96.9
20	36	30.5 ± 0.4	36	29.1 ± 0.3	0.006*	95.2
24	36	31.2 ± 0.5	35	30.8 ± 0.3	0.398	98.5
28	36	31.3 ± 0.5	25	31.1 ± 0.4	0.857	99.3
32	33	31.9 ± 0.5	2	32.7 ± 1.8	0.895	102.6
36	25	32.2 ± 0.6	0			
40	7	31.4 ± 0.9	0			
44	5	30.9 ± 1.5	0			
48	0		0			
52	0		0			
Mean for Weeks						
0-52		29.0 ± 0.3		27.9 ± 0.3		96.0
UVA						
0	36	24.1 ± 0.3	36	24.0 ± 0.3	0.923	99.8
4	36	26.2 ± 0.4	36	26.6 ± 0.3	0.492	101.3
8	35	28.5 ± 0.4	36	28.2 ± 0.4	0.505	98.9
12	34	29.3 ± 0.4	36	29.4 ± 0.3	0.730	100.5
16	34	30.0 ± 0.3	35	30.2 ± 0.3	0.644	100.7
20	34	30.3 ± 0.3	35	31.0 ± 0.3	0.178	102.2
24	34	30.3 ± 0.4	35	30.9 ± 0.3	0.305	101.8
28	34	31.0 ± 0.4	34	32.0 ± 0.3	0.071	103.1
32	34	31.3 ± 0.4	32	32.1 ± 0.4	0.177	102.7
36	32	32.3 ± 0.4	32	32.8 ± 0.3	0.373	101.6
40	31	32.3 ± 0.4	32	32.9 ± 0.4	0.478	101.7
44	31	32.0 ± 0.5	30	31.6 ± 0.5	0.665	99.0
48	28	32.6 ± 0.6	29	32.7 ± 0.6	0.921	100.2
52	26	33.4 ± 0.7	27	33.3 ± 0.6	0.944	99.8
Mean for Weeks						
0-52		29.9 ± 0.4		30.2 ± 0.3	0.565	101.3

TABLE C7
Mean Body Weights and Survival of Female Mice Administered Retinoic Acid Cream or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		0.001% Retinoic Acid Cream			
Weeks on Study	No. of Survivors	Av. Wt. (g)[a]	No. of Survivors	Av. Wt. (g)	P Value[b]	Wt. (% of controls)
UVB						
0	36	23.7 ± 0.3	36	23.9 ± 0.3	0.542	101.0
4	36	25.8 ± 0.3	35	26.0 ± 0.4	0.696	100.8
8	35	27.8 ± 0.3	34	27.6 ± 0.3	0.659	99.1
12	35	29.0 ± 0.3	34	28.8 ± 0.3	0.612	99.1
16	35	29.6 ± 0.3	33	29.6 ± 0.3	0.959	100.0
20	35	29.0 ± 0.5	33	30.1 ± 0.3	0.049*	103.9
24	35	29.8 ± 0.4	30	30.2 ± 0.3	0.468	101.4
28	34	31.4 ± 0.3	10	31.4 ± 0.4	0.683	100.0
32	26	32.4 ± 0.4	0			
36	11	31.5 ± 0.7	0			
40	6	32.6 ± 0.7	0			
44	1	32.9	0			
48	0		0			
52	0		0			
Mean for Weeks						
0-52		28.6 ± 0.3		27.9 ± 0.3		97.3

* Significant at P≤0.05
[a] Mean ± standard error
[b] P value represents pairwise comparison of body weights to control cream group at an equivalent dose of SSL or UV light.

TABLE C8
Mean Body Weights and Survival of Male Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream			0.1% Retinyl Palmitate Cream[a]				0.5% Retinyl Palmitate Cream[a]			
Week	No. of Survivors	Av. Wt. (g)[b]	P Value[c]	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
0.00 mJ•CIE/cm^2 SSL											
0	36	30.1 ± 0.5	0.218								
4	36	32.7 ± 0.5	0.007*								
8	36	34.2 ± 0.6	0.194								
12	35	35.5 ± 0.6	0.021*								
16	35	36.1 ± 0.6	0.001*								
20	35	36.8 ± 0.6	0.002*								
24	35	36.9 ± 0.6	0.022*								
28	35	37.0 ± 0.6	0.010*								
32	33	37.4 ± 0.6	0.002*								
36	33	37.2 ± 0.7	0.063								
40	33	37.4 ± 0.7	0.074								
44	33	37.5 ± 0.7	0.073								
48	30	38.5 ± 0.8	0.122								
52	29	37.4 ± 0.7	0.612								
Mean for Weeks											
0-52		35.8 ± 0.6	0.002*								

TABLE C8
Mean Body Weights and Survival of Male Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	1.0% Retinyl Palmitate Cream				2.0% Retinyl Palmitate Cream			
Week	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
0.00 mJ•CIE/cm^2 SSL								
0	36	29.3 ± 0.3	0.194	97.3	36	29.3 ± 0.4	0.218	97.5
4	36	31.9 ± 0.2	0.162	97.5	36	31.2 ± 0.5	0.007*	95.2
8	36	34.1 ± 0.3	0.831	99.6	36	33.4 ± 0.4	0.194	97.6
12	36	34.3 ± 0.3	0.104	96.7	36	33.9 ± 0.4	0.021*	95.5
16	35	34.7 ± 0.3	0.059	96.2	35	33.8 ± 0.4	0.001*	93.8
20	33	34.3 ± 0.5	0.001*	93.4	33	34.6 ± 0.4	0.002*	94.1
24	31	35.5 ± 0.4	0.028*	96.2	31	35.5 ± 0.5	0.022*	96.1
28	29	35.9 ± 0.4	0.102	97.0	30	35.0 ± 0.6	0.010*	94.8
32	26	35.8 ± 0.5	0.025*	95.6	21	34.9 ± 0.7	0.002*	93.3
36	21	35.4 ± 0.7	0.015*	95.1	11	35.9 ± 0.9	0.063	96.4
40	16	36.2 ± 0.8	0.064	96.6	8	35.8 ± 1.0	0.074	95.5
44	11	35.5 ± 1.0	0.045*	94.5	6	36.2 ± 1.0	0.073	96.5
48	9	34.7 ± 1.1	0.007*	90.1	4	36.8 ± 1.0	0.122	95.6
52	8	34.7 ± 1.1	0.082	92.8	3	37.3 ± 1.0	0.612	99.8
Mean for Weeks								
0-52		33.9 ± 0.3	0.002*	94.8		33.4 ± 0.4	0.002*	93.4

TABLE C8
Mean Body Weights and Survival of Male Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream			0.1% Retinyl Palmitate Cream[a]				0.5% Retinyl Palmitate Cream[a]			
Week	No. of Survivors	Av. Wt. (g)[b]	P Value[c]	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
6.85 mJ•CIE/cm^2 SSL											
0	36	29.0 ± 0.4	0.255	36	28.9 ± 0.4	0.798	99.5	36[e]	28.6 ± 0.5	0.408	98.4
4	34	32.8 ± 0.5	0.010*	36	32.6 ± 0.4	0.980	99.4	36[e]	31.9 ± 0.4	0.230	97.3
8	34	34.7 ± 0.5	0.086	36	34.5 ± 0.4	0.906	99.3	35	33.9 ± 0.4	0.199	97.7
12	34	36.1 ± 0.5	0.067	35	35.7 ± 0.6	0.638	98.8	35	35.0 ± 0.4	0.111	96.9
16	34	36.7 ± 0.5	0.135	35	35.9 ± 0.5	0.247	97.9	35	35.4 ± 0.4	0.028*	96.5
20	34	36.5 ± 0.5	0.918	35	36.0 ± 0.5	0.511	98.6	34	34.9 ± 0.5	0.018*	95.6
24	34	37.5 ± 0.5	0.049*	35	37.0 ± 0.5	0.487	98.6	34	36.2 ± 0.4	0.055	96.5
28	32	38.3 ± 0.6	0.010*	33	37.7 ± 0.5	0.481	98.4	32	36.6 ± 0.6	0.028*	95.5
32	30	38.8 ± 0.6	<0.001*	28	38.6 ± 0.6	0.903	99.5	23	37.0 ± 0.6	0.081	95.5
36	23	38.1 ± 0.9		13	39.2 ± 1.0	0.227	102.8	4	37.9 ± 2.2	0.638	99.4
40	11	38.3 ± 1.2		3	37.3 ± 3.0	0.650	97.6	0			
44	7	36.7 ± 0.5		1	41.0	0.002	111.6	0			
48	2	37.1 ± 0.3		0				0			
52	1	31.9		0				0			
Mean for Weeks											
0-52		35.2 ± 0.6			35.1 ± 0.4		99.7		34.0 ± 0.5		96.6

TABLE C8
Mean Body Weights and Survival of Male Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	1.0% Retinyl Palmitate Cream				2.0% Retinyl Palmitate Cream			
Week	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
6.85 mJ•CIE/cm^2 SSL								
0	36	29.5 ± 0.4	0.436	101.5	36	29.4 ± 0.4	0.555	101.2
4	36	32.5 ± 0.4	0.816	99.0	36	31.2 ± 0.4	0.013*	95.0
8	36	34.2 ± 0.4	0.609	98.6	36	33.5 ± 0.4	0.087	96.6
12	36	35.4 ± 0.4	0.440	98.1	36	34.6 ± 0.5	0.048*	95.8
16	36	36.7 ± 0.4	0.849	100.0	35	35.2 ± 0.3	0.020*	95.9
20	36	36.9 ± 0.4	0.445	101.0	32	35.9 ± 0.3	0.426	98.3
24	36	37.4 ± 0.4	0.989	99.7	30	35.8 ± 0.4	0.015*	95.4
28	33	37.2 ± 0.5	0.247	97.1	26	36.1 ± 0.6	0.006*	94.2
32	14	37.4 ± 1.0	0.181	96.3	13	35.0 ± 0.9	<0.001*	90.3
36	0				0			
40	0				0			
44	0				0			
48	0				0			
52	0				0			
Mean for Weeks								
0-52		35.1 ± 0.3		99.5		33.8 ± 0.3		95.9

TABLE C8
Mean Body Weights and Survival of Male Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream			0.1% Retinyl Palmitate Cream[a]				0.5% Retinyl Palmitate Cream[a]			
Week	No. of Survivors	Av. Wt. (g)[b]	P Value[c]	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
13.70 mJ•CIE/cm^2 SSL											
0	35	28.8 ± 0.4	0.408	36	29.0 ± 0.4	0.782	100.5	36	29.0 ± 0.4	0.705	100.6
4	35	32.5 ± 0.5	0.010*	36	32.6 ± 0.3	0.765	100.5	36	33.0 ± 0.4	0.366	101.5
8	35	33.9 ± 0.5	0.009*	36	34.2 ± 0.3	0.711	100.6	36	34.7 ± 0.4	0.198	102.2
12	35	35.3 ± 0.5	0.007*	36	35.2 ± 0.4	0.911	99.8	36	35.8 ± 0.5	0.405	101.5
16	35	36.4 ± 0.6	0.002*	36	36.6 ± 0.4	0.724	100.6	36	36.8 ± 0.4	0.429	101.3
20	35	37.3 ± 0.5	0.011*	35	36.7 ± 0.4	0.394	98.6	36	37.6 ± 0.4	0.535	100.9
24	34	37.5 ± 0.5	<0.001*	30	37.8 ± 0.5	0.505	100.8	30	38.4 ± 0.4	0.162	102.3
28	27	37.3 ± 0.6	0.077	20	37.4 ± 0.5	0.893	100.3	8	37.1 ± 0.7	0.672	99.3
32	22	37.8 ± 0.7		1	36.6	0.703	96.9	0			
36	6	38.0 ± 1.2		0				0			
40	0			0				0			
44	0			0				0			
48	0			0				0			
52	0			0				0			
Mean for Weeks											
0-52		35.0 ± 0.4			34.7 ± 0.3		99.1		35.0 ± 0.4		100.0

TABLE C8
Mean Body Weights and Survival of Male Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	1.0% Retinyl Palmitate Cream				2.0% Retinyl Palmitate Cream			
Week	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
13.70 mJ•CIE/cm^2 SSL								
0	36	29.1 ± 0.3	0.643	100.8	36	28.5 ± 0.3	0.517	98.9
4	35	32.6 ± 0.4	0.759	100.5	36	31.3 ± 0.4	0.039*	96.5
8	35	33.5 ± 0.4	0.494	98.8	36	32.9 ± 0.4	0.070	96.9
12	34	34.8 ± 0.4	0.294	98.6	36	34.0 ± 0.4	0.034*	96.3
16	34	36.2 ± 0.3	0.652	99.6	35	35.0 ± 0.4	0.015*	96.3
20	34	36.9 ± 0.3	0.454	99.1	34	36.0 ± 0.4	0.015*	96.6
24	31	37.1 ± 0.4	0.559	98.9	32	35.9 ± 0.5	0.010*	95.7
28	12	36.2 ± 0.6	0.113	97.2	8	37.5 ± 1.0	0.209	100.6
32	0				0			
36	0				0			
40	0				0			
44	0				0			
48	0				0			
52	0				0			
Mean for Weeks								
0-52		34.1 ± 0.3		97.4		33.3 ± 0.4		95.1

* Significant at P≤0.05
[a] Article not tested at 0.00 mJ•CIE/cm^2 SSL and 0.1% RP cream or 0.5% RP cream
[b] Mean ± standard error
[c] P value represents linear trend test.
[d] P value represents pairwise comparison to control cream at the same exposure to SSL.
[e] Includes one missexed animal

TABLE C9
Mean Body Weights and Survival of Female Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream			0.1% Retinyl Palmitate Cream[a]				0.5% Retinyl Palmitate Cream[a]			
Week	No. of Survivors	Av. Wt. (g)[b]	P Value[c]	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
0.00 mJ•CIE/cm^2 SSL											
0	36	24.0 ± 0.3	0.367								
4	36	26.5 ± 0.3	0.294								
8	36	27.7 ± 0.3	0.171								
12	36	28.2 ± 0.4	0.171								
16	36	28.6 ± 0.3	0.242								
20	36	29.5 ± 0.4	0.014*								
24	36	29.8 ± 0.3	0.559								
28	36	30.2 ± 0.4	0.027*								
32	36	30.6 ± 0.4	0.015*								
36	36	30.6 ± 0.4	0.051								
40	34	31.3 ± 0.4	0.001*								
44	34	31.3 ± 0.4	0.178								
48	31	31.2 ± 0.4	0.190								
52	28	31.8 ± 0.5									
Mean for Weeks											
0-52		29.3 ± 0.3									

TABLE C9
Mean Body Weights and Survival of Female Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	1.0% Retinyl Palmitate Cream				2.0% Retinyl Palmitate Cream			
Week	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
0.00 mJ•CIE/cm^2 SSL								
0	36	23.7 ± 0.3	0.539	98.9	36	23.6 ± 0.3	0.367	98.3
4	36	25.8 ± 0.3	0.152	97.3	36	26.0 ± 0.4	0.294	98.1
8	36	27.2 ± 0.3	0.308	98.3	36	27.0 ± 0.4	0.171	97.7
12	36	27.4 ± 0.3	0.098	97.2	36	27.6 ± 0.3	0.171	97.6
16	34	28.0 ± 0.4	0.175	97.7	33	27.9 ± 0.4	0.242	97.4
20	34	28.7 ± 0.3	0.097	97.3	26	28.1 ± 0.5	0.014*	95.3
24	32	29.2 ± 0.4	0.301	97.8	17	28.9 ± 1.0	0.559	96.9
28	30	29.5 ± 0.4	0.194	97.6	14	28.3 ± 0.6	0.027*	93.8
32	28	29.9 ± 0.4	0.324	97.8	9	28.1 ± 1.1	0.015*	91.9
36	20	30.0 ± 0.5	0.269	98.0	6	29.0 ± 1.1	0.051	94.8
40	14	30.9 ± 0.7	0.382	98.9	4	27.9 ± 1.7	0.001*	89.3
44	11	29.9 ± 0.7	0.076	95.8	1	30.4	0.178	97.3
48	10	29.1 ± 0.9	0.010*	93.1	1	29.6	0.190	94.8
52	9	29.2 ± 1.2	0.010*	91.8	0			
Mean for Weeks								
0-52		27.8 ± 0.3	0.016*	95.1		26.9 ± 0.3		92.1

TABLE C9
Mean Body Weights and Survival of Female Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream			0.1% Retinyl Palmitate Cream[a]				0.5% Retinyl Palmitate Cream[a]			
Week	No. of Survivors	Av. Wt. (g)[b]	P Value[c]	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
6.85 mJ•CIE/cm^2 SSL											
0	36	23.6 ± 0.3	0.470	36	23.5 ± 0.5	0.860	99.6	36	23.2 ± 0.3	0.458	98.5
4	36	26.0 ± 0.3	0.007*	36	26.7 ± 0.3	0.135	102.5	36	25.9 ± 0.3	0.765	99.5
8	36	26.9 ± 0.3	0.003*	36	27.6 ± 0.3	0.154	102.3	36	26.8 ± 0.3	0.768	99.5
12	36	28.0 ± 0.3	0.001*	36	28.7 ± 0.4	0.149	102.5	36	28.0 ± 0.3	0.982	100.0
16	36	29.0 ± 0.3	0.030*	34	29.5 ± 0.4	0.248	101.9	36	28.5 ± 0.3	0.356	98.5
20	36	29.5 ± 0.3	0.256	34	29.4 ± 0.4	0.834	99.7	36	29.1 ± 0.3	0.403	98.6
24	36	30.3 ± 0.3	0.289	33	30.3 ± 0.4	0.949	100.1	35	29.6 ± 0.4	0.203	97.9
28	36	30.8 ± 0.3	0.005*	33	30.9 ± 0.5	0.989	100.2	35	30.0 ± 0.4	0.109	97.3
32	34	30.6 ± 0.4	0.002*	33	31.6 ± 0.5	0.084	103.3	31	30.8 ± 0.4	0.832	100.7
36	33	31.6 ± 0.4	0.009*	26	31.2 ± 0.5	0.912	98.9	16	30.3 ± 0.7	0.104	96.0
40	32	31.6 ± 0.4	0.170	20	32.2 ± 0.6	0.269	102.1	2	30.0 ± 1.9	0.762	94.9
44	30	31.8 ± 0.4	0.042	14	32.1 ± 0.7	0.585	101.1	1	29.3	0.905	92.3
48	25	32.2 ± 0.5		9	31.8 ± 0.9	0.951	98.8	0			
52	24	32.7 ± 0.7		4	32.2 ± 0.8	0.751	98.5	0			
Mean for Weeks											
0-52		29.3 ± 0.3			29.0 ± 0.4	0.338	99.0		28.0 ± 0.3		95.6

TABLE C9
Mean Body Weights and Survival of Female Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	1.0% Retinyl Palmitate Cream				2.0% Retinyl Palmitate Cream			
Week	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
6.85 mJ•CIE/cm^2 SSL								
0	36	23.4 ± 0.3	0.689	99.2	36	23.2 ± 0.3	0.437	98.4
4	36	25.9 ± 0.3	0.693	99.3	36	25.3 ± 0.3	0.090	97.2
8	36	26.9 ± 0.3	0.880	99.8	36	26.0 ± 0.3	0.042*	96.7
12	36	28.1 ± 0.3	0.940	100.1	36	26.9 ± 0.4	0.018*	95.9
16	36	29.2 ± 0.3	0.567	100.9	36	28.2 ± 0.4	0.092	97.3
20	36	29.9 ± 0.3	0.478	101.2	35	28.8 ± 0.5	0.153	97.5
24	35	30.5 ± 0.3	0.609	100.7	32	29.7 ± 0.3	0.187	98.0
28	35	29.9 ± 0.3	0.079	97.0	28	29.5 ± 0.4	0.013*	95.6
32	31	30.3 ± 0.4	0.775	99.2	20	29.4 ± 0.4	0.044*	96.1
36	16	30.1 ± 0.5	0.089	95.2	4	29.3 ± 1.2	0.015*	92.7
40	2	30.2 ± 0.5	0.339	95.7	2	31.4	0.305	99.4
44	1	27.0	0.045*	85.0	1	29.7	0.118	93.5
48	0				0			
52	0				0			
Mean for Weeks								
0-52		28.3 ± 0.3		96.4		28.0 ± 0.3		95.6

TABLE C9
Mean Body Weights and Survival of Female Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream			0.1% Retinyl Palmitate Cream[a]				0.5% Retinyl Palmitate Cream[a]			
Week	No. of Survivors	Av. Wt. (g)[b]	P Value[c]	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
13.70 mJ•CIE/cm^2 SSL											
0	36	23.3 ± 0.3	0.224	36	23.2 ± 0.3	0.880	99.8	35	23.0 ± 0.3	0.388	98.6
4	36	25.8 ± 0.3	0.333	36	25.6 ± 0.3	0.624	99.2	35	25.4 ± 0.3	0.431	98.7
8	36	27.0 ± 0.3	0.132	36	26.5 ± 0.2	0.202	98.2	34	26.7 ± 0.3	0.362	98.9
12	36	28.3 ± 0.4	0.057	36	27.5 ± 0.3	0.102	97.3	34	27.9 ± 0.3	0.397	98.7
16	36	29.4 ± 0.4	0.076	36	28.8 ± 0.3	0.128	97.7	33	29.0 ± 0.3	0.355	98.7
20	36	30.5 ± 0.4	0.146	36	29.7 ± 0.2	0.063	97.1	33	29.8 ± 0.4	0.133	97.7
24	36	31.2 ± 0.5	0.027*	36	30.1 ± 0.3	0.027*	96.3	32	30.5 ± 0.4	0.168	97.8
28	36	31.3 ± 0.5	0.123	35	30.3 ± 0.3	0.091	96.9	27	30.1 ± 0.5	0.045*	96.2
32	33	31.9 ± 0.5	0.100	21	30.4 ± 0.5	0.089	95.3	6	28.8 ± 1.2	0.227	90.4
36	25	32.2 ± 0.6		3	31.9 ± 1.8	0.760	99.2	0			
40	7	31.4 ± 0.9		0				0			
44	5	30.9 ± 1.5		0				0			
48	0			0				0			
52	0			0				0			
Mean for Weeks											
0-52		29.0 ± 0.3			27.9 ± 0.2		96.1		27.6 ± 0.3		95.2

TABLE C9
Mean Body Weights and Survival of Female Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	1.0% Retinyl Palmitate Cream				2.0% Retinyl Palmitate Cream			
Week	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
13.70 mJ•CIE/cm^2 SSL								
0	36	23.2 ± 0.2	0.879	99.8	36	22.8 ± 0.2	0.198	98.0
4	36	25.7 ± 0.3	0.962	99.9	36	25.2 ± 0.2	0.216	98.0
8	36	26.6 ± 0.2	0.402	98.8	35	26.2 ± 0.2	0.051	97.3
12	36	27.7 ± 0.3	0.190	97.9	35	27.2 ± 0.3	0.018*	96.1
16	36	29.1 ± 0.3	0.495	99.0	35	28.4 ± 0.3	0.019*	96.5
20	36	29.7 ± 0.3	0.066	97.2	33	29.6 ± 0.3	0.039*	96.9
24	36	30.1 ± 0.3	0.040*	96.6	29	29.6 ± 0.3	0.004*	94.9
28	24	29.2 ± 0.3	0.015*	93.4	13	30.0 ± 0.6	0.051	95.8
32	1	31.9	0.247	100.1	1	28.5	0.072	89.4
36	0				0			
40	0				0			
44	0				0			
48	0				0			
52	0				0			
Mean for Weeks								
0-52		27.7 ± 0.3		95.3		26.9 ± 0.2		92.8

TABLE C9
Mean Body Weights and Survival of Female Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		1.0% Retinyl Palmitate Cream			
Week	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
UVA						
0	36	24.1 ± 0.3	36	24.0 ± 0.3	0.966	99.9
4	36	26.2 ± 0.4	34	26.2 ± 0.3	0.792	100.1
8	35	28.5 ± 0.4	35	27.7 ± 0.4	0.126	97.1
12	34	29.3 ± 0.4	35	29.4 ± 0.4	0.664	100.5
16	34	30.0 ± 0.3	34	30.3 ± 0.4	0.502	100.8
20	34	30.3 ± 0.3	34	30.7 ± 0.4	0.349	101.3
24	34	30.3 ± 0.4	34	30.7 ± 0.4	0.452	101.1
28	34	31.0 ± 0.4	32	31.8 ± 0.5	0.134	102.6
32	34	31.3 ± 0.4	32	31.7 ± 0.4	0.328	101.5
36	32	32.3 ± 0.4	28	32.2 ± 0.4	0.785	99.6
40	31	32.3 ± 0.4	27	32.6 ± 0.5	0.408	100.9
44	31	32.0 ± 0.5	20	31.9 ± 0.6	0.808	99.7
48	28	32.6 ± 0.6	18	32.1 ± 0.5	0.494	98.4
52	26	33.4 ± 0.7	17	33.7 ± 0.8	0.603	100.8
Mean for Weeks						
0-52		29.9 ± 0.4		29.7 ± 0.4	0.664	99.6

TABLE C9
Mean Body Weights and Survival of Female Mice Administered Retinyl Palmitate Creams or Control Cream and Exposed to 0.00, 6.85, or 13.70 mJ•CIE/cm^2 SSL or UV Light in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Control Cream		1.0% Retinyl Palmitate Cream			
Week	No. of Survivors	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	P Value[d]	Wt. (% of controls)
UVB						
0	36	23.7 ± 0.3	36	23.6 ± 0.2	0.833	99.7
4	36	25.8 ± 0.3	36	26.0 ± 0.3	0.662	100.8
8	35	27.8 ± 0.3	36	27.0 ± 0.2	0.058	97.2
12	35	29.0 ± 0.3	36	28.6 ± 0.3	0.291	98.4
16	35	29.6 ± 0.3	35	29.2 ± 0.3	0.300	98.6
20	35	29.0 ± 0.5	35	29.0 ± 0.3	0.942	100.0
24	35	29.8 ± 0.4	30	29.2 ± 0.3	0.336	98.0
28	34	31.4 ± 0.3	10	30.2 ± 0.8	0.082	96.2
32	26	32.4 ± 0.4	0			
36	11	31.5 ± 0.7	0			
40	6	32.6 ± 0.7	0			
44	1	32.9	0			
48	0		0			
52	0		0			
Mean for Weeks						
0-52		28.6 ± 0.3		27.7 ± 0.3		95.3

* Significant at P≤0.05
[a] Article not tested at 0.00 mJ•CIE/cm^2 SSL and 0.1% RP cream or 0.5% RP cream
[b] Mean ± standard error
[c] P value represents linear trend test.
[d] P value represents pairwise comparison to control cream at the same exposure to SSL or UV light.

APPENDIX D
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Test Articles

All-*trans*-retinoic acid (RA) (lot 072K1606) and all-*trans*-retinyl palmitate (RP) (lot 092K0637) were obtained from Sigma Chemical Company (St. Louis, MO). Identity and purity analyses were conducted by the Chemistry Support Unit of the National Center for Toxicological Research (NCTR, Jefferson, AR). Reports on analyses performed in support of the study on the effect of retinoic acid and retinyl palmitate on the photocarcinogenicity of simulated solar light are on file at the NCTR.

Structural characterization analyses of RA (a yellow to light-orange crystalline powder) and RP (a light yellow to yellow-red semisolid or a clear hazy to hazy golden viscous, oily liquid with a faint odor) were performed using direct exposure probe electron impact-mass spectrometry (DEP/EI-MS) and proton nuclear magnetic resonance (NMR) spectroscopy. The DEP/EI-MS revealed one major component with a base peak ion of *m/z* 300 as RA and one major component with a base peak ion of *m/z* 268 for RP. The RA and RP samples were tentatively identified by electronic comparison to the mass spectra of these compounds available in the National Institute of Standards and Technology (NIST) online spectra library. Proton NMR results for both test articles were consistent with the structures of the chemicals. Representative proton NMR spectra for RA and RP are presented in Figures D1 and D2, respectively.

The purity of lot 072K1606 of RA was determined using reverse phase high-performance liquid chromatography (HPLC) by system A; the purity of lot 092K0637 of RP was determined using reverse phase HPLC by system B and normal phase HPLC by system C (Table D1). Reverse phase purity estimates of approximately 99% and 97% were obtained for RA and RP, respectively. Normal phase analysis of RP determined an average content of approximately 88% all-*trans*, 9% 13-*cis*, and 1% 9-*cis* isomers.

To ensure stability, bulk RA was stored at –80° C in sealed amber glass vials in the original cardboard shipping container. Bulk RP was stored at 4° ± 2° C in sealed clear or amber glass vials in the original cardboard shipping container. At the end of the study, HPLC analyses of the bulk chemicals using system A (RA) or B (RP) were performed by the Chemistry Support Unit at the NCTR, and no degradation of either test chemical was detected.

Diisopropyl adipate (lot 01200070941), used as a solvent for the incorporation of RA and RP into the control cream, was obtained from International Specialty Products, Inc. (Texas City, TX). The diisopropyl adipate (a clear free-flowing liquid) was characterized using proton NMR spectroscopy, gas chromatography electron impact (GC/EI) analysis, and gas chromatography/mass spectrometry (GC/MS). Proton NMR results for the chemical were consistent with the structure of diisopropyl adipate. GC/EI analysis revealed one major component with a base peak ion of *m/z* 129 and the samples were tentatively identified by electron comparison to the mass spectrum of the *bis*(1-methylethyl) ester of hexanedioic acid in the NIST online spectra library. Lot 01200070941 was estimated to be 99.7% pure by GC/MS. To ensure stability, bulk diisopropyl adipate was stored at room temperature in its original container (a 7-gallon plastic pail) in a locked cabinet.

Base Cream

The base cream used for the control cream and dose cream formulations in this 1-year study was purchased from Cosmetech Laboratories, Inc. (Fairfield, NJ), in one lot (formulation CLI 1392901). The base cream had a pH of approximately 6.8 (range 6.75 to 6.91), a specific gravity of approximately 98% (range 97.2% to 99.0%), and a mean viscosity of 2,250 centipoise (range 2,100 cP to 2,400 cP). The base cream was formulated by the supplier to account for 85% (w/w) of the final cream formulations (Table 1), and it was stored in the original containers (high-density polypropylene pails) in a walk-in cold room at approximately 4° C.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

A contract support group (Bionetics Corporation, Jefferson, AR) located at the NCTR prepared the control cream, master batch creams, and dose creams used in this study. All creams were constituted on a weight:weight basis (Table D2).

Control Cream

The control cream was prepared twice weekly and was composed of the base cream, which accounted for 85% of the final control cream formulation, and diisopropyl adipate, which accounted for the remaining 15% of the final control cream formulation.

Master Batch Creams

Twice weekly, the Chemistry Support Unit at the NCTR prepared a 0.6667 mg/g solution of RA dissolved in diisopropyl adipate. A RA (0.01%) master batch cream was subsequently prepared twice weekly and was composed of the base cream (85%) and the 0.6667 mg/g RA solution (15%), previously prepared by the Chemistry Support Unit.

A RP (2.0%) master batch cream was prepared twice weekly and was composed of the base cream (85%), with RP (2.0%) and diisopropyl adipate (13%) accounting for the remaining 15%. The 2.0% RP master batch cream served as the high dose RP dose cream in the study and as the source of RP for the 0.1%, 0.5%, and 1.0% RP dose creams.

Retinoic Acid and Retinyl Palmitate Dose Creams

Dose creams of RA (0.001%) and RP (0.1%, 0.5%, and 1.0%) were prepared twice weekly by mixing the appropriate amount of control cream with the master batch cream of either RA or RP. Aliquots of the 2.0% RP master batch cream were used for the 2.0% RP dose cream.

In order to protect the test chemicals from degradation, cream formulations were shielded from ultraviolet light and mixed with Teflon®-coated impellers and spatulas. The dose formulations were dispensed under an argon stream into 20 mL amber-colored glass vials with Teflon®-lined screw-caps and stored at approximately 4° C for up to 3 days. Each vial contained sufficient control or dose cream for a single day of topical applications. The glass vials of the prepared creams were delivered to the NTP-FDA Center for Phototoxicology at the NCTR and stored at approximately 4° C until application to the mice.

Homogeneity and stability studies of the 0.001% RA dose cream were performed by the Chemistry Support Unit at the NCTR using HPLC by system A (Table D1), and homogeneity studies of the 0.1% RP dose cream were conducted at the same facility using HPLC by system B. Homogeneity was confirmed, and stability was confirmed for at least 7 days for dose creams stored under argon gas in amber glass vials sealed with Teflon®-lined screw caps at approximately 4° C.

Dose certification of the RA and RP dose creams were conducted approximately weekly by the Chemistry Support Unit at the NCTR using HPLC by systems A and B, respectively. The conditions of use of the test chemicals in this study dictated that dose creams be administered to the mice prior to completion of dose certification analyses. Therefore, while an acceptability range of ± 10% of target concentration was desirable, the goal of the dose certifications was to enable calculation of the dose that was administered to an animal at a specific point in time. The mean (over the 1-year study) percent target ± standard deviation for RA in the 0.001% RA dose cream was 89.4 ± 11.8% (Table D3); the corresponding results for RP in the 0.1%, 0.5%, 1.0%, and 2.0% RP dose creams were 102.2 ± 7.3%, 107.5 ± 10.5%, 100.3 ± 11.5%, and 100.3 ± 10.4%, respectively (Table D4).

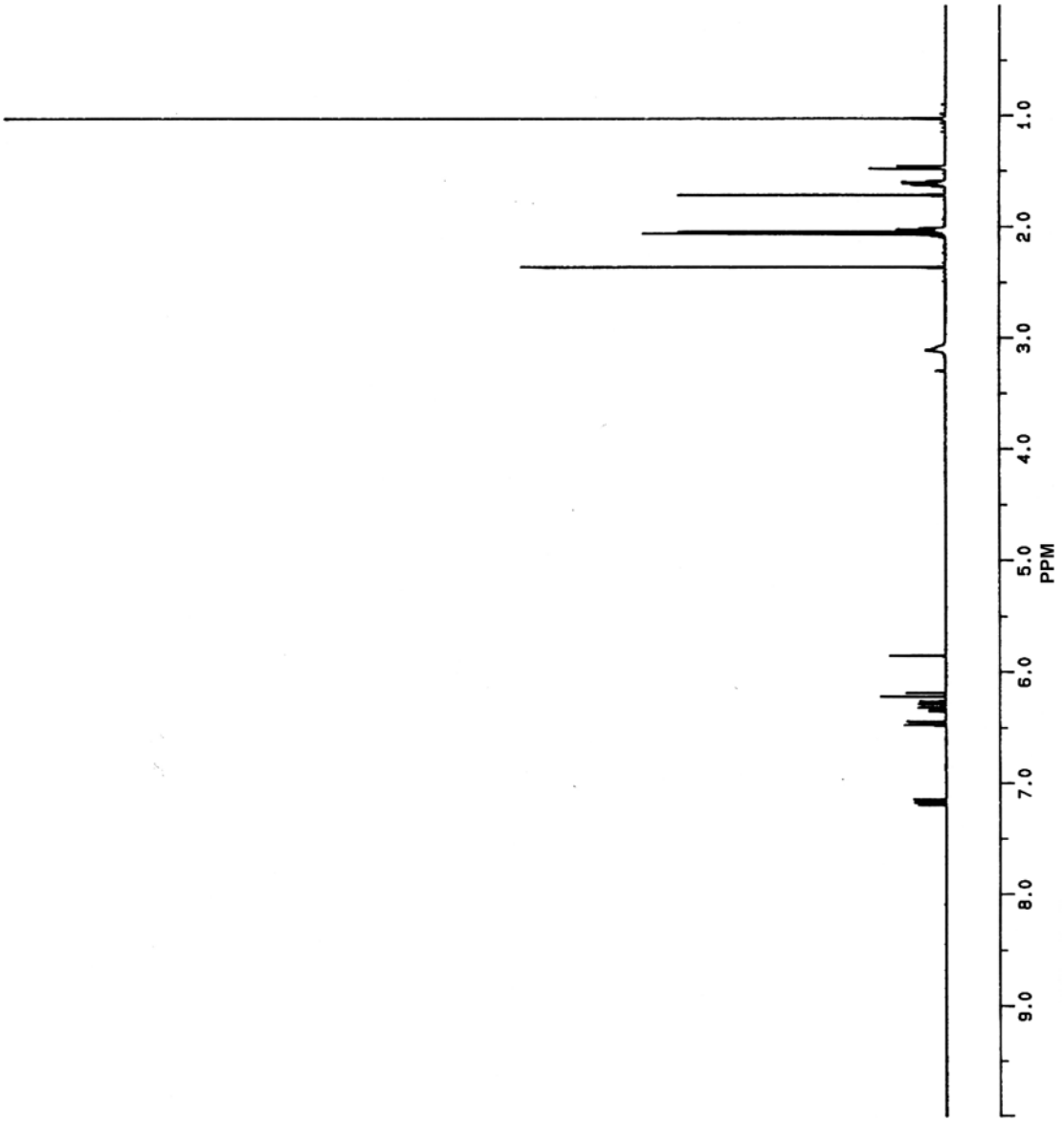

FIGURE D1
Proton Nuclear Magnetic Resonance Spectrum of Retinoic Acid

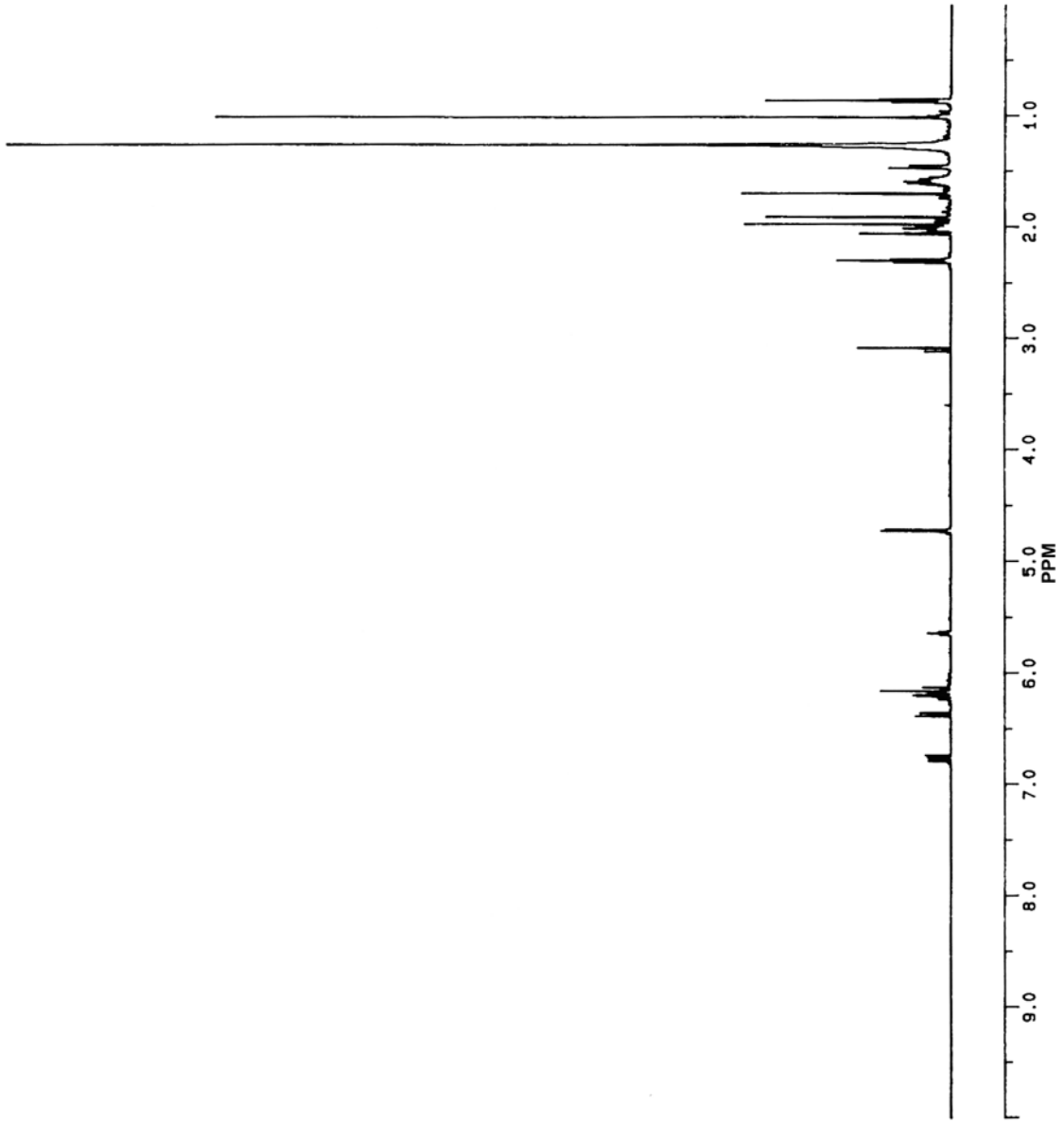

FIGURE D2
Proton Nuclear Magnetic Resonance Spectrum of Retinyl Palmitate

TABLE D1
High-Performance Liquid Chromatography Systems Used in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate[a]

Detection System	Column	Solvent System
System A Ultraviolet photodiode array with monitoring at 330 nm	Prodigy™ ODS(3), 250 mm × 4.6 mm, 5µm (Phenomenex, Torrence, CA)	Methanol:20 mM ammonium acetate:methylene chloride (80:10:10), isocratic; flow rate 1.5 mL/minute
System B Ultraviolet photodiode array with monitoring at 330 nm	Prodigy™ ODS(3), 250 mm × 4.6 mm, 5µm (Phenomenex)	Methanol: methylene chloride (85:15), isocratic; flow rate 1.5 mL/minute
System C Ultraviolet photodiode array with monitoring at 330 nm	Supelcosil®, 250 mm × 4.6 mm, 5µm (Supelco, Bellefonte, PA)	Hexanes:methylene chloride:acetic acid (80:20:0.02), isocratic; flow rate 1.0 mL/minute

[a] The high-performance liquid chromatographs were manufactured by Waters Corporation (Milford, MA).

TABLE D2
Preparation and Storage of Dose Formulations in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Preparation
Control Cream
Samples of the base cream and diisopropyl adipate were warmed to room temperature and aliquotted under ultraviolet-filtered room lighting. Appropriate quantities of each ingredient were weighed, combined, and mixed for 5 minutes under an argon atmosphere using Teflon®-coated spatulas and a mechanical stirrer (IKA® Eurostar, Wilmington, NC) equipped with a Teflon®-coated impeller. The control cream was prepared twice weekly and was composed of 85% base cream and 15% diisopropyl adipate.

Master Batch Creams
A 0.6667 mg/g (0.067%) stock solution of retinoic acid dissolved in diisopropyl adipate was prepared twice weekly. An aliquot of the stock solution was then weighed, combined, and mixed as described for the control cream to prepare the retinoic acid master batch cream. The retinoic acid (0.01%) master batch cream was prepared twice weekly and was composed of 85% base cream and 15% retinoic acid stock solution.

Samples of base cream, retinyl palmitate, and diisopropyl adipate were warmed to room temperature and then weighed, combined, and mixed as described for the control cream. The retinyl palmitate (2.0%) master batch cream was prepared twice weekly and was composed of 85% base cream, 2% retinyl palmitate, and 13% diisopropyl adipate.

Retinoic Acid and Retinyl Palmitate Dose Creams
The 0.001% retinoic acid dose cream and 0.1%, 0.5%, and 1.0% retinyl palmitate dose creams were prepared twice weekly by mixing the appropriate weights of control and master batch creams of retinoic acid or retinyl palmitate to achieve the desired concentration of test article in the cream formulations; mixing procedures for these dose creams were the same as those described for the control cream. The 2.0% retinyl palmitate master batch cream was directly aliquotted for use as the 2.0% retinyl palmitate dose cream.

Chemical Lot Numbers
072K1606 (retinoic acid)
092K0637 (retinyl palmitate)
01200070941 (diisopropyl adipate)

Formulation Number
CLI 1392901 (base cream)

Maximum Storage Time
3 days

Storage Conditions
Stored in 20 mL amber-colored glass vials with Teflon®-lined screw-caps under argon gas at approximately 4° C

Study Laboratory
National Center for Toxicological Research (Jefferson, AR)

TABLE D3
Results of Analyses of Retinoic Acid Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Date Received	Date Reported	Target Concentration (%)	Determined Concentration[a] (%)	Difference from Target (%)
June 13, 2003	June 23, 2003	0.001	0.00092 ± 0.00008	–8
June 23, 2003	July 21, 2003	0.001	0.00071 ± 0.00006	–29
July 3, 2003	July 30, 2003	0.001	0.0007 ± 0.0000	–30
July 10, 2003	July 30, 2003	0.001	0.0009 ± 0.0000	–10
July 17, 2003	July 30, 2003	0.001	0.0008 ± 0.0000	–20
July 21, 2003	August 6, 2003	0.001	0.0009 ± 0.0000	–10
July 28, 2003	August 11, 2003	0.001	0.0009 ± 0.0000	–10
August 4, 2003	August 11, 2003	0.001	0.0008 ± 0.0000	–20
August 14, 2003	August 22, 2003	0.001	0.0009 ± 0.0000	–10
August 18, 2003	August 22, 2003	0.001	0.00096 ± 0.00003	–4
August 25, 2003	September 5, 2003	0.001	0.0009 ± 0.0000	–10
September 2, 2003	September 8, 2003	0.001	0.0009 ± 0.0000	–10
September 8, 2003	September 19, 2003	0.001	0.0008 ± 0.0000	–20
September 18, 2003	October 7, 2003	0.001	0.0010 ± 0.0000	0
September 25, 2003	October 15, 2003	0.001	0.0010 ± 0.0000	0
October 2, 2003	October 28, 2003	0.001	0.0008 ± 0.0000	–20
October 6, 2003	November 7, 2003	0.001	0.0008 ± 0.0000	–20
October 14, 2003	November 10, 2003	0.001	0.0009 ± 0.0001	–10
October 20, 2003	November 10, 2003	0.001	0.0009 ± 0.0000	–10
October 27, 2003	November 25, 2003	0.001	0.0009 ± 0.0000	–10
November 6, 2003	December 1, 2003	0.001	0.0011 ± 0.0001	+10
November 10, 2003	December 1, 2003	0.001	0.0010 ± 0.0000	+103
November 18, 2003	December 2, 2003	0.001	0.0009 ± 0.0000	–10
November 24, 2003	December 8, 2003	0.001	0.0010 ± 0.0000	0
December 4, 2003	December 12, 2003	0.001	0.0010 ± 0.0000	0
December 11, 2003	December 15, 2003	0.001	0.0009 ± 0.0000	–10

TABLE D3
Results of Analyses of Retinoic Acid Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Date Received	Date Reported	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
December 18, 2003	January 7, 2004	0.001	0.0008 ± 0.0000	–20
December 24, 2003	January 26, 2004	0.001	0.0010 ± 0.0000	0
December 29, 2003	January 26, 2004	0.001	0.0007 ± 0.0000	–30
January 5, 2004	January 27, 2004	0.001	0.0006 ± 0.0000	–40
January 15, 2004	February 27, 2004	0.001	0.0009 ± 0.0000	–10
January 20, 2004	February 27, 2004	0.001	0.0011 ± 0.0001	+10
January 26, 2004	March 1, 2004	0.001	0.0006 ± 0.0000	–40
February 2, 2004	March 1, 2004	0.001	0.0009 ± 0.0000	–10
February 9, 2004	March 4, 2004	0.001	0.0012 ± 0.0000	+20
February 17, 2004	April 13, 2004	0.001	0.0010 ± 0.0000	0
February 23, 2004	May 4, 2004	0.001	0.0009 ± 0.0000	–10
March 4, 2004	May 18, 2004	0.001	0.0008 ± 0.0000	–20
March 11, 2004	June 14, 2004	0.001	0.0011 ± 0.0000	+10
March 18, 2004	June 14, 2004	0.001	0.0010 ± 0.0000	0
March 22, 2004	June 15, 2004	0.001	0.0012 ± 0.0000	+20
March 29, 2004	June 15, 2004	0.001	0.0010 ± 0.0001	0
April 5, 2004	June 16, 2004	0.001	0.0010 ± 0.0000	0
April 15, 2004	July 9, 2004	0.001	0.0004 ± 0.0000	–60
April 19, 2004	July 9, 2004	0.001	0.0008 ± 0.0000	–20
April 26, 2004	July 9, 2004	0.001	0.0007 ± 0.0000	–30
May 6, 2004	July 9, 2004	0.001	0.0010 ± 0.0000	0
May 13, 2004	July 9, 2004	0.001	0.0011 ± 0.0000	+10

[a] Results of triplicate analyses (mean ± standard deviation)

TABLE D4
Results of Analyses of Retinyl Palmitate Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Date Received	Date Reported	Target Concentration (%)	Determined Concentration[a] (%)	Difference from Target (%)
June 13, 2003	June 23, 2003	0.1	0.110 ± 0.004	+10
June 23, 2003	July 21,2003	1.0	1.01 ± 0.04	+1
		2.0	1.92 ± 0.06	–4
June 26, 2003	July 30, 2003	0.1	0.105 ± 0.003	+5
		0.5	0.498 ± 0.032	0
June 30, 2003	July 30, 2003	0.1	0.100 ± 0.005	0
		0.5	0.512 ± 0.011	+2
		1.0	1.01 ± 0.02	+1
July 3, 2003	July 30, 2003	2.0	2.06 ± 0.20	+3
July 7, 2003	July 30, 2003	1.0	0.771 ± 0.064	–23
		2.0	1.72 ± 0.02	–14
July 10, 2003	July 30, 2003	0.1	0.0926 ± 0.0011	–7
		0.5	0.454 ± 0.005	–9
July 14, 2003	August 5, 2003	0.1	0.0955 ± 0.0007	–5
		0.5	0.493 ± 0.030	–1
		2.0	1.78 ± 0.15	–11
July 17, 2003	July 30, 2003	1.0	0.939 ± 0.048	–6
July 21, 2003	August 6, 2003	0.1	0.0995 ± 0.0026	–1
July 24, 2003	December 4, 2003	0.5	0.624 ± 0.015	+25
		1.0	1.01 ± 0.04	+1
		2.0	1.80 ± 0.04	–10
July 28, 2003	August 11, 2003	0.5	0.612 ± 0.013	+22
July 31, 2003	August 11, 2003	0.1	0.102 ± 0.001	+2
		1.0	0.982 ± 0.047	–2
		2.0	2.12 ± 0.19	+6
August 4, 2003	August 11, 2003	0.1	0.0902 ± 0.0012	–10
		2.0	1.97 ± 0.13	–2
August 7, 2003	August 22, 2003	0.5	0.437 ± 0.002	–13
		1.0	0.874 ± 0.025	–13
August 11, 2003	August 22, 2003	0.1	0.102 ± 0.001	+2
		2.0	1.98 ± 0.06	–1
August 14, 2003	August 22, 2003	0.5	0.486 ± 0.005	–3
		1.0	0.931 ± 0.022	–7
August 18, 2003	August 22, 2003	0.1	0.102 ± 0.002	+2

TABLE D4
Results of Analyses of Retinyl Palmitate Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Date Received	Date Reported	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
August 21, 2003	August 25, 2003	0.5	0.444 ± 0.010	–11
		1.0	0.989 ± 0.011	–1
		2.0	1.81 ± 0.07	–10
August 25, 2003	September 5, 2003	0.1	0.0994 ± 0.0007	–1
		1.0	0.979 ± 0.052	–2
August 29, 2003	September 8, 2003	0.5	0.505 ± 0.006	+1
		2.0	1.56 ± 0.10	–22
September 2, 2003	September 8, 2003	0.1	0.0978 ± 0.0012	–2
		0.5	0.476 ± 0.018	–5
		1.0	0.960 ± 0.010	–4
		2.0	1.85 ± 0.00	–8
September 8, 2003	September 19, 2003	1.0	1.15 ± 0.02	+15
		2.0	2.24 ± 0.03	+12
September 11, 2003	October 1, 2003	0.1	0.0990 ± 0.0008	–1
		0.5	0.495 ± 0.002	–1
September 15, 2003	October 1, 2003	0.1	0.0984 ± 0.0021	–2
		0.5	0.494 ± 0.004	–1
		1.0	0.988 ± 0.023	–1
September 18, 2003	October 7, 2003	2.0	1.92 ± 0.03	–4
September 22, 2003	October 7, 2003	1.0	1.06 ± 0.04	+6
		2.0	2.05 ± 0.12	+3
September 25, 2003	October 15, 2003	0.1	0.109 ± 0.002	+9
		0.5	0.524 ± 0.010	+5
September 29, 2003	October 28, 2003	0.1	0.0940 ± 0.0020	–6
		0.5	0.472 ± 0.021	–6
		2.0	1.94 ± 0.11	–3
October 2, 2003	October 28, 2003	1.0	0.784 ± 0.032	–22
October 6, 2003	November 7, 2003	0.1	0.0842 ± 0.0021	–16
October 10, 2003	November 10, 2003	0.5	0.431 ± 0.010	–14
		1.0	0.870 ± 0.015	–13
		2.0	1.52 ± 0.08	–24
October 14, 2003	November 10, 2003	0.1	0.0690 ± 0.0003	–31
		0.5	0.437 ± 0.009	–13
		1.0	0.529 ± 0.021	–47
		1.0	0.385 ± 0.019	–62
		2.0	1.50 ± 0.02	–25

TABLE D4
Results of Analyses of Retinyl Palmitate Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Date Received	Date Reported	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
October 20, 2003	November 10, 2003	0.5	0.411 ± 0.010	–18
October 23, 2003	November 24, 2003	0.1	0.0804 ± 0.0013	–20
		1.0	0.766 ± 0.006	–23
		2.0	1.46 ± 0.01	–27
October 27, 2003	November 25, 2003	0.1	0.104 ± 0.002	+4
		2.0	1.97 ± 0.02	–2
October 30, 2003	November 26, 2003	0.5	0.507 ± 0.028	+1
		1.0	1.01 ± 0.02	+1
November 3, 2003	November 25, 2003	0.1	0.104 ± 0.002	+4
		2.0	1.42 ± 0.06	–29
November 6, 2003	December 1, 2003	0.5	0.549 ± 0.024	+10
		1.0	1.07 ± 0.02	+7
November 10, 2003	December 1, 2003	0.5	0.586 ± 0.063	+17
		2.0	1.90 ± 0.05	–5
November 13, 2003	December 1, 2003	0.1	0.108 ± 0.004	+8
		1.0	1.01 ± 0.19	+1
November 18, 2003	December 2, 2003	0.1	0.115 ± 0.002	+15
		1.0	1.11 ± 0.00	+11
November 20, 2003	December 4, 2003	0.5	0.655 ± 0.027	+31
		2.0	2.05 ± 0.08	+3
November 24, 2003	December 8, 2003	1.0	1.17 ± 0.05	+17
		2.0	2.38 ± 0.03	+19
November 26, 2003	December 9, 2003	0.1	0.117 ± 0.003	+17
		0.5	0.555 ± 0.021	+11
December 1, 2003	December 9, 2003	0.1	0.114 ± 0.001	+14
		0.5	0.573 ± 0.020	+15
		1.0	1.05 ± 0.052	+5
December 4, 2003	December 12, 2003	2.0	2.15 ± 0.04	+8
December 8, 2003	December 12, 2003	1.0	1.09 ± 0.02	+9
		2.0	2.48 ± 0.03	+24
December 11, 2003	December 15, 2003	0.1	0.117 ± 0.001	+17
		0.5	0.589 ± 0.020	+18
December 15, 2003	January 6, 2004	0.1	0.0934 ± 0.0049	–7
		0.5	0.514 ± 0.007	+3
		2.0	2.06 ± 0.13	+3

TABLE D4
Results of Analyses of Retinyl Palmitate Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Date Received	Date Reported	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
December 18, 2003	January 7, 2004	1.0	1.15 ± 0.02	+15
December 22, 2003	January 14, 2004	0.5	0.538 ± 0.009	+8
		1.0	1.04 ± 0.02	+4
		2.0	1.98 ± 0.02	–1
December 24, 2003	January 26, 2004	0.1	0.100 ± 0.002	0
December 29, 2003	January 26, 2004	0.5	0.492 ± 0.011	–2
December 31, 2003	January 27, 2004	0.1	0.105 ± 0.003	+5
		1.0	1.09 ± 0.01	+9
		2.0	1.91 ± 0.08	–5
January 5, 2004	January 27, 2004	0.1	0.114 ± 0.006	+14
		2.0	2.01 ± 0.05	+1
January 8, 2004	January 28, 2004	0.5	0.624 ± 0.002	+25
		1.0	1.06 ± 0.09	+6
January 12, 2004	January 28, 2004	0.1	0.109 ± 0.001	+9
		2.0	2.56 ± 0.19	+28
January 15, 2004	February 27, 2004	0.5	0.628 ± 0.034	+26
		1.0	1.04 ± 0.05	+4
January 20, 2004	February 27, 2004	0.1	0.104 ± 0.002	+4
January 26, 2004	March 1, 2004	0.5	0.585 ± 0.053	+17
		2.0	2.17 ± 0.0018	+9
January 29, 2004	March 1, 2004	0.1	0.100 ± 0.001	0
		1.0	1.21 ± 0.02	+21
February 2, 2004	March 1, 2004	0.1	0.0705 ± 0.0016	–30
		1.0	1.35 ± 0.07	+35
February 5, 2004	March 1, 2004	0.5	0.535 ± 0.095	+7
		2.0	1.88 ± 0.32	–6
February 9, 2004	March 4, 2004	0.1	0.107 ± 0.002	+7
		1.0	0.851 ± 0.004	–15
February 13, 2004	April 2, 2004	0.5	0.609 ± 0.039	+22
		2.0	2.41 ± 0.09	+21
February 17, 2004	April 13, 2004	0.1	0.105 ± 0.002	+5
February 23, 2004	May 4, 2004	1.0	1.04 ± 0.06	+4
		2.0	2.62 ± 0.03	+31

TABLE D4
Results of Analyses of Retinyl Palmitate Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Date Received	Date Reported	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
February 26, 2004	May 4, 2004	0.1	0.105 ± 0.000	+5
		0.5	0.588 ± 0.036	+18
March 1, 2004	May 18, 2004	0.1	0.111 ± 0.010	+11
		0.5	0.547 ± 0.015	+9
		1.0	1.26 ± 0.09	+26
March 4, 2004	May 18, 2004	2.0	2.04 ± 0.10	+2
March 8, 2004	May 18, 2004	1.0	0.964 ± 0.051	–4
		2.0	2.10 ± 0.08	+5
March 11, 2004	June 14, 2004	0.1	0.106 ± 0.003	+6
		0.5	0.552 ± 0.029	+10
March 15, 2004	June 14, 2004	0.1	0.105 ± 0.001	+5
		0.5	0.605 ± 0.022	+21
		2.0	2.23 ± 0.09	+12
March 18, 2004	June 14, 2004	1.0	1.07 ± 0.06	+7
March 22, 2004	June 15, 2004	0.1	0.108 ± 0.003	+8
March 25, 2004	June 15, 2004	0.5	0.518 ± 0.002	+4
		1.0	1.11 ± 0.05	+11
		2.0	2.14 ± 0.05	+7
March 29, 2004	June 15, 2004	0.5	0.664 ± 0.018	+33
		2.0	1.81 ± 0.14	–10
April 1, 2004	June 16, 2004	0.1	0.106 ± 0.004	+6
		1.0	1.28 ± 0.10	+28
		2.0	1.88 ± 0.18	–6
April 5, 2004	June 16, 2004	0.1	0.107 ± 0.000	+7
		2.0	1.89 ± 0.15	–6
April 8, 2004	June 16, 2004	0.5	0.450 ± 0.035	–10
		1.0	0.943 ± 0.085	–6
April 12, 2004	July 19, 2004	0.1	0.120 ± 0.002	+20
		2.0	2.65 ± 0.11	+33
April 15, 2004	July 9, 2004	0.5	0.635 ± 0.059	+27
		1.0	0.934 ± 0.019	–7
April 19, 2004	July 9, 2004	0.5	0.560 ± 0.024	+12
		2.0	2.10 ± 0.20	+5
April 22, 2004	July 9, 2004	0.1	0.109 ± 0.001	+9
		1.0	1.13 ± 0.09	+13
April 26, 2004	July 9, 2004	0.1	0.103 ± 0.000	+3
		1.0	1.05 ± 0.05	+5

TABLE D4
Results of Analyses of Retinyl Palmitate Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Date Received	Date Reported	Target Concentration (%)	Determined Concentration (%)	Difference from Target (%)
April 29, 2004	July 9, 2004	0.5	0.540 ± 0.007	+8
		2.0	2.01 ± 0.05	+1
May 3, 2004	July 9, 2004	0.1	0.104 ± 0.002	+4
		0.5	0.524 ± 0.009	+5
		1.0	0.900 ± 0.018	–10
May 6, 2004	July 9, 2004	2.0	2.02 ± 0.03	+1
May 10, 2004	July 9, 2004	1.0	1.03 ± 0.08	+3
		2.0	2.30 ± 0.03	+15
May 13, 2004	July 9, 2004	0.1	0.101 ± 0.000	+1
		0.5	0.556 ± 0.007	+11

[a] Results of triplicate analyses (mean ± standard deviation)

APPENDIX E
SPECTRAL IRRADIANCE
OF SIMULATED SOLAR LIGHT, UVA, AND UVB

SPECTRAL IRRADIANCE OF SIMULATED SOLAR LIGHT, UVA, AND UVB

METHODS

Simulated solar light (SSL) was created by filtering the output from 6.5 kilowatt (kW) xenon arc lamps (Atlas Electric, Spokane, WA) through 1 mm thick SCHOTT WG320 glass filters (SCHOTT North America, Inc., Elmsford, NY); two xenon arc lamps (SSL-1 and SSL-2) were used during the 1-year study. Ultraviolet-A (UVA) and UVB light was created using either portable 0.25 inch plate glass filtered fluorescent UVA lamps, or Kodacel-filtered fluorescent UVB lamps. At generally weekly intervals during the 1-year study, irradiance of the filtered light was measured 2 meters from the SSL light sources using a calibrated Optronics OL-754 spectroradiometer (Optronics Laboratories, Inc., Orlando, FL). Similar techniques were used to measure the irradiance of the UVA and UVB light sources except that the animal racks were positioned at a distance from the UVA and UVB lamps to achieve exposure rates approximately 1.5 to 1.8 $\mu J/cm^2$ per second for UVA or 20 to 50 $\mu J \bullet CIE/cm^2$ for UVB, and the spectroradiometric measurements were recorded at these same distances from the light sources. Excel® was used to calculate the mean and standard error of the irradiance measurements at each wavelength from 250 to 450 nm (n=46, 43, 36, and 38 for the SSL-1, SSL-2, UVA, and UVB light sources, respectively; expressed in W/cm^2 per nm units). The relative standard error for each wavelength was determined by dividing each standard error by the corresponding mean and multiplying by 100.

The average weighted irradiance and weighted standard error at each wavelength (expressed in $W \bullet CIE/cm^2$ per nm units) were determined by multiplying the average irradiance and standard error by the appropriate weighting value (S_{er}) published by the Commission Internationale de l'Éclairage (CIE) that reflects the intrinsic effectiveness of the wavelength to induce erythema (CIE, 1999). Light between 250 and 298 nm is the most effective at inducing erythema and is accordingly assigned a weighting value of 1. For the spectral range of 250 to 450 nm, the values of S_{er} derived from the human erythema action spectrum are defined as:

S_{er} Value	Wavelength (nm)
1	250 to 298
$10^{0.094 (298-wavelength)}$	299 to 328
$10^{0.015 (140-wavelength)}$	329 to 400
0	401 to 450

RESULTS

Average irradiance and average weighted irradiance values for SSL-1 are presented in Table E1, and they are graphically represented in Figures E1A (semilogarithmic scale) and E1B (linear scale), respectively. Similar data for SSL-2 are presented in Table E2 and Figures E2A and E2B, for UVA in Table E3 and Figures E3A and E3B, and for UVB in Table E4 and Figures E4A and E4B.

The spectral output for all the light sources was quite consistent over the course of the study. As shown in Tables E1 through E4, the relative standard error of the mean irradiance values during the study were highest at the low end of the spectrum, between 250 and 260 nm, and lowest at the upper wavelengths of the spectrum, between 400 and 450 nm. For the two SSL sources, the largest contribution of the spectrum of the light sources to the weighted irradiance is from light emitted between 295 and 320 nm (Figures E1B and E2B). For the filtered fluorescent UV light sources, the largest contribution of the spectrum of the light sources to the weighted irradiance is from light emitted between 325 and 375 nm for UVA and between 290 and 320 nm for UVB (Figures E3B and E4B).

TABLE E1
Irradiance and Weighted Irradiance for Light Source SSL-1 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate[a]

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance[b] (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
250	6.05E-09 ± 1.78954E-10	2.957802684	1	6.05E-09 ± 1.79E-10
251	6.44E-09 ± 1.81402E-10	2.817214575	1	6.44E-09 ± 1.81E-10
252	6.81E-09 ± 1.90869E-10	2.802691016	1	6.81E-09 ± 1.91E-10
253	7.17E-09 ± 1.97053E-10	2.750120585	1	7.17E-09 ± 1.97E-10
254	7.55E-09 ± 2.08413E-10	2.761905544	1	7.55E-09 ± 2.08E-10
255	7.92E-09 ± 2.13702E-10	2.697838737	1	7.92E-09 ± 2.14E-10
256	8.30E-09 ± 2.19731E-10	2.648007418	1	8.30E-09 ± 2.20E-10
257	8.63E-09 ± 2.24148E-10	2.598528493	1	8.63E-09 ± 2.24E-10
258	8.93E-09 ± 2.21503E-10	2.481150649	1	8.93E-09 ± 2.22E-10
259	9.27E-09 ± 2.27286E-10	2.451793764	1	9.27E-09 ± 2.27E-10
260	9.62E-09 ± 2.4035E-10	2.499375507	1	9.62E-09 ± 2.40E-10
261	1.00E-08 ± 2.43078E-10	2.431906545	1	1.00E-08 ± 2.43E-10
262	1.03E-08 ± 2.41837E-10	2.359130659	1	1.03E-08 ± 2.42E-10
263	1.05E-08 ± 2.47438E-10	2.34909735	1	1.05E-08 ± 2.47E-10
264	1.09E-08 ± 2.49232E-10	2.29035325	1	1.09E-08 ± 2.49E-10
265	1.12E-08 ± 2.53725E-10	2.269405233	1	1.12E-08 ± 2.54E-10
266	1.15E-08 ± 2.47195E-10	2.155615452	1	1.15E-08 ± 2.47E-10
267	1.18E-08 ± 2.56072E-10	2.170366831	1	1.18E-08 ± 2.56E-10
268	1.21E-08 ± 2.5869E-10	2.138945493	1	1.21E-08 ± 2.59E-10
269	1.24E-08 ± 2.64894E-10	2.140834882	1	1.24E-08 ± 2.65E-10
270	1.27E-08 ± 2.60885E-10	2.051809806	1	1.27E-08 ± 2.61E-10
271	1.32E-08 ± 2.62064E-10	1.988960428	1	1.32E-08 ± 2.62E-10
272	1.35E-08 ± 2.70449E-10	2.003943243	1	1.35E-08 ± 2.70E-10
273	1.37E-08 ± 2.70135E-10	1.974491996	1	1.37E-08 ± 2.70E-10
274	1.40E-08 ± 2.67396E-10	1.912297701	1	1.40E-08 ± 2.67E-10
275	1.43E-08 ± 2.67872E-10	1.875983822	1	1.43E-08 ± 2.68E-10
276	1.46E-08 ± 2.7258E-10	1.865789129	1	1.46E-08 ± 2.73E-10
277	1.49E-08 ± 2.68804E-10	1.800260863	1	1.49E-08 ± 2.69E-10
278	1.53E-08 ± 2.7935E-10	1.821728374	1	1.53E-08 ± 2.79E-10
279	1.57E-08 ± 2.79607E-10	1.779170947	1	1.57E-08 ± 2.80E-10
280	1.61E-08 ± 2.82412E-10	1.755317517	1	1.61E-08 ± 2.82E-10
281	1.64E-08 ± 2.78703E-10	1.698177561	1	1.64E-08 ± 2.79E-10
282	1.67E-08 ± 2.83131E-10	1.694236921	1	1.67E-08 ± 2.83E-10
283	1.71E-08 ± 2.85024E-10	1.668678677	1	1.71E-08 ± 2.85E-10
284	1.74E-08 ± 2.90574E-10	1.668921217	1	1.74E-08 ± 2.91E-10
285	1.78E-08 ± 2.90377E-10	1.631644982	1	1.78E-08 ± 2.90E-10
286	1.82E-08 ± 2.9745E-10	1.63084227	1	1.82E-08 ± 2.97E-10
287	1.87E-08 ± 3.03589E-10	1.627503915	1	1.87E-08 ± 3.04E-10
288	1.90E-08 ± 3.03295E-10	1.595215699	1	1.90E-08 ± 3.03E-10
289	1.94E-08 ± 3.10103E-10	1.601414947	1	1.94E-08 ± 3.10E-10
290	2.01E-08 ± 4.37748E-10	2.178508763	1	2.01E-08 ± 4.38E-10
291	2.16E-08 ± 4.47265E-10	2.067383313	1	2.16E-08 ± 4.47E-10
292	2.27E-08 ± 4.63367E-10	2.041076352	1	2.27E-08 ± 4.63E-10
293	2.57E-08 ± 5.3047E-10	2.06455804	1	2.57E-08 ± 5.30E-10
294	3.07E-08 ± 6.80598E-10	2.216236852	1	3.07E-08 ± 6.81E-10
295	3.89E-08 ± 9.22851E-10	2.373236054	1	3.89E-08 ± 9.23E-10
296	5.28E-08 ± 1.37891E-09	2.613780832	1	5.28E-08 ± 1.38E-09
297	7.30E-08 ± 1.87562E-09	2.569629017	1	7.30E-08 ± 1.88E-09

TABLE E1
Irradiance and Weighted Irradiance for Light Source SSL-1 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
298	1.02E-07 ± 2.65409E-09	2.593048462	1	1.02E-07 ± 2.65E-09
299	1.42E-07 ± 3.64216E-09	2.563081657	0.8053784	1.14E-07 ± 2.93E-09
300	1.92E-07 ± 4.71346E-09	2.460482396	0.6486344	1.24E-07 ± 3.06E-09
301	2.54E-07 ± 6.03179E-09	2.371058473	0.5223962	1.33E-07 ± 3.15E-09
302	3.27E-07 ± 7.33166E-09	2.243734282	0.4207266	1.37E-07 ± 3.08E-09
303	4.14E-07 ± 8.8195E-09	2.130157544	0.3388442	1.40E-07 ± 2.99E-09
304	5.09E-07 ± 1.0252E-08	2.014023501	0.2728978	1.39E-07 ± 2.80E-09
305	6.11E-07 ± 1.15995E-08	1.899981121	0.219786	1.34E-07 ± 2.55E-09
306	7.14E-07 ± 1.24701E-08	1.747358759	0.1770109	1.26E-07 ± 2.21E-09
307	8.26E-07 ± 1.57332E-08	1.905655661	0.1425608	1.18E-07 ± 2.24E-09
308	9.32E-07 ± 1.8133E-08	1.945564991	0.1148154	1.07E-07 ± 2.08E-09
309	1.06E-06 ± 1.91737E-08	1.809672747	0.0924698	9.80E-08 ± 1.77E-09
310	1.18E-06 ± 2.1043E-08	1.783880066	0.0744732	8.78E-08 ± 1.57E-09
311	1.32E-06 ± 2.21938E-08	1.68549374	0.0599791	7.90E-08 ± 1.33E-09
312	1.45E-06 ± 2.33987E-08	1.609553924	0.0483059	7.02E-08 ± 1.13E-09
313	1.56E-06 ± 2.4899E-08	1.592054161	0.0389045	6.08E-08 ± 9.69E-10
314	1.65E-06 ± 2.56395E-08	1.550387647	0.0313329	5.18E-08 ± 8.03E-10
315	1.75E-06 ± 2.71817E-08	1.553962056	0.0252348	4.41E-08 ± 6.86E-10
316	1.85E-06 ± 2.79639E-08	1.513413753	0.0203236	3.76E-08 ± 5.68E-10
317	1.94E-06 ± 2.89485E-08	1.494323826	0.0163682	3.17E-08 ± 4.74E-10
318	2.02E-06 ± 2.97597E-08	1.470281119	0.0131826	2.67E-08 ± 3.92E-10
319	2.11E-06 ± 3.08872E-08	1.464389533	0.010617	2.24E-08 ± 3.28E-10
320	2.20E-06 ± 3.19153E-08	1.453295457	0.0085507	1.88E-08 ± 2.73E-10
321	2.28E-06 ± 3.28334E-08	1.441799057	0.0068865	1.57E-08 ± 2.26E-10
322	2.38E-06 ± 3.39402E-08	1.425841297	0.0055463	1.32E-08 ± 1.88E-10
323	2.45E-06 ± 3.47296E-08	1.419262479	0.0044668	1.09E-08 ± 1.55E-10
324	2.48E-06 ± 3.5526E-08	1.430296642	0.0035975	8.94E-09 ± 1.28E-10
325	2.53E-06 ± 3.60971E-08	1.427147381	0.0028973	7.33E-09 ± 1.05E-10
326	2.58E-06 ± 3.65869E-08	1.418027079	0.0023335	6.02E-09 ± 8.54E-11
327	2.64E-06 ± 3.67875E-08	1.390950359	0.0018793	4.97E-09 ± 6.91E-11
328	2.69E-06 ± 3.77964E-08	1.404359689	0.0015136	4.07E-09 ± 5.72E-11
329	2.75E-06 ± 3.82757E-08	1.394185511	0.0014622	4.01E-09 ± 5.60E-11
330	2.79E-06 ± 3.89028E-08	1.392077373	0.0014125	3.95E-09 ± 5.50E-11
331	2.84E-06 ± 3.91534E-08	1.377465659	0.0013646	3.88E-09 ± 5.34E-11
332	2.89E-06 ± 3.92305E-08	1.357847021	0.0013183	3.81E-09 ± 5.17E-11
333	2.94E-06 ± 3.97013E-08	1.352144924	0.0012735	3.74E-09 ± 5.06E-11
334	2.98E-06 ± 4.00699E-08	1.345708949	0.0012303	3.66E-09 ± 4.93E-11
335	3.02E-06 ± 4.00005E-08	1.324892732	0.0011885	3.59E-09 ± 4.75E-11
336	3.06E-06 ± 4.04866E-08	1.322020542	0.0011482	3.52E-09 ± 4.65E-11
337	3.11E-06 ± 4.09649E-08	1.319012931	0.0011092	3.44E-09 ± 4.54E-11
338	3.15E-06 ± 4.11145E-08	1.306473948	0.0010715	3.37E-09 ± 4.41E-11
339	3.18E-06 ± 4.14324E-08	1.300862627	0.0010351	3.30E-09 ± 4.29E-11
340	3.22E-06 ± 4.12498E-08	1.28093844	0.001	3.22E-09 ± 4.12E-11
341	3.26E-06 ± 4.18833E-08	1.284016007	0.0009661	3.15E-09 ± 4.05E-11
342	3.30E-06 ± 4.19682E-08	1.272181126	0.0009333	3.08E-09 ± 3.92E-11
343	3.33E-06 ± 4.20342E-08	1.261831891	0.0009016	3.00E-09 ± 3.79E-11
344	3.37E-06 ± 4.22954E-08	1.253985447	0.000871	2.94E-09 ± 3.68E-11
345	3.48E-06 ± 1.81282E-08	0.520686448	0.0008414	2.93E-09 ± 1.53E-11

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Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
346	3.52E-06 ± 1.78625E-08	0.507803194	0.0008128	2.86E-09 ± 1.45E-11
347	3.55E-06 ± 1.77121E-08	0.498856008	0.0007852	2.79E-09 ± 1.39E-11
348	3.58E-06 ± 1.72228E-08	0.4807813	0.0007586	2.72E-09 ± 1.31E-11
349	3.61E-06 ± 1.73477E-08	0.47999039	0.0007328	2.65E-09 ± 1.27E-11
350	3.65E-06 ± 1.74317E-08	0.477869194	0.0007079	2.58E-09 ± 1.23E-11
351	3.68E-06 ± 1.71164E-08	0.46513656	0.0006839	2.52E-09 ± 1.17E-11
352	3.71E-06 ± 1.74087E-08	0.469208133	0.0006607	2.45E-09 ± 1.15E-11
353	3.74E-06 ± 1.74016E-08	0.465601907	0.0006383	2.39E-09 ± 1.11E-11
354	3.77E-06 ± 1.71607E-08	0.455659165	0.0006166	2.32E-09 ± 1.06E-11
355	3.80E-06 ± 1.73143E-08	0.456137288	0.0005957	2.26E-09 ± 1.03E-11
356	3.82E-06 ± 1.70289E-08	0.445685929	0.0005754	2.20E-09 ± 9.80E-12
357	3.84E-06 ± 1.71811E-08	0.447351142	0.0005559	2.14E-09 ± 9.55E-12
358	3.86E-06 ± 1.72497E-08	0.446742551	0.000537	2.07E-09 ± 9.26E-12
359	3.88E-06 ± 1.71629E-08	0.442164931	0.0005188	2.01E-09 ± 8.90E-12
360	3.92E-06 ± 1.68883E-08	0.431327441	0.0005012	1.96E-09 ± 8.46E-12
361	3.95E-06 ± 1.68357E-08	0.425751099	0.0004842	1.91E-09 ± 8.15E-12
362	3.97E-06 ± 1.72121E-08	0.433255601	0.0004677	1.86E-09 ± 8.05E-12
363	3.98E-06 ± 1.71611E-08	0.430745466	0.0004519	1.80E-09 ± 7.76E-12
364	4.01E-06 ± 1.70803E-08	0.425498619	0.0004365	1.75E-09 ± 7.46E-12
365	4.05E-06 ± 1.70721E-08	0.421635983	0.0004217	1.71E-09 ± 7.20E-12
366	4.09E-06 ± 1.72684E-08	0.422064024	0.0004074	1.67E-09 ± 7.04E-12
367	4.14E-06 ± 1.7469E-08	0.421760596	0.0003936	1.63E-09 ± 6.88E-12
368	4.19E-06 ± 1.75928E-08	0.419541167	0.0003802	1.59E-09 ± 6.69E-12
369	4.25E-06 ± 1.79798E-08	0.423090163	0.0003673	1.56E-09 ± 6.60E-12
370	4.28E-06 ± 1.76065E-08	0.411832156	0.0003548	1.52E-09 ± 6.25E-12
371	4.24E-06 ± 1.6983E-08	0.400931529	0.0003428	1.45E-09 ± 5.82E-12
372	4.20E-06 ± 1.71327E-08	0.407979501	0.0003311	1.39E-09 ± 5.67E-12
373	4.19E-06 ± 1.69365E-08	0.404171201	0.0003199	1.34E-09 ± 5.42E-12
374	4.21E-06 ± 1.69963E-08	0.404093437	0.000309	1.30E-09 ± 5.25E-12
375	4.23E-06 ± 1.71756E-08	0.406102863	0.0002985	1.26E-09 ± 5.13E-12
376	4.27E-06 ± 1.74049E-08	0.408063608	0.0002884	1.23E-09 ± 5.02E-12
377	4.30E-06 ± 1.73566E-08	0.403585785	0.0002786	1.20E-09 ± 4.84E-12
378	4.36E-06 ± 1.76266E-08	0.404507404	0.0002692	1.17E-09 ± 4.75E-12
379	4.43E-06 ± 1.80083E-08	0.406458052	0.00026	1.15E-09 ± 4.68E-12
380	4.53E-06 ± 1.79541E-08	0.396608468	0.0002512	1.14E-09 ± 4.51E-12
381	4.54E-06 ± 1.80506E-08	0.397598739	0.0002427	1.10E-09 ± 4.38E-12
382	4.51E-06 ± 1.78262E-08	0.395652928	0.0002344	1.06E-09 ± 4.18E-12
383	4.47E-06 ± 1.77091E-08	0.396409417	0.0002265	1.01E-09 ± 4.01E-12
384	4.44E-06 ± 1.75066E-08	0.393995202	0.0002188	9.72E-10 ± 3.83E-12
385	4.43E-06 ± 1.76188E-08	0.39742705	0.0002113	9.37E-10 ± 3.72E-12
386	4.44E-06 ± 1.73109E-08	0.390267016	0.0002042	9.06E-10 ± 3.53E-12
387	4.44E-06 ± 1.79013E-08	0.403120517	0.0001972	8.76E-10 ± 3.53E-12
388	4.49E-06 ± 1.79954E-08	0.400628802	0.0001905	8.56E-10 ± 3.43E-12
389	4.61E-06 ± 1.88294E-08	0.408878016	0.0001841	8.48E-10 ± 3.47E-12
390	4.72E-06 ± 1.89861E-08	0.402283199	0.0001778	8.39E-10 ± 3.38E-12
391	4.74E-06 ± 1.88012E-08	0.396917817	0.0001718	8.14E-10 ± 3.23E-12
392	4.77E-06 ± 1.94828E-08	0.408765331	0.000166	7.91E-10 ± 3.23E-12
393	4.87E-06 ± 1.94835E-08	0.399771802	0.0001603	7.81E-10 ± 3.12E-12

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Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
394	5.04E-06 ± 2.06164E-08	0.408895916	0.0001549	7.81E-10 ± 3.19E-12
395	5.53E-06 ± 2.38134E-08	0.430987268	0.0001496	8.27E-10 ± 3.56E-12
396	5.75E-06 ± 2.28216E-08	0.397052178	0.0001445	8.31E-10 ± 3.30E-12
397	5.82E-06 ± 2.36688E-08	0.406601724	0.0001396	8.13E-10 ± 3.30E-12
398	5.57E-06 ± 2.26924E-08	0.4075992	0.0001349	7.51E-10 ± 3.06E-12
399	5.14E-06 ± 2.05987E-08	0.400886483	0.0001303	6.70E-10 ± 2.68E-12
400	4.94E-06 ± 1.96132E-08	0.397073049	0.0001259	6.22E-10 ± 2.47E-12
401	4.89E-06 ± 1.92892E-08	0.394695338	0	—[c]
402	4.88E-06 ± 1.97015E-08	0.403952373	0	—
403	4.89E-06 ± 1.94441E-08	0.397248723	0	—
404	4.93E-06 ± 1.96805E-08	0.399559275	0	—
405	4.99E-06 ± 2.00841E-08	0.402340139	0	—
406	5.02E-06 ± 2.02745E-08	0.404222406	0	—
407	5.10E-06 ± 2.10017E-08	0.411727988	0	—
408	5.38E-06 ± 2.22801E-08	0.414320526	0	—
409	5.33E-06 ± 2.16975E-08	0.407450108	0	—
410	5.22E-06 ± 2.12174E-08	0.406795264	0	—
411	5.37E-06 ± 2.23278E-08	0.4157436	0	—
412	5.59E-06 ± 2.27456E-08	0.406689759	0	—
413	5.37E-06 ± 2.12387E-08	0.39561191	0	—
414	5.21E-06 ± 2.11326E-08	0.40556264	0	—
415	5.17E-06 ± 2.06885E-08	0.400138578	0	—
416	5.17E-06 ± 2.07218E-08	0.400762159	0	—
417	5.19E-06 ± 2.12126E-08	0.408853832	0	—
418	5.26E-06 ± 2.12589E-08	0.403895124	0	—
419	5.74E-06 ± 2.5708E-08	0.447561097	0	—
420	5.80E-06 ± 2.34285E-08	0.404212473	0	—
421	5.43E-06 ± 2.24001E-08	0.41257837	0	—
422	5.31E-06 ± 2.17633E-08	0.410119092	0	—
423	5.30E-06 ± 2.11957E-08	0.399796561	0	—
424	5.34E-06 ± 2.13804E-08	0.400204433	0	—
425	5.34E-06 ± 2.16786E-08	0.40602832	0	—
426	5.32E-06 ± 2.20064E-08	0.413281124	0	—
427	5.32E-06 ± 2.13946E-08	0.401970611	0	—
428	5.32E-06 ± 2.19607E-08	0.412791823	0	—
429	5.32E-06 ± 2.14616E-08	0.40363929	0	—
430	5.32E-06 ± 2.16974E-08	0.407610505	0	—
431	5.34E-06 ± 2.15309E-08	0.403525557	0	—
432	5.35E-06 ± 2.17976E-08	0.407185937	0	—
433	5.38E-06 ± 2.23536E-08	0.415444915	0	—
434	5.41E-06 ± 2.23733E-08	0.413746377	0	—
435	5.45E-06 ± 2.24213E-08	0.411618075	0	—
436	5.53E-06 ± 2.27146E-08	0.410576049	0	—
437	5.72E-06 ± 2.42166E-08	0.423406203	0	—
438	6.01E-06 ± 2.5476E-08	0.424068999	0	—
439	5.95E-06 ± 2.52947E-08	0.425095081	0	—
440	5.59E-06 ± 2.31393E-08	0.413841829	0	—
441	5.67E-06 ± 2.41144E-08	0.425126007	0	—

TABLE E1
Irradiance and Weighted Irradiance for Light Source SSL-1 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
442	5.76E-06 ± 2.40531E-08	0.4178634	0	—
443	5.64E-06 ± 2.37508E-08	0.421120836	0	—
444	5.60E-06 ± 2.34247E-08	0.418312385	0	—
445	5.62E-06 ± 2.35562E-08	0.418893594	0	—
446	5.57E-06 ± 2.34664E-08	0.420966486	0	—
447	5.56E-06 ± 2.31908E-08	0.417105713	0	—
448	5.61E-06 ± 2.33931E-08	0.417066871	0	—
449	5.97E-06 ± 2.70929E-08	0.453680338	0	—
450	8.63E-06 ± 4.566E-08	0.528922583	0	—

[a] Irradiance and weighted irradiance values are presented as mean ± standard error for 46 measurements at each wavelength; W=watts; S_{er}=CIE human erythema action spectrum weighting function (CIE, 1999); weighted irradiance=irradiance • S_{er}.
[b] Determined by dividing each irradiance standard error by the corresponding mean and multiplying by 100.
[c] Not applicable; S_{er}=0

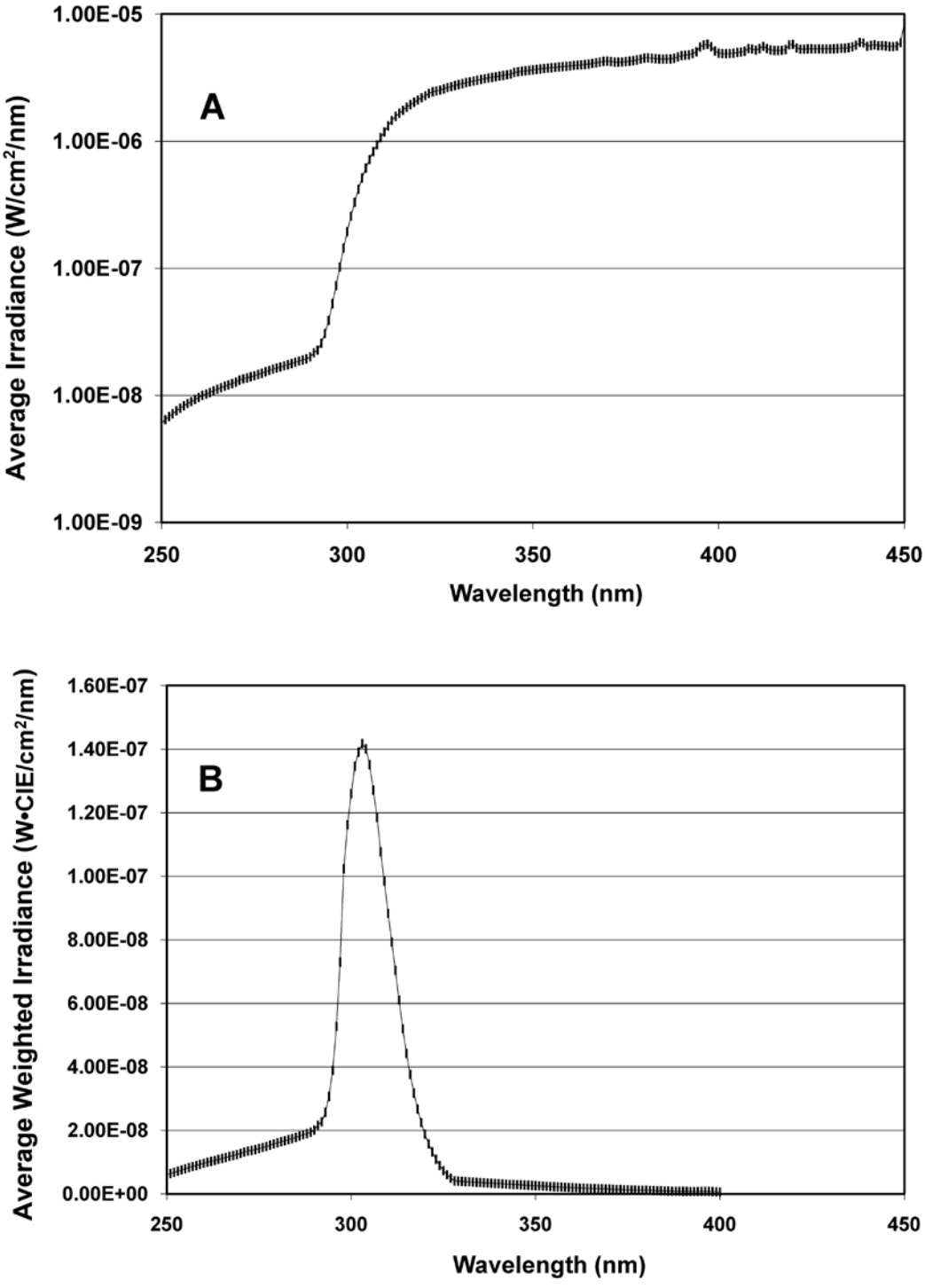


FIGURE E1
Average Irradiance (A) and Average Weighted Irradiance (B) for Light Source SSL-1 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
Average ± standard error (n=46 at each wavelength); W=watts; irradiance was weighted by application of the CIE human erythema action spectrum weighting function (CIE, 1999).

TABLE E2
Irradiance and Weighted Irradiance for Light Source SSL-2 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate[a]

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance[b] (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
250	6.18E-09 ± 1.85416E-10	2.998043657	1	6.18E-09 ± 1.85E-10
251	6.51E-09 ± 2.00432E-10	3.07689934	1	6.51E-09 ± 2.00E-10
252	6.86E-09 ± 2.02379E-10	2.951237425	1	6.86E-09 ± 2.02E-10
253	7.20E-09 ± 2.06761E-10	2.871474775	1	7.20E-09 ± 2.07E-10
254	7.51E-09 ± 2.14397E-10	2.855690485	1	7.51E-09 ± 2.14E-10
255	7.85E-09 ± 2.13354E-10	2.71742661	1	7.85E-09 ± 2.13E-10
256	8.15E-09 ± 2.16331E-10	2.654601295	1	8.15E-09 ± 2.16E-10
257	8.46E-09 ± 2.1699E-10	2.56506912	1	8.46E-09 ± 2.17E-10
258	8.74E-09 ± 2.27937E-10	2.607265065	1	8.74E-09 ± 2.28E-10
259	9.03E-09 ± 2.26168E-10	2.50479313	1	9.03E-09 ± 2.26E-10
260	9.37E-09 ± 2.38669E-10	2.547736306	1	9.37E-09 ± 2.39E-10
261	9.69E-09 ± 2.40767E-10	2.484215206	1	9.69E-09 ± 2.41E-10
262	9.94E-09 ± 2.46143E-10	2.476476449	1	9.94E-09 ± 2.46E-10
263	1.02E-08 ± 2.50154E-10	2.454163941	1	1.02E-08 ± 2.50E-10
264	1.04E-08 ± 2.4414E-10	2.337899016	1	1.04E-08 ± 2.44E-10
265	1.07E-08 ± 2.5333E-10	2.371535674	1	1.07E-08 ± 2.53E-10
266	1.10E-08 ± 2.50695E-10	2.272125288	1	1.10E-08 ± 2.51E-10
267	1.13E-08 ± 2.5153E-10	2.231305333	1	1.13E-08 ± 2.52E-10
268	1.15E-08 ± 2.52075E-10	2.196616328	1	1.15E-08 ± 2.52E-10
269	1.18E-08 ± 2.61734E-10	2.222816803	1	1.18E-08 ± 2.62E-10
270	1.21E-08 ± 2.64652E-10	2.186036475	1	1.21E-08 ± 2.65E-10
271	1.25E-08 ± 2.67844E-10	2.140260197	1	1.25E-08 ± 2.68E-10
272	1.28E-08 ± 2.70385E-10	2.110145911	1	1.28E-08 ± 2.70E-10
273	1.30E-08 ± 2.69471E-10	2.071291009	1	1.30E-08 ± 2.69E-10
274	1.33E-08 ± 2.76951E-10	2.089548492	1	1.33E-08 ± 2.77E-10
275	1.35E-08 ± 2.74672E-10	2.032978468	1	1.35E-08 ± 2.75E-10
276	1.38E-08 ± 2.69323E-10	1.951019878	1	1.38E-08 ± 2.69E-10
277	1.41E-08 ± 2.76035E-10	1.951504732	1	1.41E-08 ± 2.76E-10
278	1.45E-08 ± 2.8111E-10	1.944507865	1	1.45E-08 ± 2.81E-10
279	1.48E-08 ± 2.75219E-10	1.856535363	1	1.48E-08 ± 2.75E-10
280	1.52E-08 ± 2.89035E-10	1.896589625	1	1.52E-08 ± 2.89E-10
281	1.55E-08 ± 2.92611E-10	1.8878346	1	1.55E-08 ± 2.93E-10
282	1.58E-08 ± 2.84934E-10	1.804649868	1	1.58E-08 ± 2.85E-10
283	1.61E-08 ± 2.96785E-10	1.839363652	1	1.61E-08 ± 2.97E-10
284	1.64E-08 ± 3.00649E-10	1.831557083	1	1.64E-08 ± 3.01E-10
285	1.68E-08 ± 3.01802E-10	1.792685709	1	1.68E-08 ± 3.02E-10
286	1.72E-08 ± 3.02981E-10	1.761932124	1	1.72E-08 ± 3.03E-10
287	1.76E-08 ± 3.05586E-10	1.734437059	1	1.76E-08 ± 3.06E-10
288	1.80E-08 ± 3.06823E-10	1.706847089	1	1.80E-08 ± 3.07E-10
289	1.83E-08 ± 3.17219E-10	1.736452617	1	1.83E-08 ± 3.17E-10
290	2.00E-08 ± 3.82545E-10	1.912335049	1	2.00E-08 ± 3.83E-10
291	2.13E-08 ± 3.69071E-10	1.729728351	1	2.13E-08 ± 3.69E-10
292	2.24E-08 ± 3.88192E-10	1.729803104	1	2.24E-08 ± 3.88E-10
293	2.50E-08 ± 4.07839E-10	1.630261309	1	2.50E-08 ± 4.08E-10
294	2.97E-08 ± 4.28247E-10	1.439901507	1	2.97E-08 ± 4.28E-10
295	3.79E-08 ± 5.06765E-10	1.336701594	1	3.79E-08 ± 5.07E-10
296	5.13E-08 ± 6.82331E-10	1.330175909	1	5.13E-08 ± 6.82E-10

TABLE E2
Irradiance and Weighted Irradiance for Light Source SSL-2 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
297	7.14E-08 ± 9.76715E-10	1.36840197	1	7.14E-08 ± 9.77E-10
298	1.00E-07 ± 1.31729E-09	1.310899216	1	1.00E-07 ± 1.32E-09
299	1.39E-07 ± 1.65307E-09	1.190547497	0.8053784	1.12E-07 ± 1.33E-09
300	1.88E-07 ± 2.16406E-09	1.152792426	0.6486344	1.22E-07 ± 1.40E-09
301	2.49E-07 ± 2.74953E-09	1.105165572	0.5223962	1.30E-07 ± 1.44E-09
302	3.20E-07 ± 3.30375E-09	1.032401877	0.4207266	1.35E-07 ± 1.39E-09
303	4.05E-07 ± 3.7287E-09	0.91998379	0.3388442	1.37E-07 ± 1.26E-09
304	4.98E-07 ± 4.39939E-09	0.882945642	0.2728978	1.36E-07 ± 1.20E-09
305	5.99E-07 ± 4.7913E-09	0.799286126	0.219786	1.32E-07 ± 1.05E-09
306	7.01E-07 ± 5.05879E-09	0.721446067	0.1770109	1.24E-07 ± 8.95E-10
307	8.03E-07 ± 5.04158E-09	0.627463501	0.1425608	1.15E-07 ± 7.19E-10
308	9.13E-07 ± 7.7911E-09	0.853210727	0.1148154	1.05E-07 ± 8.95E-10
309	1.04E-06 ± 9.06026E-09	0.869625962	0.0924698	9.63E-08 ± 8.38E-10
310	1.15E-06 ± 1.0349E-08	0.896616979	0.0744732	8.60E-08 ± 7.71E-10
311	1.28E-06 ± 1.05188E-08	0.819355042	0.0599791	7.70E-08 ± 6.31E-10
312	1.42E-06 ± 8.6762E-09	0.609855219	0.0483059	6.87E-08 ± 4.19E-10
313	1.53E-06 ± 9.14587E-09	0.597258299	0.0389045	5.96E-08 ± 3.56E-10
314	1.62E-06 ± 1.01441E-08	0.625660567	0.0313329	5.08E-08 ± 3.18E-10
315	1.71E-06 ± 1.0588E-08	0.61841312	0.0252348	4.32E-08 ± 2.67E-10
316	1.81E-06 ± 1.07122E-08	0.592500552	0.0203236	3.67E-08 ± 2.18E-10
317	1.90E-06 ± 1.10005E-08	0.58028945	0.0163682	3.10E-08 ± 1.80E-10
318	1.98E-06 ± 1.18863E-08	0.599209233	0.0131826	2.61E-08 ± 1.57E-10
319	2.07E-06 ± 1.14603E-08	0.554586899	0.010617	2.19E-08 ± 1.22E-10
320	2.15E-06 ± 1.14887E-08	0.534573801	0.0085507	1.84E-08 ± 9.82E-11
321	2.23E-06 ± 1.2143E-08	0.54446793	0.0068865	1.54E-08 ± 8.36E-11
322	2.33E-06 ± 1.17265E-08	0.503339665	0.0055463	1.29E-08 ± 6.50E-11
323	2.40E-06 ± 1.24696E-08	0.519812732	0.0044668	1.07E-08 ± 5.57E-11
324	2.43E-06 ± 1.24132E-08	0.510199974	0.0035975	8.75E-09 ± 4.47E-11
325	2.48E-06 ± 1.27114E-08	0.512851037	0.0028973	7.18E-09 ± 3.68E-11
326	2.53E-06 ± 1.31722E-08	0.520353801	0.0023335	5.91E-09 ± 3.07E-11
327	2.59E-06 ± 1.34649E-08	0.519742806	0.0018793	4.87E-09 ± 2.53E-11
328	2.64E-06 ± 1.35416E-08	0.512236149	0.0015136	4.00E-09 ± 2.05E-11
329	2.69E-06 ± 1.34006E-08	0.49824591	0.0014622	3.93E-09 ± 1.96E-11
330	2.74E-06 ± 1.27827E-08	0.466472827	0.0014125	3.87E-09 ± 1.81E-11
331	2.78E-06 ± 1.35105E-08	0.485198524	0.0013646	3.80E-09 ± 1.84E-11
332	2.83E-06 ± 1.37544E-08	0.485671927	0.0013183	3.73E-09 ± 1.81E-11
333	2.88E-06 ± 1.39669E-08	0.485161175	0.0012735	3.67E-09 ± 1.78E-11
334	2.92E-06 ± 1.38303E-08	0.473688848	0.0012303	3.59E-09 ± 1.70E-11
335	2.96E-06 ± 1.41073E-08	0.476012988	0.0011885	3.52E-09 ± 1.68E-11
336	3.01E-06 ± 1.35554E-08	0.450980002	0.0011482	3.45E-09 ± 1.56E-11
337	3.05E-06 ± 1.389E-08	0.455988616	0.0011092	3.38E-09 ± 1.54E-11
338	3.09E-06 ± 1.43393E-08	0.463878274	0.0010715	3.31E-09 ± 1.54E-11
339	3.13E-06 ± 1.41359E-08	0.451958597	0.0010351	3.24E-09 ± 1.46E-11
340	3.16E-06 ± 1.45321E-08	0.459461176	0.001	3.16E-09 ± 1.45E-11
341	3.20E-06 ± 1.47919E-08	0.461760077	0.0009661	3.09E-09 ± 1.43E-11
342	3.24E-06 ± 1.50019E-08	0.462896908	0.0009333	3.02E-09 ± 1.40E-11
343	3.27E-06 ± 1.50137E-08	0.458490341	0.0009016	2.95E-09 ± 1.35E-11
344	3.31E-06 ± 1.49337E-08	0.450624111	0.000871	2.89E-09 ± 1.30E-11

TABLE E2
Irradiance and Weighted Irradiance for Light Source SSL-2
in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
345	3.40E-06 ± 1.82759E-08	0.537199941	0.0008414	2.86E-09 ± 1.54E-11
346	3.44E-06 ± 1.8616E-08	0.541497772	0.0008128	2.79E-09 ± 1.51E-11
347	3.47E-06 ± 1.83958E-08	0.530113569	0.0007852	2.72E-09 ± 1.44E-11
348	3.50E-06 ± 1.83264E-08	0.52330496	0.0007586	2.66E-09 ± 1.39E-11
349	3.54E-06 ± 1.82557E-08	0.516403416	0.0007328	2.59E-09 ± 1.34E-11
350	3.57E-06 ± 1.83492E-08	0.51409456	0.0007079	2.53E-09 ± 1.30E-11
351	3.60E-06 ± 1.86013E-08	0.516563567	0.0006839	2.46E-09 ± 1.27E-11
352	3.63E-06 ± 1.89885E-08	0.523068552	0.0006607	2.40E-09 ± 1.25E-11
353	3.66E-06 ± 1.89877E-08	0.518919247	0.0006383	2.34E-09 ± 1.21E-11
354	3.69E-06 ± 1.86307E-08	0.505310441	0.0006166	2.27E-09 ± 1.15E-11
355	3.72E-06 ± 1.86268E-08	0.501033369	0.0005957	2.21E-09 ± 1.11E-11
356	3.74E-06 ± 1.85914E-08	0.49679417	0.0005754	2.15E-09 ± 1.07E-11
357	3.76E-06 ± 1.90316E-08	0.50587957	0.0005559	2.09E-09 ± 1.06E-11
358	3.78E-06 ± 1.87452E-08	0.496057576	0.000537	2.03E-09 ± 1.01E-11
359	3.80E-06 ± 1.9209E-08	0.504947251	0.0005188	1.97E-09 ± 9.97E-12
360	3.84E-06 ± 1.87485E-08	0.488440283	0.0005012	1.92E-09 ± 9.40E-12
361	3.88E-06 ± 1.86521E-08	0.480952173	0.0004842	1.88E-09 ± 9.03E-12
362	3.90E-06 ± 1.89467E-08	0.486255028	0.0004677	1.82E-09 ± 8.86E-12
363	3.91E-06 ± 1.88705E-08	0.483011544	0.0004519	1.77E-09 ± 8.53E-12
364	3.94E-06 ± 1.86032E-08	0.472615282	0.0004365	1.72E-09 ± 8.12E-12
365	3.97E-06 ± 1.87308E-08	0.471606698	0.0004217	1.67E-09 ± 7.90E-12
366	4.01E-06 ± 1.87425E-08	0.466962731	0.0004074	1.64E-09 ± 7.64E-12
367	4.07E-06 ± 1.89538E-08	0.466159691	0.0003936	1.60E-09 ± 7.46E-12
368	4.12E-06 ± 1.87457E-08	0.455359862	0.0003802	1.57E-09 ± 7.13E-12
369	4.17E-06 ± 1.8342E-08	0.439603437	0.0003673	1.53E-09 ± 6.74E-12
370	4.20E-06 ± 1.85525E-08	0.441691741	0.0003548	1.49E-09 ± 6.58E-12
371	4.16E-06 ± 1.82147E-08	0.438060621	0.0003428	1.43E-09 ± 6.24E-12
372	4.12E-06 ± 1.73419E-08	0.420975224	0.0003311	1.36E-09 ± 5.74E-12
373	4.11E-06 ± 1.71441E-08	0.417600467	0.0003199	1.31E-09 ± 5.48E-12
374	4.12E-06 ± 1.72772E-08	0.41911448	0.000309	1.27E-09 ± 5.34E-12
375	4.15E-06 ± 1.72598E-08	0.416003001	0.0002985	1.24E-09 ± 5.15E-12
376	4.18E-06 ± 1.70024E-08	0.406530785	0.0002884	1.21E-09 ± 4.90E-12
377	4.22E-06 ± 1.73995E-08	0.41241181	0.0002786	1.18E-09 ± 4.85E-12
378	4.28E-06 ± 1.75509E-08	0.410385628	0.0002692	1.15E-09 ± 4.72E-12
379	4.35E-06 ± 1.75355E-08	0.402751272	0.00026	1.13E-09 ± 4.56E-12
380	4.45E-06 ± 1.75431E-08	0.394048862	0.0002512	1.12E-09 ± 4.41E-12
381	4.47E-06 ± 1.77802E-08	0.397907365	0.0002427	1.08E-09 ± 4.32E-12
382	4.43E-06 ± 1.7873E-08	0.403286609	0.0002344	1.04E-09 ± 4.19E-12
383	4.40E-06 ± 1.75951E-08	0.40021779	0.0002265	9.96E-10 ± 3.99E-12
384	4.37E-06 ± 1.73685E-08	0.397337939	0.0002188	9.56E-10 ± 3.80E-12
385	4.36E-06 ± 1.73442E-08	0.397766679	0.0002113	9.21E-10 ± 3.66E-12
386	4.36E-06 ± 1.69653E-08	0.388811651	0.0002042	8.91E-10 ± 3.46E-12
387	4.37E-06 ± 1.66769E-08	0.381447354	0.0001972	8.62E-10 ± 3.29E-12
388	4.42E-06 ± 1.70431E-08	0.385398923	0.0001905	8.42E-10 ± 3.25E-12
389	4.53E-06 ± 1.73677E-08	0.382981946	0.0001841	8.35E-10 ± 3.20E-12
390	4.65E-06 ± 1.79785E-08	0.386412069	0.0001778	8.27E-10 ± 3.20E-12
391	4.67E-06 ± 1.83024E-08	0.39184385	0.0001718	8.02E-10 ± 3.14E-12
392	4.70E-06 ± 1.76911E-08	0.376585719	0.000166	7.80E-10 ± 2.94E-12

TABLE E2
Irradiance and Weighted Irradiance for Light Source SSL-2 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
393	4.81E-06 ± 1.80319E-08	0.375063094	0.0001603	7.71E-10 ± 2.89E-12
394	4.98E-06 ± 1.82901E-08	0.367287919	0.0001549	7.71E-10 ± 2.83E-12
395	5.47E-06 ± 2.06454E-08	0.377391807	0.0001496	8.18E-10 ± 3.09E-12
396	5.71E-06 ± 2.10807E-08	0.369246805	0.0001445	8.25E-10 ± 3.05E-12
397	5.78E-06 ± 2.07854E-08	0.35950939	0.0001396	8.07E-10 ± 2.90E-12
398	5.54E-06 ± 2.07326E-08	0.374462952	0.0001349	7.47E-10 ± 2.80E-12
399	5.10E-06 ± 1.88267E-08	0.369510331	0.0001303	6.64E-10 ± 2.45E-12
400	4.89E-06 ± 1.7364E-08	0.354749366	0.0001259	6.16E-10 ± 2.19E-12
401	4.84E-06 ± 1.69077E-08	0.349422329	0	—[c]
402	4.83E-06 ± 1.63778E-08	0.338937758	0	—
403	4.85E-06 ± 1.66938E-08	0.344396819	0	—
404	4.88E-06 ± 1.62552E-08	0.33316195	0	—
405	4.95E-06 ± 1.64841E-08	0.333334876	0	—
406	4.98E-06 ± 1.68191E-08	0.338051924	0	—
407	5.06E-06 ± 1.71379E-08	0.338904085	0	—
408	5.34E-06 ± 1.84434E-08	0.345243941	0	—
409	5.30E-06 ± 1.83128E-08	0.345792443	0	—
410	5.17E-06 ± 1.77009E-08	0.342092539	0	—
411	5.33E-06 ± 1.82347E-08	0.341809151	0	—
412	5.57E-06 ± 1.82929E-08	0.328567674	0	—
413	5.34E-06 ± 1.81656E-08	0.340097403	0	—
414	5.18E-06 ± 1.65461E-08	0.319426454	0	—
415	5.14E-06 ± 1.6213E-08	0.315610032	0	—
416	5.14E-06 ± 1.62537E-08	0.316446036	0	—
417	5.15E-06 ± 1.62579E-08	0.315385926	0	—
418	5.23E-06 ± 1.63579E-08	0.312951574	0	—
419	5.70E-06 ± 1.96141E-08	0.344049982	0	—
420	5.78E-06 ± 1.96498E-08	0.339793422	0	—
421	5.40E-06 ± 1.68728E-08	0.312186467	0	—
422	5.27E-06 ± 1.64595E-08	0.31214511	0	—
423	5.27E-06 ± 1.63927E-08	0.31122013	0	—
424	5.31E-06 ± 1.61574E-08	0.30432483	0	—
425	5.31E-06 ± 1.58029E-08	0.297503976	0	—
426	5.30E-06 ± 1.60516E-08	0.303022953	0	—
427	5.29E-06 ± 1.62402E-08	0.30680633	0	—
428	5.29E-06 ± 1.60423E-08	0.30299469	0	—
429	5.29E-06 ± 1.59195E-08	0.300766284	0	—
430	5.30E-06 ± 1.54414E-08	0.291507855	0	—
431	5.31E-06 ± 1.55677E-08	0.293154961	0	—
432	5.33E-06 ± 1.5793E-08	0.296555145	0	—
433	5.35E-06 ± 1.56338E-08	0.292054647	0	—
434	5.38E-06 ± 1.60834E-08	0.298855165	0	—
435	5.42E-06 ± 1.60888E-08	0.296658078	0	—
436	5.50E-06 ± 1.60726E-08	0.29196534	0	—
437	5.69E-06 ± 1.68543E-08	0.296029574	0	—
438	5.98E-06 ± 1.78323E-08	0.298250057	0	—
439	5.94E-06 ± 1.89133E-08	0.318215787	0	—
440	5.57E-06 ± 1.61537E-08	0.289933354	0	—

TABLE E2
Irradiance and Weighted Irradiance for Light Source SSL-2 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
441	5.65E-06 ± 1.65352E-08	0.292704491	0	—
442	5.74E-06 ± 1.64797E-08	0.287128652	0	—
443	5.62E-06 ± 1.62606E-08	0.289216617	0	—
444	5.58E-06 ± 1.58196E-08	0.283481326	0	—
445	5.61E-06 ± 1.59925E-08	0.285143009	0	—
446	5.56E-06 ± 1.59968E-08	0.287929321	0	—
447	5.54E-06 ± 1.62785E-08	0.293668194	0	—
448	5.59E-06 ± 1.6164E-08	0.289039569	0	—
449	5.94E-06 ± 1.95646E-08	0.329164869	0	—
450	8.61E-06 ± 3.72147E-08	0.432418851	0	—

[a] Irradiance and weighted irradiance values are presented as mean ± standard error for 43 measurements at each wavelength; W=watts; S_{er}=CIE human erythema action spectrum weighting function (CIE, 1999); weighted irradiance=irradiance • S_{er}.
[b] Determined by dividing each irradiance standard error by the corresponding mean and multiplying by 100.
[c] Not applicable; S_{er}=0

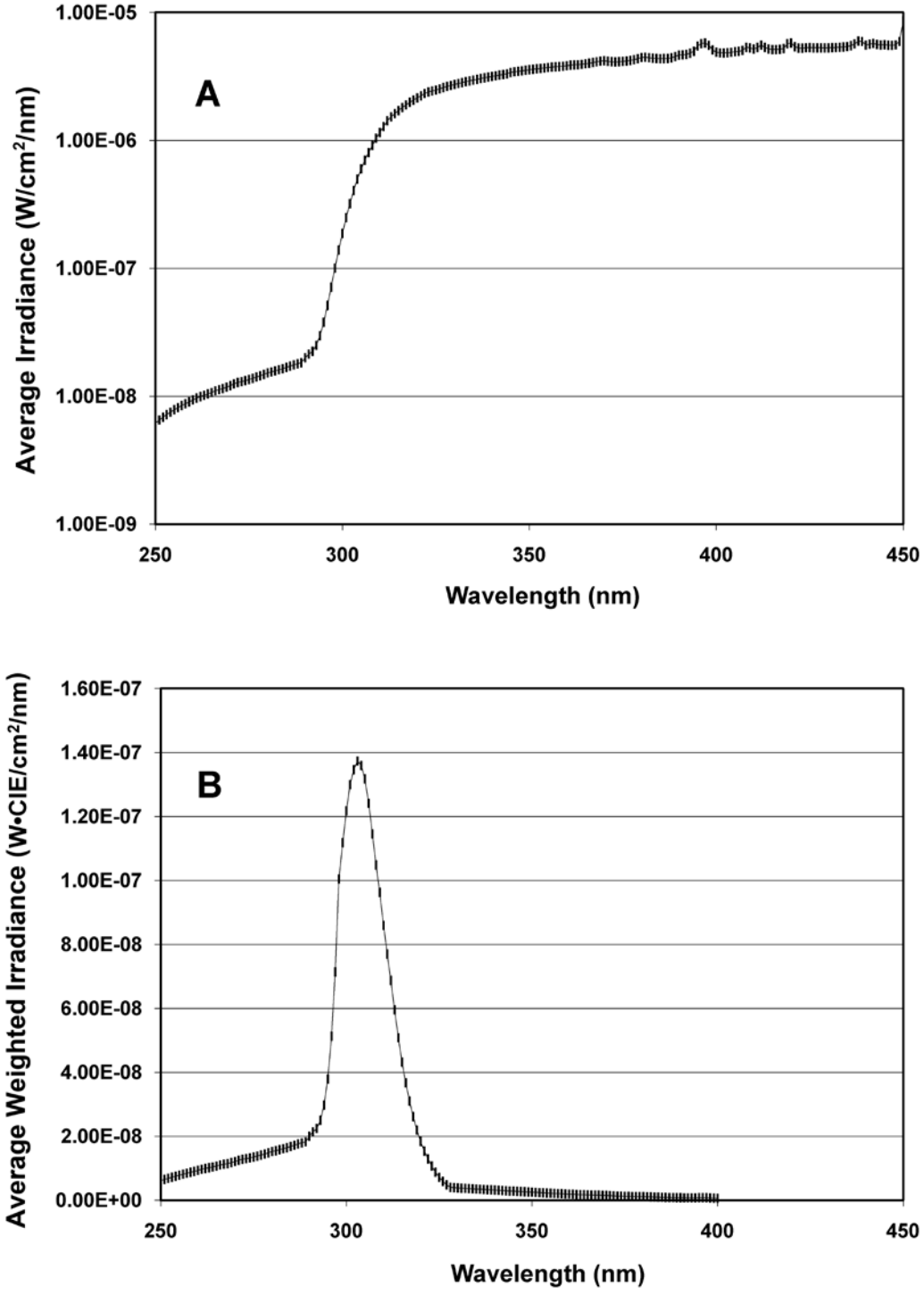


FIGURE E2
Average Irradiance (A) and Average Weighted Irradiance (B) for Light Source SSL-2 in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
Average ± standard error (n=43 at each wavelength); W=watts; irradiance was weighted by application of the CIE human erythema action spectrum weighting function (CIE, 1999).

TABLE E3
Irradiance and Weighted Irradiance for Light Source UVA in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate[a]

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance[b] (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
250	3.11E-11 ± 9.82911E-12	31.63709513	1	3.11E-11 ± 9.83E-12
251	3.14E-11 ± 8.88675E-12	28.31763073	1	3.14E-11 ± 8.89E-12
252	3.15E-11 ± 9.73438E-12	30.92855077	1	3.15E-11 ± 9.73E-12
253	3.51E-11 ± 1.00131E-11	28.51057732	1	3.51E-11 ± 1.00E-11
254	3.88E-11 ± 1.04873E-11	27.06343811	1	3.88E-11 ± 1.05E-11
255	3.57E-11 ± 9.00276E-12	25.24928978	1	3.57E-11 ± 9.00E-12
256	3.51E-11 ± 8.84564E-12	25.1900791	1	3.51E-11 ± 8.85E-12
257	3.69E-11 ± 9.24433E-12	25.05982839	1	3.69E-11 ± 9.24E-12
258	2.99E-11 ± 8.31283E-12	27.80202355	1	2.99E-11 ± 8.31E-12
259	3.13E-11 ± 8.61513E-12	27.50515252	1	3.13E-11 ± 8.62E-12
260	2.86E-11 ± 8.09601E-12	28.34104241	1	2.86E-11 ± 8.10E-12
261	3.20E-11 ± 8.36812E-12	26.15834748	1	3.20E-11 ± 8.37E-12
262	3.01E-11 ± 7.47563E-12	24.85846854	1	3.01E-11 ± 7.48E-12
263	3.43E-11 ± 7.61802E-12	22.21894978	1	3.43E-11 ± 7.62E-12
264	3.10E-11 ± 7.89977E-12	25.45259246	1	3.10E-11 ± 7.90E-12
265	3.20E-11 ± 8.4243E-12	26.32239235	1	3.20E-11 ± 8.42E-12
266	2.80E-11 ± 7.13713E-12	25.45681372	1	2.80E-11 ± 7.14E-12
267	2.93E-11 ± 7.09374E-12	24.24865741	1	2.93E-11 ± 7.09E-12
268	2.98E-11 ± 7.70333E-12	25.87773377	1	2.98E-11 ± 7.70E-12
269	2.90E-11 ± 6.9028E-12	23.79302868	1	2.90E-11 ± 6.90E-12
270	3.05E-11 ± 7.2315E-12	23.71161673	1	3.05E-11 ± 7.23E-12
271	2.82E-11 ± 6.70349E-12	23.75732209	1	2.82E-11 ± 6.70E-12
272	2.68E-11 ± 6.92874E-12	25.8975381	1	2.68E-11 ± 6.93E-12
273	3.11E-11 ± 6.74396E-12	21.70669641	1	3.11E-11 ± 6.74E-12
274	3.18E-11 ± 8.22107E-12	25.89034455	1	3.18E-11 ± 8.22E-12
275	3.50E-11 ± 6.92631E-12	19.78640501	1	3.50E-11 ± 6.93E-12
276	3.31E-11 ± 7.51972E-12	22.7244913	1	3.31E-11 ± 7.52E-12
277	2.87E-11 ± 6.56374E-12	22.87005514	1	2.87E-11 ± 6.56E-12
278	2.63E-11 ± 6.41163E-12	24.3818986	1	2.63E-11 ± 6.41E-12
279	3.40E-11 ± 7.13049E-12	20.98795537	1	3.40E-11 ± 7.13E-12
280	4.07E-11 ± 7.42452E-12	18.24734044	1	4.07E-11 ± 7.42E-12
281	4.12E-11 ± 7.63328E-12	18.52761138	1	4.12E-11 ± 7.63E-12
282	3.96E-11 ± 6.6778E-12	16.88325233	1	3.96E-11 ± 6.68E-12
283	3.73E-11 ± 7.62101E-12	20.4246602	1	3.73E-11 ± 7.62E-12
284	2.80E-11 ± 6.65541E-12	23.72969001	1	2.80E-11 ± 6.66E-12
285	3.42E-11 ± 6.90626E-12	20.19218953	1	3.42E-11 ± 6.91E-12
286	3.95E-11 ± 7.29326E-12	18.44826043	1	3.95E-11 ± 7.29E-12
287	3.99E-11 ± 7.7433E-12	19.42119037	1	3.99E-11 ± 7.74E-12
288	7.78E-11 ± 8.98974E-12	11.5540692	1	7.78E-11 ± 8.99E-12
289	3.19E-10 ± 1.90758E-11	5.974866906	1	3.19E-10 ± 1.91E-11
290	1.08E-09 ± 2.38329E-10	22.04883908	1	1.08E-09 ± 2.38E-10
291	1.14E-09 ± 2.36029E-10	20.79153046	1	1.14E-09 ± 2.36E-10
292	1.10E-09 ± 2.34792E-10	21.31315036	1	1.10E-09 ± 2.35E-10
293	1.19E-09 ± 2.38824E-10	20.10599145	1	1.19E-09 ± 2.39E-10
294	1.29E-09 ± 2.52517E-10	19.56679598	1	1.29E-09 ± 2.53E-10
295	1.58E-09 ± 2.21799E-10	14.07916258	1	1.58E-09 ± 2.22E-10
296	2.13E-09 ± 2.5163E-10	11.81800925	1	2.13E-09 ± 2.52E-10
297	2.88E-09 ± 2.85865E-10	9.939926702	1	2.88E-09 ± 2.86E-10

TABLE E3
Irradiance and Weighted Irradiance for Light Source UVA in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
298	1.96E-09 ± 2.28445E-10	11.64970946	1	1.96E-09 ± 2.28E-10
299	1.80E-09 ± 2.49912E-10	13.89122353	0.8053784	1.45E-09 ± 2.01E-10
300	2.12E-09 ± 2.47147E-10	11.6823309	0.6486344	1.37E-09 ± 1.60E-10
301	2.64E-09 ± 2.62843E-10	9.95874759	0.5223962	1.38E-09 ± 1.37E-10
302	3.51E-09 ± 2.69215E-10	7.665644166	0.4207266	1.48E-09 ± 1.13E-10
303	3.51E-09 ± 2.71235E-10	7.721069032	0.3388442	1.19E-09 ± 9.19E-11
304	3.50E-09 ± 2.56057E-10	7.314981588	0.2728978	9.55E-10 ± 6.99E-11
305	3.99E-09 ± 2.53493E-10	6.351378811	0.219786	8.77E-10 ± 5.57E-11
306	4.83E-09 ± 2.57496E-10	5.336262983	0.1770109	8.54E-10 ± 4.56E-11
307	5.81E-09 ± 2.71962E-10	4.681053139	0.1425608	8.28E-10 ± 3.88E-11
308	7.28E-09 ± 2.97332E-10	4.084150262	0.1148154	8.36E-10 ± 3.41E-11
309	9.79E-09 ± 3.78522E-10	3.865920844	0.0924698	9.05E-10 ± 3.50E-11
310	1.51E-08 ± 5.12295E-10	3.387702529	0.0744732	1.13E-09 ± 3.82E-11
311	2.73E-08 ± 9.8063E-10	3.592039025	0.0599791	1.64E-09 ± 5.88E-11
312	6.46E-08 ± 2.58844E-09	4.008057775	0.0483059	3.12E-09 ± 1.25E-10
313	1.13E-07 ± 4.04527E-09	3.575810789	0.0389045	4.40E-09 ± 1.57E-10
314	8.26E-08 ± 2.68814E-09	3.254919643	0.0313329	2.59E-09 ± 8.42E-11
315	8.66E-08 ± 2.82329E-09	3.261081093	0.0252348	2.18E-09 ± 7.12E-11
316	1.16E-07 ± 3.9168E-09	3.370529471	0.0203236	2.36E-09 ± 7.96E-11
317	1.65E-07 ± 5.80943E-09	3.525697266	0.0163682	2.70E-09 ± 9.51E-11
318	2.34E-07 ± 8.0057E-09	3.419126392	0.0131826	3.09E-09 ± 1.06E-10
319	3.29E-07 ± 1.11617E-08	3.38806529	0.010617	3.50E-09 ± 1.19E-10
320	4.57E-07 ± 1.58434E-08	3.469589203	0.0085507	3.90E-09 ± 1.35E-10
321	6.23E-07 ± 2.18292E-08	3.505491872	0.0068865	4.29E-09 ± 1.50E-10
322	8.37E-07 ± 2.94076E-08	3.515056519	0.0055463	4.64E-09 ± 1.63E-10
323	1.12E-06 ± 3.88513E-08	3.466833138	0.0044668	5.01E-09 ± 1.74E-10
324	1.47E-06 ± 5.01305E-08	3.412147236	0.0035975	5.29E-09 ± 1.80E-10
325	1.89E-06 ± 6.38766E-08	3.381783402	0.0028973	5.47E-09 ± 1.85E-10
326	2.40E-06 ± 8.16471E-08	3.403710581	0.0023335	5.60E-09 ± 1.91E-10
327	3.01E-06 ± 1.01255E-07	3.363195276	0.0018793	5.66E-09 ± 1.90E-10
328	3.72E-06 ± 1.25533E-07	3.377650437	0.0015136	5.63E-09 ± 1.90E-10
329	4.54E-06 ± 1.52659E-07	3.360225112	0.0014622	6.64E-09 ± 2.23E-10
330	5.47E-06 ± 1.80908E-07	3.308486481	0.0014125	7.72E-09 ± 2.56E-10
331	6.52E-06 ± 2.14445E-07	3.287910909	0.0013646	8.90E-09 ± 2.93E-10
332	7.68E-06 ± 2.50397E-07	3.258642019	0.0013183	1.01E-08 ± 3.30E-10
333	9.00E-06 ± 2.94507E-07	3.27224144	0.0012735	1.15E-08 ± 3.75E-10
334	1.05E-05 ± 3.44292E-07	3.265077003	0.0012303	1.30E-08 ± 4.24E-10
335	1.18E-05 ± 3.85386E-07	3.260668533	0.0011885	1.40E-08 ± 4.58E-10
336	1.32E-05 ± 4.29178E-07	3.246994923	0.0011482	1.52E-08 ± 4.93E-10
337	1.48E-05 ± 4.76464E-07	3.22486887	0.0011092	1.64E-08 ± 5.28E-10
338	1.64E-05 ± 5.28588E-07	3.220423082	0.0010715	1.76E-08 ± 5.66E-10
339	1.81E-05 ± 5.7781E-07	3.200567778	0.0010351	1.87E-08 ± 5.98E-10
340	1.97E-05 ± 6.2972E-07	3.190038468	0.001	1.97E-08 ± 6.30E-10
341	2.15E-05 ± 6.81333E-07	3.175609111	0.0009661	2.07E-08 ± 6.58E-10
342	2.31E-05 ± 7.34612E-07	3.1787062	0.0009333	2.16E-08 ± 6.86E-10
343	2.48E-05 ± 7.79521E-07	3.143597656	0.0009016	2.24E-08 ± 7.03E-10
344	2.64E-05 ± 8.28296E-07	3.142812487	0.000871	2.30E-08 ± 7.21E-10
345	2.83E-05 ± 8.46655E-07	2.994941001	0.0008414	2.38E-08 ± 7.12E-10

TABLE E3
Irradiance and Weighted Irradiance for Light Source UVA in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
346	2.97E-05 ± 8.83461E-07	2.976416397	0.0008128	2.41E-08 ± 7.18E-10
347	3.10E-05 ± 9.14383E-07	2.953791021	0.0007852	2.43E-08 ± 7.18E-10
348	3.21E-05 ± 9.4011E-07	2.929411962	0.0007586	2.43E-08 ± 7.13E-10
349	3.30E-05 ± 9.63945E-07	2.916713188	0.0007328	2.42E-08 ± 7.06E-10
350	3.39E-05 ± 9.84876E-07	2.907160171	0.0007079	2.40E-08 ± 6.97E-10
351	3.46E-05 ± 1.04028E-06	3.00879642	0.0006839	2.36E-08 ± 7.11E-10
352	3.51E-05 ± 1.04752E-06	2.987840835	0.0006607	2.32E-08 ± 6.92E-10
353	3.54E-05 ± 1.05276E-06	2.975573805	0.0006383	2.26E-08 ± 6.72E-10
354	3.55E-05 ± 1.05378E-06	2.965673926	0.0006166	2.19E-08 ± 6.50E-10
355	3.55E-05 ± 1.05226E-06	2.960926117	0.0005957	2.12E-08 ± 6.27E-10
356	3.54E-05 ± 1.04543E-06	2.951791596	0.0005754	2.04E-08 ± 6.02E-10
357	3.52E-05 ± 1.04017E-06	2.956764576	0.0005559	1.96E-08 ± 5.78E-10
358	3.48E-05 ± 1.02689E-06	2.950600963	0.000537	1.87E-08 ± 5.51E-10
359	3.42E-05 ± 1.0112E-06	2.953303743	0.0005188	1.78E-08 ± 5.25E-10
360	3.36E-05 ± 9.88095E-07	2.943254873	0.0005012	1.68E-08 ± 4.95E-10
361	3.28E-05 ± 9.67941E-07	2.949701511	0.0004842	1.59E-08 ± 4.69E-10
362	3.19E-05 ± 9.4336E-07	2.953663157	0.0004677	1.49E-08 ± 4.41E-10
363	3.10E-05 ± 9.11184E-07	2.938323355	0.0004519	1.40E-08 ± 4.12E-10
364	3.15E-05 ± 9.29502E-07	2.94893502	0.0004365	1.38E-08 ± 4.06E-10
365	4.11E-05 ± 1.2216E-06	2.975587289	0.0004217	1.73E-08 ± 5.15E-10
366	3.31E-05 ± 9.62018E-07	2.902564558	0.0004074	1.35E-08 ± 3.92E-10
367	2.76E-05 ± 7.98576E-07	2.893869094	0.0003936	1.09E-08 ± 3.14E-10
368	2.51E-05 ± 7.31196E-07	2.907517489	0.0003802	9.56E-09 ± 2.78E-10
369	2.38E-05 ± 6.94515E-07	2.915629159	0.0003673	8.75E-09 ± 2.55E-10
370	2.25E-05 ± 6.53048E-07	2.900026629	0.0003548	7.99E-09 ± 2.32E-10
371	2.12E-05 ± 6.16394E-07	2.906079975	0.0003428	7.27E-09 ± 2.11E-10
372	1.99E-05 ± 5.77942E-07	2.902225177	0.0003311	6.59E-09 ± 1.91E-10
373	1.87E-05 ± 5.41741E-07	2.902243764	0.0003199	5.97E-09 ± 1.73E-10
374	1.75E-05 ± 5.05398E-07	2.891570713	0.000309	5.40E-09 ± 1.56E-10
375	1.63E-05 ± 4.72791E-07	2.897191332	0.0002985	4.87E-09 ± 1.41E-10
376	1.52E-05 ± 4.41194E-07	2.897305802	0.0002884	4.39E-09 ± 1.27E-10
377	1.42E-05 ± 4.10279E-07	2.887601984	0.0002786	3.96E-09 ± 1.14E-10
378	1.33E-05 ± 3.81466E-07	2.877235709	0.0002692	3.57E-09 ± 1.03E-10
379	1.23E-05 ± 3.54465E-07	2.870279127	0.00026	3.21E-09 ± 9.22E-11
380	1.15E-05 ± 3.28976E-07	2.863928903	0.0002512	2.89E-09 ± 8.26E-11
381	1.07E-05 ± 3.07337E-07	2.877897146	0.0002427	2.59E-09 ± 7.46E-11
382	9.92E-06 ± 2.84219E-07	2.864680931	0.0002344	2.33E-09 ± 6.66E-11
383	9.20E-06 ± 2.62729E-07	2.854881244	0.0002265	2.08E-09 ± 5.95E-11
384	8.53E-06 ± 2.42553E-07	2.842400795	0.0002188	1.87E-09 ± 5.31E-11
385	7.91E-06 ± 2.25415E-07	2.849723219	0.0002113	1.67E-09 ± 4.76E-11
386	7.33E-06 ± 2.07399E-07	2.827721715	0.0002042	1.50E-09 ± 4.24E-11
387	6.79E-06 ± 1.9282E-07	2.841708795	0.0001972	1.34E-09 ± 3.80E-11
388	6.27E-06 ± 1.77604E-07	2.834167586	0.0001905	1.19E-09 ± 3.38E-11
389	5.79E-06 ± 1.6374E-07	2.829655492	0.0001841	1.07E-09 ± 3.01E-11
390	5.38E-06 ± 1.52262E-07	2.832408716	0.0001778	9.56E-10 ± 2.71E-11
391	4.96E-06 ± 1.39614E-07	2.81347467	0.0001718	8.53E-10 ± 2.40E-11
392	4.54E-06 ± 1.28287E-07	2.828676987	0.000166	7.53E-10 ± 2.13E-11
393	4.18E-06 ± 1.18368E-07	2.832703072	0.0001603	6.70E-10 ± 1.90E-11

TABLE E3
Irradiance and Weighted Irradiance for Light Source UVA in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
394	3.85E-06 ± 1.08808E-07	2.823432647	0.0001549	5.97E-10 ± 1.69E-11
395	3.55E-06 ± 1.0015E-07	2.817250013	0.0001496	5.32E-10 ± 1.50E-11
396	3.28E-06 ± 9.17423E-08	2.797596575	0.0001445	4.74E-10 ± 1.33E-11
397	3.03E-06 ± 8.4435E-08	2.786208562	0.0001396	4.23E-10 ± 1.18E-11
398	2.81E-06 ± 7.82714E-08	2.786547854	0.0001349	3.79E-10 ± 1.06E-11
399	2.59E-06 ± 7.17671E-08	2.769889399	0.0001303	3.38E-10 ± 9.35E-12
400	2.39E-06 ± 6.61276E-08	2.771253023	0.0001259	3.00E-10 ± 8.33E-12
401	2.21E-06 ± 6.11076E-08	2.767254081	0	—[c]
402	2.06E-06 ± 5.65033E-08	2.747026322	0	—
403	2.86E-06 ± 9.3173E-08	3.257775604	0	—
404	1.53E-05 ± 6.53077E-07	4.267833851	0	—
405	3.89E-05 ± 1.10917E-06	2.850283282	0	—
406	2.95E-06 ± 1.01801E-06	34.53488544	0	—
407	2.31E-06 ± 6.59682E-08	2.859771972	0	—
408	5.24E-06 ± 1.55373E-07	2.96622835	0	—
409	1.34E-06 ± 1.12186E-07	8.385586068	0	—
410	1.08E-06 ± 2.94318E-08	2.719938798	0	—
411	1.02E-06 ± 2.72578E-08	2.673809841	0	—
412	9.13E-07 ± 2.46024E-08	2.693713634	0	—
413	8.42E-07 ± 2.26244E-08	2.68839939	0	—
414	7.80E-07 ± 2.09808E-08	2.69116774	0	—
415	7.21E-07 ± 1.92626E-08	2.671259192	0	—
416	6.71E-07 ± 1.79741E-08	2.67742728	0	—
417	6.18E-07 ± 1.64616E-08	2.661815772	0	—
418	5.74E-07 ± 1.53349E-08	2.672884371	0	—
419	5.33E-07 ± 1.41622E-08	2.655148176	0	—
420	5.00E-07 ± 1.32692E-08	2.656050685	0	—
421	4.59E-07 ± 1.20701E-08	2.631489951	0	—
422	4.27E-07 ± 1.11061E-08	2.601536864	0	—
423	3.98E-07 ± 1.0403E-08	2.611195076	0	—
424	3.72E-07 ± 9.57017E-09	2.570485245	0	—
425	3.51E-07 ± 9.03811E-09	2.576621232	0	—
426	3.33E-07 ± 8.55634E-09	2.570453805	0	—
427	3.16E-07 ± 8.10377E-09	2.567304463	0	—
428	2.97E-07 ± 7.59729E-09	2.554781261	0	—
429	2.83E-07 ± 7.22385E-09	2.549798304	0	—
430	2.73E-07 ± 6.91126E-09	2.53601231	0	—
431	2.61E-07 ± 6.66851E-09	2.55204501	0	—
432	2.61E-07 ± 6.58483E-09	2.526987264	0	—
433	3.66E-07 ± 1.03199E-08	2.823210332	0	—
434	1.96E-06 ± 9.00463E-08	4.586542502	0	—
435	2.57E-05 ± 1.12081E-06	4.354481552	0	—
436	1.21E-04 ± 4.03537E-06	3.329958128	0	—
437	8.03E-06 ± 3.38488E-06	42.1700254	0	—
438	3.96E-07 ± 1.12022E-07	28.29640808	0	—
439	2.24E-07 ± 5.8315E-09	2.603553328	0	—
440	2.08E-07 ± 5.21141E-09	2.504233316	0	—
441	2.03E-07 ± 5.04205E-09	2.483451462	0	—

TABLE E3
Irradiance and Weighted Irradiance for Light Source UVA in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
442	1.98E-07 ± 4.88467E-09	2.462313294	0	—
443	1.94E-07 ± 4.76297E-09	2.46137569	0	—
444	1.88E-07 ± 4.58693E-09	2.433616588	0	—
445	1.84E-07 ± 4.44302E-09	2.415869185	0	—
446	1.80E-07 ± 4.29007E-09	2.382476185	0	—
447	1.76E-07 ± 4.17516E-09	2.366278077	0	—
448	1.72E-07 ± 4.02857E-09	2.335647762	0	—
449	1.69E-07 ± 4.00009E-09	2.362695488	0	—
450	1.67E-07 ± 3.9667E-09	2.372382441	0	—

[a] Irradiance and weighted irradiance values are presented as mean ± standard error for 36 measurements at each wavelength; W=watts; S_{er}=CIE human erythema action spectrum weighting function (CIE, 1999); weighted irradiance=irradiance • S_{er}.
[b] Determined by dividing each irradiance standard error by the corresponding mean and multiplying by 100.
[c] Not applicable; S_{er}=0

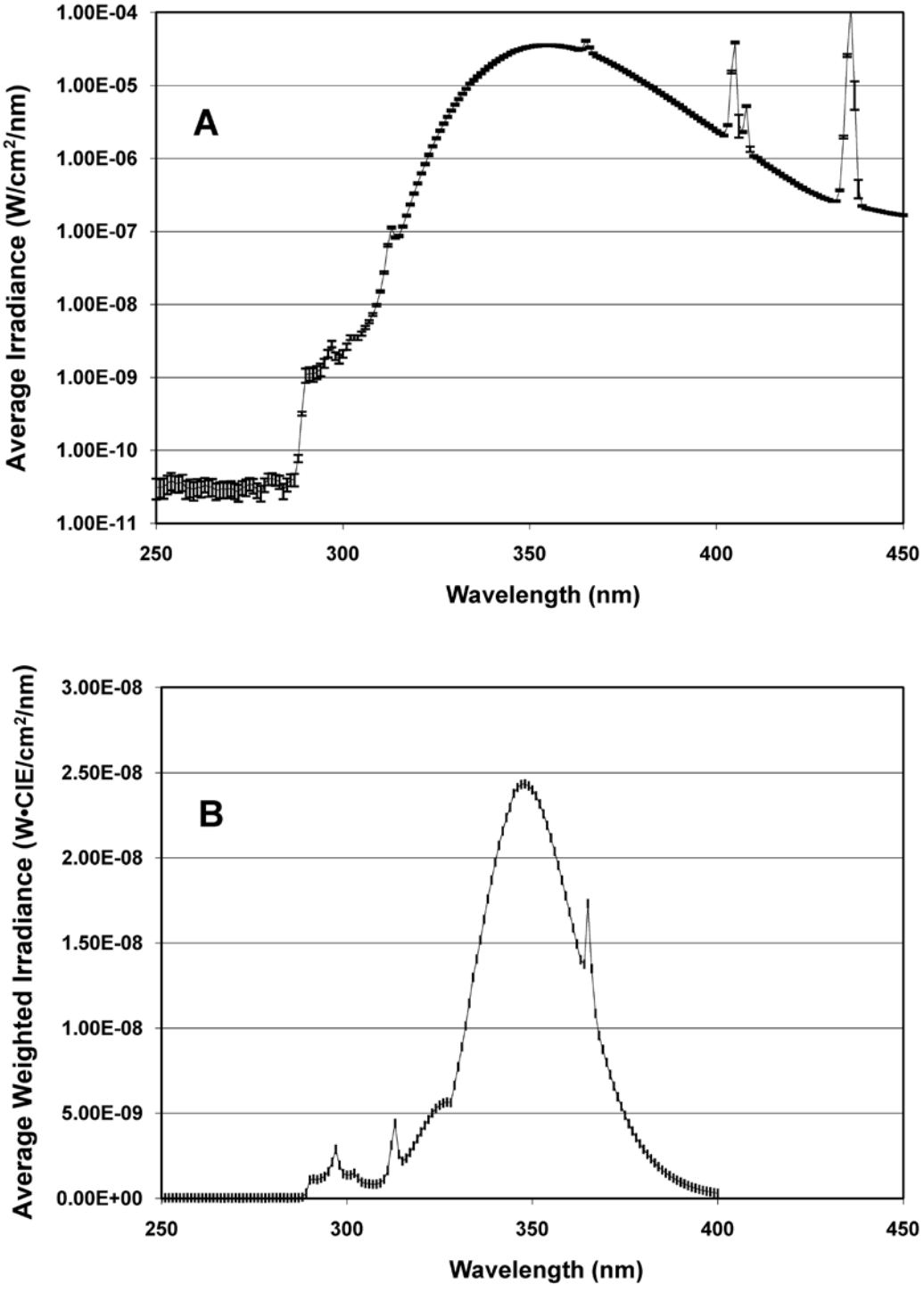


FIGURE E3
Average Irradiance (A) and Average Weighted Irradiance (B) for Light Source UVA in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
Average ± standard error (n=36 at each wavelength); W=watts; irradiance was weighted by application of the CIE human erythema action spectrum weighting function (CIE, 1999).

TABLE E4
Irradiance and Weighted Irradiance for Light Source UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate[a]

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance[b] (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
250	4.20E-11 ± 1.10695E-11	26.32782016	1	4.20E-11 ± 1.11E-11
251	4.77E-11 ± 1.09073E-11	22.85268742	1	4.77E-11 ± 1.09E-11
252	4.22E-11 ± 1.08551E-11	25.72822891	1	4.22E-11 ± 1.09E-11
253	4.60E-11 ± 1.04376E-11	22.71332011	1	4.60E-11 ± 1.04E-11
254	4.69E-11 ± 1.06787E-11	22.75089794	1	4.69E-11 ± 1.07E-11
255	4.41E-11 ± 1.09673E-11	24.87772429	1	4.41E-11 ± 1.10E-11
256	4.16E-11 ± 1.09753E-11	26.38476268	1	4.16E-11 ± 1.10E-11
257	4.61E-11 ± 1.08361E-11	23.49690515	1	4.61E-11 ± 1.08E-11
258	4.26E-11 ± 9.31653E-12	21.89081069	1	4.26E-11 ± 9.32E-12
259	4.24E-11 ± 1.00802E-11	23.78354307	1	4.24E-11 ± 1.01E-11
260	4.59E-11 ± 9.41605E-12	20.53192331	1	4.59E-11 ± 9.42E-12
261	4.81E-11 ± 9.63264E-12	20.04354589	1	4.81E-11 ± 9.63E-12
262	4.24E-11 ± 9.35081E-12	22.05194654	1	4.24E-11 ± 9.35E-12
263	3.94E-11 ± 8.81482E-12	22.39884937	1	3.94E-11 ± 8.81E-12
264	4.28E-11 ± 9.04465E-12	21.12118759	1	4.28E-11 ± 9.04E-12
265	4.57E-11 ± 8.16129E-12	17.86875775	1	4.57E-11 ± 8.16E-12
266	4.19E-11 ± 8.43036E-12	20.1275927	1	4.19E-11 ± 8.43E-12
267	3.64E-11 ± 7.93206E-12	21.79187007	1	3.64E-11 ± 7.93E-12
268	4.94E-11 ± 7.84506E-12	15.88262353	1	4.94E-11 ± 7.85E-12
269	4.94E-11 ± 8.10871E-12	16.41892273	1	4.94E-11 ± 8.11E-12
270	6.81E-11 ± 9.25682E-12	13.58921481	1	6.81E-11 ± 9.26E-12
271	8.49E-11 ± 1.06454E-11	12.53155515	1	8.49E-11 ± 1.06E-11
272	1.17E-10 ± 1.31405E-11	11.24631446	1	1.17E-10 ± 1.31E-11
273	1.63E-10 ± 1.7436E-11	10.69249731	1	1.63E-10 ± 1.74E-11
274	2.22E-10 ± 2.3927E-11	10.77491592	1	2.22E-10 ± 2.39E-11
275	3.36E-10 ± 3.78696E-11	11.2714267	1	3.36E-10 ± 3.79E-11
276	4.18E-10 ± 4.67624E-11	11.19272526	1	4.18E-10 ± 4.68E-11
277	5.38E-10 ± 6.10556E-11	11.35907882	1	5.38E-10 ± 6.11E-11
278	6.93E-10 ± 8.05214E-11	11.62445368	1	6.93E-10 ± 8.05E-11
279	8.76E-10 ± 1.03507E-10	11.82250715	1	8.76E-10 ± 1.04E-10
280	1.15E-09 ± 1.35045E-10	11.71980407	1	1.15E-09 ± 1.35E-10
281	1.40E-09 ± 1.64553E-10	11.78371836	1	1.40E-09 ± 1.65E-10
282	1.70E-09 ± 2.04939E-10	12.02266594	1	1.70E-09 ± 2.05E-10
283	2.06E-09 ± 2.41429E-10	11.74132479	1	2.06E-09 ± 2.41E-10
284	2.46E-09 ± 2.87424E-10	11.67751665	1	2.46E-09 ± 2.87E-10
285	2.97E-09 ± 3.40353E-10	11.46507611	1	2.97E-09 ± 3.40E-10
286	3.73E-09 ± 3.97458E-10	10.64807489	1	3.73E-09 ± 3.97E-10
287	5.77E-09 ± 4.69909E-10	8.146818674	1	5.77E-09 ± 4.70E-10
288	1.23E-08 ± 6.50973E-10	5.281363991	1	1.23E-08 ± 6.51E-10
289	3.33E-08 ± 1.80603E-09	5.423378113	1	3.33E-08 ± 1.81E-09
290	9.56E-08 ± 6.81422E-09	7.130974746	1	9.56E-08 ± 6.81E-09
291	1.95E-07 ± 1.54634E-08	7.91709941	1	1.95E-07 ± 1.55E-08
292	3.62E-07 ± 3.01319E-08	8.317641784	1	3.62E-07 ± 3.01E-08
293	6.06E-07 ± 5.24666E-08	8.661598429	1	6.06E-07 ± 5.25E-08
294	9.07E-07 ± 7.83371E-08	8.634179807	1	9.07E-07 ± 7.83E-08
295	1.28E-06 ± 1.10895E-07	8.684638156	1	1.28E-06 ± 1.11E-07
296	1.71E-06 ± 1.49271E-07	8.725167525	1	1.71E-06 ± 1.49E-07
297	2.10E-06 ± 1.79122E-07	8.517077266	1	2.10E-06 ± 1.79E-07

TABLE E4
Irradiance and Weighted Irradiance for Light Source UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
298	2.37E-06 ± 2.00979E-07	8.465878633	1	2.37E-06 ± 2.01E-07
299	2.68E-06 ± 2.22341E-07	8.292867988	0.8054	2.16E-06 ± 1.79E-07
300	3.00E-06 ± 2.45099E-07	8.173619623	0.6486	1.95E-06 ± 1.59E-07
301	3.27E-06 ± 2.62005E-07	8.001060847	0.5224	1.71E-06 ± 1.37E-07
302	3.58E-06 ± 2.83402E-07	7.918227519	0.4207	1.51E-06 ± 1.19E-07
303	3.74E-06 ± 2.90263E-07	7.759323474	0.3388	1.27E-06 ± 9.84E-08
304	3.88E-06 ± 2.97911E-07	7.679452871	0.2729	1.06E-06 ± 8.13E-08
305	4.01E-06 ± 3.04101E-07	7.581552099	0.2198	8.82E-07 ± 6.68E-08
306	4.15E-06 ± 3.15117E-07	7.599198826	0.177	7.34E-07 ± 5.58E-08
307	4.25E-06 ± 3.17063E-07	7.459406504	0.1426	6.06E-07 ± 4.52E-08
308	4.32E-06 ± 3.20329E-07	7.414361247	0.1148	4.96E-07 ± 3.68E-08
309	4.37E-06 ± 3.19468E-07	7.309415773	0.0925	4.04E-07 ± 2.95E-08
310	4.44E-06 ± 3.21439E-07	7.235994034	0.0745	3.31E-07 ± 2.39E-08
311	4.60E-06 ± 3.35697E-07	7.302824864	0.06	2.76E-07 ± 2.01E-08
312	5.10E-06 ± 3.73413E-07	7.317929452	0.0483	2.46E-07 ± 1.80E-08
313	5.64E-06 ± 4.07003E-07	7.213089585	0.0389	2.20E-07 ± 1.58E-08
314	4.77E-06 ± 3.35935E-07	7.03669378	0.0313	1.50E-07 ± 1.05E-08
315	4.41E-06 ± 3.12884E-07	7.098155273	0.0252	1.11E-07 ± 7.90E-09
316	4.24E-06 ± 3.01391E-07	7.108177695	0.0203	8.62E-08 ± 6.13E-09
317	4.15E-06 ± 2.97091E-07	7.15554863	0.0164	6.80E-08 ± 4.86E-09
318	4.08E-06 ± 2.88114E-07	7.069890334	0.0132	5.37E-08 ± 3.80E-09
319	3.98E-06 ± 2.81345E-07	7.077487814	0.0106	4.22E-08 ± 2.99E-09
320	3.88E-06 ± 2.73839E-07	7.065060967	0.0086	3.31E-08 ± 2.34E-09
321	3.77E-06 ± 2.67898E-07	7.107955815	0.0069	2.60E-08 ± 1.84E-09
322	3.65E-06 ± 2.57583E-07	7.05807921	0.0055	2.02E-08 ± 1.43E-09
323	3.53E-06 ± 2.5106E-07	7.103078296	0.0045	1.58E-08 ± 1.12E-09
324	3.41E-06 ± 2.41868E-07	7.10211679	0.0036	1.23E-08 ± 8.70E-10
325	3.27E-06 ± 2.31631E-07	7.076772189	0.0029	9.48E-09 ± 6.71E-10
326	3.15E-06 ± 2.23505E-07	7.095585269	0.0023	7.35E-09 ± 5.22E-10
327	3.02E-06 ± 2.12426E-07	7.027900541	0.0019	5.68E-09 ± 3.99E-10
328	2.89E-06 ± 2.02409E-07	7.007310671	0.0015	4.37E-09 ± 3.06E-10
329	2.76E-06 ± 1.93631E-07	7.013325569	0.0015	4.04E-09 ± 2.83E-10
330	2.64E-06 ± 1.83062E-07	6.947280245	0.0014	3.72E-09 ± 2.59E-10
331	2.52E-06 ± 1.75323E-07	6.961737611	0.0014	3.44E-09 ± 2.39E-10
332	2.40E-06 ± 1.66441E-07	6.930143989	0.0013	3.17E-09 ± 2.19E-10
333	2.32E-06 ± 1.60598E-07	6.92014481	0.0013	2.96E-09 ± 2.05E-10
334	2.31E-06 ± 1.5919E-07	6.900104997	0.0012	2.84E-09 ± 1.96E-10
335	2.12E-06 ± 1.44498E-07	6.826264144	0.0012	2.52E-09 ± 1.72E-10
336	1.97E-06 ± 1.3392E-07	6.784501714	0.0011	2.27E-09 ± 1.54E-10
337	1.87E-06 ± 1.26431E-07	6.770434007	0.0011	2.07E-09 ± 1.40E-10
338	1.78E-06 ± 1.20759E-07	6.79588399	0.0011	1.90E-09 ± 1.29E-10
339	1.68E-06 ± 1.12582E-07	6.697744197	0.001	1.74E-09 ± 1.17E-10
340	1.59E-06 ± 1.05899E-07	6.652023339	0.001	1.59E-09 ± 1.06E-10
341	1.51E-06 ± 9.98632E-08	6.621043857	0.001	1.46E-09 ± 9.65E-11
342	1.43E-06 ± 9.42628E-08	6.601919174	0.0009	1.33E-09 ± 8.80E-11
343	1.35E-06 ± 8.77228E-08	6.51669187	0.0009	1.21E-09 ± 7.91E-11
344	1.27E-06 ± 8.16992E-08	6.443559802	0.0009	1.10E-09 ± 7.12E-11
345	1.19E-06 ± 7.67375E-08	6.47349025	0.0008	9.97E-10 ± 6.46E-11

TABLE E4
Irradiance and Weighted Irradiance for Light Source UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
346	1.12E-06 ± 7.17067E-08	6.420995938	0.0008	9.08E-10 ± 5.83E-11
347	1.05E-06 ± 6.65153E-08	6.341276355	0.0008	8.24E-10 ± 5.22E-11
348	9.86E-07 ± 6.17704E-08	6.267697393	0.0008	7.48E-10 ± 4.69E-11
349	9.24E-07 ± 5.73761E-08	6.209395945	0.0007	6.77E-10 ± 4.20E-11
350	8.67E-07 ± 5.33121E-08	6.146253196	0.0007	6.14E-10 ± 3.77E-11
351	8.13E-07 ± 4.95502E-08	6.09524366	0.0007	5.56E-10 ± 3.39E-11
352	7.62E-07 ± 4.59429E-08	6.026988165	0.0007	5.04E-10 ± 3.04E-11
353	7.15E-07 ± 4.26053E-08	5.96013273	0.0006	4.56E-10 ± 2.72E-11
354	6.71E-07 ± 3.95173E-08	5.89055504	0.0006	4.14E-10 ± 2.44E-11
355	6.29E-07 ± 3.66887E-08	5.831173929	0.0006	3.75E-10 ± 2.19E-11
356	5.92E-07 ± 3.41885E-08	5.778174518	0.0006	3.40E-10 ± 1.97E-11
357	5.57E-07 ± 3.18677E-08	5.718703805	0.0006	3.10E-10 ± 1.77E-11
358	5.25E-07 ± 2.96304E-08	5.64669693	0.0005	2.82E-10 ± 1.59E-11
359	4.94E-07 ± 2.77005E-08	5.610795977	0.0005	2.56E-10 ± 1.44E-11
360	4.65E-07 ± 2.57912E-08	5.547482443	0.0005	2.33E-10 ± 1.29E-11
361	4.38E-07 ± 2.40503E-08	5.488787	0.0005	2.12E-10 ± 1.16E-11
362	4.14E-07 ± 2.24108E-08	5.413998679	0.0005	1.94E-10 ± 1.05E-11
363	4.05E-07 ± 2.19986E-08	5.437144981	0.0005	1.83E-10 ± 9.94E-12
364	7.85E-07 ± 4.59544E-08	5.854005337	0.0004	3.43E-10 ± 2.01E-11
365	3.46E-06 ± 1.87645E-07	5.427229779	0.0004	1.46E-09 ± 7.91E-11
366	1.58E-06 ± 7.45345E-08	4.732326884	0.0004	6.42E-10 ± 3.04E-11
367	5.54E-07 ± 2.55277E-08	4.608781501	0.0004	2.18E-10 ± 1.00E-11
368	2.83E-07 ± 1.45604E-08	5.140517922	0.0004	1.08E-10 ± 5.54E-12
369	2.63E-07 ± 1.35176E-08	5.143064361	0.0004	9.65E-11 ± 4.97E-12
370	2.46E-07 ± 1.25984E-08	5.115064973	0.0004	8.74E-11 ± 4.47E-12
371	2.28E-07 ± 1.15619E-08	5.066915759	0.0003	7.82E-11 ± 3.96E-12
372	2.11E-07 ± 1.06329E-08	5.038304496	0.0003	6.99E-11 ± 3.52E-12
373	1.96E-07 ± 9.79995E-09	4.998246625	0.0003	6.27E-11 ± 3.14E-12
374	1.82E-07 ± 9.07367E-09	4.977378167	0.0003	5.63E-11 ± 2.80E-12
375	1.69E-07 ± 8.40867E-09	4.966630979	0.0003	5.05E-11 ± 2.51E-12
376	1.57E-07 ± 7.75924E-09	4.92989358	0.0003	4.54E-11 ± 2.24E-12
377	1.46E-07 ± 7.21246E-09	4.928310867	0.0003	4.08E-11 ± 2.01E-12
378	1.37E-07 ± 6.67343E-09	4.888240208	0.0003	3.68E-11 ± 1.80E-12
379	1.27E-07 ± 6.19095E-09	4.863685259	0.0003	3.31E-11 ± 1.61E-12
380	1.19E-07 ± 5.76926E-09	4.848751066	0.0003	2.99E-11 ± 1.45E-12
381	1.10E-07 ± 5.33645E-09	4.840544728	0.0002	2.68E-11 ± 1.30E-12
382	1.02E-07 ± 4.95131E-09	4.833574754	0.0002	2.40E-11 ± 1.16E-12
383	9.49E-08 ± 4.581E-09	4.825218472	0.0002	2.15E-11 ± 1.04E-12
384	8.85E-08 ± 4.3006E-09	4.86111431	0.0002	1.94E-11 ± 9.41E-13
385	8.25E-08 ± 3.9959E-09	4.841022424	0.0002	1.74E-11 ± 8.44E-13
386	7.72E-08 ± 3.75606E-09	4.867330325	0.0002	1.58E-11 ± 7.67E-13
387	7.21E-08 ± 3.48758E-09	4.838390622	0.0002	1.42E-11 ± 6.88E-13
388	6.74E-08 ± 3.28123E-09	4.865701669	0.0002	1.28E-11 ± 6.25E-13
389	6.42E-08 ± 3.1624E-09	4.924222977	0.0002	1.18E-11 ± 5.82E-13
390	6.92E-08 ± 3.41292E-09	4.930850564	0.0002	1.23E-11 ± 6.07E-13
391	6.68E-08 ± 3.16973E-09	4.747790063	0.0002	1.15E-11 ± 5.45E-13
392	5.31E-08 ± 2.63766E-09	4.965901414	0.0002	8.82E-12 ± 4.38E-13
393	5.03E-08 ± 2.53571E-09	5.041401037	0.0002	8.06E-12 ± 4.06E-13

TABLE E4
Irradiance and Weighted Irradiance for Light Source UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
394	4.79E-08 ± 2.43706E-09	5.086123688	0.0002	7.42E-12 ± 3.78E-13
395	4.59E-08 ± 2.34368E-09	5.106083873	0.0001	6.87E-12 ± 3.51E-13
396	4.38E-08 ± 2.27459E-09	5.192327936	0.0001	6.33E-12 ± 3.29E-13
397	4.25E-08 ± 2.23189E-09	5.251206682	0.0001	5.93E-12 ± 3.12E-13
398	4.33E-08 ± 2.30109E-09	5.315476937	0.0001	5.84E-12 ± 3.10E-13
399	4.12E-08 ± 2.18406E-09	5.305920335	0.0001	5.36E-12 ± 2.85E-13
400	3.87E-08 ± 2.07911E-09	5.366700586	0.0001	4.88E-12 ± 2.62E-13
401	3.89E-08 ± 2.10192E-09	5.403229887	0	—[c]
402	4.26E-08 ± 2.28143E-09	5.349400219	0	—
403	2.92E-07 ± 1.65078E-08	5.647416778	0	—
404	3.53E-06 ± 1.67417E-07	4.745778357	0	—
405	9.45E-06 ± 3.27238E-07	3.462949885	0	—
406	1.48E-07 ± 5.528E-09	3.745498266	0	—
407	2.88E-07 ± 1.33865E-08	4.641563444	0	—
408	1.07E-06 ± 3.47587E-08	3.245421115	0	—
409	5.69E-08 ± 2.41144E-09	4.238611533	0	—
410	4.11E-08 ± 2.19097E-09	5.334547849	0	—
411	4.78E-08 ± 2.4068E-09	5.032417017	0	—
412	4.03E-08 ± 2.12204E-09	5.268146377	0	—
413	4.12E-08 ± 2.14298E-09	5.20725232	0	—
414	4.25E-08 ± 2.17775E-09	5.119738928	0	—
415	4.37E-08 ± 2.20425E-09	5.048097457	0	—
416	4.58E-08 ± 2.2822E-09	4.979268781	0	—
417	4.63E-08 ± 2.26375E-09	4.894478386	0	—
418	4.70E-08 ± 2.25899E-09	4.806461261	0	—
419	4.85E-08 ± 2.33027E-09	4.808493174	0	—
420	5.07E-08 ± 2.37949E-09	4.695734551	0	—
421	5.05E-08 ± 2.35636E-09	4.666396718	0	—
422	5.15E-08 ± 2.32568E-09	4.517753945	0	—
423	5.29E-08 ± 2.36059E-09	4.466365415	0	—
424	5.42E-08 ± 2.39871E-09	4.425912808	0	—
425	5.58E-08 ± 2.42794E-09	4.354456293	0	—
426	5.80E-08 ± 2.46186E-09	4.241013601	0	—
427	5.96E-08 ± 2.49708E-09	4.187529333	0	—
428	6.04E-08 ± 2.49718E-09	4.131000256	0	—
429	6.19E-08 ± 2.53777E-09	4.097595311	0	—
430	6.36E-08 ± 2.57869E-09	4.055624719	0	—
431	6.48E-08 ± 2.59049E-09	3.999270866	0	—
432	6.87E-08 ± 2.73489E-09	3.978516522	0	—
433	1.02E-07 ± 4.11694E-09	4.032782893	0	—
434	5.63E-07 ± 2.97576E-08	5.287426827	0	—
435	7.20E-06 ± 3.31078E-07	4.596125276	0	—
436	3.26E-05 ± 1.12887E-06	3.463667018	0	—
437	1.21E-06 ± 5.16208E-08	4.259327264	0	—
438	9.41E-08 ± 3.23781E-09	3.440066506	0	—
439	7.90E-08 ± 2.77391E-09	3.512034482	0	—
440	7.72E-08 ± 2.74088E-09	3.550563146	0	—
441	7.79E-08 ± 2.73666E-09	3.513658748	0	—

TABLE E4
Irradiance and Weighted Irradiance for Light Source UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Wavelength (nm)	Irradiance ($W/cm^2/nm$)	Relative Standard Error for Irradiance (%)	S_{er}	Weighted Irradiance ($W•CIE/cm^2/nm$)
442	7.86E-08 ± 2.74676E-09	3.492871963	0	—
443	7.93E-08 ± 2.72381E-09	3.434658866	0	—
444	7.97E-08 ± 2.71841E-09	3.411533082	0	—
445	8.00E-08 ± 2.68879E-09	3.36000052	0	—
446	8.06E-08 ± 2.70277E-09	3.352682522	0	—
447	8.09E-08 ± 2.67941E-09	3.310115225	0	—
448	8.12E-08 ± 2.66924E-09	3.285843965	0	—
449	8.14E-08 ± 2.6672E-09	3.276974284	0	—
450	8.17E-08 ± 2.64249E-09	3.234104513	0	—

[a] Irradiance and weighted irradiance values are presented as mean ± standard error for 38 measurements at each wavelength; W=watts; S_{er}=CIE human erythema action spectrum weighting function (CIE, 1999); weighted irradiance=irradiance • S_{er}.
[b] Determined by dividing each irradiance standard error by the corresponding mean and multiplying by 100.
[c] Not applicable; S_{er}=0

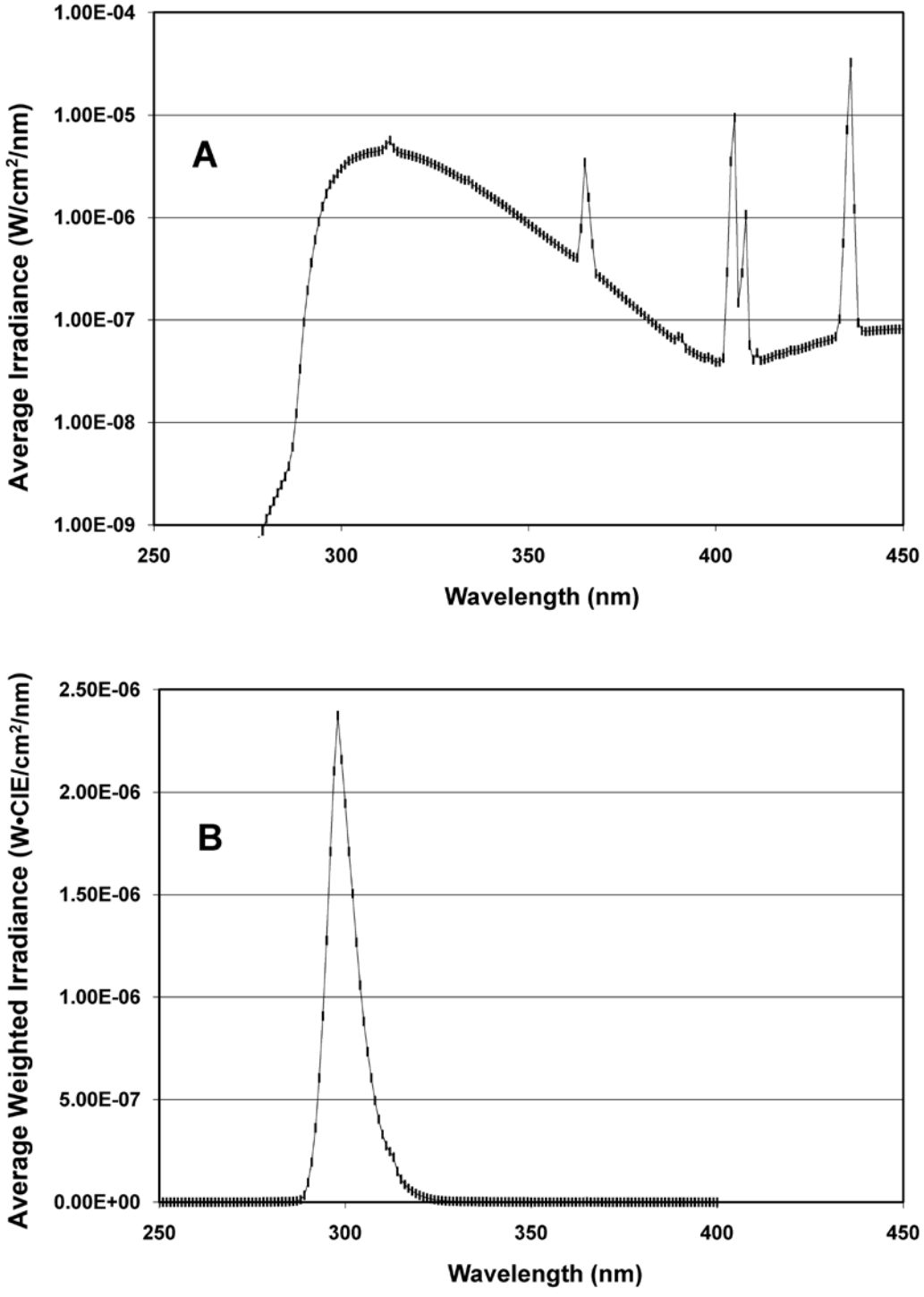


FIGURE E4
Average Irradiance (A) and Average Weighted Irradiance (B) for Light Source UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
Average ± standard error (n=38 at each wavelength); W=watts; irradiance was weighted by application of the CIE human erythema action spectrum weighting function (CIE, 1999).

APPENDIX F
DOSIMETRY
OF SIMULATED SOLAR LIGHT, UVA, AND UVB

DOSIMETRY OF SIMULATED SOLAR LIGHT, UVA, AND UVB

METHODS AND RESULTS

SKH-1 mice were housed in Lenderking EXP355-72 (Lenderking Caging Products, Millersville, MD) animal racks. Each animal rack had 72 individual animal compartments, and animals housed in a single rack received the same dose of simulated solar light (SSL), ultraviolet (UV) A or UVB light. Mice were administered SSL, UVA, or UVB each weekday morning for a period of 40 weeks. An individual animal rack may have housed mice from more than one treatment group; however, the mice on a given animal rack all received the same dose of SSL, UVA, or UVB, and were all of the same sex.

As described in Appendix E, the spectral irradiance of the SSL from the two filtered 6.5 kilowatt (kW) xenon arc light sources, and of the UVA and UVB light from glass-filtered fluorescent UVA lamps or Kodacel-filtered fluorescent UVB lamps, respectively, was measured using a spectroradiometer and recorded in units of W/cm^2 per nm. Measured irradiance was multiplied by human erythema action spectrum weighting factors defined by the Commission Internationale de l'Éclairage (CIE) to generate full-spectrum weighted irradiance with units of $W•CIE/cm^2$ (CIE, 1999). Because 1 W/second equals 1 joule (J), weighted irradiances can be converted to units of $mJ•CIE/cm^2$ following timed exposures to SSL, UVA, or UVB.

The target dose of irradiation administered to an animal rack was based on a weekly accumulation of doses that were dispensed in approximately equivalent increments Monday through Friday of the same week. The target doses of irradiance for the SSL portion of the retinoic acid and retinyl palmitate study were based on historical data from published studies conducted at the Argus Research Laboratories (Sambuco *et al.*, 2003). The doses selected were 0 SSL, 0.3 $MED^{instrumental}$ SSL, 0.6 $MED^{instrumental}$ SSL, and 0.9 $MED^{instrumental}$ SSL, where the minimal erythma dose (MED) was defined as the minimal amount of radiation that causes slight erythema within 24 hours after irradiation. The target doses of irradiance for the UVA/UVB portion of the retinoic acid and retinyl palmitate study were based on the spectral distribution of the SSL-1 and SSL-2 lamps used to produce SSL. Irradiance values were determined using a Solar Light PMA-1101 (Solar Light Company, Inc., Glenside, PA) erythemally weighted dosimeter and were determined to be equivalent to the following daily doses.

SSL

0.3 $MED^{instrumental}$ SSL ≅ 6.85 $mJ•CIE/cm^2$
0.6 $MED^{instrumental}$ SSL ≅ 13.70 $mJ•CIE/cm^2$
0.9 $MED^{instrumental}$ SSL ≅ 20.55 $mJ•CIE/cm^2$

UVA or UVB

UVA and UVB lamps delivered daily doses equivalent to the amounts of UVA and UVB radiation delivered by SSL lamps at 13.70 $mJ•CIE/cm^2$. For the current study, the daily targeted dose of UVA was 1.471 $mJ•CIE/cm^2$ and that of UVB was 13.70 $mJ•CIE/cm^2$.

A summary of the doses of SSL delivered to each treatment group throughout the study is presented in Table F1. The results indicate that male mice were exposed to 99.81% to 100.28% of the targeted SSL doses with relative standard error values ranging from 0.16% to 0.47%. Female mice were exposed to 99.85% to 100.28% of the targeted SSL doses with relative standard error values ranging from 0.16% to 0.44%. Overall, the results indicated that mice were exposed to 99.81 to 100.28% of the targeted SSL doses with a relative standard error less than 0.5% in all dose groups.

A summary of the doses of UVA or UVB delivered to each treatment group throughout the study is presented in Table F2. The results indicate that female mice were exposed to 100.02% to 100.17% of the targeted UVA dose with a relative standard error value of 0.20% in all the dose groups. Female mice were exposed to 99.99% to 100.01% of the targeted UVB dose with relative standard error values ranging from 0.20% to 0.23%.

TABLE F1
Doses of Light for Light Sources SSL-1 and SSL-2
in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate[a]

Group	Animal Rack Number	Daily Light Dose[b]	Targeted Daily Weighted Irradiance (mJ•CIE/cm^2)	Determined Daily Weighted Irradiance (mJ•CIE/cm^2)[c]	Relative Standard Error (%)	Percent of Target
Male						
No cream	31	0.3 MED	6.85	6.8576 ± 0.0300	0.44	100.11
Control cream	31	0.3 MED	6.85	6.8576 ± 0.0300	0.44	100.11
Retinyl palmitate 0.1%	32	0.3 MED	6.85	6.8369 ± 0.0309	0.45	99.81
Retinyl palmitate 0.5%	32	0.3 MED	6.85	6.8369 ± 0.0309	0.45	99.81
Retinyl palmitate 1.0%	33	0.3 MED	6.85	6.8689 ± 0.0323	0.47	100.28
Retinyl palmitate 2.0%	33	0.3 MED	6.85	6.8689 ± 0.0323	0.47	100.28
Retinoic acid 0.001%	34	0.3 MED	6.85	6.8612 ± 0.0323	0.47	100.16
No cream	35	0.6 MED	13.70	13.7244 ± 0.0298	0.22	100.18
Control cream	35	0.6 MED	13.70	13.7244 ± 0.0298	0.22	100.18
Retinyl palmitate 0.1%	36	0.6 MED	13.70	13.7185 ± 0.0340	0.25	100.14
Retinyl palmitate 0.5%	36	0.6 MED	13.70	13.7185 ± 0.0340	0.25	100.14
Retinyl palmitate 1.0%	37	0.6 MED	13.70	13.7388 ± 0.0340	0.25	100.28
Retinyl palmitate 2.0%	37	0.6 MED	13.70	13.7388 ± 0.0340	0.25	100.28
Retinoic acid 0.001%	38	0.6 MED	13.70	13.7061 ± 0.0372	0.27	100.04
No cream	39	0.9 MED	20.55	20.5658 ± 0.0329	0.16	100.08
Female						
No cream	45	0.3 MED	6.85	6.8695 ± 0.0294	0.43	100.28
Control cream	45	0.3 MED	6.85	6.8695 ± 0.0294	0.43	100.28
Retinyl palmitate 0.1%	46	0.3 MED	6.85	6.8573 ± 0.0294	0.43	100.11
Retinyl palmitate 0.5%	46	0.3 MED	6.85	6.8573 ± 0.0294	0.43	100.11
Retinyl palmitate 1.0%	47	0.3 MED	6.85	6.8514 ± 0.0295	0.43	100.02
Retinyl palmitate 2.0%	47	0.3 MED	6.85	6.8514 ± 0.0295	0.43	100.02
Retinoic acid 0.001%	48	0.3 MED	6.85	6.8555 ± 0.0298	0.44	100.08
No cream	49	0.6 MED	13.70	13.6961 ± 0.0294	0.21	99.97
Control cream	49	0.6 MED	13.70	13.6961 ± 0.0294	0.21	99.97
Retinyl palmitate 0.1%	50	0.6 MED	13.70	13.7089 ± 0.0319	0.23	100.06
Retinyl palmitate 0.5%	50	0.6 MED	13.70	13.7089 ± 0.0319	0.23	100.06
Retinyl palmitate 1.0%	51	0.6 MED	13.70	13.6798 ± 0.0334	0.24	99.85
Retinyl palmitate 2.0%	51	0.6 MED	13.70	13.6798 ± 0.0334	0.24	99.85
Retinoic acid 0.001%	52	0.6 MED	13.70	13.7371 ± 0.0334	0.24	100.27
No cream	53	0.9 MED	20.55	20.5393 ± 0.0321	0.16	99.95

[a] Groups of male (racks 29, 30, and 42) and female (racks 43, 44, and 56) mice exposed to 0.00 mJ•CIE/cm^2 of simulated solar light are not presented in this table.
[b] MED=minimal erythemal dose
[c] Mean daily rack dose ± standard error

TABLE F2
Doses of Light for Light Sources UVA and UVB Administered to Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Group	Animal Rack Number	Daily Light Dose	Targeted Daily Weighted Irradiance (mJ•CIE/cm^2)	Determined Daily Weighted Irradiance (mJ•CIE/cm^2)[a]	Relative Standard Error (%)	Percent of Target
No cream	54	UVA	1.471	1.4713 ± 0.0030	0.20	100.02
Control cream	54	UVA	1.471	1.4713 ± 0.0030	0.20	100.02
Retinyl palmitate 1.0%	55	UVA	1.471	1.4735 ± 0.0030	0.20	100.17
Retinoic acid 1.0%	55	UVA	1.471	1.4735 ± 0.0030	0.20	100.17
No cream	40	UVB	13.70	13.7014 ± 0.0277	0.20	100.01
Control cream	40	UVB	13.70	13.7014 ± 0.0277	0.20	100.01
Retinyl palmitate 1.0%	41	UVB	13.70	13.6993 ± 0.0321	0.23	99.99
Retinoic acid 1.0%	41	UVB	13.70	13.6993 ± 0.0321	0.23	99.99

[a] Mean daily rack dose ± standard error

APPENDIX G
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-31 RAT AND MOUSE RATION

TABLE G1
Ingredients of NIH-31 Rat and Mouse Ration

Ingredients[a]	Percent by Weight
Ground whole hard wheat	35.5
Ground #2 yellow shelled corn	21.0
Ground whole oats	10.0
Wheat middlings	10.0
Fish meal (60% protein)	9.0
Soybean meal (48.5% protein)	5.0
Alfalfa meal (17% protein)	2.0
Corn gluten meal (60% protein)	2.0
Dicalcium phosphate[b]	1.5
Soy oil	1.5
Dried brewer's yeast	1.0
Ground limestone[b]	0.5
Premixes	0.5
Salt	0.5

[a] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before mixing.
[b] Specific ingredient requirement is for cadmium content not to exceed 1 mg/kg.

TABLE G2
Vitamins and Minerals in NIH-31 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	22,000,000 IU	Vitamin A palmitate or acetate
D_3	3,800,000 IU	D-activated animal sterol
K_3	20 g	Menadione activity
Choline	700 g	Choline chloride
dl-α-tocopheryl acetate	15 g	
Folic acid	1 g	
Niacin	20 g	
d-Pantothenic acid	25 g	*d*-Calcium pantothenate
Riboflavin	5 g	
Thiamine	65 g	Thiamine mononitrate
B_{12}	14 g	
Pyridoxine	2 g	Pyridoxine hydrochloride
Biotin	0.12 g	*d*-Biotin
Minerals		
Magnesium	400 g	Magnesium oxide
Manganese	100 g	Manganese oxide
Iron	60 g	Iron sulfate
Zinc	10 g	Zinc oxide
Copper	4 g	Copper sulfate
Iodine	1.5 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 pounds) of finished product

TABLE G3
Nutrient Composition of NIH-31 Rat and Mouse Ration[a]

Nutrient	Mean ± Standard Deviation	Number of Samples
Crude protein (% by weight)	20.9 ± 0.83	14
Crude fat (% by weight)	5.60 ± 0.87	14
Volatiles (% by weight)	6.83 ± 1.13	14
Vitamins		
A (µg/g)	10.75 ± 1.9	14
E (µg/g)	56.0 ± 4.52	14
B_1 (mg/g)	0.092 ± 0.00	14
Minerals		
Selenium (µg/g)	0.40 ± 0.11	14

[a] Analyses for nutrient content of NIH-31 diet were performed by standard operating procedures developed and/or validated by the NCTR Division of Chemistry.

TABLE G4
Contaminant Levels in NIH-31 Rat and Mouse Ration[a]

	Mean ± Standard Deviation	Number of Lots (Number Positive)
Arsenic (µg/g)	0.14 ± 0.03	14 (12)
Cadmium (µg/g)	<MDL	14 (0)
Lead (µg/g)	0.52 ± 0.12	14 (11)
Aflatoxin B_1 (ppb)	<MDL	14 (0)
Aflatoxin B_2 (ppb)	<MDL	14 (0)
Aflatoxin G_1 (ppb)	<MDL	14 (0)
Aflatoxin G_2 (ppb)	<MDL	14 (0)
Fumonisin B_1	no data	14 (0)
Total fumonisin	457 ± 213	14 (14)
Pesticides (ppb)		
Heptachlor	<MDL	14 (0)
Total DDT	<MDL	14 (0)
Dieldrin	<MDL	14 (0)
PCB	<MDL	14 (0)
Malathion	<MDL	14 (0)
Lindane	<MDL	14 (0)

[a] Analysis for contamination levels in NIH-31 diet were performed by standard operating procedures developed and/or validated by the NCTR Division of Chemistry. MDL = minimum detectable level.

APPENDIX H
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from two pairs of sentinel mice at each time point during the 1-year study. Blood from each animal was collected and allowed to clot, and the serum was separated. The serum was analyzed by enzyme-linked immunosorbent assay (ELISA) for the presence of specific antibodies by the Research Animal Diagnostic Laboratory (University of Missouri, Columbia, MO). The laboratory serology methods and viral/mycoplasma agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Collection
ELISA	
Ectromelia virus	3, 6, and 9 months
EDIM (epizootic diarrhea of infant mice)	3, 6, and 9 months
GDVII (mouse encephalomyelitis virus)	3, 6, and 9 months
LCM (lymphocytic choriomeningitis virus)	3, 6, and 9 months
MHV (mouse hepatitis virus)	3, 6, and 9 months
Mycoplasma pulmonis	3, 6, and 9 months
Parvo NS-l	3, 6, and 9 months
Parvovirus	3, 6, and 9 months
PVM (pneumonia virus of mice)	3, 6, and 9 months
Polyoma virus	3, 6, and 9 months
Reovirus 3	3, 6, and 9 months
Sendai	3, 6, and 9 months

RESULTS

All test results were negative.

APPENDIX I
THE RANGE-FINDING STUDY OF RETINOIC ACID AND RETINYL PALMITATE AND THE MINIMAL ERYTHEMAL DOSE STUDY OF RETINYL PALMITATE

THE RANGE-FINDING STUDY OF RETINOIC ACID AND RETINYL PALMITATE AND THE MINIMAL ERYTHEMAL DOSE STUDY OF RETINYL PALMITATE

INTRODUCTION

The phototoxicity of topically applied health and cosmetic ingredients is of concern because of the large body surface area that is potentially exposed to sunlight. There is increased interest in the cutaneous photochemistry and photobiology of retinyl esters, such as all-*trans*-retinyl palmitate (RP), because of the physiological importance of retinyl esters and their widespread use in skin care products applied to sun-exposed skin. These studies investigated the biological consequences of 13 weeks of topical applications of creams containing different concentrations of RP or all-*trans*-retinoic acid (RA) to the dorsal skin of SKH-1 mice in the presence and absence of simulated solar light (SSL) to determine their effects on SSL-induced skin damage and to determine appropriate doses of RA and RP to use in the 1-year photococarcinogenesis study.

MATERIALS AND METHODS

Procurement and Characterization

Test Articles

The RP and RA test chemicals were obtained from Sigma Chemical Company (St. Louis, MO). RP (lot 091K10851) was received as 92 sealed amber glass ampules (5 g each) and 56 sealed amber glass ampules (25 g each) for a total of 1,860 g RP. The sealed ampules of the RP test article were stored in their original cardboard shipping container at 4° ± 2° C in a walk-in cold room maintained by the Chemistry Support Unit in the Division of Biochemical Toxicology at the National Center for Toxicological Research (NCTR, Jefferson, AR). RA (lot 042K1680) was received as 30 sealed amber glass ampules (50 mg each) and 110 sealed amber glass ampules (100 mg each) for a total of 12.5 g of RA. The sealed glass ampules of the RA test article were stored in their original cardboard shipping container at −80° C. The environmental temperatures of the test chemical storage facilities were monitored with a JC-85 Control System (Johnson Controls, Inc., Milwaukee, WI) by the Division of Engineering, Operations, and Maintenance at the NCTR. Characterization analyses were conducted on the RP and RA test materials during the month of October 2002 and again during the months of April and May 2003.

Diisopropyl adipate (CAS No. 6938-94-9; Ceraphyl® 230) was used as a solvent for the incorporation of RP and RA into the control cream base and was obtained from International Specialty Products, Inc. (Wayne, NJ). The diisopropyl adipate was received as a single 7-gallon (50 pound) plastic pail of the clear free-flowing liquid (lot 01100056360). The diisopropyl adipate was stored in the original container in a cabinet under lock at room temperature. Characterization analyses were conducted on diisopropyl adipate during the month of October 2002 and again in April 2003.

Custody of the RP and RA test chemicals and the diisopropyl adipate solvent was maintained by the Chemistry Support Unit, Division of Biochemical Toxicology, NCTR. Twice weekly, the Chemistry Support Unit prepared approximately 20 g of a solution of RA dissolved in diisopropyl adipate (0.6667 mg RA/g diisopropyl adipate), and this solution and aliquots of the RP test article in sealed ampules were transferred biweekly to a contract support group (The Bionetics Corporation, Jefferson, AR) for the preparation of dosed cream formulations. The diisopropyl adipate was dispensed into 4-liter amber screw-capped bottles and transferred to Bionetics staff members as needed for the preparation of master batch cream formulations. Chemical usage logs along with chain-of-custody sheets that documented each removal of test chemical were maintained by the Chemistry Support Unit at the NCTR, and copies of the documentation and the Standard Operating Procedures (SOPs) appear in the analytical chemistry summary reports on file at the NCTR.

Test article characterization and analyses to determine the purity of the test chemicals were performed in October 2002 and in May 2003 by the Chemistry Support Unit, NCTR. Structural characterization analyses of the

RA and RP test chemicals was performed on samples of RP (lot 091K10851) and RA (lot 042K1680) using direct exposure probe electron impact-mass spectrometry (DEP/EI-MS) and nuclear magnetic resonance (NMR) spectroscopy. The DEP/EI-MS revealed one major component with a base peak ion as *m/z* 268 for RP and also identified one test article as RA with a base peak ion as *m/z* 300. The RP and RA were tentatively identified by electronic comparison to the mass spectra of these compounds listed in the National Institute of Standards and Technology online library.

The diisopropyl adipate was characterized using gas chromatography electron impact analyses (GC/EI) and gas chromatography mass spectral analyses (GC/MS). The diisopropyl adipate had a base peak ion as *m/z* 129 and was estimated to be 99.7% pure by GC/MS. Results of NMR analyses performed on samples of the RP and RA test chemicals and on the diisopropyl adipate solvent were consistent with the structures of these compounds.

Reverse phase high-performance liquid chromatography (HPLC) was performed on samples of RP and RA to determine the purity of each test article. The purity was determined to be approximately 94.6% for RP and approximately 99% for RA. Based on the results of mass spectral and NMR analyses, diisopropyl adipate had an estimated purity of 99.5%. At the end of the study, HPLC analyses of RP, RA, and diisopropyl adipate were performed by the Chemistry Support Unit at the NCTR; no significant degradation of the test chemicals was detected.

Base Cream

The base cream used for the control cream and dose cream formulations in these studies was purchased from Cosmetech Laboratories, Inc. (Fairfield, NJ), and was received in 12 batches of formulation CLI 1392901 that were labeled CLI 1392901B, C, and E to N. Each of the batches of formulation CLI 1392901 consisted of one high-density white polypropylene pail (batch B and C consisted of one pail each at 2,500 g of the base cream; batches E to N consisted of one pail each at 3,500 g) for a total of 40 kg of base cream. The different batches of base cream had pH values that were approximately 7.0 and a mean viscosity of 3,500 centipoise. The base cream was stored in the original containers, which were numbered 1 to 10 in a walk-in cold room at 4° C. The base cream was formulated by the supplier to account for 85% (wt/wt) of the final cream formulations (Table I1).

Preparation and Analysis of Dose Formulations

Control Cream

The Bionetics Corporation support group staff prepared the control and dose cream formulations used in this study. The control cream was prepared twice weekly and was composed of the base cream, which accounted for 85% of the final control cream formulation, and diisopropyl adipate, which accounted for the remaining 15% (wt/wt) of the final control cream formulation.

Master Batch Dose Creams

An RP (13.0%) master batch formulation was prepared twice weekly and was composed of the base cream (85%, wt/wt), with RP (13.0%, wt/wt) and diisopropyl adipate (2.0%, wt/wt) accounting for the remaining 15%. The RP (13.0%) master batch formulation served both as the RP high dose cream in the study and as the source of RP for dose formulations of lower RP concentrations.

An RA (0.1%) master batch formulation was prepared twice weekly. The base cream comprised 85% (wt/wt) of the RA master batch cream and the RA solution, previously prepared by the Chemistry Support Unit, was incorporated into the base cream in an amount equal to the remaining 15% (wt/wt). The RA (0.1%) master batch formulation served as the RA high-dose cream and the source of RA for the 0.01% (wt/wt) RA dose formulation.

Dose Creams

The final concentrations of the RP test chemical (0.1%, 0.5%, 1.0%, 2.0%, 5.0%, 10.0%, or 13.0%; wt/wt) and of the RA test chemical (0.1% or 0.01%; wt/wt) in the dose formulations were prepared twice weekly by mixing the appropriate amount of control cream with the master batch formulations of RP (13.0%, wt/wt) cream or RA (0.1%, wt/wt) cream to achieve the desired concentration of test article in the cream formulations.

In order to protect the test chemicals from degradation, the dose formulations were shielded from ultraviolet light and mixed with plastic impellers and spatulas. The dose formulations were dispensed into 20 mL amber-colored glass vials with Teflon®-lined screw-caps, under an argon stream, and stored at approximately 4° C for up to 3 days. Each vial contained sufficient control or dose cream for a single day of applications. The glass vials of the prepared creams were delivered to the National Toxicology Program Food and Drug Administration (NTP-FDA) Center for Phototoxicology at the NCTR and stored at 4° ± 6° C until application to the skins of mice. The vials of creams from the previously issued batch of control and dose cream formulations were collected at the time of delivery of the newly prepared creams, and the time and date of issuance of the current batch of creams were recorded, along with the date and time of collection of the previously prepared creams.

The homogeneity of RP and RA in dose cream formulations was assessed on the 13.0%, 5.0%, 1.0%, and 0.1% dose formulations of RP and on the 0.1% and 0.01% dose formulations of RA. The results for approximately nine replicate samples of the 13.0%, 5.0%, and 1.0% RP creams were 90.0% ± 4.4% [mean % target ± standard deviation (s.d.); 11.70 ± 0.57 with a 4.8 coefficient of variation (CV)], 96.0% ± 4.6% (mean % target ± s.d.; 4.48 ± 0.23 with a 5.1 CV), and 107.0% ± 5.0% (mean % target ± s.d.; 1.07 ± 0.05 with a 4.4 CV), respectively; and for the 0.1% RA cream the results were 98.0% ± 3.0% (mean % target ± s.d.; 0.098 ± 0.003 with a 3.2 CV). The homogeneity of the low dose of each of the RP and RA test articles was conducted at three timepoints during the study. The results for the 13 samples of the 0.1% RP creams and the 18 samples of the 0.01% RA creams were 103% ± 7.0% (mean % target ± s.d.; 0.103 ± 0.007 with a 6.8 CV) and 90.0% ± 8.3% (mean % target ± s.d.; 0.009 ± 0.0008 with a 9.1 CV), respectively. Stability studies on the 0.001% formulation of RA were conducted by the Chemistry Support Unit using HPLC. Three-day stability was confirmed for samples stored at 2° to 8° C in the absence of light and sealed in amber glass vials with Teflon®-lined screw-caps. The recoveries of RP (13.0%, 5.0%, 1.0%, and 0.1%) were 100% for day 0, 93.7% and 78.8%, respectively, for the 5.0% and 1.0% RP creams at 1 day, 100% and 84.5% for the 13.0% and 0.1% RP creams at 2 days, and 83.8% and 92.6% for the 13.0% and 0.1% RP creams at 3 days, respectively. Both dose levels of RA remained at 100% for the 3 days of sampling.

Samples of the control and each level of dose creams for each test chemical were collected at the twice-weekly batch preparations and submitted to the Chemistry Support Unit for dose certification analyses. Weekly dose certifications of the control cream, the RA and RP master batch cream formulations, and the dose cream formulations for the RP and RA test chemicals were conducted using HPLC. Dose formulations were directly measured for the concentrations of the test chemicals, and quantitation of RA or RP was made based on the retention times and peak areas of known standards.

The conditions of use of the test chemicals in this study dictated that dose creams be administered to the mice prior to completion of dose certification analyses. Therefore, while an acceptability range of ± 10% of target was desirable, the goal of the dose certification was to enable calculation of the dose that was administered to an animal as a specific point in time. The median percentages of target and the CV% for RP in the 0.1%, 0.5%, 1.0%, 2.0%, 5.0%, 10.0%, and 13.0% RP dose creams over the 13-week study were 100.0% ± 2.5%, 99.21% ± 3.5%, 104.0% ± 4.0%, 106.0% ± 4.5%, 96.6% ± 4.7%, 96.4% ± 6.9%, and 100.00% ± 5.7%, respectively; and those for RA in the 0.1% master cream formulation and the 0.01% dose cream formulation were 96.0% ± 4.9% and 99.4% ± 2.3%, respectively.

Test Facility

The 13-week range-finding study on RA and RP and the minimal erythemal dose (MED) study on RP were conducted in the NTP-FDA Center for Phototoxicology within the Division of Biochemical Toxicology at the NCTR, Jefferson, AR. For the range-finding study, SKH-1 male and female mice were stagger-loaded over four weekly allocations and randomly assigned to treatment groups on a weight-ranked basis. The range of body weights of mice over the four allocations was 28.2 to 31.59 g for male mice and 22.8 to 24.0 for female mice. Body weights of mice for each of the four loads did not differ by greater than 1.0 or 1.7 grams for female or male mice, respectively. The first load of mice went on dose October 28, 2002, and the last mouse was euthanized on February 18, 2003.

For the MED study, female SKH-1 mice were stagger-loaded over three weekly allocations and randomly assigned to treatment groups on a weight-ranked basis. The range of body weights for the mice over the three allocations was

21.6 to 25.9 g. Body weights of mice for each of the three loads did not differ by greater than 3.7 g. The first load of mice went on dose November 18, 2002, and the last mouse was euthanized on March 6, 2003.

Light Source and Irradiance Dosimetry

These studies were conducted in a similar manner as other phototoxicity studies conducted in the NTP-FDA Center for Phototoxicology at NCTR (NTP, 2007). The sources of irradiance were glass-filtered (WG320, 1 mm; SCHOTT North America, Inc., Elmsford, NY) 6.5 kW xenon arc lamps (Atlas Electric, Spokane, WA). The xenon arc lamp source of irradiance is commonly referred to as simulated solar light (SSL). The output spectra emitted from the irradiance sources were measured on a weekly basis using a calibrated spectroradiometer. Exposures were monitored with solar light PMA-1101 broad-band dosimeters (Solar Light Company, Inc., Glenside, PA) that were attached to the center-front of each animal rack.

In the range-finding study, mice were exposed to filtered SSL at 0 or 0.6 (medium) minimal erythema doses (MED) of light for 13 weeks, while in the MED study, mice were exposed only to the 0.6 MED of light for 13 weeks. One MED is defined as the minimal amount of radiation that causes slight erythema within 24 hours after irradiation. The actual measured exposure to light in this study was based on the convention of the Commission Internationale de l'Eclairage (CIE, 1987, 1999). The light exposures were determined by measuring the irradiance from the SSL source in mW/cm^2 and multiplying the irradiance by the human erythema action spectrum to obtain a weighted irradiance in $mW \cdot CIE/cm^2$. Since exposure to 1 $mW \cdot CIE/cm^2$ is equivalent to 1 $mJ \cdot CIE/cm^2$, the weighted irradiances from the SSL lamp source are multiplied by the duration of exposure to calculate the daily exposures received by the mice. Based on this convention, 0.0 and the medium dose of SSL were equivalent to 0.00 and 13.70 $mJ \cdot CIE/cm^2$, respectively. Daily exposures of mice to SSL were recorded in this report as $mJ \cdot CIE/cm^2$. The dose levels of SSL administered each weekday to male and female mice on the range-finding study were 0.00 or 13.70 $mJ \cdot CIE/cm^2$. The selection of levels of SSL administered to mice in this study was based on previous National Toxicology Program photococarcinogenesis studies conducted at this same test facility (NTP, 2007, 2010).

13-Week Range-Finding and MED Studies

Study Design

Humans apply retinoids, especially RA, generally at night and, therefore, have a period of time between application and sun exposure. The range-finding study was designed to mimic human use. Groups of 12 male and 12 female mice were irradiated with 13.70 $mJ \cdot CIE/cm^2$ light emitted from SSL sources in the morning, 5 days per week, including holidays, for 13 weeks; additional groups of mice received no SSL exposure. The mice were then treated in the afternoons of the same days, 5 days per week, with approximately 75 µL (approximately 2 mg/cm^2) of control cream, 0.1%, 0.5%, 1.0%, 5.0%, 10.0%, or 13.0% RP cream, or 0.01% or 0.1% RA cream; additional groups of mice received no cream (Table I2).

The induction of edema and epidermal basal cell proliferation were examined in the MED study. Groups of 42 female mice were exposed to the SSL source at a level of 13.70 $mJ \cdot CIE/cm^2$ in the morning, 5 days per week, including holidays, for 13 weeks. The mice were then treated in the afternoons of the same days, 5 days per week, with no cream or approximately 75 µL (approximately 2 mg/cm^2) of control cream, 2.0%, 10.0%, or 13.0% RP cream. Twenty-four hours after the final exposure to SSL at 13.70 $mJ \cdot CIE/cm^2$ and the final application of creams, six mice from each treatment group, with the exception of the 13.0% RP cream-treated animals, were exposed to a single level of SSL at 0, 60, 100, 140, 180, 220, or 260 $mJ \cdot CIE/cm^2$ (Table I3).

The topical creams were dispensed with a positive-displacement repeater pipette (Eppendorf Repeater® Plus; Fisher Scientific, Houston, TX) equipped with a 2.5 mL reservoir and applied with a gloved finger to the dorsal skin region of the animal for 30 seconds. The site of application extended from the nape of the neck to the base of the tail and midway along both sides of the animal. Untreated animals were not handled. The mice were housed in stainless steel racks that allowed horizontal exposure to the SSL source. The racks were placed at preset positions approximately 2 meters from the light source with the front of the animal cage facing the light source. The duration of the exposure of mice to the light source was based on the dose of SSL administered, the rack position from the lamp source, and the PMA dosimeter output. A typical duration for SSL exposure at a level of 13.70 $mJ \cdot CIE/cm^2$ was 70 minutes.

Source and Specification of Animals
Male and female Crl:SKH-1 (*hr*$^{-}$/*hr*$^{-}$) BR hairless mice were obtained from Charles River Laboratories (Wilmington, MA). The SKH-1 mouse was selected based on its historical use in photocarcinogenesis studies (Kligman, 1996; NTP, 2007, 2010). Mice were approximately 4 weeks old upon receipt, quarantined for 2 weeks, and acclimated for 1 week to the animal room environment prior to the start of the studies. Mice were approximately 8 weeks old at the beginning of the studies. Nine mice were examined during the quarantine period for serological pathogens, parasites, and bacterial pathogens.

Animal Maintenance
Mice were identified by an 11-digit unique animal identification number, the last four digits of which were tattooed onto the mouse tail (AIMS, Inc., Bud Lake, NJ). Mice were housed individually in a stainless steel compartment with a stainless steel wire mesh front. Each cage rack had six compartments per cage, six cages per column, and two columns per rack (EXP355-72; Lenderking Caging Products, Millersville, MD). Cage positions in each cage rack were rotated daily within each column, and column positions were interchanged at weekly rack changes.

Male and female mice were housed in a room with a 12-hour light/dark cycle. The environment of the animal room was monitored by a JC-85 air handler computer system with controls set to maintain a temperature of 25° ± 3° C, a relative humidity of 50% ± 20%, and a minimum of 10 air changes per hour. Feed (autoclaved NIH-31 rodent pellets; Purina Mills, Richmond, NJ) and water (Millipore-filtered Jefferson County municipal tap water via an automated watering system; Edstrom Industries, Waterford, WI) were available *ad libitum*, except during periods of light exposure. Samples of feed lots and processed drinking water for the animals were tested on a regular basis for specified pathogens and mold. Additionally, swabs of all solid surfaces in the animal rooms were monitored quarterly for mold and bacterial pathogens. Microbiology surveillance results indicated the feed lots, water, and room swabs met the NCTR standard with less than 200 cfu of bacteria and 20 cfu of mold. Due to the design of the racks, neither feed consumption nor water consumption was measured during the course of the study.

Clinical Examinations and Pathology
Visual inspection of mouse cages for animal well-being was conducted twice daily, and body weights were recorded on individual animals initially, at weekly intervals during the study, and when an animal was removed from the study. Clinical findings were recorded weekly and when an animal was removed from the study.

At the end of the 13-week studies, mice that were scheduled for terminal kill were fasted overnight and, with the exception of mice that received the 13.0% RP creams, injected intraperitoneally with 200 mg/kg 5-bromo-2′-deoxyuridine (BrdU) (Sigma Chemical Company, St. Louis, MO) dissolved in phosphate-buffered saline (pH 7.4) 2 hours prior to euthanasia by carbon dioxide asphyxiation. Anthropometric measurements of bifold skin thicknesses of mice on the MED study were obtained with a micrometer (Dyer Instruments Company, Lancaster, PA) on left and right rear dorsal and ventral skin sites. At necropsy, all protocol-specified tissues including the duodenum, liver, skin (left and right anterior and posterior, and ventral), spleen, and gross lesions, were examined, removed, and placed in 10% neutral buffered formalin fixative. Additional sections of skin were snap-frozen in liquid nitrogen and archived for RNA, DNA, and protein expression analysis. The protocol-designated tissues and gross lesions were trimmed, processed, mounted in paraffin-plastic blocks, sectioned at 5 µm, and stained with hematoxylin and eosin. Additional samples of control (normal) skin from the right and left front and rear dorsal skin and from the abdominal ventral skin were removed and similarly fixed and processed. When applicable, nonneoplastic lesions were graded for severity.

Microscopic evaluations were completed by the study pathologist. Microscopic findings were tabulated by the individual animal record in the pathology report and classified as skin (site of application), skin (untreated), liver, or spleen. After completion of all microscopic evaluations, the tissue slides, paraffin blocks, and residual wet tissues were stored in the NCTR pathology archives.

Statistical Methods

Survival Analyses

A Cox proportional hazards regression model was used to analyze the survival data for this study (Cox, 1972). This analysis examined the effects of all cream treatments within each SSL exposure for each sex to determine differences among cream groups. Pairwise comparisons of each cream treatment group to the control cream group were performed. An analysis was also performed on the range-finding data to determine the effects of cream (no cream, control cream, 13.0% RP cream, or 0.1% RA cream) and SSL level (0.00 or 13.70 mJ•CIE/cm^2). Pairwise comparisons of cream treatment groups to the control cream group were performed for each SSL exposure.

All decreases in risk relative to the control group were expressed with a Cox hazard ratio between 0 and 1, while all possible increases in risk relative to the baseline group were expressed with a Cox hazard ratio between 1 and infinity. Two-sided P values less than or equal to 0.05 were considered statistically significant. Kaplan-Meier estimator results were used to generate Kaplan-Meier estimates of mean survival times.

Body Weight Analyses

The analysis of mouse body weight data collected during the 13-week studies was conducted using a repeated measures, mixed model analysis of covariance (ANCOVA) with cream treatment group, SSL level, week, and interactions, with baseline weight as the covariate. Due to missing values at the later weeks, only data through week 11 were used. Pairwise comparisons of mean weekly values were obtained using contrasts within a repeated measures, mixed model analysis of variance (ANOVA) for each sex and each light exposure by treatment group, week, and their interactions. Due to missing values at the later weeks, only data through week 11 were used for the analysis with SSL = 0.00 mJ•CIE/cm^2. Week of study was treated as the repeated measure. For comparison tests between treatment groups at each level of SSL exposure, the control cream was the reference group. P values less than or equal to 0.05 were considered statistically significant.

Skinfold Thickness, Epidermal Thickness, and Basal Epithelial Cell Proliferation

Epidermal basal epithelial cell proliferation was determined by the immunohistochemical detection of BrdU incorporation into cellular DNA, using an automated research microscope system (DM/LA; Leica Corp., Wetzlar, Germany) with motorized stage, an integrated color digital camera, optical measuring software (Image-Pro Plus, version 4.5, Media Cybernetics, Inc., Silver Spring, MD), and Microsoft Excel (version 2002 SP3). The ratios of BrdU-positive to the total number of epidermal basal cells counted in 20 frames (~ 240 µm/frame) were determined for each of the two posterior and anterior skin sections of each mouse and are reported as the BrdU labeling index. For epidermal skin thicknesses, the microscopic measures of 10 fields of view were analyzed per mouse. The measurements of skinfold thicknesses, epidermal skin thicknesses, and basal cell proliferation were compiled into Microsoft Excel spreadsheets. Statistical analyses were conducted on these data using a two-way analysis of variance (ANOVA) in experiments where two parameters were tested, e.g., test article and dose of SSL. Analyses were conducted using *SAS*® System for Windows (release 8.02 TS Level 02M0), and comparisons were considered significant at the probability level of $P \leq 0.05$. The data were reported as least square mean values ± standard error of the mean.

Analysis of Incidence and Severity of Histopathology Findings

Nonneoplastic lesions were analyzed using the Poly-k method of Bailer and Portier as modified by Bieler and Williams (1993) and the NIEHS continuity-correction with k=3 to analyze age-adjusted incidence and severity score averages (Bailer and Portier, 1988a,b; Portier and Bailer, 1989). In addition, the distribution-free method of Jonckheere (1954) and Terpstra (1952) was used to compute monotonic trend tests for lesion severity scores, and the method of Shirley (1977) as modified by Williams (1986) was used to compute comparisons of severity scores to those of control cream groups.

Quality Assurance Methods

The 13-week range-finding and MED studies on retinoic acid and retinyl palmitate were conducted in compliance with the FDA Good Laboratory Practice Regulations (21 CFR, Part 58). The Quality Assurance Unit of the NCTR performed audits and inspections of protocols, procedures, data, and reports throughout the course of these studies,

with the exception of the procedures used to determine skin bifold thickness, epidermal thickness, and those used to determine epidermal incorporation of BrdU.

RESULTS

Survival

The disposition of mice on the range-finding study that died early or were removed when moribund, those that reached the terminal kill, and those that were examined microscopically are found in Table I4 for male mice and Table I5 for female mice. Early deaths and moribund animals in both sexes were mainly confined to the 0.1% RA and 13.0% RP treatment groups, with mice that received no SSL treatment having increased incidences. The disposition of female mice on the MED study that died early or were removed when moribund, those that reached the terminal kill, and those that were examined microscopically are found in Table I6. Early deaths and moribund animals were mainly confined to the 13.0% RP treatment group, with all but four mice withdrawn from the study and not examined microscopically.

No Cream

For the range-finding study, 12 male and 12 female mice were initially allocated to each of 14 different treatment groups. No differences in survival were observed in comparison tests between groups of mice that received no cream when compared with mice that received control cream (Table I7).

Retinoic Acid

The topical application of 0.1% RA cream, but not 0.01% RA cream, significantly decreased the survival of mice, and increased Cox survival estimates and hazard ratios of male and female mice in comparison tests with control cream counterparts, especially in the absence of SSL exposure (Table I8).

Retinyl Palmitate

There were no significant differences in Cox estimates or hazard ratios in male or female mice treated with creams containing RP at concentrations of 0.1%, 0.5%, 1.0%, 5.0%, 10.0%, or 13.0% in the presence of SSL exposure or in male mice not exposed to SSL; however, significant increases in the Cox survival estimate and hazard ratio were observed in female mice that received the 13.0% RP cream and were not exposed to SSL (Table I9).

MED Study

Mice on the MED study that received no cream, control cream, or the 2.0%, 10.0%, and 13.0% RP creams had similar survival times and no significant treatment effects were observed for any level of SSL (Table I10).

Body Weight

Summary tables of mean body weights, percentage of mean body weights relative to control weights, survival of mice over the 13 weeks of study, and statistical tests of dose trends and control comparisons are shown for male and female mice on the range-finding study in Tables I11 to I14 and for female mice on the MED study in Tables I15 and I16.

No Cream

In the absence or presence of SSL exposure, no differences in body weight were observed between control cream and no cream treatment groups of male and female mice (Table I11).

Retinoic Acid

The body weights of male and female mice that received topical applications of RA creams are compared to control cream groups in the absence and presence of SSL in Table I12. Sporadic differences in body weights were observed in comparison tests between the RA and control cream groups; however, body weights throughout the study were within 10% of control values. These differences were small and not considered biologically relevant.

Retinyl Palmitate

In the absence of SSL, the body weights of male and female mice were significantly decreased by topical treatments with 13.0% RP cream in comparison tests with control cream treated mice Table I13. For many of the weekly measurements, the body weights of 13.0% RP treatment groups were less than 90% of the control cream animals.

Body weights were also significantly lower than control values in the presence of SSL for mice that received 5.0%, 10.0%, and 13.0% RP cream treatments (Table I14).

MED Study
As found for the range-finding study, no differences in body weights were observed between no cream and control cream treated mice on the MED study (Table I15); however, mice treated with 10.0% or 13.0% RP creams had significantly lower mean weekly body weights in comparison tests with control cream mice (Table I16).

Skinfold Thickness, Epidermal Skin Thickness, and Basal Cell Proliferation

Range-Finding Study

Skinfold Thickness

The results of the skin bifold measurements are shown in Figure I1. In the absence of SSL, the skinfold thickness of male and female mice treated with control creams did not differ from the skinfold thickness of male and female mice that received no cream treatment. In contrast, significantly thicker skinfold measurements were obtained in male mice that received the 0.1% RA cream treatment and in male and female mice that received the 13.0% RP cream treatment compared to mice that received control cream treatment. In male and female mice exposed to 13.70 mJ•CIE/cm^2, significantly greater skinfold thickness measures were observed for the RA cream treatments and for the RP cream treatments at concentrations greater than 5.0%.

Epidermal Skin Thickness

Epidermal skin thickness was measured using a calibrated microscope system in 10 fields of view for each skin site (left rear dorsal, right rear dorsal, and ventral). The results of the ventral, left rear dorsal, and right rear dorsal epidermal skin measurements are shown in Figures I2, I3, and I4, respectively.

There were no differences between the ventral epidermal skin thicknesses of no cream and control cream treated mice in the absence or presence of SSL exposure (Figure I2).

In the presence of SSL, the ventral epidermis of male mice was significantly thicker in mice treated with RP creams at concentrations greater than 0.1% when compared with mice that received control cream treatment (Figure I2). In female mice exposed to SSL, only the 5.0% RP cream treatment resulted in significantly thicker epidermal thickness in the ventral skin compared to control cream treated mice. Since mice tend to remain on their feet during SSL exposure episodes, these results suggest that RP-containing creams enhanced epidermal cell proliferation irrespective of SSL exposure.

In male mice that received no SSL exposure, treatment with control cream significantly enhanced the thickness of the epidermis in left (Figure I3) and right (Figure I4) rear dorsal skin. The epidermis of the left and right rear dorsal skin of male and female mice was significantly thicker in mice that were treated with RP creams at concentrations greater than 0.1% and exposed to SSL at 13.70 mJ•CIE/cm^2.

BrdU Proliferation Index

The BrdU proliferation index was significantly enhanced by control cream treatment in male and female mice in both the absence and presence of SSL exposure (Figure I5). Additionally, the BrdU index was significantly increased in male mice by 5.0% and 10.0% RP cream treatments when exposed to SSL at 13.70 mJ•CIE/cm^2. RP cream treatment had no effect on the BrdU proliferation index in female mice exposed to SSL.

MED Study

Skinfold Thickness

The skin bifold measurements of mice on the MED study are shown in Figure I6. The data were analyzed in two ways; first by treatment to determine the effects of SSL exposure on skin thickness within treatment groups and then by SSL level to determine the effects of treatment at the different light levels.

The skinfold thickness of female mice that received the 10.0% RP cream did not differ by SSL exposure level; however, the level of SSL had a significant effect on the skinfold thickness of female mice that received no cream, control cream, or 2.0% RP cream treatments. As the level of SSL was increased, the bifold skin thickness also

increased, and significantly thicker bifold skin measurements were observed when the level of SSL was equal to or greater than 180 mJ•CIE/cm^2.

When treatments were compared at the same level of SSL, the 10.0% RP treatment group had significantly thicker bifold skin measures than those of the no cream or control cream groups at each level of SSL (except at 260 mJ•CIE/cm^2). These results suggest that the 10.0% RP cream enhanced the bifold skin thickness irrespective of SSL level (Figure I6).

Epidermal Skin Thickness
The results of the microscopic evaluations of epidermal skin thickness are shown for female mice on the MED study in Figure I7. The topical application of 2.0% RP cream resulted in significantly thicker skin epidermis in both the absence and presence of SSL exposure, when compared with the control cream or no cream groups.

BrdU Proliferation Index
The results of the microscopic examination of mouse basal epidermal skin cells for incorporation of BrdU as a marker of cell proliferation are shown in Figure I8. There were no differences in basal cell proliferation among treatment groups in the absence of SSL exposure. The treatment of mouse skin with topical cream that contained 2.0% RP resulted in significantly elevated cell proliferation when exposed to SSL at levels between 60 and 180 mJ•CIE/cm^2. At the higher levels of SSL, all treatment groups were similar in their response to epidermal cell proliferation.

Pathology Findings

The pathology results were based on the 158 male and 164 female mice from the range-finding study and the 168 female mice from the MED study that were examined microscopically. Summaries of their disposition and distribution are presented in Tables I4 through I6.

Nonneoplastic Skin Lesions
Range-Finding Study
The 13-week range-finding study was conducted to determine the test compound doses for the chronic photococarcinogenicity bioassay. The skin from the dorsal region was removed from mice at necropsy, sectioned, and fixed in formalin for microscopic evaluations of lesions. The microscopic findings for male and female mice on the range-finding study are summarized by treatment group in Tables I17 to I22.

The skin of SKH-1 mice has a number of unique histologic characteristics. The epidermis usually consists of one or two layers of squamous cells and, in the untreated animal, is unremarkable. Hair shafts and adnexal structures such as sebaceous glands are either absent or are atypical in location and development. There are often prominent cystic structures in the dermis, which appear to be remnants of hair follicles. The cysts are usually lined by squamous or low cuboidal epithelium and are either empty or contain small amounts of keratinized debris. Fragmented hair shafts are occasionally present within cysts. A minimal inflammatory change in the dermis is characterized by infiltration of lymphocytes, macrophages, and occasional multinucleated foreign body giant cells, and a few plasma cells are frequently associated with smaller hair shaft/cystic structures. These infiltrates are likely due to rupture or leakage of cyst contents into the dermis and were coded as inflammation, granulomatous, of the dermis when more than two foci were noted.

The dermal application of the RP and RA cream formulations in the absence or presence of SSL exposure was associated with diffuse thickening of the epidermis. This change was documented using the term acanthosis. Squamous hyperplasia was only used when there was a focal nodular proliferation of squamous cells. The severity of acanthosis was graded according to the number of epithelial cell layers in the epidermis 1) minimal if three to four cell layers were present; 2) mild if five to six cells layers; 3) moderate if seven to nine cell layers; or 4) marked if greater than nine cell layers.

The incidences and severity scores for skin acanthosis at the site of topical cream application were significantly increased in male (Table I17) and female (Table I18) mice that received topical applications of control cream in both the absence and presence of SSL exposure when compared to the incidences and severity scores in mice that received no cream treatment and the same level of SSL exposure.

The effects of topical application of creams containing RA on the incidences and average severity scores for acanthosis are shown for male mice in Table I19 and female mice in Table I20. The incidences of acanthosis at the site of application were 100% in male and female mice that received either RA or control creams (one exception: female mice, 0.1% RA, no SSL), and no differences in incidences were detected. However, male and female mice that received topical RA cream applications showed significantly increased incidences of acanthosis in untreated skin when compared with control cream mice. In male mice that were not exposed to SSL and in male and female mice that were exposed to SSL, significant dose-related trend increases were observed in the severity scores for skin acanthosis at both treated and untreated skin sites. Additionally, dose-related trend increases in the incidences and severities of dermal inflammation, epidermal necrosis, hematopoietic cell proliferation, and hepatic inflammation were observed in male and female mice that received the RA creams in both the absence and presence of SSL exposure.

The effects of topical application of creams containing RP on the incidences and average severity scores for acanthosis are shown for male mice in Table I21 and female mice in Table I22. In male and female mice that received either no SSL or 13.70 mJ•CIE/cm^2 of SSL, the severity scores for skin acanthosis in treated and untreated skin showed significant dose-related trend increases, and significantly higher severity scores for skin acanthosis were observed in mice that received the RP creams and compared to mice that received control cream treatments. Significant dose-related increases were also observed in male mice that received RP creams in the incidences and severity scores for inflammation of the dermis and epidermal necrosis in the both the absence and presence of SSL. Dose-related trend increases were also observed in the average severity scores for hematopoietic cell proliferation and hepatic inflammation.

MED Study

The 13-week MED study was conducted to determine the effects of RP to alter the minimum dose level of SSL to induce edema in the skin of mice. There were five cream treatment groups (no cream, control cream, and 2.0%, 10.0%, and 13.0% RP) of female mice. The mice in the five cream treatment groups were exposed to 13.70 mJ•CIE/cm^2 of SSL 5 days per week for 13 weeks and, subsequently, were subdivided into seven subgroups based on level of SSL (0, 60, 100, 140, 180, 220, or 260 mJ•CIE/cm^2) administered at the final exposure. The mice were killed by carbon dioxide asphyxiation and necropsied 48 hours after the final administration of SSL. The skin from the dorsal region was removed from mice at necropsy, sectioned, and fixed in formalin for microscopic evaluations of lesions. The microscopic findings for female mice on the MED study are summarized by treatment groups in Tables I23 to I26.

The incidences and severity scores of skin acanthosis in treated and untreated skin are shown in Table I23. The topical application of control cream significantly induced skin acanthosis at the site of application, but not in untreated skin, and higher severity scores for acanthosis were observed in control cream treated mice at each level of SSL and compared to mice that received no cream treatment. There was no incidence of skin acanthosis observed at the site of cream application in mice that received no cream treatment, but acanthosis was observed in 100% of the animals treated with the control cream. Similarly, 100% incidence and significantly higher severity scores for acanthosis were observed in mice that received the RP cream treatments at each level of SSL exposure and both in treated and untreated skin, when compared to mice that received the control cream.

The incidences and severity scores for inflammation of the dermis are shown in Table I24. Inflammation of the dermis was observed in 100% of mice that received the RP cream treatments irrespective of SSL level. The severity scores for this skin lesion showed significant dose-related trend increases at the site of application irrespective of SSL level when compared with severity scores of mice that received the control cream treatment. There were no significant differences in the incidences dermal inflammation in the untreated skin of the same animals.

The incidences and severity scores of suppurative inflammation and necrosis in epidermal skin layers are shown in Tables I25 and I26, respectively. Significant RP dose-related trend increases in incidence and severity scores were observed at levels of SSL below 180 mJ•CIE/cm^2, and significant differences from control cream groups were observed in mice that received the 10% RP creams. Significantly higher severity scores were also observed at SSL levels above 140 mJ•CIE/cm^2 for mice that received the 10% RP creams. Differences in incidences were not observed, since incidence reached 100% in most groups.

CONCLUSIONS

These experiments investigated the potential of topical applications of creams containing retinoic acid or retinyl palmitate to alter the appearance and responses of skin to SSL. The goal of the range-finding study was to determine appropriate dose levels of RA and RP for the photococarcinogenesis bioassay, while the MED study was designed to evaluate the effects of RP on skin structure. Data on skin lesions were collected by histopathlogic evaluation at necropsy.

The results of these preliminary experiments indicated that the incidences and severities of skin acanthosis, inflammation, and necrosis increased in a dose-related manner with the application of RA and RP creams to SKH-1 mice, in the absence and presence of SSL. The topical application of 5.0%, 10.0%, or 13.0% RP and of 0.01% or 0.1% RA was not well tolerated by the SKH-1 mouse irrespective of light treatment. This was evidenced by marked acanthosis, dermal inflammation, and epidermal necrosis. Groups of mice that received RP doses lower than 5.0% in the creams featured less dermal inflammation and no epidermal necrosis. Skin acanthosis was observed in all cream treatment groups, including the control cream treatment.

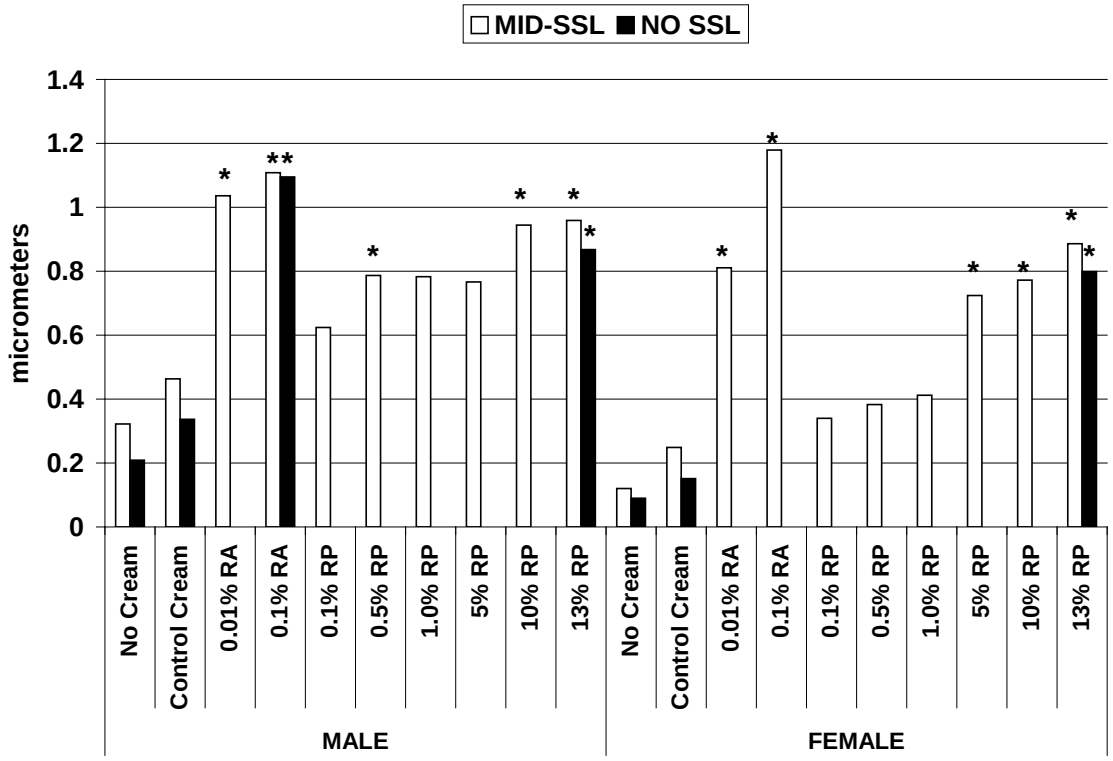


FIGURE I1
Bifold Skin Thickness of Mice on the Range-Finding Study of Retinyl Palmitate
Bars represent the mean of triplicate bifold skin measurements on each mouse, n=7 to 12.
P values are the results of multiple comparison tests (Tukey), and asterisks represent $P \leq 0.05$.

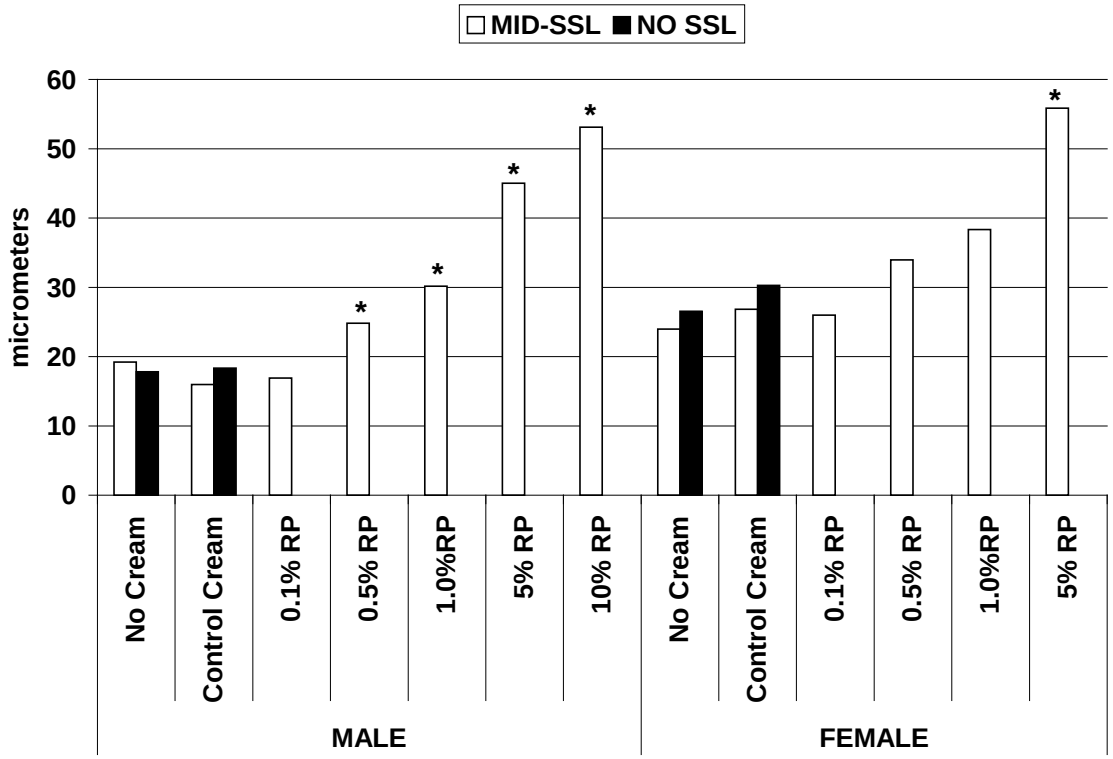


FIGURE I2
Mean Epidermal Thickness of Ventral Skin in Mice on the Range-Finding Study of Retinyl Palmitate
Bars represent the mean epidermal thickness measurements of 10 microscope slide view fields for each mouse, n=7 to 12. P values are the results of multiple comparison tests (Tukey), and asterisks represent $P \leq 0.05$.

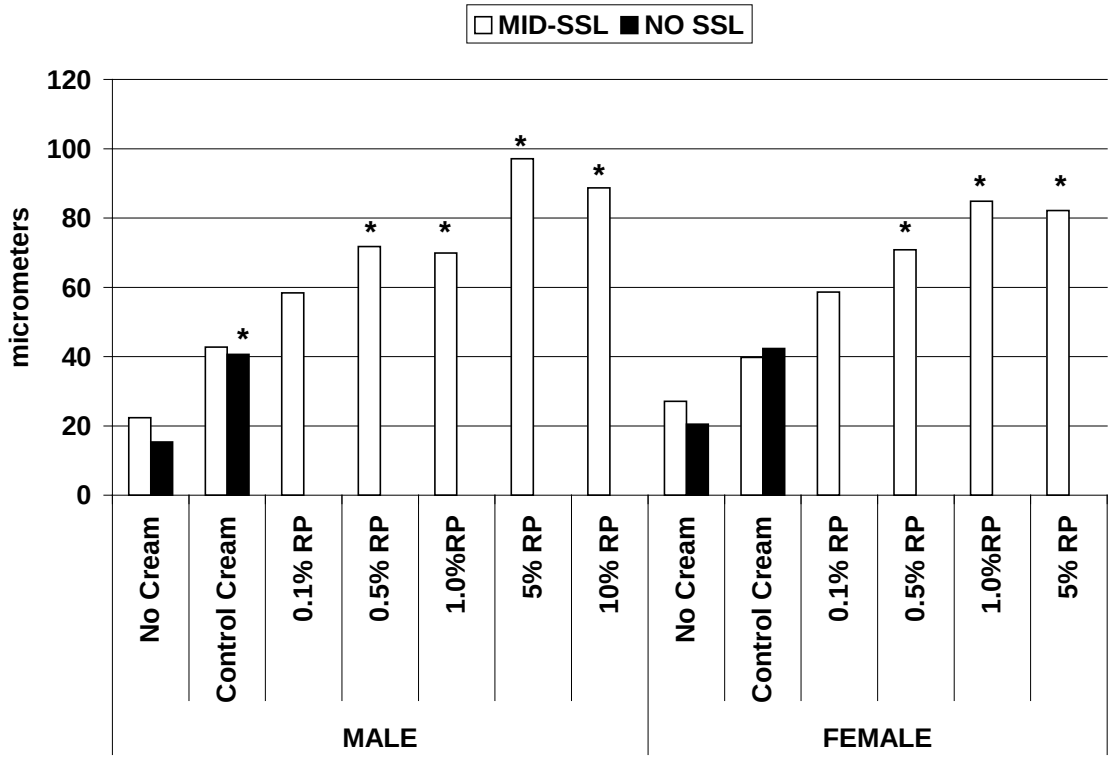


FIGURE I3
Mean Epidermal Thickness of Left Dorsal Skin in Mice on the Range-Finding Study of Retinyl Palmitate
Bars represent the mean epidermal thickness measurements of 10 microscope slide view fields for each mouse, n=7 to 12. P values are the results of multiple comparison tests (Tukey), and asterisks represent $P \leq 0.05$.

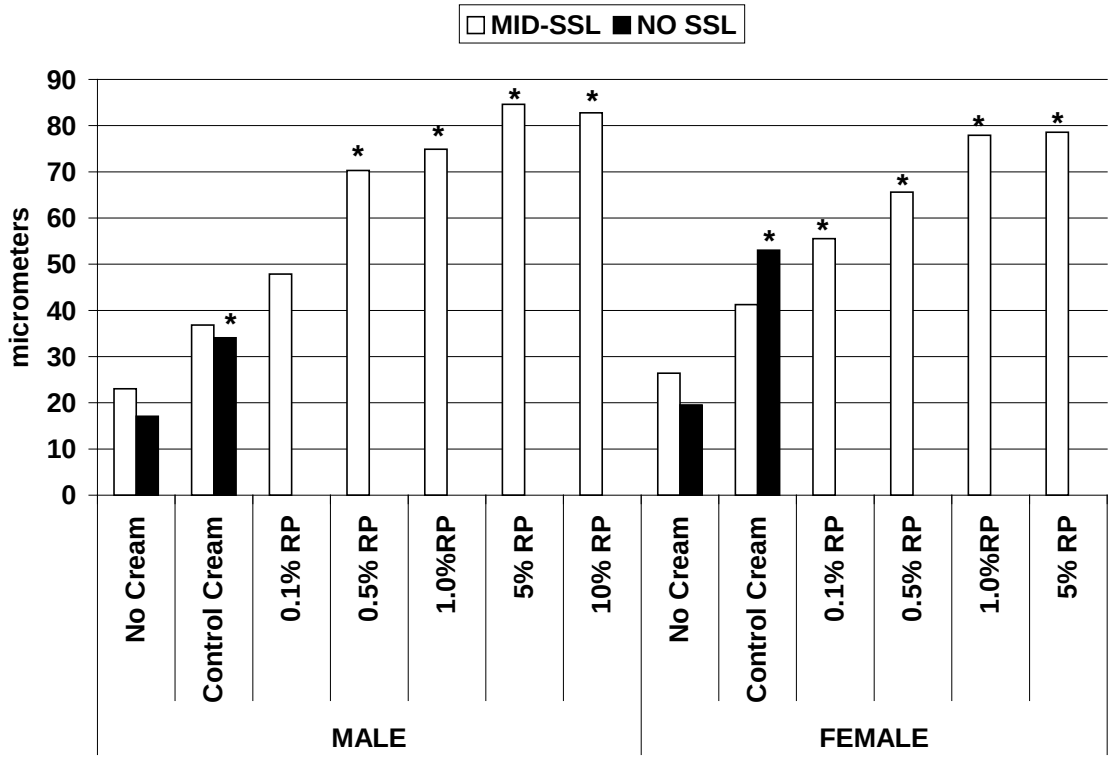


FIGURE I4
Mean Epidermal Thickness of Right Dorsal Skin of Mice on the Range-Finding Study of Retinyl Palmitate
Bars represent the mean epidermal thickness measurements of 10 microscope slide view fields for each mouse, n=7 to 12. P values are the results of multiple comparison tests (Tukey), and asterisks represent $P \leq 0.05$.

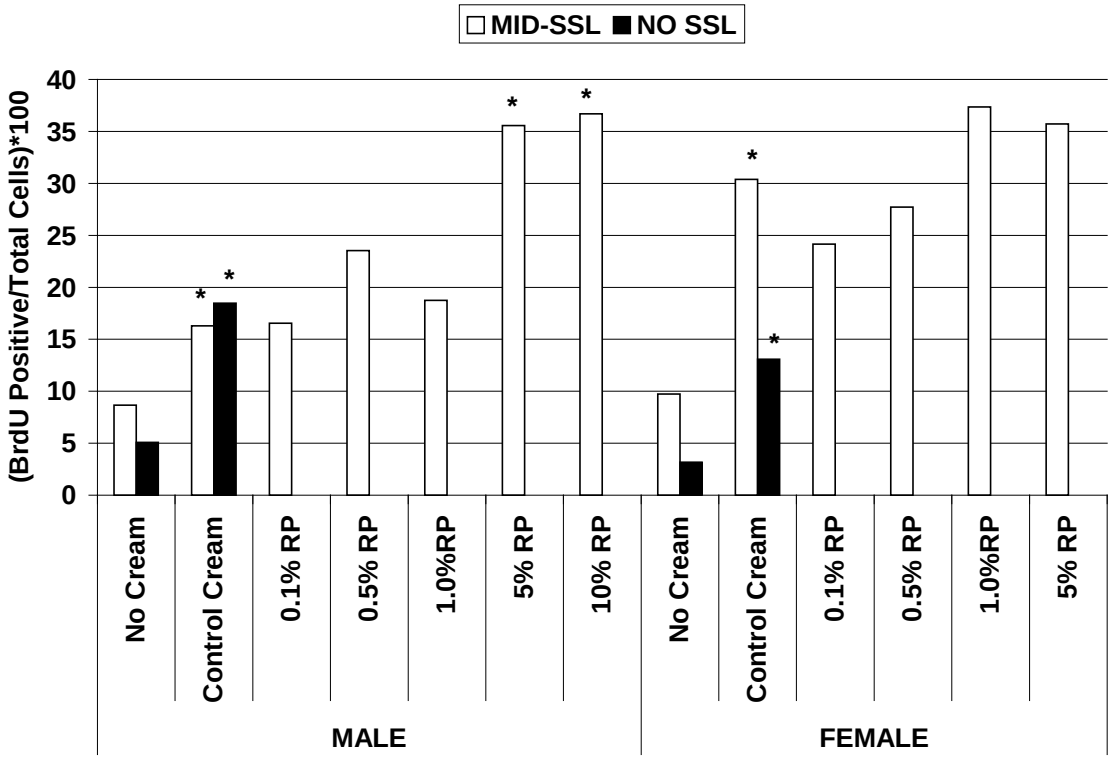


FIGURE I5
Mean BrdU Proliferation Index of Epidermal Basal Cells in the Skin of Mice on the Range-Finding Study of Retinyl Palmitate
Bars represent the mean ratios of BrdU positive to total epidermal basal cells counted in 20 microscope slide view fields of mouse skin (~240 µm/field) per mouse, n=7 to 12. P values are the results of multiple comparison tests (Tukey), and asterisks represent $P \leq 0.05$.

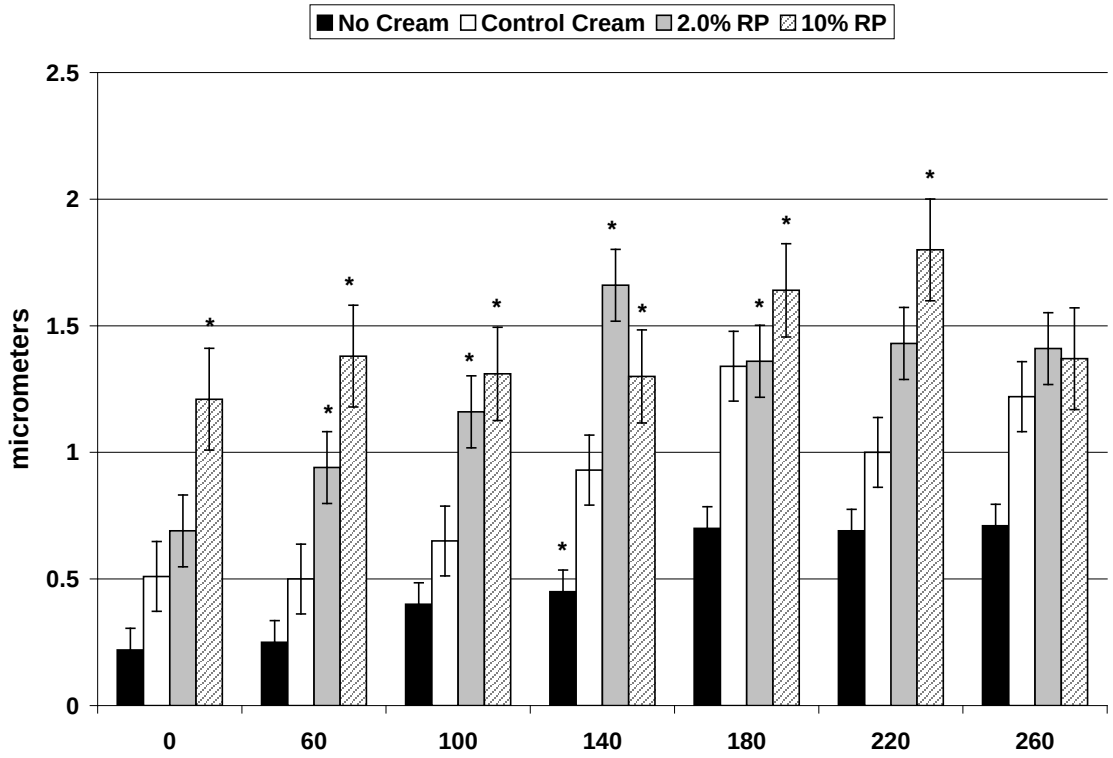


FIGURE I6
Bifold Skin Thickness of Female Mice on the MED Study of Retinyl Palmitate
Bars represent the mean of triplicate bifold skin measurements on each mouse, n=7 to 12.
P values are the results of multiple comparison tests (Tukey), and asterisks represent $P \leq 0.05$.

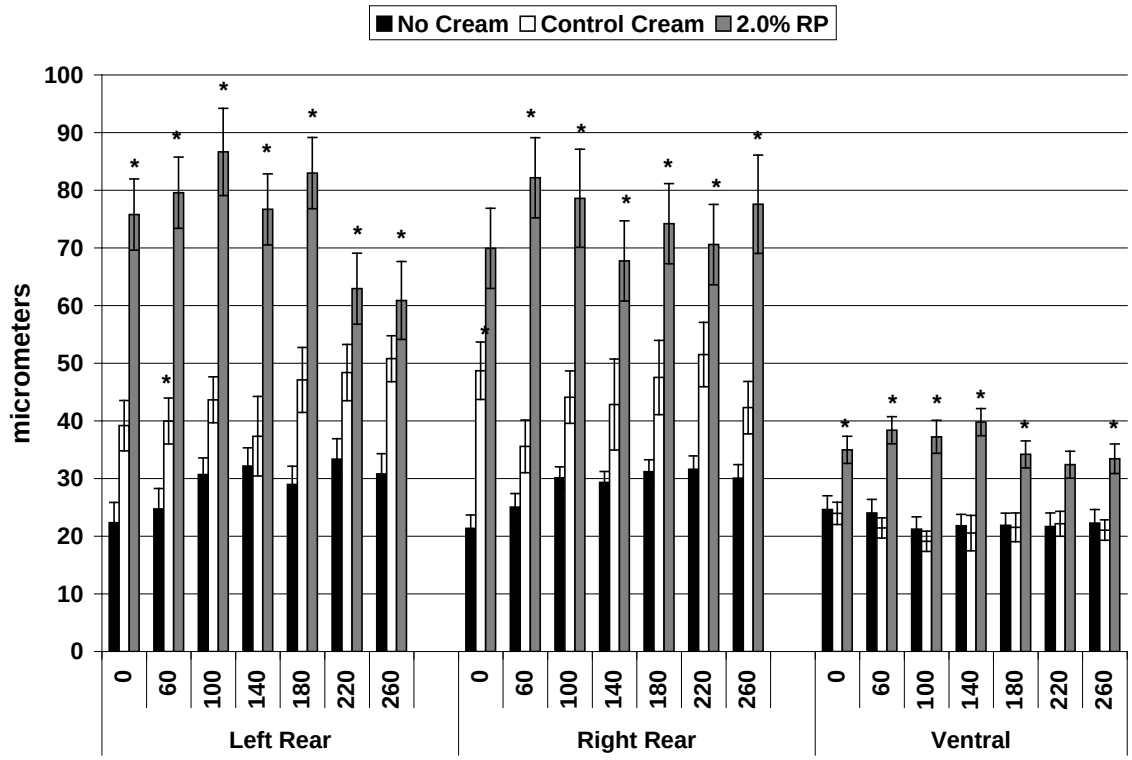


FIGURE I7
Mean Epidermal Skin Thickness in Female Mice on the MED Study of Retinyl Palmitate
Bars represent the mean epidermal thickness measurements of 10 microscope slide view fields for each mouse, n=7 to 12. P values are the results of multiple comparison tests (Tukey), and asterisks represent $P \leq 0.05$.

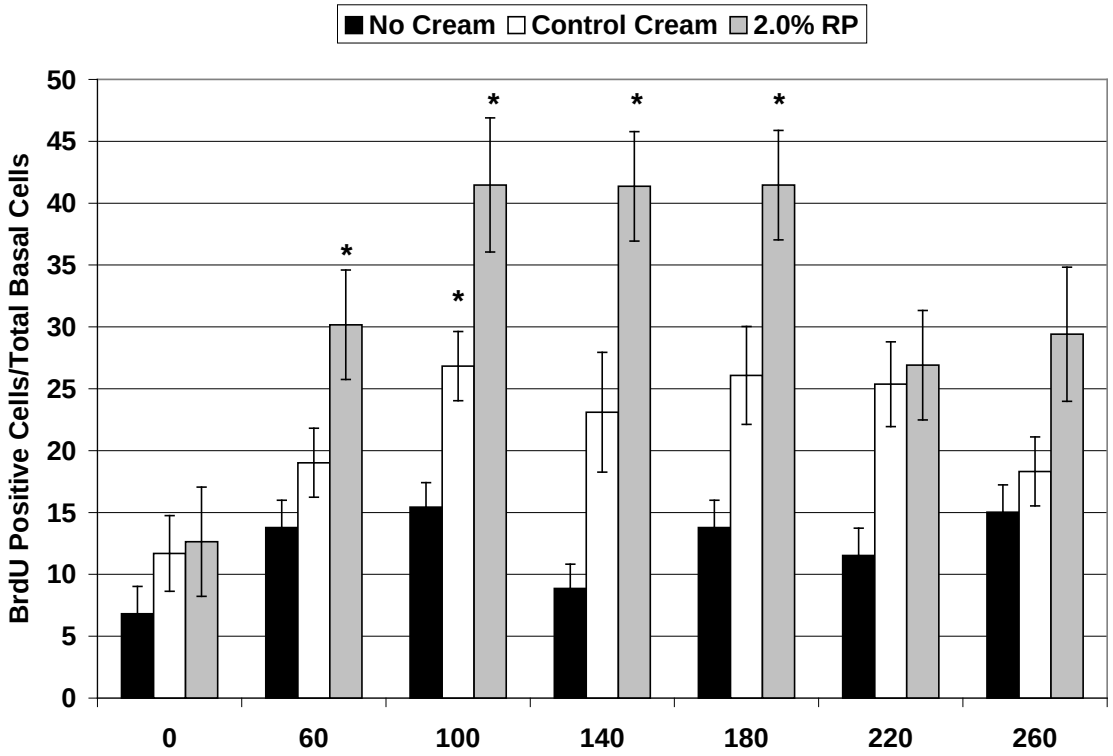


FIGURE I8
Mean BrdU Proliferation Index of Epidermal Basal Cells in the Skin of Female Mice on the MED Study of Retinyl Palmitate
Bars represent the mean ratios of BrdU positive to total epidermal basal cells counted in 20 microscope slide view fields of mouse skin (~240 µm/field) per mouse, n=7 to 12. P values are the results of multiple comparison tests (Tukey), and asterisks represent $P \leq 0.05$.

TABLE I1
Formulation of the Base Cream Used in the 13-Week Study of Retinoic Acid and Retinyl Palmitate

Item No.	Phase[a]	Ingredient	% (w/w)
1	A	Water, deionized	59.65
2	A	Disodium EDTA	0.10
3	A	Glycerin 96%	2.50
4	A	Carbopol 981 (2% solution)	7.50
5	B	Mineral oil 65/75	7.50
6	B	BRIJ 721	1.50
7	B	Stearic acid XXX	2.00
8	B	Cetearyl alcohol	0.25
9	B	Octyl palmitate	2.50
10	C	NaOH (20% solution), sufficient quantity to adjust pH to 7.0	0.50
11	D	Germaben II	1.00
Total			85.00

[a] Manufacturing instructions: Heat phase A to 75° C. Add phase B to phase A. Add phase C. Cool to 40° C and add phase D. Homogenize mixture and package cream at 35° C.

TABLE I2
Treatment and Level of Light Exposure Administered to Mice on the Range-Finding Study of Retinoic Acid and Retinyl Palmitate

Cream Application	Simulated Solar Light (SSL) Exposure Levels	
	0.00 mJ•CIE/cm^2/day	**13.70 mJ•CIE/cm^2/day**
No cream	12 males 12 females	12 males 12 females
Control cream	12 males 12 females	12 males 12 females
0.1% Retinyl palmitate		12 males 12 females
0.5% Retinyl palmitate		12 males 12 females
1.0% Retinyl palmitate		12 males 12 females
5.0% Retinyl palmitate		12 males 12 females
10.0% Retinyl palmitate		12 males 12 females
13.0% Retinyl palmitate	12 males 12 females	12 males 12 females
0.01% Retinoic acid		12 males 12 females
0.1% Retinoic acid	12 males 12 females	12 males 12 females

TABLE I3
Treatment and Level of Final Light Exposure Administered to Female Mice on the MED Study of Retinyl Palmitate

	Simulated Solar Light (SSL) Exposure Levels						
Cream Application	**0 mJ•CIE/cm^2**	**60 mJ•CIE/cm^2**	**100 mJ•CIE/cm^2**	**140 mJ•CIE/cm^2**	**180 mJ•CIE/cm^2**	**220 mJ•CIE/cm^2**	**260 mJ•CIE/cm^2**
No cream	6 females	6 females	6 females	6 females	6 females	6 females	6 females
Control cream	6 females	6 females	6 females	6 females	6 females	6 females	6 females
2.0% Retinyl palmitate	6 females	6 females	6 females	6 females	6 females	6 females	6 females
10.0% Retinyl palmitate	6 females	6 females	6 females	6 females	6 females	6 females	6 females
13.0% Retinyl palmitate	—[a]	—	—	—	—	—	—

[a] Due to severe skin damage, the 13.0% group was not administered the final light exposure.

TABLE I4
Disposition of Male Mice on the 13-Week Range-Finding Study of Retinoic Acid and Retinyl Palmitate

SSL/Test Substance	Mice Initially in Study	Natural Death	Moribund	Terminal Kill	Examined Microscopically
0.00 mJ•CIE/cm^2					
No cream	12	0	0	12	12
Control cream	12	0	0	12	12
0.1% Retinyl palmitate					
0.5% Retinyl palmitate					
1.0% Retinyl palmitate					
5.0% Retinyl palmitate					
10.0% Retinyl palmitate					
13.0% Retinyl palmitate	12	1	2	9	12
0.01% Retinoic acid					
0.1% Retinoic acid	12	0	6	6	10
13.70 mJ•CIE/cm^2					
No cream	12	0	0	12	12
Control cream	12	1	0	11	12
0.1% Retinyl palmitate	12	0	0	12	12
0.5% Retinyl palmitate	12	0	0	12	12
1.0% Retinyl palmitate	12	0	0	12	12
5.0% Retinyl palmitate	12	1	0	12	12
10.0% Retinyl palmitate	12	1	0	11	11
13.0% Retinyl palmitate	12	0	0	12	12
0.01% Retinoic acid	12	0	0	12	12
0.1% Retinoic acid	12	0	2	10	11

TABLE I5
Disposition of Female Mice on the 13-Week Range-Finding Study of Retinoic Acid and Retinyl Palmitate

SSL/Test Substance	Mice Initially in Study	Natural Death	Moribund	Terminal Kill	Examined Microscopically
0.00 mJ•CIE/cm^2					
No cream	12	0	0	12	12
Control cream	12	0	0	12	12
0.1% Retinyl palmitate					
0.5% Retinyl palmitate					
1.0% Retinyl palmitate					
5.0% Retinyl palmitate					
10.0% Retinyl palmitate					
13.0% Retinyl palmitate	12	0	5	7	11
0.01% Retinoic acid					
0.1% Retinoic acid	12	2	10	0	6
13.70 mJ•CIE/cm^2					
No cream	12	0	0	12	12
Control cream	12	0	0	12	12
0.1% Retinyl palmitate	12	0	0	12	12
0.5% Retinyl palmitate	12	0	0	12	12
1.0% Retinyl palmitate	12	0	0	12	12
5.0% Retinyl palmitate	12	1	0	11	10
10.0% Retinyl palmitate	12	0	1	11	12
13.0% Retinyl palmitate	12	0	1	11	11
0.01% Retinoic acid	12	0	0	12	12
0.1% Retinoic acid	12	0	5	7	12

TABLE I6
Disposition of Female Mice on the MED Study

SSL/Test Substance	Mice Initially in Study	Natural Death	Moribund	Terminal Kill	Examined Microscopically
0.00 mJ•CIE/cm^2					
No cream	6	0	0	6	6
Control cream	6	0	0	6	6
2.0% Retinyl palmitate	6	0	0	6	6
10.0% Retinyl palmitate	6	1	0	5	5
13.0% Retinyl palmitate	6	0	2	4	1
60 mJ•CIE/cm^2					
No cream	6	0	0	6	6
Control cream	6	0	0	6	6
2.0% Retinyl palmitate	6	0	0	6	6
10.0% Retinyl palmitate	6	1	0	5	5
13.0% Retinyl palmitate	6	0	0	6	1
100 mJ•CIE/cm^2					
No cream	6	0	0	6	6
Control cream	6	0	0	6	6
2.0% Retinyl palmitate	6	0	0	6	6
10.0% Retinyl palmitate	6	0	0	6	6
13.0% Retinyl palmitate	6	1	1	4	0
140 mJ•CIE/cm^2					
No cream	6	0	0	6	6
Control cream	6	0	0	6	6
2.0% Retinyl palmitate	6	0	0	6	6
10.0% Retinyl palmitate	6	0	0	6	6
13.0% Retinyl palmitate	6	0	1	5	0
180 mJ•CIE/cm^2					
No cream	6	0	0	6	6
Control cream	6	0	0	6	6
2.0% Retinyl palmitate	6	0	0	6	6
10.0% Retinyl palmitate	6	0	0	6	6
13.0% Retinyl palmitate	6	0	0	6	1
220 mJ•CIE/cm^2					
No cream	6	0	0	6	6
Control cream	6	0	0	6	6
2.0% Retinyl palmitate	6	0	0	6	6
10.0% Retinyl palmitate	6	1	0	5	5
13.0% Retinyl palmitate	6	0	0	6	0
260 mJ•CIE/cm^2					
No cream	6	0	0	6	6
Control cream	6	0	0	6	6
2.0% Retinyl palmitate	6	0	0	6	6
10.0% Retinyl palmitate	6	0	1	5	5
13.0% Retinyl palmitate	6	0	2	4	1

TABLE I7
Cox Survival Estimates and Hazard Ratios of No Cream Compared to Control Cream Treatment Groups of Mice on the Range-Finding Study

SSL Exposure Level	Treatment	P Value[a]	Cox Survival Estimate	Standard Error	Hazard Ratio
Male					
0.00 mJ•CIE/cm^2	No cream	0.522	0.66	1.04	1.94
13.70 mJ•CIE/cm^2	No cream	0.536	−0.76	1.22	0.47
Female					
0.00 mJ•CIE/cm^2	No cream	0.477	0.73	1.03	2.08
13.70 mJ•CIE/cm^2	No cream	1.000	0.00	1.41	1.00

[a] Tests formed by suitable contrasts with the control cream group, which was assigned a Cox survival estimate of 0.00 and a Cox hazard ratio of 1.00

TABLE I8
Cox Survival Estimates and Hazard Ratios of Retinoic Acid Cream Compared to Control Cream Treatment Groups of Mice on the Range-Finding Study

Treatment	P Value[a]	Cox Survival Estimate	Standard Error	Hazard Ratio
Male				
0.00 mJ•CIE/cm^2				
0.1% Retinoic acid	**0.022**	2.46	1.07	11.69
13.70 mJ•CIE/cm^2				
0.01% Retinoic acid	0.536	-0.76	1.22	0.47
0.1% Retinoic acid	0.648	0.42	0.91	1.52
Female				
0.00 mJ•CIE/cm^2				
0.1% Retinoic acid	**<0.001**	4.24	1.06	69.09
13.70 mJ•CIE/cm^2				
0.01% Retinoic acid	1.000	0.00	1.41	1.00
0.1% Retinoic acid	**0.048**	2.14	1.08	8.46

[a] Tests formed by suitable contrasts with the control cream group, which was assigned a Cox survival estimate of 0.00 and a Cox hazard ratio of 1.00. Significant P values appear in bold-faced type.

TABLE I9
Cox Survival Estimates and Hazard Ratios of Retinyl Palmitate Cream Compared to Control Cream Treatment Groups of Mice on the Range-Finding Study

Treatment	P Value[a]	Cox Survival Estimate	Standard Error	Hazard Ratio
Male				
0.00 mJ•CIE/cm^2				
13.0% Retinyl palmitate	0.182	1.49	1.12	4.45
13.70 mJ•CIE/cm^2				
0.1% Retinyl palmitate	0.536	−0.76	1.22	0.47
0.5% Retinyl palmitate	0.536	−0.76	1.22	0.47
1.0% Retinyl palmitate	0.536	−0.76	1.22	0.47
5.0% Retinyl palmitate	0.536	−0.76	1.22	0.47
10.0% Retinyl palmitate	0.995	0.01	1.00	1.01
13.0% Retinyl palmitate	0.536	−0.76	1.22	0.47
Female				
0.00 mJ•CIE/cm^2				
13.0% Retinyl palmitate	**0.045**	2.17	1.08	8.76
13.70 mJ•CIE/cm^2				
0.1% Retinyl palmitate	1.000	0.00	1.41	1.00
0.5% Retinyl palmitate	1.000	0.00	1.41	1.00
1.0% Retinyl palmitate	1.000	0.00	1.41	1.00
5.0% Retinyl palmitate	0.529	0.77	1.22	2.16
10.0% Retinyl palmitate	0.541	0.75	1.22	2.11
13.0% Retinyl palmitate	0.531	0.77	1.22	2.15

[a] Tests formed by suitable contrasts with the control cream group, which was assigned a Cox survival estimate of 0.00 and a Cox hazard ratio of 1.00. Significant P values appear in bold-faced type.

TABLE I10
Cox Survival Estimates and Hazard Ratios of Retinyl Palmitate Cream Compared to Control Cream Treatment Groups of Female Mice on the MED Study

SSL Exposure Level	Treatment	P Value[a]	Cox Survival Estimate	Standard Error	Hazard Ratio
0 mJ•CIE/cm^2	No cream	1.000	0.00	1.00	1.00
	2.0% Retinyl palmitate	1.000	0.00	1.00	1.00
	10.0% Retinyl palmitate	0.551	0.54	0.91	1.72
	13.0% Retinyl palmitate	0.250	1.00	0.87	2.71
60 mJ•CIE/cm^2	No cream	1.000	0.00	1.00	1.00
	2.0% Retinyl palmitate	1.000	0.00	1.00	1.00
	10.0% Retinyl palmitate	0.548	0.55	0.91	1.73
	13.0% Retinyl palmitate	1.000	0.00	1.00	1.00
100 mJ•CIE/cm^2	No cream	1.000	0.00	1.00	1.00
	2.0% Retinyl palmitate	1.000	0.00	1.00	1.00
	10.0% Retinyl palmitate	1.000	0.00	1.00	1.00
	13.0% Retinyl palmitate	0.248	1.00	0.87	2.72
140 mJ•CIE/cm^2	No cream	1.000	0.00	1.00	1.00
	2.0% Retinyl palmitate	1.000	0.00	1.00	1.00
	10.0% Retinyl palmitate	1.000	0.00	1.00	1.00
	13.0% Retinyl palmitate	0.552	0.54	0.91	1.72
180 mJ•CIE/cm^2	No cream	1.000	0.00	1.00	1.00
	2.0% Retinyl palmitate	1.000	0.00	1.00	1.00
	10.0% Retinyl palmitate	1.000	0.00	1.00	1.00
	13.0% Retinyl palmitate	1.000	0.00	1.00	1.00
220 mJ•CIE/cm^2	No cream	1.000	0.00	1.00	1.00
	2.0% Retinyl palmitate	1.000	0.00	1.00	1.00
	10.0% Retinyl palmitate	0.550	0.55	0.91	1.73
	13.0% Retinyl palmitate	1.000	0.00	1.00	1.00
260 mJ•CIE/cm^2	No cream	1.000	0.00	1.00	1.00
	2.0% Retinyl palmitate	1.000	0.00	1.00	1.00
	10.0% Retinyl palmitate	0.545	0.55	0.91	1.74
	13.0% Retinyl palmitate	0.244	1.01	0.87	2.75

[a] Tests formed by suitable contrasts with the control cream group, which was assigned a Cox survival estimate of 0.00 and a Cox hazard ratio of 1.00

TABLE I11
Mean Body Weights and Survival of No Cream Compared to Control Cream Treatment Groups of Mice on the Range-Finding Study

	Control Cream		No Cream			
Week	No of Survivors	Mean Body Wt. ± SE[a]	No of Survivors	Mean Body Wt. ± SE	P Value[b]	Wt. (%) of Controls
0.00 mJ•CIE/cm^2						
Male						
1	12	31.5 ± 0.4	12	31.4 ± 0.4	0.841	99.7
2	12	32.1 ± 0.4	12	32.0 ± 0.4	0.811	99.6
3	12	32.9 ± 0.4	12	33.1 ± 0.4	0.768	100.5
4	12	33.4 ± 0.4	12	33.3 ± 0.4	0.870	99.7
5	12	34.2 ± 0.4	12	34.6 ± 0.4	0.445	101.4
6	12	33.5 ± 0.4	12	33.8 ± 0.4	0.594	101.0
7	12	34.6 ± 0.5	12	34.7 ± 0.5	0.837	100.4
8	12	34.0 ± 0.5	12	34.0 ± 0.5	0.952	99.9
9	12	34.6 ± 0.5	12	34.6 ± 0.5	0.992	100.0
10	12	34.5 ± 0.6	12	34.6 ± 0.6	0.867	100.4
11	12	34.7 ± 0.5	12	34.7 ± 0.5	0.989	100.0
Mean (1–11)		33.6 ± 0.3		33.7 ± 0.3	0.842	100.2
Female						
1	12	24.8 ± 0.3	12	24.3 ± 0.3	0.198	97.9
2	12	25.1 ± 0.3	12	25.1 ± 0.3	0.851	99.7
3	12	25.3 ± 0.4	12	24.9 ± 0.4	0.449	98.5
4	12	26.1 ± 0.4	12	26.3 ± 0.4	0.761	100.7
5	12	25.9 ± 0.5	12	25.8 ± 0.5	0.890	99.7
6	12	26.7 ± 0.5	12	26.7 ± 0.5	0.986	100.0
7	12	26.5 ± 0.5	12	25.9 ± 0.5	0.467	98.0
8	12	27.3 ± 0.5	12	27.0 ± 0.5	0.651	98.8
9	12	27.3 ± 0.6	12	27.0 ± 0.6	0.765	99.1
10	12	27.3 ± 0.5	12	26.9 ± 0.5	0.593	98.5
11	12	28.2 ± 0.6	12	27.5 ± 0.6	0.461	97.8
Mean (1–11)		26.4 ± 0.3		26.1 ± 0.3	0.501	99.0

TABLE I11
Mean Body Weights and Survival of No Cream Compared to Control Cream Treatment Groups of Mice on the Range-Finding Study

		Control Cream		No Cream			
	Week	No. of Survivors	Mean Body Wt. ± SE	No. of Survivors	Mean Body Wt. ± SE	P Value	Wt. (%) of Controls
13.70 mJ•CIE/cm^2							
Male							
	1	12	31.8 ± 0.3	12	31.5 ± 0.4	0.540	99.0
	2	12	32.8 ± 0.3	12	32.0 ± 0.4	0.249	97.8
	3	12	33.1 ± 0.4	12	32.9 ± 0.5	0.808	99.5
	4	12	33.5 ± 0.3	12	33.7 ± 0.5	0.804	100.5
	5	12	34.2 ± 0.4	12	34.5 ± 0.5	0.725	100.7
	6	12	33.9 ± 0.4	12	33.9 ± 0.5	0.996	100.0
	7	12	34.9 ± 0.5	12	35.0 ± 0.5	0.810	100.5
	8	12	34.7 ± 0.5	12	34.5 ± 0.6	0.785	99.4
	9	12	35.7 ± 0.5	12	35.2 ± 0.5	0.414	98.4
	10	12	35.5 ± 0.5	12	34.5 ± 0.6	0.228	97.2
	11	12	35.9 ± 0.5	12	35.1 ± 0.5	0.287	97.7
	12	12	36.3 ± 0.5	12	35.6 ± 0.5	0.334	98.0
	13	12	36.7 ± 0.5	12	35.5 ± 0.5	0.100	96.6
	Mean (1–13)		34.5 ± 0.3		34.1 ± 0.3	0.377	98.8
Female							
	1	12	25.2 ± 0.3	12	25.2 ± 0.3	0.953	100.1
	2	12	25.5 ± 0.3	12	25.8 ± 0.3	0.500	101.0
	3	12	25.3 ± 0.4	12	27.3 ± 0.4	**<0.001**	107.9
	4	12	26.5 ± 0.4	12	28.2 ± 0.3	**<0.001**	106.4
	5	12	25.9 ± 0.5	12	25.4 ± 0.4	0.429	98.1
	6	12	27.2 ± 0.5	12	26.2 ± 0.4	0.074	96.1
	7	12	26.9 ± 0.5	12	26.8 ± 0.5	0.827	99.5
	8	12	28.0 ± 0.5	12	27.7 ± 0.5	0.656	99.0
	9	12	27.8 ± 0.6	12	28.2 ± 0.5	0.617	101.2
	10	12	28.1 ± 0.5	12	28.5 ± 0.5	0.646	101.2
	11	12	28.5 ± 0.6	12	28.8 ± 0.5	0.722	100.8
	12	12	28.4 ± 0.5	12	28.6 ± 0.5	0.771	100.7
	13	12	28.8 ± 0.5	12	28.8 ± 0.5	0.914	99.7
	Mean (1–13)		27.1 ± 0.3		27.3 ± 0.3	0.531	100.9

[a] Least squares means and standard errors are presented in grams.
[b] P values represent pairwise comparisons of group body weight to that of the control cream group. Significant P values (P≤0.05) are shown in bold-faced type.

TABLE I12
Mean Body Weights and Survival of Retinoic Acid Compared to Control Cream Treatment Groups of Mice on the Range-Finding Study

Week	Control Cream		0.01% Retinoic Acid Cream				0.1% Retinoic Acid Cream			
	No. of Survivors	Mean Body Wt. ± SE[a]	No. of Survivors	Mean Body Wt. ± SE	P Value[b]	Wt. (%) of Controls	No. of Survivors	Mean Body Wt. ± SE	P Value[b]	Wt. (%) of Controls
0.00 mJ•CIE/cm^2										
Male										
1	12	31.5 ± 0.4					12	31.0 ± 0.4	0.314	98.4
2	12	32.1 ± 0.4					12	30.7 ± 0.4	**0.014**	95.7
3	12	32.9 ± 0.4					12	32.3 ± 0.4	0.296	98.2
4	12	33.4 ± 0.4					12	33.2 ± 0.4	0.702	99.3
5	12	34.2 ± 0.4					12	34.3 ± 0.4	0.839	100.4
6	12	33.5 ± 0.4					12	33.7 ± 0.4	0.670	100.8
7	12	34.6 ± 0.5					12	35.5 ± 0.5	0.200	102.7
8	12	34.0 ± 0.5					10	33.9 ± 0.5	0.841	99.6
9	12	34.6 ± 0.5					10	35.6 ± 0.5	0.156	102.9
10	12	34.5 ± 0.6					9	35.6 ± 0.6	0.178	103.3
11	12	34.7 ± 0.5					7	36.7 ± 0.6	**0.010**	105.6
Mean (1-11)		33.6 ± 0.3						33.9 ± 0.3	0.564	100.7
Female										
1	12	24.8 ± 0.3					12	24.5 ± 0.3	0.456	98.8
2	12	25.1 ± 0.3					12	25.8 ± 0.3	0.102	102.8
3	12	25.3 ± 0.4					12	25.9 ± 0.4	0.305	102.1
4	12	26.1 ± 0.4					12	27.6 ± 0.4	**0.013**	105.6
5	12	25.9 ± 0.5					12	27.8 ± 0.5	**0.003**	107.3
6	12	26.7 ± 0.5					12	29.1 ± 0.5	**<0.001**	108.7
7	12	26.5 ± 0.5					10	28.6 ± 0.5	**0.005**	107.9
8	12	27.3 ± 0.5					10	30.2 ± 0.6	**<0.001**	110.7
9	12	27.3 ± 0.6					8	27.6 ± 0.7	0.748	101.1
10	12	27.3 ± 0.5					5	28.5 ± 0.8	0.184	104.5
11	12	28.2 ± 0.6					5	28.5 ± 0.9	0.761	101.2
Mean (1-11)		26.4 ± 0.3						27.6 ± 0.3	**0.005**	104.6

TABLE I12
Mean Body Weights and Survival of Retinoic Acid Compared to Control Cream Treatment Groups of Mice on the Range-Finding Study

	Control Cream		0.01% Retinoic Acid Cream				0.1% Retinoic Acid Cream			
Week	No. of Survivors	Mean Body Wt. ± SE	No. of Survivors	Mean Body Wt. ± SE	P Value	Wt. (%) of Controls	No. of Survivors	Mean Body Wt. ± SE	P Value	Wt. (%) of Controls
13.70 mJ•CIE/cm^2										
Male										
1	12	31.8 ± 0.4	12	31.8 ± 0.4	0.912	99.8	12	31.7 ± 0.4	0.764	99.5
2	12	32.8 ± 0.4	12	32.4 ± 0.4	0.562	98.9	12	32.1 ± 0.4	0.303	98.0
3	12	33.1 ± 0.5	12	32.6 ± 0.5	0.440	98.5	11	33.3 ± 0.5	0.749	100.6
4	12	33.5 ± 0.5	12	33.4 ± 0.5	0.866	99.7	11	32.9 ± 0.5	0.330	98.1
5	12	34.2 ± 0.5	12	34.8 ± 0.5	0.385	101.7	11	34.4 ± 0.5	0.835	100.4
6	12	33.9 ± 0.5	12	33.0 ± 0.5	0.232	97.5	11	32.9 ± 0.5	0.158	97.0
7	12	34.9 ± 0.5	12	35.0 ± 0.5	0.843	100.4	11	35.1 ± 0.5	0.771	100.6
8	12	34.7 ± 0.6	12	34.7 ± 0.6	0.966	99.9	11	32.6 ± 0.6	**0.009**	93.8
9	12	35.7 ± 0.5	12	35.5 ± 0.5	0.693	99.2	11	35.0 ± 0.5	0.301	97.9
10	12	35.5 ± 0.6	12	36.1 ± 0.6	0.441	101.8	11	35.4 ± 0.6	0.900	99.7
11	11	35.9 ± 0.6	12	36.2 ± 0.5	0.786	100.6	11	34.4 ± 0.6	0.057	95.8
12	11	36.3 ± 0.5	12	36.3 ± 0.5	0.977	99.9	11	35.1 ± 0.5	0.123	96.8
13	11	36.7 ± 0.5	12	36.4 ± 0.5	0.709	99.2	10	35.2 ± 0.6	**0.047**	95.7
Mean (1-13)		34.5 ± 0.3		34.5 ± 0.3	0.875	99.8		33.8 ± 0.3	0.129	98.0
Female										
1	12	25.2 ± 0.3	12	25.3 ± 0.3	0.729	100.6	12	25.7 ± 0.3	0.271	101.9
2	12	25.5 ± 0.3	12	25.8 ± 0.3	0.424	101.2	12	26.0 ± 0.3	0.203	101.9
3	12	25.3 ± 0.4	12	26.4 ± 0.4	**0.033**	104.4	12	26.6 ± 0.4	**0.017**	105.0
4	12	26.5 ± 0.3	12	26.9 ± 0.3	0.400	101.5	12	27.4 ± 0.3	0.052	103.5
5	12	25.9 ± 0.4	12	26.9 ± 0.4	0.120	103.8	12	27.3 ± 0.4	**0.031**	105.3
6	12	27.2 ± 0.4	12	27.7 ± 0.4	0.400	101.8	12	27.6 ± 0.4	0.506	101.5
7	12	26.9 ± 0.5	11	27.4 ± 0.5	0.518	101.6	12	27.6 ± 0.5	0.310	102.4
8	12	28.0 ± 0.5	12	28.4 ± 0.5	0.500	101.6	12	28.9 ± 0.5	0.170	103.2
9	12	27.8 ± 0.5	12	29.0 ± 0.5	0.075	104.3	12	29.7 ± 0.5	**0.006**	106.6
10	12	28.1 ± 0.5	12	28.8 ± 0.5	0.364	102.4	9	30.0 ± 0.6	**0.016**	106.7
11	12	28.5 ± 0.5	12	29.2 ± 0.5	0.304	102.5	9	30.4 ± 0.5	**0.011**	106.4
12	12	28.4 ± 0.5	12	29.3 ± 0.5	0.197	103.1	8	30.8 ± 0.6	**0.002**	108.3
13	12	28.8 ± 0.5	12	29.8 ± 0.5	0.220	103.2	7	30.6 ± 0.7	**0.046**	106.0
Mean (1-13)		27.1 ± 0.3		27.8 ± 0.3	0.074	102.5		28.3 ± 0.3	**0.001**	104.6

[a] Least squares means and standard errors are presented in grams.
[b] P values represent pairwise comparisons of group body weight to that of the control cream group. Significant P values ($P \leq 0.05$) are shown in bold-faced type.

TABLE I13
Mean Body Weights and Survival of Retinyl Palmitate Compared to Control Cream Treatment Groups of Mice on the Range-Finding Study – 0.00 mJ•CIE/cm^2 SSL

Week	Control Cream		13.0% Retinyl Palmitate Cream			
	No. of Survivors	Mean Body Wt. ± SE[a]	No. of Survivors	Mean Body Wt. ± SE	P Value[b]	Wt. (%) of Controls
Male						
1	12	31.5 ± 0.4	12	28.6 ± 0.4	**<0.001**	90.9
2	12	32.1 ± 0.4	12	28.6 ± 0.4	**<0.001**	89.0
3	12	32.9 ± 0.4	12	28.7 ± 0.4	**<0.001**	87.1
4	12	33.4 ± 0.4	12	29.2 ± 0.4	**<0.001**	87.4
5	12	34.2 ± 0.4	12	29.6 ± 0.4	**<0.001**	86.6
6	12	33.5 ± 0.4	12	29.4 ± 0.4	**<0.001**	87.9
7	12	34.6 ± 0.5	12	31.0 ± 0.5	**<0.001**	89.7
8	12	34.0 ± 0.5	12	30.5 ± 0.5	**<0.001**	89.7
9	12	34.6 ± 0.5	12	32.1 ± 0.5	**<0.001**	92.6
10	12	34.5 ± 0.6	12	30.5 ± 0.6	**<0.001**	88.5
11	12	34.7 ± 0.5	11	31.4 ± 0.5	**<0.001**	90.5
Mean (1-11)		33.6 ± 0.3		30.0 ± 0.3	**<0.001**	89.1
Female						
1	12	24.8 ± 0.3	12	23.1 ± 0.3	**<0.001**	93.2
2	12	25.1 ± 0.3	12	22.3 ± 0.3	**<0.001**	88.8
3	12	25.3 ± 0.4	12	22.8 ± 0.4	**<0.001**	90.2
4	12	26.1 ± 0.4	12	23.5 ± 0.4	**<0.001**	90.0
5	12	25.9 ± 0.5	12	23.7 ± 0.5	**0.001**	91.5
6	12	26.7 ± 0.5	12	24.6 ± 0.5	**0.001**	92.0
7	12	26.5 ± 0.5	11	23.8 ± 0.5	**<0.001**	89.9
8	12	27.3 ± 0.5	11	25.3 ± 0.5	**0.007**	92.6
9	12	27.3 ± 0.6	11	24.8 ± 0.6	**0.004**	90.9
10	12	27.3 ± 0.5	11	25.7 ± 0.6	**0.043**	94.1
11	12	28.2 ± 0.6	10	25.2 ± 0.6	**0.001**	89.5
Mean (1-11)		26.4 ± 0.3		24.1 ± 0.3	**<0.001**	91.2

[a] Least squares means and standard errors are presented in grams.
[b] P values represent pairwise comparisons of group body weight to that of the control cream group. Significant P values (P≤0.05) are shown in bold-faced type.

TABLE I14
Mean Body Weights and Survival of Retinyl Palmitate Compared to Control Cream Treatment Groups of Mice on the Range-Finding Study – 13.70 mJ•CIE/cm^2 SSL

	Control Cream		0.1% Retinyl Palmitate Cream				0.5% Retinyl Palmitate Cream				1.0% Retinyl Palmitate Cream			
Week	No.	Mean Wt. ± SE[a]	No.	Mean Wt. ± SE	P Value[b]	% Wt. Control	No.	Mean Wt. ± SE	P Value	% Wt. Control	No.	Mean Wt. ± SE	P Value	% Wt. Control
Male														
1	12	31.8 ± 0.4	12	33.7 ± 0.4	**0.001**	105.8	12	31.5 ± 0.4	0.510	98.9	12	31.6 ± 0.4	0.629	99.2
2	12	32.8 ± 0.4	12	34.0 ± 0.4	0.057	103.7	12	32.8 ± 0.4	0.994	100.0	12	31.4 ± 0.4	**0.035**	95.9
3	12	33.1 ± 0.5	12	34.6 ± 0.5	**0.017**	104.6	12	33.5 ± 0.5	0.493	101.3	12	31.9 ± 0.5	0.063	96.4
4	12	33.5 ± 0.5	12	35.0 ± 0.5	**0.030**	104.2	12	34.3 ± 0.5	0.262	102.2	12	32.4 ± 0.5	0.088	96.7
5	12	34.2 ± 0.5	12	35.5 ± 0.5	0.062	103.6	12	34.1 ± 0.5	0.812	99.5	12	33.2 ± 0.5	0.093	96.8
6	12	33.9 ± 0.5	12	35.4 ± 0.5	**0.031**	104.5	12	33.9 ± 0.5	0.976	100.1	12	32.9 ± 0.5	0.165	97.1
7	12	34.9 ± 0.5	12	36.4 ± 0.5	**0.036**	104.3	12	35.0 ± 0.5	0.865	100.3	12	33.7 ± 0.5	0.109	96.7
8	12	34.7 ± 0.6	12	35.9 ± 0.6	0.138	103.5	12	34.3 ± 0.6	0.619	98.8	12	32.9 ± 0.6	**0.030**	94.9
9	12	35.7 ± 0.5	12	36.6 ± 0.5	0.229	102.4	12	35.8 ± 0.5	0.939	100.2	12	34.5 ± 0.5	0.082	96.6
10	12	35.5 ± 0.6	12	36.6 ± 0.6	0.197	103.0	12	35.6 ± 0.6	0.907	100.3	12	34.2 ± 0.6	0.106	96.3
11	11	35.9 ± 0.6	12	37.5 ± 0.5	**0.042**	104.4	12	36.0 ± 0.5	0.914	100.2	12	35.1 ± 0.5	0.294	97.7
12	11	36.3 ± 0.5	12	37.4 ± 0.5	0.141	103.0	12	36.0 ± 0.5	0.725	99.3	12	35.0 ± 0.5	0.077	96.4
13	11	36.7 ± 0.5	12	37.5 ± 0.5	0.279	102.3	12	36.3 ± 0.5	0.565	98.8	12	35.0 ± 0.5	**0.028**	95.4
Mean (1–13)		34.5 ± 0.3		35.8 ± 0.3	**0.005**	103.8		34.5 ± 0.3	0.990	100.0		33.4 ± 0.3	**0.011**	96.6
Female														
1	12	25.2 ± 0.3	12	24.6 ± 0.3	0.187	97.8	12	25.5 ± 0.3	0.434	101.3	12	24.8 ± 0.3	0.355	98.4
2	12	25.5 ± 0.3	12	25.6 ± 0.3	0.894	100.2	12	25.2 ± 0.3	0.463	98.9	12	25.3 ± 0.3	0.535	99.1
3	12	25.3 ± 0.4	12	25.6 ± 0.4	0.556	101.2	12	25.7 ± 0.4	0.464	101.5	12	25.5 ± 0.4	0.701	100.8
4	12	26.5 ± 0.3	12	26.2 ± 0.3	0.532	98.9	12	26.6 ± 0.3	0.818	100.4	12	26.6 ± 0.3	0.777	100.5
5	12	25.9 ± 0.4	12	26.0 ± 0.4	0.831	100.5	12	25.9 ± 0.4	0.939	99.8	12	26.0 ± 0.4	0.892	100.3
6	12	27.2 ± 0.4	12	27.1 ± 0.4	0.825	99.5	12	26.8 ± 0.4	0.487	98.5	12	27.4 ± 0.4	0.724	100.8
7	12	26.9 ± 0.5	12	26.9 ± 0.5	0.981	99.9	12	26.5 ± 0.5	0.546	98.6	12	26.7 ± 0.5	0.731	99.2
8	12	28.0 ± 0.5	12	27.8 ± 0.5	0.722	99.2	12	26.3 ± 0.5	**0.010**	94.0	12	27.7 ± 0.5	0.623	98.8
9	12	27.8 ± 0.5	12	28.1 ± 0.5	0.688	101.0	12	27.4 ± 0.5	0.501	98.4	12	28.0 ± 0.5	0.790	100.6
10	12	28.1 ± 0.5	12	28.3 ± 0.5	0.813	100.6	12	27.5 ± 0.5	0.422	97.9	12	28.3 ± 0.5	0.846	100.5
11	12	28.5 ± 0.5	12	28.7 ± 0.5	0.805	100.6	12	28.0 ± 0.5	0.393	98.0	12	28.6 ± 0.5	0.890	100.3
12	12	28.4 ± 0.5	12	28.6 ± 0.5	0.817	100.6	12	27.7 ± 0.5	0.256	97.3	12	28.5 ± 0.5	0.901	100.3
13	12	28.8 ± 0.5	12	29.0 ± 0.5	0.870	100.4	12	27.9 ± 0.5	0.201	96.6	12	28.5 ± 0.5	0.675	98.9
Mean (1–13)		27.1 ± 0.3		27.1 ± 0.3	0.976	100.0		26.7 ± 0.3	0.266	98.5		27.1 ± 0.3	0.940	99.9

TABLE I14
Mean Body Weights and Survival of Retinyl Palmitate Compared to Control Cream Treatment Groups of Mice on the Range-Finding Study – 13.70 mJ•CIE/cm^2 SSL

	5.0% Retinyl Palmitate Cream				10.0% Retinyl Palmitate Cream				13.0% Retinyl Palmitate Cream			
Week	No.	Mean Wt. ± SE	P Value	% Wt. Control	No.	Mean Wt. ± SE	P Value	% Wt. Control	No.	Mean Wt. ± SE	P Value	% Wt. Control
Male												
1	12	30.8 ± 0.4	0.062	96.8	12	29.9 ± 0.4	**<0.001**	94.0	12	30.2 ± 0.4	**0.002**	94.8
2	12	31.1 ± 0.4	**0.008**	94.8	12	28.8 ± 0.4	**<0.001**	87.8	12	30.3 ± 0.4	**<0.001**	92.5
3	12	31.3 ± 0.5	**0.006**	94.7	12	29.9 ± 0.5	**<0.001**	90.6	12	31.0 ± 0.5	**0.001**	93.7
4	12	31.0 ± 0.5	**<0.001**	92.3	12	30.3 ± 0.5	**<0.001**	90.3	12	30.2 ± 0.5	**<0.001**	90.0
5	12	31.6 ± 0.5	**<0.001**	92.3	12	31.3 ± 0.5	**<0.001**	91.3	12	31.0 ± 0.5	**<0.001**	90.6
6	12	31.1 ± 0.5	**<0.001**	91.9	12	29.9 ± 0.5	**<0.001**	88.2	12	29.5 ± 0.5	**<0.001**	87.2
7	12	32.8 ± 0.5	**0.003**	93.9	12	32.1 ± 0.5	**<0.001**	92.1	12	31.7 ± 0.5	**<0.001**	90.9
8	12	31.2 ± 0.6	**<0.001**	89.9	12	31.3 ± 0.6	**<0.001**	90.2	12	30.4 ± 0.6	**<0.001**	87.5
9	12	33.3 ± 0.5	**0.001**	93.2	12	32.5 ± 0.5	**<0.001**	91.1	12	31.7 ± 0.5	**<0.001**	88.7
10	12	32.8 ± 0.6	**0.001**	92.3	12	32.2 ± 0.6	**<0.001**	90.7	12	31.9 ± 0.6	**<0.001**	89.8
11	12	33.3 ± 0.5	**0.001**	92.8	11	32.4 ± 0.6	**<0.001**	90.1	12	31.7 ± 0.5	**<0.001**	88.1
12	12	33.2 ± 0.5	**<0.001**	91.5	11	32.6 ± 0.5	**<0.001**	89.9	12	32.4 ± 0.5	**<0.001**	89.2
13	12	33.0 ± 0.5	**<0.001**	90.0	11	33.1 ± 0.5	**<0.001**	90.1	12	32.4 ± 0.5	**<0.001**	88.4
Mean (1–13)		32.0 ± 0.3	**<0.001**	92.8		31.3 ± 0.3	**<0.001**	90.5		31.1 ± 0.3	**<0.001**	90.0
Female												
1	11	24.6 ± 0.3	0.209	97.8	12	24.4 ± 0.3	0.084	97.1	12	23.9 ± 0.3	**0.004**	95.0
2	11	24.2 ± 0.3	**0.001**	94.8	12	24.5 ± 0.3	**0.007**	96.0	12	23.8 ± 0.3	**<0.001**	93.3
3	11	24.4 ± 0.4	0.104	96.5	12	24.9 ± 0.4	0.385	98.2	12	24.2 ± 0.4	**0.046**	95.8
4	11	25.1 ± 0.4	**0.004**	94.7	12	25.8 ± 0.3	0.170	97.5	11	24.9 ± 0.3	**0.001**	93.9
5	11	24.7 ± 0.5	0.052	95.1	12	25.7 ± 0.4	0.723	99.1	11	25.1 ± 0.5	0.204	96.8
6	11	25.8 ± 0.4	**0.023**	94.9	12	25.6 ± 0.4	**0.007**	94.1	11	25.3 ± 0.4	**0.001**	92.8
7	11	25.3 ± 0.5	**0.013**	93.9	12	25.6 ± 0.5	**0.034**	94.9	11	25.1 ± 0.5	**0.006**	93.2
8	11	26.0 ± 0.5	**0.003**	92.9	12	26.4 ± 0.5	**0.016**	94.4	11	26.0 ± 0.5	**0.003**	92.8
9	11	26.5 ± 0.5	**0.044**	95.1	12	27.0 ± 0.5	0.236	97.2	11	26.7 ± 0.5	0.103	96.0
10	11	27.3 ± 0.5	0.288	97.1	12	27.1 ± 0.5	0.183	96.5	11	26.6 ± 0.6	**0.049**	94.7
11	11	27.4 ± 0.5	0.103	96.0	12	27.2 ± 0.5	**0.041**	95.1	11	26.3 ± 0.5	**0.002**	92.2
12	11	26.9 ± 0.5	**0.025**	94.5	11	27.7 ± 0.5	0.265	97.3	11	26.5 ± 0.5	**0.007**	93.3
13	11	27.1 ± 0.6	**0.028**	94.0	11	27.6 ± 0.6	0.115	95.7	11	26.4 ± 0.6	**0.002**	91.5
Mean (1–13)		25.8 ± 0.3	**0.001**	95.2		26.1 ± 0.3	**0.009**	96.4		25.5 ± 0.3	**<0.001**	93.9

[a] Least squares means and standard errors are presented in grams.
[b] P values represent pairwise comparisons of mean body weights to that of the control group. Significant P values (P≤0.05) are shown in bold-faced type.

TABLE I15
Mean Body Weights and Survival of No Cream Compared to Control Cream Treatment Groups of Female Mice on the MED Study

	Control Cream			No Cream			
	Week	No. of Survivors	Mean Body Wt. ± SE[a]	No. of Survivors	Mean Body Wt. ± SE	P Value[b]	Wt. (%) of Controls
0 mJ•CIE/cm^2							
	1	6	25.0 ± 0.6	6	25.7 ± 0.6	0.372	103.0
	2	6	25.7 ± 0.6	6	25.9 ± 0.6	0.809	100.8
	3	6	26.0 ± 0.7	6	26.2 ± 0.7	0.880	100.5
	4	6	26.8 ± 0.7	6	27.4 ± 0.7	0.528	102.2
	5	6	27.1 ± 0.7	6	27.0 ± 0.7	0.938	99.7
	6	6	27.0 ± 0.7	6	27.2 ± 0.7	0.840	100.8
	7	6	27.3 ± 0.7	6	27.7 ± 0.7	0.668	101.6
	8	6	27.7 ± 0.7	6	27.5 ± 0.7	0.848	99.3
	9	6	27.6 ± 0.7	6	27.7 ± 0.7	0.940	100.3
	10	6	28.3 ± 0.7	6	28.1 ± 0.7	0.816	99.2
	11	6	28.1 ± 0.7	6	27.9 ± 0.7	0.881	99.5
	12	6	28.2 ± 0.8	6	28.5 ± 0.8	0.826	100.9
	13	6	29.3 ± 0.7	6	28.7 ± 0.7	0.606	98.1
	Mean (0–13)		27.2 ± 0.5		27.3 ± 0.5	0.863	100.4
60 mJ•CIE/cm^2							
	1	6	25.4 ± 0.6	6	24.9 ± 0.6	0.589	98.2
	2	6	25.6 ± 0.6	6	25.1 ± 0.6	0.547	98.0
	3	6	25.9 ± 0.7	6	25.5 ± 0.7	0.591	98.1
	4	6	26.3 ± 0.7	6	26.4 ± 0.7	0.954	100.2
	5	6	26.8 ± 0.7	6	26.4 ± 0.7	0.664	98.4
	6	6	26.7 ± 0.7	6	26.8 ± 0.7	0.933	100.3
	7	6	27.4 ± 0.7	6	27.5 ± 0.7	0.943	100.3
	8	6	27.3 ± 0.7	6	27.3 ± 0.7	0.984	100.1
	9	6	26.8 ± 0.7	6	27.1 ± 0.7	0.732	101.3
	10	6	27.9 ± 0.7	6	27.7 ± 0.7	0.840	99.3
	11	6	27.7 ± 0.7	6	27.9 ± 0.7	0.831	100.7
	12	6	27.8 ± 0.8	6	28.3 ± 0.8	0.656	101.7
	13	6	28.2 ± 0.7	6	28.4 ± 0.7	0.834	100.8
	Mean (0–13)		26.9 ± 0.5		26.9 ± 0.5	0.942	99.8
100 mJ•CIE/cm^2							
	1	6	25.0 ± 0.6	6	24.7 ± 0.6	0.693	98.7
	2	6	25.8 ± 0.6	6	25.5 ± 0.6	0.746	98.9
	3	6	26.1 ± 0.7	6	25.7 ± 0.7	0.657	98.4
	4	6	26.7 ± 0.7	6	26.5 ± 0.7	0.808	99.2
	5	6	26.9 ± 0.7	6	26.2 ± 0.7	0.494	97.5
	6	6	27.1 ± 0.7	6	26.9 ± 0.7	0.863	99.3
	7	6	27.4 ± 0.7	6	27.0 ± 0.7	0.690	98.6
	8	6	26.8 ± 0.7	6	26.8 ± 0.7	0.953	99.8
	9	6	28.1 ± 0.7	6	26.9 ± 0.7	0.238	95.9
	10	6	28.0 ± 0.7	6	27.2 ± 0.7	0.445	97.3
	11	6	28.1 ± 0.7	6	27.4 ± 0.7	0.467	97.5
	12	6	28.3 ± 0.8	6	27.4 ± 0.8	0.405	96.8
	13	6	28.9 ± 0.7	6	27.6 ± 0.7	0.213	95.5
	Mean (0–13)		27.2 ± 0.5		26.6 ± 0.5	0.375	97.9

TABLE I15
Mean Body Weights and Survival of No Cream Compared to Control Cream Treatment Groups of Female Mice on the MED Study

	Control Cream			No Cream			
	Week	No. of Survivors	Mean Body Wt. ± SE	No. of Survivors	Mean Body Wt. ± SE	P Value	Wt. (%) of Controls
140 mJ•CIE/cm^2							
	1	6	25.8 ± 0.6	6	24.8 ± 0.6	0.236	96.2
	2	6	26.1 ± 0.6	6	25.7 ± 0.6	0.587	98.2
	3	6	26.1 ± 0.7	6	26.0 ± 0.7	0.902	99.6
	4	6	26.5 ± 0.7	6	26.6 ± 0.7	0.870	100.6
	5	6	27.0 ± 0.7	6	26.4 ± 0.7	0.569	97.9
	6	6	27.0 ± 0.7	6	26.6 ± 0.7	0.687	98.5
	7	6	27.0 ± 0.7	6	27.8 ± 0.7	0.435	102.9
	8	6	27.2 ± 0.7	6	27.3 ± 0.7	0.958	100.2
	9	6	27.1 ± 0.7	6	27.1 ± 0.7	0.957	100.2
	10	6	26.8 ± 0.7	6	27.8 ± 0.7	0.303	103.7
	11	6	27.7 ± 0.7	6	27.6 ± 0.7	0.919	99.7
	12	6	27.9 ± 0.8	6	26.7 ± 0.8	0.267	95.7
	13	6	28.3 ± 0.7	6	28.0 ± 0.7	0.766	98.9
	Mean (0–13)		27.0 ± 0.5		26.8 ± 0.5	0.798	99.4
180 mJ•CIE/cm^2							
	1	6	25.4 ± 0.6	6	25.0 ± 0.6	0.629	98.4
	2	6	25.6 ± 0.6	6	25.3 ± 0.6	0.770	99.0
	3	6	26.0 ± 0.7	6	25.8 ± 0.7	0.829	99.2
	4	6	26.4 ± 0.7	6	26.6 ± 0.7	0.830	100.8
	5	6	26.5 ± 0.7	6	26.9 ± 0.7	0.673	101.6
	6	6	26.9 ± 0.7	6	27.4 ± 0.7	0.626	101.9
	7	6	27.4 ± 0.7	6	27.9 ± 0.7	0.577	102.0
	8	6	27.6 ± 0.7	6	27.9 ± 0.7	0.754	101.1
	9	6	28.1 ± 0.7	6	27.8 ± 0.7	0.812	99.2
	10	6	27.9 ± 0.7	6	28.0 ± 0.7	0.918	100.4
	11	6	28.0 ± 0.7	6	28.4 ± 0.7	0.727	101.2
	12	6	28.2 ± 0.8	6	28.7 ± 0.8	0.604	102.0
	13	6	29.5 ± 0.7	6	29.4 ± 0.7	0.924	99.7
	Mean (0–13)		27.2 ± 0.5		27.3 ± 0.5	0.828	100.5
220 mJ•CIE/cm^2							
	1	6	25.5 ± 0.6	6	25.3 ± 0.6	0.763	99.0
	2	6	25.5 ± 0.6	6	26.3 ± 0.6	0.391	102.9
	3	6	25.7 ± 0.7	6	26.7 ± 0.7	0.249	104.2
	4	6	26.2 ± 0.7	6	27.4 ± 0.7	0.181	104.8
	5	6	26.7 ± 0.7	6	27.7 ± 0.7	0.346	103.5
	6	6	26.6 ± 0.7	6	27.9 ± 0.7	0.184	105.1
	7	6	26.9 ± 0.7	6	28.3 ± 0.7	0.142	105.4
	8	6	27.4 ± 0.7	6	28.1 ± 0.7	0.542	102.2
	9	6	27.7 ± 0.7	6	28.4 ± 0.7	0.488	102.5
	10	6	27.6 ± 0.7	6	28.4 ± 0.7	0.422	102.8
	11	6	27.8 ± 0.7	6	28.8 ± 0.7	0.287	103.7
	12	6	27.5 ± 0.8	6	29.1 ± 0.8	0.157	105.6
	13	6	28.6 ± 0.7	6	29.4 ± 0.7	0.476	102.6
	Mean (0–13)		26.9 ± 0.5		27.8 ± 0.5	0.152	103.4

TABLE I15
Mean Body Weights and Survival of No Cream Compared to Control Cream Treatment Groups of Female Mice on the MED Study

	Control Cream			No Cream			
	Week	No. of Survivors	Mean Body Wt. ± SE	No. of Survivors	Mean Body Wt. ± SE	P Value	Wt. (%) of Controls
260 mJ•CIE/cm^2							
	1	6	24.4 ± 0.6	6	24.7 ± 0.6	0.757	101.0
	2	6	25.2 ± 0.6	6	25.5 ± 0.6	0.705	101.3
	3	6	25.6 ± 0.7	6	26.4 ± 0.7	0.424	102.9
	4	6	26.1 ± 0.7	6	26.9 ± 0.7	0.398	103.0
	5	6	26.4 ± 0.7	6	27.9 ± 0.7	0.128	105.7
	6	6	26.7 ± 0.7	6	27.5 ± 0.7	0.423	103.1
	7	6	26.8 ± 0.7	6	28.1 ± 0.7	0.221	104.5
	8	6	27.0 ± 0.7	6	28.0 ± 0.7	0.344	103.5
	9	6	27.4 ± 0.7	6	28.6 ± 0.7	0.240	104.2
	10	6	27.4 ± 0.7	6	28.5 ± 0.7	0.256	104.0
	11	6	27.6 ± 0.7	6	28.9 ± 0.7	0.188	104.5
	12	6	27.5 ± 0.8	6	28.8 ± 0.8	0.227	104.8
	13	6	28.1 ± 0.7	6	29.3 ± 0.7	0.272	104.1
	Mean (0–13)		26.6 ± 0.5		27.6 ± 0.5	0.131	103.6

[a] Least squares means and standard errors are presented in grams.
[b] P values represent pairwise comparisons of group body weight to that of the control cream group.

TABLE I16
Body Weight and Survival of Retinyl Palmitate Compared to Control Cream Treatment Groups of Female Mice on the MED Study

	Control Cream		2.0% Retinyl Palmitate Cream				10.0% Retinyl Palmitate Cream				13.0% Retinyl Palmitate Cream			
Week	No.	Mean Wt. ± SE[a]	No.	Mean Wt. ± SE	P Value[b]	% Wt. Control	No.	Mean Wt. ± SE	P Value	% Wt. Control	No.	Mean Wt. ± SE	P Value	% Wt. Control
0 mJ•CIE/cm^2														
1	6	25.0 ± 0.6	6	25.8 ± 0.6	0.329	103.2	6	24.0 ± 0.6	0.244	96.1	6	24.6 ± 0.6	0.616	98.3
2	6	25.7 ± 0.6	6	25.7 ± 0.6	0.978	100.1	6	23.6 ± 0.6	**0.013**	91.7	6	24.2 ± 0.6	0.074	94.0
3	6	26.0 ± 0.7	6	25.9 ± 0.7	0.905	99.6	6	23.5 ± 0.7	**0.007**	90.4	6	24.3 ± 0.7	0.055	93.2
4	6	26.8 ± 0.7	6	26.4 ± 0.7	0.610	98.2	6	24.4 ± 0.7	**0.010**	91.0	6	24.1 ± 0.7	**0.003**	89.8
5	6	27.1 ± 0.7	6	26.9 ± 0.7	0.858	99.3	6	24.8 ± 0.7	**0.020**	91.5	6	25.3 ± 0.7	0.070	93.4
6	6	27.0 ± 0.7	6	27.0 ± 0.7	0.969	100.1	6	25.6 ± 0.7	0.184	94.9	5	25.2 ± 0.8	0.101	93.6
7	6	27.3 ± 0.7	6	27.6 ± 0.7	0.730	101.2	6	25.4 ± 0.7	0.061	93.2	5	25.4 ± 0.7	0.076	93.3
8	6	27.7 ± 0.7	6	27.1 ± 0.7	0.614	98.2	6	25.5 ± 0.7	**0.035**	92.3	5	25.3 ± 0.8	**0.025**	91.5
9	6	27.6 ± 0.7	6	27.9 ± 0.7	0.729	101.2	5	25.8 ± 0.7	0.081	93.6	5	25.2 ± 0.8	**0.019**	91.3
10	6	28.3 ± 0.7	6	27.6 ± 0.7	0.487	97.6	5	25.9 ± 0.7	**0.017**	91.5	5	26.2 ± 0.8	**0.046**	92.8
11	6	28.1 ± 0.7	6	27.8 ± 0.7	0.799	99.1	5	26.0 ± 0.7	**0.036**	92.6	4	24.3 ± 0.8	**<0.001**	86.6
12	6	28.2 ± 0.8	6	27.8 ± 0.8	0.674	98.4	5	26.7 ± 0.8	0.172	94.5	4	25.4 ± 0.9	**0.019**	90.0
13	6	29.3 ± 0.7	6	28.3 ± 0.7	0.353	96.7	5	27.0 ± 0.8	**0.037**	92.1	4	25.2 ± 0.9	**<0.001**	86.0
Mean (0–13)		27.2 ± 0.5		27.1 ± 0.5	0.802	99.4		25.2 ± 0.5	**0.002**	92.7		25.0 ± 0.5	**0.001**	91.7
60 mJ•CIE/cm^2														
1	6	25.4 ± 0.6	6	25.9 ± 0.6	0.483	102.3	6	24.7 ± 0.6	0.416	97.3	6	24.2 ± 0.6	0.166	95.5
2	6	25.6 ± 0.6	6	25.8 ± 0.6	0.758	101.0	6	24.4 ± 0.6	0.169	95.4	6	23.1 ± 0.6	**0.003**	90.2
3	6	25.9 ± 0.7	6	26.1 ± 0.7	0.874	100.6	6	24.4 ± 0.7	0.092	94.0	6	22.7 ± 0.7	**<0.001**	87.4
4	6	26.3 ± 0.7	6	26.5 ± 0.7	0.875	100.6	6	24.5 ± 0.7	0.053	93.1	6	23.5 ± 0.7	**0.002**	89.2
5	6	26.8 ± 0.7	6	26.9 ± 0.7	0.922	100.4	6	25.1 ± 0.7	0.073	93.4	6	26.6 ± 0.7	0.803	99.1
6	6	26.7 ± 0.7	6	27.2 ± 0.7	0.663	101.7	5	25.5 ± 0.8	0.252	95.5	6	24.8 ± 0.7	0.065	92.9
7	6	27.4 ± 0.7	6	27.6 ± 0.7	0.789	101.0	5	25.8 ± 0.7	0.110	94.1	6	24.9 ± 0.7	**0.010**	90.8
8	6	27.3 ± 0.7	6	27.6 ± 0.7	0.807	100.9	5	25.6 ± 0.8	0.099	93.7	6	25.2 ± 0.7	**0.037**	92.3
9	6	26.8 ± 0.7	6	27.9 ± 0.7	0.237	104.3	5	24.9 ± 0.8	0.070	93.1	6	25.0 ± 0.7	0.066	93.2
10	6	27.9 ± 0.7	6	28.1 ± 0.7	0.853	100.6	5	25.9 ± 0.7	**0.048**	92.8	6	25.5 ± 0.7	**0.013**	91.3
11	6	27.7 ± 0.7	6	28.3 ± 0.7	0.532	102.2	5	26.1 ± 0.7	0.110	94.2	6	25.7 ± 0.7	**0.037**	92.8
12	6	27.8 ± 0.8	6	28.3 ± 0.8	0.672	101.7	5	26.2 ± 0.8	0.153	94.1	6	26.0 ± 0.8	0.098	93.5
13	6	28.2 ± 0.7	6	28.4 ± 0.7	0.877	100.6	5	26.2 ± 0.8	0.073	93.0	6	26.0 ± 0.7	**0.034**	92.1
Mean (0–13)		26.9 ± 0.5		27.3 ± 0.5	0.566	101.4		25.3 ± 0.5	**0.016**	94.1		24.8 ± 0.5	**0.001**	92.3
100 mJ•CIE/cm^2														
1	6	25.0 ± 0.6	6	26.6 ± 0.6	0.064	106.1	6	23.4 ± 0.6	0.053	93.6	6	22.9 ± 0.6	**0.009**	91.3
2	6	25.8 ± 0.6	6	27.1 ± 0.6	0.133	105.0	6	23.9 ± 0.6	**0.032**	92.8	5	23.5 ± 0.6	**0.009**	91.1
3	6	26.1 ± 0.7	6	27.3 ± 0.7	0.195	104.6	6	23.7 ± 0.7	**0.012**	91.1	5	24.2 ± 0.7	0.055	93.0
4	6	26.7 ± 0.7	6	27.5 ± 0.7	0.363	103.2	6	24.2 ± 0.7	**0.010**	90.9	5	24.2 ± 0.7	**0.012**	90.9
5	6	26.9 ± 0.7	6	28.0 ± 0.7	0.266	104.1	6	24.4 ± 0.7	**0.011**	90.7	5	25.1 ± 0.8	0.079	93.3
6	6	27.1 ± 0.7	6	28.0 ± 0.7	0.338	103.6	6	24.6 ± 0.7	**0.017**	90.9	5	25.0 ± 0.8	**0.050**	92.2
7	6	27.4 ± 0.7	6	28.2 ± 0.7	0.427	102.9	6	24.9 ± 0.7	**0.014**	91.1	5	24.7 ± 0.8	**0.011**	90.4
8	6	26.8 ± 0.7	6	28.5 ± 0.7	0.106	106.1	6	24.5 ± 0.7	**0.024**	91.4	5	25.0 ± 0.8	0.090	93.3
9	6	28.1 ± 0.7	6	28.5 ± 0.7	0.623	101.7	6	24.7 ± 0.7	**0.001**	88.1	5	25.2 ± 0.8	**0.006**	89.9
10	6	28.0 ± 0.7	6	28.5 ± 0.7	0.561	102.0	6	25.5 ± 0.7	**0.014**	91.4	5	25.6 ± 0.8	**0.021**	91.6
11	6	28.1 ± 0.7	6	29.1 ± 0.7	0.320	103.4	6	25.5 ± 0.7	**0.008**	90.9	4	24.4 ± 0.8	**<0.001**	86.7
12	6	28.3 ± 0.8	6	28.8 ± 0.8	0.670	101.7	6	25.2 ± 0.8	**0.005**	89.0	4	25.0 ± 0.9	**0.006**	88.4
13	6	28.9 ± 0.7	6	29.0 ± 0.7	0.937	100.3	6	25.3 ± 0.7	**0.001**	87.5	4	24.7 ± 0.9	**<0.001**	85.3
Mean (0–13)		27.2 ± 0.5		28.1 ± 0.5	0.153	103.4		24.6 ± 0.5	**<0.001**	90.7		24.6 ± 0.5	**<0.001**	90.5

TABLE I16
Body Weight and Survival of Retinyl Palmitate Compared to Control Cream Treatment Groups of Female Mice on the MED Study

	Control Cream		2.0% Retinyl Palmitate Cream				10.0% Retinyl Palmitate Cream				13.0% Retinyl Palmitate Cream			
Week	No.	Mean Wt. ± SE	No.	Mean Wt. ± SE	P Value	% Wt. Control	No.	Mean Wt. ± SE	P Value	% Wt. Control	No.	Mean Wt. ± SE	P Value	% Wt. Control
140 mJ•CIE/cm²														
1	6	25.8 ± 0.6	6	24.2 ± 0.6	0.056	93.9	6	24.5 ± 0.6	0.113	94.9	6	23.5 ± 0.6	**0.004**	90.9
2	6	26.1 ± 0.6	6	24.7 ± 0.6	0.094	94.5	6	24.3 ± 0.6	**0.036**	93.1	6	23.5 ± 0.6	**0.002**	89.8
3	6	26.1 ± 0.7	6	24.5 ± 0.7	0.098	94.1	6	24.0 ± 0.7	**0.025**	92.0	6	24.0 ± 0.7	**0.023**	91.9
4	6	26.5 ± 0.7	6	24.6 ± 0.7	**0.042**	92.8	6	24.7 ± 0.7	0.060	93.4	6	24.1 ± 0.7	**0.011**	91.0
5	6	27.0 ± 0.7	6	25.1 ± 0.7	0.060	93.1	6	24.5 ± 0.7	**0.012**	90.8	6	24.6 ± 0.7	**0.014**	91.0
6	6	27.0 ± 0.7	6	25.7 ± 0.7	0.189	95.0	6	25.2 ± 0.7	0.070	93.1	6	24.7 ± 0.7	**0.023**	91.4
7	6	27.0 ± 0.7	6	25.8 ± 0.7	0.224	95.6	6	25.7 ± 0.7	0.207	95.4	6	24.5 ± 0.7	**0.011**	90.7
8	6	27.2 ± 0.7	6	26.3 ± 0.7	0.339	96.5	6	26.0 ± 0.7	0.231	95.6	6	24.4 ± 0.7	**0.006**	89.8
9	6	27.1 ± 0.7	6	26.5 ± 0.7	0.554	97.8	5	26.4 ± 0.7	0.481	97.4	6	24.3 ± 0.7	**0.005**	89.6
10	6	26.8 ± 0.7	6	26.3 ± 0.7	0.633	98.3	5	25.9 ± 0.7	0.387	96.8	6	24.4 ± 0.7	**0.018**	91.1
11	6	27.7 ± 0.7	6	26.2 ± 0.7	0.121	94.6	5	26.1 ± 0.7	0.092	94.2	6	25.0 ± 0.7	**0.008**	90.5
12	6	27.9 ± 0.8	6	26.6 ± 0.8	0.229	95.3	5	26.3 ± 0.8	0.141	94.2	6	24.3 ± 0.8	**0.002**	87.1
13	6	28.3 ± 0.7	6	27.2 ± 0.7	0.327	96.3	5	26.4 ± 0.7	0.083	93.5	6	24.9 ± 0.8	**0.002**	88.1
Mean (0–13)		27.0 ± 0.5		25.7 ± 0.5	**0.046**	95.2		25.4 ± 0.5	**0.015**	94.2		24.3 ± 0.5	**<0.001**	90.2
180 mJ•CIE/cm²														
1	6	25.4 ± 0.6	6	24.3 ± 0.6	0.186	95.7	6	24.0 ± 0.6	0.091	94.5	6	24.2 ± 0.6	0.163	95.5
2	6	25.6 ± 0.6	6	24.3 ± 0.6	0.151	95.2	6	23.7 ± 0.6	**0.029**	92.7	6	23.8 ± 0.6	**0.033**	92.9
3	6	26.0 ± 0.7	6	24.7 ± 0.7	0.146	94.8	6	23.4 ± 0.7	**0.004**	89.8	6	23.2 ± 0.7	**0.002**	89.1
4	6	26.4 ± 0.7	6	25.5 ± 0.7	0.348	96.7	6	23.9 ± 0.7	**0.006**	90.3	6	24.4 ± 0.7	**0.031**	92.4
5	6	26.5 ± 0.7	6	25.7 ± 0.7	0.422	97.0	6	24.0 ± 0.7	**0.011**	90.5	6	24.7 ± 0.7	0.066	93.1
6	6	26.9 ± 0.7	6	25.7 ± 0.7	0.252	95.6	6	24.7 ± 0.7	**0.029**	91.7	6	24.6 ± 0.7	**0.023**	91.3
7	6	27.4 ± 0.7	6	25.8 ± 0.7	0.106	94.2	6	23.8 ± 0.7	**<0.001**	87.0	6	24.9 ± 0.7	**0.012**	91.0
8	6	27.6 ± 0.7	6	26.5 ± 0.7	0.272	96.0	6	24.4 ± 0.7	**0.002**	88.5	6	24.9 ± 0.7	**0.008**	90.3
9	6	28.1 ± 0.7	6	26.7 ± 0.7	0.167	95.2	6	25.0 ± 0.7	**0.002**	89.0	6	25.0 ± 0.7	**0.002**	89.2
10	6	27.9 ± 0.7	6	27.0 ± 0.7	0.359	96.8	6	24.6 ± 0.7	**0.001**	88.3	6	25.0 ± 0.7	**0.003**	89.6
11	6	28.0 ± 0.7	6	26.9 ± 0.7	0.238	96.0	6	25.0 ± 0.7	**0.002**	89.3	6	24.7 ± 0.7	**0.001**	88.2
12	6	28.2 ± 0.8	6	26.8 ± 0.8	0.225	95.3	6	24.7 ± 0.8	**0.002**	87.8	6	24.1 ± 0.8	**<0.001**	85.4
13	6	29.5 ± 0.7	6	27.3 ± 0.7	**0.037**	92.6	6	24.4 ± 0.7	**<0.001**	82.7	6	23.8 ± 0.7	**<0.001**	80.5
Mean (0–13)		27.2 ± 0.5		26.0 ± 0.5	0.053	95.4		24.3 ± 0.5	**<0.001**	89.3		24.4 ± 0.5	**<0.001**	89.7
220 mJ•CIE/cm²														
1	6	25.5 ± 0.6	6	25.0 ± 0.6	0.499	97.8	6	23.5 ± 0.6	**0.016**	92.2	6	24.1 ± 0.6	0.088	94.5
2	6	25.5 ± 0.6	6	24.0 ± 0.6	0.068	93.9	6	23.6 ± 0.6	**0.026**	92.6	6	22.7 ± 0.6	**0.001**	88.7
3	6	25.7 ± 0.7	6	23.9 ± 0.7	0.053	93.0	6	23.8 ± 0.7	**0.045**	92.8	6	24.0 ± 0.7	0.078	93.6
4	6	26.2 ± 0.7	6	24.6 ± 0.7	0.085	93.9	6	24.3 ± 0.7	**0.042**	92.7	6	23.9 ± 0.7	**0.014**	91.2
5	6	26.7 ± 0.7	6	25.1 ± 0.7	0.087	93.7	6	24.0 ± 0.7	**0.005**	89.6	6	24.9 ± 0.7	0.067	93.2
6	6	26.6 ± 0.7	6	25.3 ± 0.7	0.214	95.2	6	23.0 ± 0.7	**0.001**	86.6	6	25.3 ± 0.7	0.201	95.1
7	6	26.9 ± 0.7	6	24.9 ± 0.7	**0.042**	92.5	5	23.7 ± 0.7	**0.001**	88.1	6	26.1 ± 0.7	0.391	96.9
8	6	27.4 ± 0.7	6	25.2 ± 0.7	**0.026**	91.8	5	24.3 ± 0.8	**0.002**	88.5	6	26.4 ± 0.7	0.293	96.1
9	6	27.7 ± 0.7	6	25.6 ± 0.7	**0.030**	92.3	5	24.6 ± 0.7	**0.002**	88.8	6	26.4 ± 0.7	0.166	95.1
10	6	27.6 ± 0.7	6	25.8 ± 0.7	0.066	93.5	5	24.7 ± 0.7	**0.004**	89.4	6	26.4 ± 0.7	0.207	95.5
11	6	27.8 ± 0.7	6	26.0 ± 0.7	0.054	93.4	5	25.5 ± 0.7	**0.020**	91.7	6	26.7 ± 0.7	0.223	95.8
12	6	27.5 ± 0.8	6	26.1 ± 0.8	0.182	94.7	5	25.6 ± 0.8	0.088	92.9	6	26.1 ± 0.8	0.192	94.8
13	6	28.6 ± 0.7	6	26.2 ± 0.7	**0.021**	91.5	5	25.5 ± 0.8	**0.004**	89.0	6	25.9 ± 0.7	**0.009**	90.4
Mean (0–13)		26.9 ± 0.5		25.2 ± 0.5	**0.008**	93.6		24.3 ± 0.5	**<0.001**	90.3		25.3 ± 0.5	**0.012**	93.9

TABLE I16
Body Weight and Survival of Retinyl Palmitate Compared to Control Cream Treatment Groups of Female Mice on the MED Study

	Control Cream		2.0% Retinyl Palmitate Cream				10.0% Retinyl Palmitate Cream				13.0% Retinyl Palmitate Cream			
Week	No.	Mean Wt. ± SE	No.	Mean Wt. ± SE	P Value	% Wt. Control	No.	Mean Wt. ± SE	P Value	% Wt. Control	No.	Mean Wt. ± SE	P Value	% Wt. Control
260 mJ•CIE/cm^2														
1	6	24.4 ± 0.6	6	25.4 ± 0.6	0.254	103.9	6	24.4 ± 0.6	0.920	99.7	6	25.0 ± 0.6	0.522	102.2
2	6	25.2 ± 0.6	6	25.8 ± 0.6	0.512	102.2	6	24.3 ± 0.6	0.283	96.4	6	24.7 ± 0.6	0.517	97.8
3	6	25.6 ± 0.7	6	25.6 ± 0.7	0.980	99.9	6	24.3 ± 0.7	0.144	94.7	6	24.7 ± 0.7	0.303	96.3
4	6	26.1 ± 0.7	6	26.6 ± 0.7	0.635	101.7	6	25.0 ± 0.7	0.239	95.8	6	25.7 ± 0.7	0.666	98.5
5	6	26.4 ± 0.7	6	26.8 ± 0.7	0.654	101.7	6	25.2 ± 0.7	0.232	95.5	5	26.0 ± 0.7	0.710	98.6
6	6	26.7 ± 0.7	6	27.3 ± 0.7	0.531	102.4	5	24.7 ± 0.8	0.061	92.6	5	26.5 ± 0.8	0.880	99.4
7	6	26.8 ± 0.7	6	27.6 ± 0.7	0.421	103.0	5	24.9 ± 0.7	0.056	92.8	4	26.6 ± 0.8	0.853	99.3
8	6	27.0 ± 0.7	6	27.6 ± 0.7	0.590	102.0	5	25.5 ± 0.8	0.137	94.2	4	26.5 ± 0.8	0.662	98.2
9	6	27.4 ± 0.7	6	27.6 ± 0.7	0.844	100.7	5	25.4 ± 0.8	**0.046**	92.5	4	27.2 ± 0.8	0.842	99.2
10	6	27.4 ± 0.7	6	27.4 ± 0.7	0.954	99.8	5	25.8 ± 0.7	0.105	94.0	4	26.6 ± 0.8	0.476	97.2
11	6	27.6 ± 0.7	6	27.3 ± 0.7	0.696	98.6	5	26.2 ± 0.7	0.145	94.7	4	26.9 ± 0.8	0.469	97.2
12	6	27.5 ± 0.8	6	28.2 ± 0.8	0.526	102.5	5	25.8 ± 0.8	0.150	94.0	4	26.4 ± 0.9	0.374	96.1
13	6	28.1 ± 0.7	6	28.1 ± 0.7	0.992	100.0	5	26.4 ± 0.8	0.127	94.0	4	26.5 ± 0.9	0.177	94.4
Mean (0–13)		26.6 ± 0.5		27.0 ± 0.5	0.254	101.4		25.2 ± 0.5	**0.029**	94.6		26.1 ± 0.5	0.420	98.0

[a] Least squares means and standard errors are presented in grams.
[b] P values represent pairwise comparisons of mean body weights to that of the control group. Significant P values (P≤0.05) are shown in bold-faced type.

TABLE I17
Incidence and Severity of Nonneoplastic Lesions in No Cream Compared to Control Cream Treatment Groups of Male Mice on the Range-Finding Study[a]

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**
Skin, Site of Application, Acanthosis				
Simple Incidence	0/12 (0.0%)	12/12 (100.0%)	4/12 (33.3%)	12/12 (100.0%)
Poly-3 Incidence	0/12.0 (0.0%)	12/12.0 (100.0%)	4/12.0 (33.3%)	12/12.0 (100.0%)
Terminal Incidence	0/12 (0.0%)	12/12 (100.0%)	4/12 (33.3%)	11/11 (100.0%)
Time-to-First	—	94	94	76
Poly-3 P Value		**< 0.001**		**< 0.001**
Average Severity	—	1.0	1.0	1.3
Inflammation, Granulomatous, Dermis				
Simple Incidence	2/12 (16.7%)	5/12 (41.7%)	4/12 (33.3%)	2/12 (16.7%)
Poly-3 Incidence	2/12.0 (16.7%)	5/12.0 (41.7%)	4/12.0 (33.3%)	2/11.5 (17.3%)
Terminal Incidence	2/12 (16.7%)	5/12 (41.7%)	4/12 (33.3%)	2/11 (18.2%)
Time-to-First	94	94	94	94
Poly-3 P Value		0.186		0.342N
Average Severity	1.0	1.0	1.0	1.0
Skin, Dermis, Inflammation				
Simple Incidence	3/12 (25.0%)	6/12 (50.0%)	4/12 (33.3%)	3/12(25.0%)
Poly-3 Incidence	3/12.0 (25.0%)	6/12.0 (50.0%)	4/12.0 (33.3%)	3/11.5(26.0%)
Terminal Incidence	3/12 (25.0%)	6/12 (50.0%)	4/12 (33.3%)	3/11(27.3%)
Time-to-First	94	94	94	94
Poly-3 P Value		0.202		0.524N
Average Severity	1.0	1.0	1.0	1.0
Skin, Untreated Inflammation, Granulomatous, Dermis				
Simple Incidence	2/12 (16.7%)	3/12 (25.0%)	4/12 (33.3%)	0/12 (0.0%)
Poly-3 Incidence	2/12.0 (16.7%)	3/12.0 (25.0%)	4/12.0 (33.3%)	0/11.5 (0.0%)
Terminal Incidence	2/12 (16.7%)	3/12 (25.0%)	4/12 (33.3%)	0/11 (0.0%)
Time-to-First	94	94	94	—
Poly-3 P Value		0.500		**0.044N**
Average Severity	1.0	1.0	1.3	—
Skin, Dermis, Inflammation				
Simple Incidence	4/12 (33.3%)	4/12 (33.3%)	4/12 (33.3%)	0/12 (0.0%)
Poly-3 Incidence	4/12.0 (33.3%)	4/12.0 (33.3%)	4/12.0 (33.3%)	0/11.5 (0.0%)
Terminal Incidence	4/12 (33.3%)	4/12 (33.3%)	4/12 (33.3%)	0/11 (0.0%)
Time-to-First	94	94	94	—
Poly-3 P Value		0.661		**0.044N**
Average Severity	1.0	1.0	1.3	—
Spleen, Hyperplasia, Lymphoid				
Simple Incidence	1/12 (8.3%)	2/12 (16.7%)	0/12 (0.0%)	1/12 (8.3%)
Poly-3 Incidence	1/12.0 (8.3%)	2/12.0 (16.7%)	0/12.0 (0.0%)	1/11.5 (8.7%)
Terminal Incidence	1/12 (8.3%)	2/12 (16.7%)	0/12 (0.0%)	1/11 (9.1%)
Time-to-First	94	94	—	94
Poly-3 P Value		0.500		0.492
Average Severity	2.0	2.5	—	1.0

[a] Pairwise comparison tests of incidences are made to control cream groups. P values are based on one-sided tests. Significant P values ($P \leq 0.05$) appear in bold-faced type. Negative P values are appended with "**N**".

TABLE I18
Incidence and Severity of Nonneoplastic Lesions in No Cream Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study[a]

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2	
	No Cream	**Control Cream**	**No Cream**	**Control Cream**
Skin, Site of Application, Acanthosis				
Simple Incidence	1/12 (8.3%)	12/12 (100.0%)	4/12 (33.3%)	12/12 (100.0%)
Poly-3 Incidence	1/12.0 (8.3%)	12/12.0 (100.0%)	4/12.0 (33.3%)	12/12.0 (100.0%)
Terminal Incidence	1/12 (8.3%)	12/12 (100.0%)	4/12 (33.3%)	12/12 (100.0%)
Time-to-First	94	94	94	94
Poly-3 P Value		**< 0.001**		**<0.001**
Average Severity	1.0	1.4	1.0	1.3
Inflammation, Chronic/Active, Dermis				
Simple Incidence	0/12 (0.0%)	2/12 (16.7%)	0/12 (0.0%)	3/12 (25.0%)
Poly-3 Incidence	0/12.0 (0.0%)	2/12.0 (16.7%)	0/12.0 (0.0%)	3/12.0 (25.0%)
Terminal Incidence	0/12 (0.0%)	2/12 (16.7%)	0/12 (0.0%)	3/12 (25.0%)
Time-to-First	—	94	—	94
Poly-3 P Value		0.229		0.101
Average Severity	—	1.5	—	1.0

[a] Pairwise comparison tests of incidences are made to control cream groups. P values are based on one-sided tests. Significant P values ($P \leq 0.05$) appear in bold-faced type.

TABLE I19
Incidence and Severity of Nonneoplastic Lesions in Retinoic Acid Compared to Control Cream Treatment Groups of Male Mice on the Range-Finding Study[a]

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2		
	Control Cream	0.1% RA	Control Cream	0.01% RA	0.1% RA
Skin, Site of Application, Acanthosis					
Overall incidence	12/12 (100.0%)	10/10 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	12/12.0 (100.0%)	10/10.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	12/12 (100.0%)	6/6 (100.0%)	11/11 (100.0%)	12/12 (100.0%)	10/10 (100.0%)
Lesion onset (days)	94	69	76	94	93
Poly-3 P value		—	—	—	—
Average severity score	1.0	3.1	1.3	3.4	4.0
Inflammation, Chronic/Active, Dermis					
Overall incidence	0/12 (0.0%)	10/10 (100.0%)	1/12 (8.3%)	10/12 (83.3%)	11/11 (100.0%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	10/10.0 (100.0%)	1/11.5 (8.7%)	10/12.0 (83.3%)	11/11.0 (100.0%)
Terminal incidence	0/12 (0.0%)	6/6 (100.0%)	1/11 (9.1%)	10/12 (83.3%)	10/10 (100.0%)
Lesion onset (days)	—	69	94	94	93
Poly-3 P value		**<0.001**	**<0.001**	**<0.001**	**<0.001**
Average severity score	—	3.4	1.0	2.4	4.0
Inflammation, Granulomatous, Dermis					
Overall incidence	5/12 (41.7%)	0/10 (0.0%)	2/12 (16.7%)	1/12 (8.3%)	0/11 (0.0%)
Poly-3 adjusted incidence	5/12.0 (41.7%)	0/8.2 (0.0%)	2/11.5 (17.3%)	1/12.0 (8.3%)	0/11.0 (0.0%)
Terminal incidence	5/12 (41.7%)	0/6 (0.0%)	2/11 (18.2%)	1/12 (8.3%)	0/10 (0.0%)
Lesion onset (days)	94	—	94	94	—
Poly-3 P value		**0.044N**	0.251N	0.486N	0.240N
Average severity score	1.0	—	1.0	1.0	—
Skin, Dermis, Inflammation					
Overall incidence	6/12 (50.0%)	10/10 (100.0%)	3/12 (25.0%)	12/12 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	6/12.0 (50.0%)	10/10.0 (100.0%)	3/11.5 (26.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	6/12 (50.0%)	6/6 (100.0%)	3/11 (27.3%)	12/12 (100.0%)	10/10 (100.0%)
Lesion onset (days)	94	69	94	94	93
Poly-3 P value		**0.007**	**<0.001**	**<0.001**	**<0.001**
Average severity score	1.0	3.4	1.0	2.3	4.0
Necrosis, Epithelium					
Overall incidence	0/12 (0.0%)	8/10 (80.0%)	0/12 (0.0%)	12/12 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	8/9.2 (86.6%)	0/11.5 (0.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	0/12 (0.0%)	6/6 (100.0%)	0/11 (0.0%)	12/12 (100.0%)	10/10 (100.0%)
Lesion onset (days)	—	69	—	94	93
Poly-3 P value		**<0.001**	**<0.001**	**<0.001**	**<0.001**
Average severity score	—	3.5	—	2.0	4.0

TABLE I19
Incidence and Severity of Nonneoplastic Lesions in Retinoic Acid Compared to Control Cream Treatment Groups of Male Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2		
	Control Cream	0.1% RA	Control Cream	0.01% RA	0.1% RA
Skin, Untreated, Acanthosis					
Overall incidence	0/12 (0.0%)	9/9 (100.0%)	0/12 (0.0%)	10/12 (83.3%)	11/11 (100.0%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	9/9.0 (100.0%)	0/11.5 (0.0%)	10/12.0 (83.3%)	11/11.0 (100.0%)
Terminal incidence	0/12 (0.0%)	6/6 (100.0%)	0/11 (0.0%)	10/12 (83.3%)	10/10 (100.0%)
Lesion onset (days)	—	69	—	94	93
Poly-3 P value		**<0.001**	**<0.001**	**<0.001**	**<0.001**
Average severity score	—	1.9	—	1.0	2.0
Inflammation, Chronic/Active Dermis					
Overall incidence	1/12 (8.3%)	7/9 (7.8%)	0/12 (0.0%)	1/12 (8.3%)	10/11 (90.9%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	7/8.6 (81.0%)	0/11.5 (0.0%)	1/12.0 (8.3%)	10/11.0 (90.9%)
Terminal incidence	1/12 (8.3%)	5/6 (3.3%)	0/11 (0.0%)	1/12 (8.3%)	9/10 (90.0%)
Lesion onset (days)	94	69	—	94	93
Poly-3 P value		**<0.001**	**<0.001**	0.508	**<0.001**
Average severity score	1.0	1.6	—	2.0	1.7
Skin, Dermis, Inflammation					
Overall incidence	4/12 (33.3%)	8/9 (88.9%)	0/12 (0.0%)	3/12 (25.0%)	10/11 (90.9%)
Poly-3 adjusted incidence	4/12.0 (33.3%)	8/8.6 (92.6%)	0/11.5 (0.0%)	3/12.0 (25.0%)	10/11.0 (90.9%)
Terminal incidence	4/12 (33.3%)	6/6 (100.0%)	0/11 (0.0%)	3/12 (25.0%)	9/10 (90.0%)
Lesion onset (days)	94	69	—	94	93
Poly-3 P value		**0.004**	**<0.001**	0.108	**<0.001**
Average severity score	1.0	1.5	—	1.3	1.7
Skin, Epithelium, Necrosis					
Overall incidence	0/12 (0.0%)	1/9 (11.1%)	0/12 (0.0%)	0/12 (0.0%)	4/11 (36.4%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	1/7.6 (13.1%)	0/11.5 (0.0%)	0/12.0 (0.0%)	4/11.0 (36.5%)
Terminal incidence	0/12 (0.0%)	1/6 (16.7%)	0/11 (0.0%)	0/12 (0.0%)	4/10 (40.0%)
Lesion onset (days)	—	94	—	—	94
Poly-3 P value		0.410	**0.002**	—	**0.032**
Average severity score	—	2.0	—	—	1.8

TABLE I19
Incidence and Severity of Nonneoplastic Lesions in Retinoic Acid Compared to Control Cream Treatment Groups of Male Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2		
	Control Cream	0.1%RA	Control Cream	0.01% RA	0.1% RA
Liver, Hematopoietic Cell Proliferation					
Overall incidence	1/12 (8.3%)	10/10 (100.0%)	1/12 (8.3%)	2/12 (16.7%)	9/11 (81.8%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	10/10.0 (100.0%)	1/11.5 (8.7%)	2/12.0 (16.7%)	9/11.0 (81.8%)
Terminal incidence	1/12 (8.3%)	6/6 (100.0%)	1/11 (9.1%)	2/12 (16.7%)	8/10 (80.0%)
Lesion onset (days)	94	69	94	94	93
Poly-3 P value		**<0.001**	**<0.001**	0.514	**<0.001**
Average severity score	1.0	3.9	1.0	1.0	2.7
Infiltration, Cellular, Lymphocyte					
Overall incidence			0/12 (0.0%)	0/12 (0.0%)	4/11 (36.4%)
Poly-3 adjusted incidence			0/11.5 (0.0%)	0/12.0 (0.0%)	4/11.0 (36.5%)
Terminal incidence			0/11 (0.0%)	0/12 (0.0%)	4/10 (40.0%)
Lesion onset (days)			—	—	94
Poly-3 P value			**0.002**	—	**0.032**
Average severity score			—	—	2.0
Inflammation, Chronic, Active					
Overall incidence	0/12 (0.0%)	8/10 (80.0%)	1/12 (8.3%)	1/12 (8.3%)	2/11 (18.2%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	8/9.6 (83.0%)	1/11.5 (8.7%)	1/12.0 (8.3%)	2/11.0 (18.2%)
Terminal incidence	0/12 (0.0%)	5/6 (83.3%)	1/11 (9.1%)	1/12 (8.3%)	1/10 (10.0%)
Lesion onset (days)	---	69	94	94	93
Poly-3 P value		**<0.001**	0.393	0.752N	0.483
Average severity score	---	3.6	1.0	3.0	3.0
Lymphocyte Infiltration					
Overall incidence			0/12 (0.0%)	0/12 (0.0%)	4/11 (36.4%)
Poly-3 adjusted incidence			0/11.5 (0.0%)	0/12.0 (0.0%)	4/11.0 (36.5%)
Terminal incidence			0/11 (0.0%)	0/12 (0.0%)	4/10 (40.0%)
Lesion onset (days)			—	—	94
Poly-3 P value			**0.002**	—	**0.032**
Average severity score			—	—	2.0
Lymph Node, Axillary, Hyperplasia, Lymphoid					
Overall incidence	4/4 (100.0%)	10/10 (100.0%)	6/7 (85.7%)	12/12 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	4/4.0 (100.0%)	10/10.0 (100.0%)	6/7.0 (85.7%)	12/12.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	4/4 (100.0%)	6/6 (100.0%)	6/7 (85.7%)	12/12 (100.0%)	10/10 (100.0%)
Lesion onset (days)	94	69	94	94	93
Poly-3 P value		—	0.539	0.390	0.408
Average severity score	2.5	3.8	2.8	3.5	3.8

TABLE I19
Incidence and Severity of Nonneoplastic Lesions in Retinoic Acid Compared to Control Cream Treatment Groups of Male Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2		
	Control Cream	0.1% RA	Control Cream	0.01% RA	0.1% RA
Lymph Node, Inguinal, Hyperplasia, Lymphoid					
Overall incidence	3/4 (75.0%)	8/10 (80.0%)	2/7 (28.6%)	9/12 (75.0%)	10/11 (90.9%)
Poly-3 adjusted incidence	3/4.0 (75.0%)	8/10.0 (80.0%)	2/7.0 (28.6%)	9/12.0 (75.0%)	10/11.0 (90.9%)
Terminal incidence	3/4 (75.0%)	4/6 (66.7%)	2/7 (28.6%)	9/12 (75.0%)	9/10 (90.0%)
Lesion onset (days)	94	69	94	94	93
Poly-3 P value		0.683	**0.031**	0.056	**0.003**
Average severity score	2.7	3.8	2.5	3.9	3.7
Lymph Node, Axillary, Polymorphonuclear Cell Infiltrate					
Overall incidence	0/4 (0.0%)	7/10 (70.0%)	0/7 (0.0%)	0/12 (0.0%)	4/11 (36.4%)
Poly-3 adjusted incidence	0/4.0 (0.0%)	7/10.0 (70.0%)	0/7.0 (0.0%)	0/12.0 (0.0%)	4/11.0 (36.4%)
Terminal incidence	0/4 (0.0%)	3/6 (50.0%)	0/7 (0.0%)	0/12 (0.0%)	3/10 (30.0%)
Lesion onset (days)	—	69	—	—	93
Poly-3 P value		**0.017**	**0.006**	—	0.100
Average severity score	—	3.9	—	—	3.0
Lymph Node, Inguinal, Polymorphonuclear Cell Infiltrate					
Overall incidence	0/4 (0.0%)	6/10 (60.0%)	0/7 (0.0%)	1/12 (8.3%)	4/11 (36.4%)
Poly-3 adjusted incidence	0/4.0 (0.0%)	6/10.0 (60.0%)	0/7.0 (0.0%)	1/12.0 (8.3%)	4/11.0 (36.4%)
Terminal incidence	0/4 (0.0%)	2/6 (33.3%)	0/7 (0.0%)	1/12 (8.3%)	3/10 (30.0%)
Lesion onset (days)	—	69	—	94	93
Poly-3 P value		0.054	**0.034**	0.606	0.100
Average severity score	—	3.7	—	2.0	3.0
Spleen, Hematopoietic Cell Proliferation					
Overall incidence	1/12 (8.3%)	10/10 (100.0%)	0/12 (0.0%)	8/12 (66.7%)	11/11 (100.0%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	10/10.0 (100.0%)	0/11.5 (0.0%)	8/12.0 (66.7%)	11/11.0 (100.0%)
Terminal incidence	1/12 (8.3%)	6/6 (100.0%)	0/11 (0.0%)	8/12 (66.7%)	10/10 (100.0%)
Lesion onset (days)	94	69	—	94	93
Poly-3 P value		**<0.001**	**<0.001**	**<0.001**	**<0.001**
Average severity score	2.0	3.9	—	2.5	3.7
Hyperplasia, Lymphoid					
Overall incidence	2/12 (16.7%)	6/10 (60.0%)	1/12 (8.3%)	5/12 (41.7%)	4/11 (36.4%)
Poly-3 adjusted incidence	2/12.0 (16.7%)	6/8.6 (69.9%)	1/11.5 (8.7%)	5/12.0 (41.7%)	4/11.0 (36.5%)
Terminal incidence	2/12 (16.7%)	5/6 (83.3%)	1/11 (9.1%)	5/12 (41.7%)	4/10 (40.0%)
Lesion onset (days)	94	81	94	94	94
Poly-3 P value		**0.013**	0.336	0.079	0.137
Average severity score	2.5	3.8	1.0	2.4	2.8

[a] Pairwise comparison tests of incidences are made to control cream groups. P values are based on one-sided tests. Significant P values ($P \leq 0.05$) appear in bold-faced type. Negative P values are appended with "**N**". P values for the control cream group represent dose trend effects for incidence with increasing doses of retinoic acid.

TABLE I20
Incidence and Severity of Nonneoplastic Lesions in Retinoic Acid Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study[a]

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2		
	Control Cream	0.1%RA	Control Cream	0.01% RA	0.1% RA
Skin, Site of Application, Acanthosis					
Overall incidence	12/12 (100.0%)	4/5 (80.0%)	12/12 (100.0%)	12/12 (100.0%)	12/12 (100.0%)
Poly-3 adjusted incidence	12/12.0 (100.0%)	4/4.8 (82.7%)	12/12.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)
Terminal incidence	12/12 (100.0%)		12/12 (100.0%)	12/12 (100.0%)	7/7 (100.0%)
Lesion onset (days)	94	72	94	94	72
Poly-3 P value		0.397N	—	—	—
Average severity score	1.4	4.0	1.3	3.6	4.0
Inflammation, Chronic/Active, Dermis					
Overall incidence	2/12 (16.7%)	5/5 (100.0%)	3/12 (25.0%)	12/12 (100.0%)	12/12 (100.0%)
Poly-3 adjusted incidence	2/12.0 (16.7%)	5/5.0 (100.0%)	3/12.0 (25.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)
Terminal incidence	2/12 (16.7%)		3/12 (25.0%)	12/12 (100.0%)	7/7 (100.0%)
Lesion onset (days)	94	72	94	94	72
Poly-3 P value		**<0.001**	**<0.001**	**<0.001**	**<0.001**
Average severity score	1.5	4.0	1.0	2.9	4.0
Skin, Dermis, Inflammation Pyogranulomatous					
Overall incidence			2/12 (16.7%)	0/12 (0.0%)	0/12 (0.0%)
Poly-3 adjusted incidence			2/12.0 (16.7%)	0/12.0 (0.0%)	0/10.0 (0.0%)
Terminal incidence			2/12 (16.7%)	0/12 (0.0%)	0/7 (0.0%)
Lesion onset (days)			94	—	—
Poly-3 P value			0.356N	0.229N	0.274N
Average severity score			1.0	—	—
Skin, Dermis, Inflammation					
Overall incidence	3/12 (25.0%)	5/5 (100.0%)	6/12 (50.0%)	12/12 (100.0%)	12/12 (100.0%)
Poly-3 adjusted incidence	3/12.0 (25.0%)	5/5.0 (100.0%)	6/12.0 (50.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)
Terminal incidence	3/12 (25.0%)		6/12 (50.0%)	12/12 (100.0%)	7/7 (100.0%)
Lesion onset (days)	94	72	94	94	72
Poly-3 P value		**0.002**	**0.016**	**0.003**	**0.003**
Average severity score	1.3	4.0	1.0	2.9	4.0
Necrosis, Epithelium					
Overall incidence	0/12 (0.0%)	5/5 (100.0%)	0/12 (0.0%)	12/12 (100.0%)	12/12 (100.0%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	5/5.0 (100.0%)	0/12.0 (0.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)
Terminal incidence	0/12 (0.0%)		0/12 (0.0%)	12/12 (100.0%)	7/7 (100.0%)
Lesion onset (days)	—	72	—	94	72
Poly-3 P value		**<0.001**	**<0.001**	**<0.001**	**<0.001**
Average severity score	—	4.0	—	2.3	**3.9**

TABLE I20
Incidence and Severity of Nonneoplastic Lesions in Retinoic Acid Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2		
	Control Cream	0.1%RA	Control Cream	0.01% RA	0.1% RA
Skin, Untreated, Acanthosis					
Overall incidence	3/12 (25.0%)	5/5 (100.0%)	1/12 (8.3%)	11/12 (91.7%)	9/9 (100.0%)
Poly-3 adjusted incidence	3/12.0 (25.0%)	5/5.0 (100.0%)	1/12.0 (8.3%)	11/12.0 (91.7%)	9/9.0 (100.0%)
Terminal incidence	3/12 (25.0%)		1/12 (8.3%)	11/12 (91.7%)	7/7 (100.0%)
Lesion onset (days)	94	72	94	94	72
Poly-3 P value		**0.002**	**<0.001**	**<0.001**	**<0.001**
Average severity score	1.0	1.8	1.0	1.2	2.1
Inflammation, Chronic/Active Dermis					
Overall incidence	0/12 (0.0%)	4/5 (80.0%)	0/12 (0.0%)	1/12 (8.3%)	5/9 (55.6%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	4/5.0 (80.0%)	0/12.0 (0.0%)	1/12.0 (8.3%)	5/8.8 (56.5%)
Terminal incidence	0/12 (0.0%)		0/12 (0.0%)	1/12 (8.3%)	4/7 (57.1%)
Lesion onset (days)	—	72	—	94	72
Poly-3 P value		**<0.001**	**<0.001**	0.500	**<0.001**
Average severity score	—	1.5	—	1.0	1.2
Inflammation, Granulomatous, Dermis					
Overall incidence			2/12 (16.7%)	2/12 (16.7%)	1/9 (11.1%)
Poly-3 adjusted incidence			2/12.0 (16.7%)	2/12.0 (16.7%)	1/8.3 (12.1%)
Terminal incidence			2/12 (16.7%)	2/12 (16.7%)	1/7 (14.3%)
Lesion onset (days)			94	94	94
Poly-3 P value			0.577N	0.700	0.629N
Average severity score			1.0	1.0	1.0
Skin, Dermis, Inflammation					
Overall incidence	0/12 (0.0%)	4/5 (80.0%)	2/12 (16.7%)	3/12 (25.0%)	6/9 (66.7%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	4/5.0 (80.0%)	2/12.0 (16.7%)	3/12.0 (25.0%)	6/8.8 (67.8%)
Terminal incidence	0/12 (0.0%)		2/12 (16.7%)	3/12 (25.0%)	5/7 (71.4%)
Lesion onset (days)	---	72	94	94	72
Poly-3 P value		**<0.001**	**0.011**	0.500	**0.016**
Average severity score	---	1.5	1.0	1.0	1.2
Liver, Hematopoietic Cell Proliferation					
Overall incidence	1/12 (8.3%)	6/6 (100.0%)	0/12 (0.0%)	1/12 (8.3%)	10/12 (83.3%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	6/6.0 (100.0%)	0/12.0 (0.0%)	1/12.0 (8.3%)	10/11.8 (84.4%)
Terminal incidence	1/12 (8.3%)		0/12 (0.0%)	1/12 (8.3%)	6/7 (85.7%)
Lesion onset (days)	94	72	—	94	72
Poly-3 P value		**<0.001**	**<0.001**	0.500	**<0.001**
Average severity score	1.0	4.0	—	2.0	3.2

TABLE I20
Incidence and Severity of Nonneoplastic Lesions in Retinoic Acid Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2		
	Control Cream	**0.1%RA**	**Control Cream**	**0.01% RA**	**0.1% RA**
Infiltration, Cellular, Lymphocyte					
Overall incidence	1/12 (8.3%)	0/6 (0.0%)	0/12 (0.0%)	2/12 (16.7%)	1/12 (8.3%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	0/5.3 (0.0%)	0/12.0 (0.0%)	2/12.0 (16.7%)	1/10.0 (10.0%)
Terminal incidence	1/12 (8.3%)		0/12 (0.0%)	2/12 (16.7%)	1/7 (14.3%)
Lesion onset (days)	94	—	—	94	94
Poly-3 P value		0.657N	0.614	0.229	0.463
Average severity score	2.0	—	—	1.0	2.0
Inflammation, Chronic Active					
Overall incidence	0/12 (0.0%)	6/6 (100.0%)	0/12 (0.0%)	1/12 (8.3%)	8/12 (66.7%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	6/6.0 (100.0%)	0/12.0 (0.0%)	1/12.0 (8.3%)	8/11.8 (67.5%)
Terminal incidence	0/12 (0.0%)		0/12 (0.0%)	1/12 (8.3%)	4/7 (57.1%)
Lesion onset (days)	—	72	—	94	72
Poly-3 P value		**<0.001**	**<0.001**	0.500	**<0.001**
Average severity score	—	3.8	—	1.0	3.1
Liver, Necrosis					
Overall incidence	0/12 (0.0%)	3/6 (50.0%)	0/12 (0.0%)	0/12 (0.0%)	2/12 (16.7%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	3/5.9 (50.6%)	0/12.0 (0.0%)	0/12.0 (0.0%)	2/10.7 (18.6%)
Terminal incidence	0/12 (0.0%)		0/12 (0.0%)	0/12 (0.0%)	0/7 (0.0%)
Lesion onset (days)	—	72	—	—	72
Poly-3 P value		**0.007**	0.076	—	0.203
Average severity score	—	3.7	—	—	3.5
Lymph Node, Axillary, Hyperplasia, Lymphoid					
Overall incidence	3/4 (75.0%)	5/6 (83.3%)	10/10 (100.0%)	12/12 (100.0%)	11/12 (91.7%)
Poly-3 adjusted incidence	3/4.0 (75.0%)	5/5.6 (89.5%)	10/10.0 (100.0%)	12/12.0 (100.0%)	11/11.4 (96.1%)
Terminal incidence	3/4 (75.0%)		10/10 (100.0%)	12/12 (100.0%)	7/7 (100.0%)
Lesion onset (days)	94	81	94	94	72
Poly-3 P value		0.611	0.793N	—	0.896N
Average severity score	3.7	4.0	2.6	3.8	4.0
Lymph Node, Inguinal, Hyperplasia, Lymphoid					
Overall incidence	2/4 (50.0%)	5/6 (83.3%)	9/10 (90.0%)	10/12 (83.3%)	9/12 (75.0%)
Poly-3 adjusted incidence	2/4.0 (50.0%)	5/6.0 (83.3%)	9/10.0 (90.0%)	10/12.0 (83.3%)	9/10.7 (83.7%)
Terminal incidence	2/4 (50.0%)		9/10 (90.0%)	10/12 (83.3%)	7/7 (100.0%)
Lesion onset (days)	94	72	94	94	72
Poly-3 P value		0.343	0.601N	0.565N	0.596N
Average severity score	2.5	3.6	3.0	4.0	3.7

TABLE I20
Incidence and Severity of Nonneoplastic Lesions in Retinoic Acid Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2		
	Control Cream	0.1%RA	Control Cream	0.01% RA	0.1% RA
Lymph Node, Axillary, Necrosis					
Overall incidence			0/10 (0.0%)	0/12 (0.0%)	6/12 (50.0%)
Poly-3 adjusted incidence			0/10.0 (0.0%)	0/12.0 (0.0%)	6/10.0 (60.2%)
Terminal incidence			0/10 (0.0%)	0/12 (0.0%)	6/7 (85.7%)
Lesion onset (days)			---	—	94
Poly-3 P value			**<0.001**	—	**0.001**
Average severity score			—	—	1.8
Lymph Node, Axillary, Polymorphonuclear Cell Infiltration					
Overall incidence	0/4 (0.0%)	5/6 (83.3%)	0/10 (0.0%)	4/12 (33.3%)	8/12 (66.7%)
Poly-3 adjusted incidence	0/4.0 (0.0%)	5/5.6 (89.5%)	0/10.0 (0.0%)	4/12.0 (33.3%)	8/10.7 (74.4%)
Terminal incidence	0/4 (0.0%)		0/10 (0.0%)	4/12 (33.3%)	6/7 (85.7%)
Lesion onset (days)	—	81	—	94	72
Poly-3 P value		**<0.001**	**<0.001**	0.061	**<0.001**
Average severity score	—	4.0	—	2.0	2.5
Lymph Node, Inguinal, Polymorphonuclear Cell Infiltration					
Overall incidence	0/4 (0.0%)	5/6 (83.3%)	0/10 (0.0%)	2/12 (16.7%)	4/12 (33.3%)
Poly-3 adjusted incidence	0/4.0 (0.0%)	5/6.0 (83.3%)	0/10.0 (0.0%)	2/12.0 (16.7%)	4/10.7 (37.2%)
Terminal incidence	0/4 (0.0%)		0/10 (0.0%)	2/12 (16.7%)	2/7 (28.6%)
Lesion onset (days)	—	72	—	94	72
Poly-3 P value		**0.001**	0.054	0.272	**0.043**
Average severity score	—	3.6	—	2.0	2.8
Spleen, Hematopoietic Cell Proliferation					
Overall incidence	2/12 (16.7%)	6/6 (100.0%)	1/12 (8.3%)	9/12 (75.0%)	12/12 (100.0%)
Poly-3 adjusted incidence	2/12.0 (16.7%)	6/6.0 (100.0%)	1/12.0 (8.3%)	9/12.0 (75.0%)	12/12.0 (100.0%)
Terminal incidence	2/12 (16.7%)		1/12 (8.3%)	9/12 (75.0%)	7/7 (100.0%)
Lesion onset (days)	94	72	94	94	72
Poly-3 P value		**<0.001**	**<0.001**	**<0.001**	**<0.001**
Average severity score	2.0	4.0	2.0	2.8	3.8

[a] Pairwise comparison tests of incidences are made to control cream groups. P values are based on one-sided tests. Significant P values ($P \leq 0.05$) appear in bold-faced type. Negative P values are appended with "**N**". P values for the control cream group represent dose trend effects for incidence with increasing doses of retinoic acid.

TABLE I21
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Male Mice on the Range-Finding Study[a]

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Skin, Site of Application, Acanthosis									
Overall incidence	12/12 (100.0%)	5/12 (41.7%)	12/12 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	11/11 (100.0%)	12/12 (100.0%)
Poly-3 adjusted incidence	12/12.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)	12/12.0 (100.0%)
Terminal incidence	12/12 (100.0%)	9/9 (100.0%)	11/11 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	11/11 (100.0%)	12/12 (100.0%)
Lesion onset (days)	94	73	76	94	94	94	94	94	94
Poly-3 P value		—	—	—	—	—	—	—	—
Average severity score	1	3.3	1.3	2.0	2.4	2.3	3.2	3.3	3.5
Inflammation, Chronic/Active, Dermis									
Overall incidence	0/12 (0.0%)	12/12 (100.0%)	1/12 (8.3%)	2/12 (16.7%)	5/12 (41.7%)	6/12 (50.0%)	12/12 (100.0%)	11/11 (100.0%)	12/12 (100.0%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	12/12.0 (100.0%)	1/11.5 (8.7%)	2/12.0 (16.7%)	5/12.0 (41.7%)	6/12.0 (50.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)	12/12.0 (100.0%)
Terminal incidence	0/12 (0.0%)	9/9 (100.0%)	1/11 (9.1%)	2/12 (16.7%)	5/12 (41.7%)	6/12 (50.0%)	12/12 (100.0%)	11/11 (100.0%)	12/12 (100.0%)
Lesion onset (days)	—	73	94	94	94	94	94	94	94
Poly-3 P value		**<0.001**	**<0.001**	0.514	0.079	**0.031**	**<0.001**	**<0.001**	**<0.001**
Average severity score	—	2.8	1.0	1.0	1.0	1.2	2.6	3.1	3.2
Inflammation, Granulomatous, Dermis									
Overall incidence	5/12 (41.7%)	0/12 (0.0%)	2/12 (16.7%)	4/12 (33.3%)	1/12 (8.3%)	2/12 (16.7%)	0/12 (0.0%)	0/11 (0.0%)	0/12 (0.0%)
Poly-3 adjusted incidence	5/12.0 (41.7%)	0/11.3 (0.0%)	2/11.5 (17.3%)	4/12.0 (33.3%)	1/12.0 (8.3%)	2/12.0 (16.7%)	0/12.0 (0.0%)	0/11.0 (0.0%)	0/12.0 (0.0%)
Terminal incidence	5/12 (41.7%)	0/9 (0.0%)	2/11 (18.2%)	4/12 (33.3%)	1/12 (8.3%)	2/12 (16.7%)	0/12 (0.0%)	0/11 (0.0%)	0/12 (0.0%)
Lesion onset (days)	94	—	94	94	94	94	—	—	—
Poly-3 P value		**0.015N**	**0.008N**	0.342	0.486N	0.686N	0.219N	0.239N	0.219N
Average severity score	1.0	—	1.0	1.0	2.0	1.0	—	—	—
Skin, Dermis, Inflammation									
Overall incidence	6/12 (50.0%)	12/12 (100.0%)	3/12 (25.0%)	6/12 (50.0%)	9/12 (75.0%)	10/12 (83.3%)	12/12 (100.0%)	11/11 (100.0%)	12/12 (100.0%)
Poly-3 adjusted incidence	6/12.0 (50.0%)	12/12.0 (100.0%)	3/11.5 (26.0%)	6/12.0 (50.0%)	9/12.0 (75.0%)	10/12.0 (83.3%)	12/12.0 (100.0%)	11/11.0 (100.0%)	12/12.0 (100.0%)
Terminal incidence	6/12 (50.0%)	9/9 (100.0%)	3/11 (27.3%)	6/12 (50.0%)	9/12 (75.0%)	10/12 (83.3%)	12/12 (100.0%)	11/11 (100.0%)	12/12 (100.0%)
Lesion onset (days)	94	73	94	94	94	94	94	94	94
Poly-3 P value		**0.003**	**<0.001**	0.222	**0.015**	**0.003**	**<0.001**	**<0.001**	**<0.001**
Average severity score	1.0	2.8	1.0	1.0	1.1	1.2	2.6	3.1	3.2

TABLE I21
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Male Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Necrosis, Epithelium									
Overall incidence	0/12 (0.0%)	8/12 (66.7%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	6/12 (50.0%)	7/11 (63.6%)	11/12 (91.7%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	8/11.3 (70.5%)	0/11.5 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	6/12.0 (50.0%)	7/11.0 (63.6%)	11/12.0 (91.7%)
Terminal incidence	0/12 (0.0%)	8/9 (88.9%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	6/12 (50.0%)	7/11 (63.6%)	11/12 (91.7%)
Lesion onset (days)	—	94	—	—	—	—	94	94	94
Poly-3 P value		**<0.001**	**<0.001**	—	—	—	**0.004**	**<0.001**	**<0.001**
Average severity score	—	1.8	—	—	—	—	2.3	1.9	2.7
Skin, Epithelium, Hyperplasia- Squamous									
Overall incidence			0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	2/12 (16.7%)	0/11 (0.0%)	0/12 (0.0%)
Poly-3 adjusted incidence			0/11.5 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	2/12.0 (16.7%)	0/11.0 (0.0%)	0/12.0 (0.0%)
Terminal incidence			0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	2/12 (16.7%)	0/11 (0.0%)	0/12 (0.0%)
Lesion onset (days)			—	—	—	—	94	—	—
Poly-3 P value			0.555	—	—	—	0.238	—	—
Average severity score			—	—	—	—	4.0	—	—
Skin, Hyperplasia- Squamous									
Overall incidence			0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	2/12 (16.7%)	0/11 (0.0%)	0/12 (0.0%)
Poly-3 adjusted incidence			0/11.5 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	2/12.0 (16.7%)	0/11.0 (0.0%)	0/12.0 (0.0%)
Terminal incidence			0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	2/12 (16.7%)	0/11 (0.0%)	0/12 (0.0%)
Lesion onset (days)			—	—	—	—	94	—	—
Poly-3 P value			0.555	—	—	—	0.238	—	—
Average severity score			—	—	—	—	4.0	—	—
Skin, Untreated									
Skin, Acanthosis									
Overall incidence	0/12 (0.0%)	10/11 (90.9%)	0/12 (0.0%)	0/12 (0.0%)	5/12 (41.7%)	6/12 (50.0%)	12/12 (100.0%)	11/11 (100.0%)	12/12 (100.0%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	10/10.5 (95.5%)	0/11.5 (0.0%)	0/12.0 (0.0%)	5/12.0 (41.7%)	6/12.0 (50.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)	12/12.0 (100.0%)
Terminal incidence	0/12 (0.0%)	9/9 (100.0%)	0/11 (0.0%)	0/12 (0.0%)	5/12 (41.7%)	6/12 (50.0%)	12/12 (100.0%)	11/11 (100.0%)	12/12 (100.0%)
Lesion onset (days)	—	91	—	—	94	94	94	94	94
Poly-3 P value		**<0.001**	**<0.001**	—	**0.015**	**0.004**	**<0.001**	**<0.001**	**<0.001**
Average severity score	—	1.4	—	—	1.0	1.0	1.3	1.6	1.5

TABLE I21
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Male Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Inflammation, Chronic/Active, Dermis									
Overall incidence	1/12 (8.3%)	4/11 (36.4%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	5/12 (41.7%)	5/11 (45.5%)	4/12 (33.3%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	4/10.4 (38.6%)	0/11.5 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	5/12.0 (41.7%)	5/11.0 (45.5%)	4/12.0 (33.3%)
Terminal incidence	1/12 (8.3%)	4/9 (44.4%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	5/12 (41.7%)	5/11 (45.5%)	4/12 (33.3%)
Lesion onset (days)	94	94	—	—	—	—	94	94	94
Poly-3 P value		0.109	**<0.001**	—	—	—	**0.015**	**0.009**	**0.044**
Average severity score	1.0	1.3	—	—	—	—	1.0	1.0	1.0
Skin, Dermis, Inflammation									
Overall incidence	4/12 (33.3%)	7/11 (63.6%)	0/12 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	1/12 (8.3%)	5/12 (41.7%)	6/11 (54.5%)	5/12 (41.7%)
Poly-3 adjusted incidence	4/12.0 (33.3%)	7/10.4 (67.5%)	0/11.5 (0.0%)	0/12.0 (0.0%)	1/12.0 (8.3%)	1/12.0 (8.3%)	5/12.0 (41.7%)	6/11.0 (54.5%)	5/12.0 (41.7%)
Terminal incidence	4/12 (33.3%)	7/9 (77.8%)	0/11 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	1/12 (8.3%)	5/12 (41.7%)	6/11 (54.5%)	5/12 (41.7%)
Lesion onset (days)	94	94	—	—	94	94	94	94	94
Poly-3 P value		0.113	**<0.001**	—	0.508	0.508	**0.015**	**0.001**	**0.015**
Average severity score	1.0	1.1	—	—	1.0	1.0	1.0	1.0	1.0
Liver, Vacuolization, Cytoplasmic									
Overall incidence	1/12 (8.3%)	1/12 (8.3%)	0/12 (0.0%)	1/12 (8.3%)	3/12 (25.0%)	0/12 (0.0%)	3/12 (25.0%)	1/11 (9.1%)	2/12 (16.7%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	1/11.3 (8.8%)	0/11.5 (0.0%)	1/12.0 (8.3%)	3/12.0 (25.0%)	0/12.0 (0.0%)	3/12.0 (25.0%)	1/11.0 (9.1%)	2/12.0 (16.7%)
Terminal incidence	1/12 (8.3%)	1/9 (11.1%)	0/11 (0.0%)	1/12 (8.3%)	3/12 (25.0%)	0/12 (0.0%)	3/12 (25.0%)	1/11 (9.1%)	2/12 (16.7%)
Lesion onset (days)	94	94	—	94	94	—	94	94	94
Poly-3 P value		0.748	0.289	0.508	0.108	—	0.108	0.491	0.238
Average severity score	1.0	2.0	—	1.0	1.0	—	1.3	1.0	1.5
Hematopoietic Cell Proliferation									
Overall incidence	1/12 (8.3%)	9/12 (75.0%)	1/12 (8.3%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	3/12 (25.0%)	1/11 (9.1%)	7/12 (58.3%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	9/11.5 (78.5%)	1/11.5 (8.7%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	3/12.0 (25.0%)	1/11.0 (9.1%)	7/12.0 (58.3%)
Terminal incidence	1/12 (8.3%)	7/9 (77.8%)	1/11 (9.1%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	3/12 (25.0%)	1/11 (9.1%)	7/12 (58.3%)
Lesion onset (days)	94	91	94	—	—	—	94	94	94
Poly-3 P value		**<0.001**	**<0.001**	0.492N	0.492N	0.492N	0.310	0.750	**0.009**
Average severity score	1.0	2.3	1.0	—	---—	—	1.7	2.0	2.3

TABLE I21
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Male Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Lymphocyte, Cell Infiltration									
Overall incidence	0/12 (0.0%)	3/12 (25.0%)	0/12 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	0/12 (0.0%)	2/12 (16.7%)	4/11 (36.4%)	2/12 (16.7%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	3/11.3 (26.4%)	0/11.5 (0.0%)	0/12.0 (0.0%)	1/12.0 (8.3%)	0/12.0 (0.0%)	2/12.0 (16.7%)	4/11.0 (36.4%)	2/12.0 (16.7%)
Terminal incidence	0/12 (0.0%)	3/9 (33.3%)	0/11 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	0/12 (0.0%)	2/12 (16.7%)	4/11 (36.4%)	2/12 (16.7%)
Lesion onset (days)	—	94	—	—	94	—	94	94	94
Poly-3 P value		0.090	**0.003**	—	0.508	—	0.238	**0.032**	0.238
Average severity score	—	1.3	—	—	1.0	—	1.5	1.5	1.0
Inflammation, Chronic, Active									
Overall incidence	0/12 (0.0%)	5/12 (41.7%)	1/12 (8.3%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/11 (0.0%)	1/12 (8.3%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	5/11.5 (43.6%)	1/11.5 (8.7%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/11.0 (0.0%)	1/12.0 (8.3%)
Terminal incidence	0/12 (0.0%)	3/9 (33.3%)	1/11 (9.1%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/11 (0.0%)	1/12 (8.3%)
Lesion onset (days)	—	91	94	—	—	—	—	—	94
Poly-3 P value		**0.010**	0.372	0.492N	0.492N	0.492N	0.492N	0.509N	0.752N
Average severity score	—	2.2	1.0	—	—	—	—	—	2.0
Lymph Node, Axillary, Hyperplasia, Lymphoid									
Overall incidence	4/4 (100.0%)	12/12 (100.0%)	6/7 (85.7%)	8/9 (88.9%)	9/9 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	11/11 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	4/4.0 (100.0%)	12/12.0 (100.0%)	6/7.0 (85.7%)	8/9.0 (88.9%)	9/9.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	4/4 (100.0%)	9/9 (100.0%)	6/7 (85.7%)	8/9 (88.9%)	9/9 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	11/11 (100.0%)	11/11 (100.0%)
Lesion onset (days)	94	73	94	94	94	94	94	94	94
Poly-3 P value		—	0.165	0.704	0.449	0.390	0.390	0.408	0.408
Average severity score	2.5	3.3	2.8	2.8	3.3	3.4	3.2	3.3	3.6
Lymph Node, Axillary , Polymorphonuclear Cell Infiltration									
Overall incidence	0/4 (0.0%)	5/12 (41.7%)	0/7 (0.0%)	0/9 (0.0%)	0/9 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	1/11 (9.1%)	2/11 (18.2%)
Poly-3 adjusted incidence	0/4.0 (0.0%)	5/12.0 (41.7%)	0/7.0 (0.0%)	0/9.0 (0.0%)	0/9.0 (0.0%)	0/12.0 (0.0%)	1/12.0 (8.3%)	1/11.0 (9.1%)	2/11.0 (18.2%)
Terminal incidence	0/4 (0.0%)	2/9 (22.2%)	0/7 (0.0%)	0/9 (0.0%)	0/9 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	1/11 (9.1%)	2/11 (18.2%)
Lesion onset (days)	—	73	—	—	—	—	94	94	94
Poly-3 P value		0.171	**0.020**	—	—	—	0.606	0.589	0.337
Average severity score	—	3.0	—	—	—	—	1.0	2.0	3.0

TABLE I21
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Male Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Lymph Node, Inguinal, Hyperplasia, Lymphoid									
Overall incidence	3/4 (75.0%)	12/12 (100.0%)	2/7 (28.6%)	6/9 (66.7%)	7/9 (77.8%)	9/12 (75.0%)	11/12 (91.7%)	9/11 (81.8%)	11/11 (100.0%)
Poly-3 adjusted incidence	3/4.0 (75.0%)	12/12.0 (100.0%)	2/7.0 (28.6%)	6/9.0 (66.7%)	7/9.0 (77.8%)	9/12.0 (75.0%)	11/12.0 (91.7%)	9/11.0 (81.8%)	11/11.0 (100.0%)
Terminal incidence	3/4 (75.0%)	9/9 (100.0%)	2/7 (28.6%)	6/9 (66.7%)	7/9 (77.8%)	9/12 (75.0%)	11/12 (91.7%)	9/11 (81.8%)	11/11 (100.0%)
Lesion onset (days)	94	73	94	94	94	94	94	94	94
Poly-3 P value		0.266	**0.004**	0.154	0.058	0.056	**0.002**	**0.025**	**<0.001**
Average severity score	2.7	3.5	2.5	3.0	3.4	3.1	3.4	3.6	3.7
Lymph Node, Inguinal, Polymorphonuclear Cell Infiltration									
Overall incidence	0/4 (0.0%)	5/12 (41.7%)	0/7 (0.0%)	0/9 (0.0%)	0/9 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/11 (0.0%)	2/11 (18.2%)
Poly-3 adjusted incidence	0/4.0 (0.0%)	5/12.0 (41.7%)	0/7.0 (0.0%)	0/9.0 (0.0%)	0/9.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/11.0 (0.0%)	2/11.0 (18.2%)
Terminal incidence	0/4 (0.0%)	2/9 (22.2%)	0/7 (0.0%)	0/9 (0.0%)	0/9 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/11 (0.0%)	2/11 (18.2%)
Lesion onset (days)	—	73	—	—	—	—	—	—	94
Poly-3 P value		0.171	**0.017**	—	—	—	—	—	0.337
Average severity score	—	3.0	—	—	—	—	—	—	2.5
Spleen, Hematopoietic Cell Proliferation									
Overall incidence	1/12 (8.3%)	8/12 (66.7%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	7/12 (58.3%)	5/11 (45.5%)	10/12 (83.3%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	8/11.5 (69.8%)	0/11.5 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	7/12.0 (58.3%)	5/11.0 (45.5%)	10/12.0 (83.3%)
Terminal incidence	1/12 (8.3%)	6/9 (66.7%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	7/12 (58.3%)	5/11 (45.5%)	10/12 (83.3%)
Lesion onset (days)	94	91	—	—	—	—	94	94	94
Poly-3 P value		**<0.001**	**<0.001**	—	—	—	**<0.001**	**0.009**	**<0.001**
Average severity score	2.0	3.1	—	—	—	—	2.9	2.0	3.5
Hyperplasia, Lymphoid									
Overall incidence	2/12 (16.7%)	5/12 (41.7%)	1/12 (8.3%)	0/12 (0.0%)	5/12 (41.7%)	6/12 (50.0%)	7/12 (58.3%)	4/11 (36.4%)	7/12 (58.3%)
Poly-3 adjusted incidence	2/12.0 (16.7%)	5/11.4 (43.7%)	1/11.5 (8.7%)	0/12.0 (0.0%)	5/12.0 (41.7%)	6/12.0 (50.0%)	7/12.0 (58.3%)	4/11.0 (36.4%)	7/12.0 (58.3%)
Terminal incidence	2/12 (16.7%)	4/9 (44.4%)	1/11 (9.1%)	0/12 (0.0%)	5/12 (41.7%)	6/12 (50.0%)	7/12 (58.3%)	4/11 (36.4%)	7/12 (58.3%)
Lesion onset (days)	94	91	94	—	94	94	94	94	94
Poly-3 P value		0.163	**0.011**	0.492N	0.079	**0.031**	**0.009**	0.138	**0.009**
Average severity score	2.5	2.4	1.0	—	2.2	2.5	2.9	2.5	3.0

[a] Pairwise comparison tests of incidences are made to control cream groups. P values are based on one-sided tests. Significant P values ($P \leq 0.05$) appear in bold-faced type. Negative P values are appended with "**N**". P values for the control cream group represent dose trend effects for incidence with increasing doses of retinyl palmitate.

TABLE I22
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study[a]

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Skin, Site of Application, Acanthosis									
Overall incidence	12/12 (100.0%)	11/11 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	10/10 (100.0%)	12/12 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	12/12.0 (100.0%)	11/11.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)	12/12.0 (100.0%)	10/10.0 (100.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	12/12 (100.0%)	7/7 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	12/12 (100.0%)	10/10 (100.0%)	11/11 (100.0%)	11/11 (100.0%)
Lesion onset (days)	94	74	94	94	94	94	94	86	94
Poly-3 P value		—	—	—	—	—	—	—	—
Average severity score	1.4	3.7	1.3	2.0	2.4	2.9	3.9	3.7	3.9
Inflammation, Chronic/Active, Dermis									
Overall incidence	2/12 (16.7%)	11/11 (100.0%)	3/12 (25.0%)	8/12 (66.7%)	11/12 (91.7%)	12/12 (100.0%)	10/10 (100.0%)	12/12 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	2/12.0 (16.7%)	11/11.0 (100.0%)	3/12.0 (25.0%)	8/12.0 (66.7%)	11/12.0 (91.7%)	12/12.0 (100.0%)	10/10.0 (100.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	2/12 (16.7%)	7/7 (100.0%)	3/12 (25.0%)	8/12 (66.7%)	11/12 (91.7%)	12/12 (100.0%)	10/10 (100.0%)	11/11 (100.0%)	11/11 (100.0%)
Lesion onset (days)	94	74	94	94	94	94	94	86	94
Poly-3 P value		**<0.001**	**<0.001**	**0.042**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Average severity score	1.5	3.7	1.0	1.5	1.5	1.9	3.4	3.4	3.8
Inflammation, Granulomatous, Dermis									
Overall incidence	1/12 (8.3%)	0/11 (0.0%)	1/12 (8.3%)	1/12 (8.3%)	1/12 (8.3%)	0/12 (0.0%)	0/10 (0.0%)	0/12 (0.0%)	0/11 (0.0%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	0/9.7 (0.0%)	1/12.0 (8.3%)	1/12.0 (8.3%)	1/12.0 (8.3%)	0/12.0 (0.0%)	0/10.0 (0.0%)	0/11.8 (0.0%)	0/11.0 (0.0%)
Terminal incidence	1/12 (8.3%)	0/7 (0.0%)	1/12 (8.3%)	1/12 (8.3%)	1/12 (8.3%)	0/12 (0.0%)	0/10 (0.0%)	0/11 (0.0%)	0/11 (0.0%)
Lesion onset (days)	94	—	94	94	94	—	—	—	—
Poly-3 P value		0.542N	0.141N	0.760	0.760	0.500N	0.536N	0.504N	0.517N
Average severity score	1.0	—	1.0	1.0	1.0	—	—	—	—
Inflammation, Pyogranulomatous, Dermis									
Overall incidence			2/12 (16.7%)	1/12 (8.3%)	0/12 (0.0%)	0/12 (0.0%)	0/10 (0.0%)	0/12 (0.0%)	0/11 (0.0%)
Poly-3 adjusted incidence			2/12.0 (16.7%)	1/12.0 (8.3%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/10.0 (0.0%)	0/11.8 (0.0%)	0/11.0 (0.0%)
Terminal incidence			2/12 (16.7%)	1/12 (8.3%)	0/12 (0.0%)	0/12 (0.0%)	0/10 (0.0%)	0/11 (0.0%)	0/11 (0.0%)
Lesion onset (days)			94	94	—	—	—	—	—
Poly-3 P value			0.121N	0.500N	0.229N	0.229N	0.272N	0.234N	0.249N
Average severity score			1.0	1.0	—	—	—	—	—

TABLE I22
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Skin, Dermis, Inflammation, Suppurative									
Overall incidence	0/12 (0.0%)	1/11 (9.1%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	1/10 (10.0%)	0/12 (0.0%)	0/11 (0.0%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	1/10.2 (9.8%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	1/10.0 (10.0%)	0/11.8 (0.0%)	0/11.0 (0.0%)
Terminal incidence	0/12 (0.0%)	0/7 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	1/10 (10.0%)	0/11 (0.0%)	0/11 (0.0%)
Lesion onset (days)	—	74	—	—	—	—	94	—	—
Poly-3 P value		0.468	0.622	—	—	—	0.463	—	—
Average severity score	—	4.0	—	—	—	—	3.0	—	—
Skin, Dermis, Inflammation									
Overall incidence	3/12 (25.0%)	11/11 (100.0%)	6/12 (50.0%)	10/12 (83.3%)	12/12 (100.0%)	12/12 (100.0%)	10/10 (100.0%)	12/12 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	3/12.0 (25.0%)	11/11.0 (100.0%)	6/12.0 (50.0%)	10/12.0 (83.3%)	12/12.0 (100.0%)	12/12.0 (100.0%)	10/10.0 (100.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	3/12 (25.0%)	7/7 (100.0%)	6/12 (50.0%)	10/12 (83.3%)	12/12 (100.0%)	12/12 (100.0%)	10/10 (100.0%)	11/11 (100.0%)	11/11 (100.0%)
Lesion onset (days)	94	74	94	94	94	94	94	86	94
Poly-3 P value		**<0.001**	**0.003**	0.092	**0.003**	**0.003**	**0.007**	**0.003**	**0.004**
Average severity score	1.3	3.7	1.0	1.4	1.4	1.9	3.4	3.4	3.8
Necrosis, Epithelium									
Overall incidence	0/12 (0.0%)	9/11 (81.8%)	0/12 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	1/12 (8.3%)	9/10 (90.0%)	11/12 (91.7%)	11/11 (100.0%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	9/10.3 (87.8%)	0/12.0 (0.0%)	0/12.0 (0.0%)	1/12.0 (8.3%)	1/12.0 (8.3%)	9/10.0 (90.0%)	11/12.0 (91.7%)	11/11.0 (100.0%)
Terminal incidence	0/12 (0.0%)	7/7 (100.0%)	0/12 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	1/12 (8.3%)	9/10 (90.0%)	10/11 (90.9%)	11/11 (100.0%)
Lesion onset (days)	—	83	—	—	94	94	94	86	94
Poly-3 P value		**<0.001**	**<0.001**	—	0.500	0.500	**<0.001**	**<0.001**	**<0.001**
Average severity score	—	3.0	—	—	1.0	1.0	3.0	3.0	3.3
Skin, Epithelium, Hyperplasia–Squamous									
Overall incidence			1/12 (8.3%)	1/12 (8.3%)	0/12 (0.0%)	0/12 (0.0%)	0/10 (0.0%)	0/12 (0.0%)	0/11 (0.0%)
Poly-3 adjusted incidence			1/12.0 (8.3%)	1/12.0 (8.3%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/10.0 (0.0%)	0/11.8 (0.0%)	0/11.0 (0.0%)
Terminal incidence			1/12 (8.3%)	1/12 (8.3%)	0/12 (0.0%)	0/12 (0.0%)	0/10 (0.0%)	0/11 (0.0%)	0/11 (0.0%)
Lesion onset (days)			94	94	—	—	—	—	—
Poly-3 P value			0.210N	0.760	0.500N	0.500N	0.536N	0.504N	0.517N
Average severity score			3.0	4.0	—	—	—	—	—

TABLE I22
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Skin, Hyperplasia- Squamous									
Overall incidence			1/12 (8.3%)	1/12 (8.3%)	0/12 (0.0%)	0/12 (0.0%)	0/10 (0.0%)	0/12 (0.0%)	0/11 (0.0%)
Poly-3 adjusted incidence			1/12.0 (8.3%)	1/12.0 (8.3%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/10.0 (0.0%)	0/11.8 (0.0%)	0/11.0 (0.0%)
Terminal incidence			1/12 (8.3%)	1/12 (8.3%)	0/12 (0.0%)	0/12 (0.0%)	0/10 (0.0%)	0/11 (0.0%)	0/11 (0.0%)
Lesion onset (days)			94	94	—	—	—	—	—
Poly-3 P value			0.210N	0.760	0.500N	0.500N	0.536N	0.504N	0.517N
Average severity score			3.0	4.0	—	—	—	—	—
Skin, Untreated									
Skin, Acanthosis									
Overall incidence	3/12 (25.0%)	11/11 (100.0%)	1/12 (8.3%)	9/12 (75.0%)	9/12 (75.0%)	10/12 (83.3%)	10/10 (100.0%)	11/11 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	3/12.0 (25.0%)	11/11.0 (100.0%)	1/12.0 (8.3%)	9/12.0 (75.0%)	9/12.0 (75.0%)	10/12.0 (83.3%)	10/10.0 (100.0%)	11/11.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	3/12 (25.0%)	7/7 (100.0%)	1/12 (8.3%)	9/12 (75.0%)	9/12 (75.0%)	10/12 (83.3%)	10/10 (100.0%)	11/11 (100.0%)	11/11 (100.0%)
Lesion onset (days)	94	74	94	94	94	94	94	94	94
Poly-3 P value		**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Average severity score	1.0	2.1	1.0	1.0	1.0	1.2	1.8	1.5	1.6
Inflammation, Chronic/Active, Dermis									
Overall incidence	0/12 (0.0%)	9/11 (81.8%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	4/10 (40.0%)	5/11 (45.5%)	5/11 (45.5%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	9/10.7 (84.2%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	4/10.0 (40.0%)	5/11.0 (45.5%)	5/11.0 (45.5%)
Terminal incidence	0/12 (0.0%)	6/7 (85.7%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	4/10 (40.0%)	5/11 (45.5%)	5/11 (45.5%)
Lesion onset (days)	—	74	—	—	—	—	94	94	94
Poly-3 P value		**<0.001**	**<0.001**	—	—	—	**0.019**	**0.007**	**0.007**
Average severity score	---	1.4	—	—	—	—	1.0	1.2	1.0
Inflammation, Granulomatous, Dermis									
Overall incidence			2/12 (16.7%)	3/12 (25.0%)	0/12 (0.0%)	1/12 (8.3%)	0/10 (0.0%)	0/11 (0.0%)	1/11 (9.1%)
Poly-3 adjusted incidence			2/12.0 (16.7%)	3/12.0 (25.0%)	0/12.0 (0.0%)	1/12.0 (8.3%)	0/10.0 (0.0%)	0/11.0 (0.0%)	1/11.0 (9.1%)
Terminal incidence			2/12 (16.7%)	3/12 (25.0%)	0/12 (0.0%)	1/12 (8.3%)	0/10 (0.0%)	0/11 (0.0%)	1/11 (9.1%)
Lesion onset (days)			94	94	—	94	—	—	94
Poly-3 P value			0.177N	0.500	0.229N	0.500N	0.272N	0.249N	0.531N
Average severity score			1.0	1.3	—	1.0	—	—	1.0

TABLE I22
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Skin, Dermis, Inflammation									
Overall incidence	0/12 (0.0%)	10/11 (90.9%)	2/12 (16.7%)	3/12 (25.0%)	0/12 (0.0%)	1/12 (8.3%)	4/10 (40.0%)	6/11 (54.5%)	6/11 (54.5%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	10/10.7 (93.6%)	2/12.0 (16.7%)	3/12.0 (25.0%)	0/12.0 (0.0%)	1/12.0 (8.3%)	4/10.0 (40.0%)	6/11.0 (54.5%)	6/11.0 (54.5%)
Terminal incidence	0/12 (0.0%)	7/7 (100.0%)	2/12 (16.7%)	3/12 (25.0%)	0/12 (0.0%)	1/12 (8.3%)	4/10 (40.0%)	6/11 (54.5%)	6/11 (54.5%)
Lesion onset (days)	—	74	94	94	—	94	94	94	94
Poly-3 P value		**<0.001**	**<0.001**	0.500	0.229N	0.500N	0.232	0.063	0.063
Average severity score	—	1.4	1.0	1.3	—	1.0	1.0	1.2	1.0
Liver, Vacuolization, Cytoplasmic									
Overall incidence	0/12 (0.0%)	3/11 (27.3%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	4/10 (40.0%)	9/12 (75.0%)	8/11 (72.7%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	3/9.7 (30.9%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	4/10.0 (40.0%)	9/11.8 (76.5%)	8/11.0 (72.7%)
Terminal incidence	0/12 (0.0%)	3/7 (42.9%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	4/10 (40.0%)	9/11 (81.8%)	8/11 (72.7%)
Lesion onset (days)	—	94	—	—	—	—	94	94	94
Poly-3 P value		0.063	**<0.001**	—	—	—	**0.019**	**<0.001**	**<0.001**
Average severity score	—	2.0	—	—	—	—	2.0	1.9	2.0
Hematopoietic Cell Proliferation									
Overall incidence	1/12 (8.3%)	11/11 (100.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	8/10 (80.0%)	8/12 (66.7%)	8/11 (72.7%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	11/11.0 (100.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	8/10.0 (80.0%)	8/12.0 (66.7%)	8/11.0 (72.7%)
Terminal incidence	1/12 (8.3%)	7/7 (100.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	8/10 (80.0%)	7/11 (63.6%)	8/11 (72.7%)
Lesion onset (days)	94	74	—	—	—	—	94	86	94
Poly-3 P value		**<0.001**	**<0.001**	—	—	—	**<0.001**	**<0.001**	**<0.001**
Average severity score	1.0	2.5	—	—	—	—	1.9	1.8	2.5
Lymphocyte, Cell Infiltration									
Overall incidence	1/12 (8.3%)	2/11 (18.2%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	5/10 (50.0%)	3/12 (25.0%)	3/11 (27.3%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	2/9.7 (20.6%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	1/12.0 (8.3%)	5/10.0 (50.0%)	3/11.8 (25.5%)	3/11.0 (27.3%)
Terminal incidence	1/12 (8.3%)	2/7 (28.6%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	1/12 (8.3%)	5/10 (50.0%)	3/11 (27.3%)	3/11 (27.3%)
Lesion onset (days)	94	94	—	—	—	94	94	94	94
Poly-3 P value		0.424	**0.001**	—	—	0.500	**0.003**	0.097	0.084
Average severity score	2.0	1.5	—	—	—	1.0	2.0	1.3	2.3

TABLE I22
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Inflammation, Chronic, Active									
Overall incidence	0/12 (0.0%)	3/11 (27.3%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/10 (0.0%)	2/12 (16.7%)	1/11 (9.1%)
Poly-3 adjusted incidence	0/12.0 (0.0%)	3/10.7 (28.1%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	0/10.0 (0.0%)	2/11.8 (17.0%)	1/11.0 (9.1%)
Terminal incidence	0/12 (0.0%)	0/7 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	0/10 (0.0%)	2/11 (18.2%)	1/11 (9.1%)
Lesion onset (days)	—	74	—	—	—	—	—	94	94
Poly-3 P value		0.079	**0.014**	—	—	—	—	0.224	0.483
Average severity score	—	4.0	—	—	—	—	—	2.0	2.0
Lymph Node, Axillary, Hyperplasia, Lymphoid									
Overall incidence	3/4 (75.0%)	9/11 (81.8%)	10/10 (100.0%)	10/11 (90.9%)	12/12 (100.0%)	12/12 (100.0%)	10/10 (100.0%)	12/12 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	3/4.0 (75.0%)	9/10.3 (87.8%)	10/10.0 (100.0%)	10/11.0 (90.9%)	12/12.0 (100.0%)	12/12.0 (100.0%)	10/10.0 (100.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	3/4 (75.0%)	7/7 (100.0%)	10/10 (100.0%)	10/11 (90.9%)	12/12 (100.0%)	12/12 (100.0%)	10/10 (100.0%)	11/11 (100.0%)	11/11 (100.0%)
Lesion onset (days)	94	83	94	94	94	94	94	86	94
Poly-3 P value		0.589	0.369	0.519N	—	—	—	—	—
Average severity score	3.7	3.6	2.6	3.0	3.2	3.3	3.8	3.5	3.3
Lymph Node, Axillary Necrosis									
Overall incidence	0/4 (0.0%)	4/11 (36.4%)	0/10 (0.0%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	1/10 (10.0%)	2/12 (16.7%)	3/11 (27.3%)
Poly-3 adjusted incidence	0/4.0 (0.0%)	4/9.7 (41.2%)	0/10.0 (0.0%)	0/11.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	1/10.0 (10.0%)	2/11.8 (17.0%)	3/11.0 (27.3%)
Terminal incidence	0/4 (0.0%)	4/7 (57.1%)	0/10 (0.0%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	1/10 (10.0%)	2/11 (18.2%)	3/11 (27.3%)
Lesion onset (days)	—	94	—	—	—	—	94	94	94
Poly-3 P value		0.177	**<0.001**	—	—	—	0.500	0.267	0.116
Average severity score	—	2.0	—	—	—	—	2.0	3.0	2.3
Lymph Node, Axillary, Polymorphonuclear Cell Infiltration									
Overall incidence	0/4 (0.0%)	9/11 (81.8%)	0/10 (0.0%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	6/10 (60.0%)	5/12 (41.7%)	8/11 (72.7%)
Poly-3 adjusted incidence	0/4.0 (0.0%)	9/11.0 (81.8%)	0/10.0 (0.0%)	0/11.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	6/10.0 (60.0%)	5/12.0 (41.7%)	8/11.0 (72.7%)
Terminal incidence	0/4 (0.0%)	5/7 (71.4%)	0/10 (0.0%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	6/10 (60.0%)	4/11 (36.4%)	8/11 (72.7%)
Lesion onset (days)	—	74	—	—	—	—	94	86	94
Poly-3 P value		**<0.001**	**<0.001**	—	—	—	**0.001**	**0.023**	**<0.001**
Average severity score	—	3.2	—	—	—	—	2.3	2.8	2.5

TABLE I22
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Lymph Node, Inguinal, Hyperplasia, Lymphoid									
Overall incidence	2/4 (50.0%)	9/11 (81.8%)	9/10 (90.0%)	11/11 (100.0%)	8/12 (66.7%)	11/12 (91.7%)	10/10 (100.0%)	12/12 (100.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	2/4.0 (50.0%)	9/10.3 (87.8%)	9/10.0 (90.0%)	11/11.0 (100.0%)	8/12.0 (66.7%)	11/12.0 (91.7%)	10/10.0 (100.0%)	12/12.0 (100.0%)	11/11.0 (100.0%)
Terminal incidence	2/4 (50.0%)	7/7 (100.0%)	9/10 (90.0%)	11/11 (100.0%)	8/12 (66.7%)	11/12 (91.7%)	10/10 (100.0%)	11/11 (100.0%)	11/11 (100.0%)
Lesion onset (days)	94	83	94	94	94	94	94	86	94
Poly-3 P value		0.182	**0.034**	0.481	0.217N	0.719	0.500	0.463	0.481
Average severity score	2.5	3.0	3.0	3.2	3.6	3.4	4.0	3.7	3.5
Lymph Node, Inguinal, Necrosis									
Overall incidence			0/10 (0.0%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	1/10 (10.0%)	2/12 (16.7%)	4/11 (36.4%)
Poly-3 adjusted incidence			0/10.0 (0.0%)	0/11.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	1/10.0 (10.0%)	2/11.8 (17.0%)	4/11.0 (36.4%)
Terminal incidence			0/10 (0.0%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	1/10 (10.0%)	2/11 (18.2%)	4/11 (36.4%)
Lesion onset (days)			—	—	—	—	94	94	94
Poly-3 P value			**<0.001**	—	—	—	0.500	0.267	**0.047**
Average severity score			—	—	—	—	2.0	2.5	2.3
Lymph Node, Inguinal, Polymorphonuclear Cell Infiltration									
Overall incidence	0/4 (0.0%)	7/11 (63.6%)	0/10 (0.0%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	8/10 (80.0%)	6/12 (50.0%)	9/11 (81.8%)
Poly-3 adjusted incidence	0/4.0 (0.0%)	7/10.8 (65.0%)	0/10.0 (0.0%)	0/11.0 (0.0%)	0/12.0 (0.0%)	0/12.0 (0.0%)	8/10.0 (80.0%)	6/12.0 (50.0%)	9/11.0 (81.8%)
Terminal incidence	0/4 (0.0%)	4/7 (57.1%)	0/10 (0.0%)	0/11 (0.0%)	0/12 (0.0%)	0/12 (0.0%)	8/10 (80.0%)	5/11 (45.5%)	9/11 (81.8%)
Lesion onset (days)	—	74	—	—	—	—	94	86	94
Poly-3 P value		**0.029**	**<0.001**	—	—	—	**<0.001**	**0.007**	**<0.001**
Average severity score	—	3.3	—	—	—	—	2.1	3.0	2.7

TABLE I22
Incidence and Severity of Nonneoplastic Lesions in Retinyl Palmitate Compared to Control Cream Treatment Groups of Female Mice on the Range-Finding Study

	0.00 mJ•CIE/cm^2		13.70 mJ•CIE/cm^2						
	Control Cream	13.0% Retinyl Palmitate	Control Cream	0.1% Retinyl Palmitate	0.5% Retinyl Palmitate	1.0% Retinyl Palmitate	5.0% Retinyl Palmitate	10.0% Retinyl Palmitate	13.0% Retinyl Palmitate
Spleen, Hematopoietic Cell Proliferation									
Overall incidence	2/12 (16.7%)	10/11 (90.9%)	1/12 (8.3%)	2/12 (16.7%)	2/12 (16.7%)	3/12 (25.0%)	9/10 (90.0%)	9/12 (75.0%)	11/11 (100.0%)
Poly-3 adjusted incidence	2/12.0 (16.7%)	10/11.0 (90.9%)	1/12.0 (8.3%)	2/12.0 (16.7%)	2/12.0 (16.7%)	3/12.0 (25.0%)	9/10.0 (90.0%)	9/12.0 (75.0%)	11/11.0 (100.0%)
Terminal incidence	2/12 (16.7%)	6/7 (85.7%)	1/12 (8.3%)	2/12 (16.7%)	2/12 (16.7%)	3/12 (25.0%)	9/10 (90.0%)	8/11 (72.7%)	11/11 (100.0%)
Lesion onset (days)	94	74	94	94	94	94	94	86	94
Poly-3 P value		**<0.001**	**<0.001**	0.500	0.500	0.295	**<0.001**	**<0.001**	**<0.001**
Average severity score	2.0	3.7	2.0	2.0	2.0	2.7	3.3	3.2	3.5
Hyperplasia, Lymphoid									
Overall incidence	1/12 (8.3%)	5/11 (45.5%)	5/12 (41.7%)	5/12 (41.7%)	2/12 (16.7%)	3/12 (25.0%)	4/10 (40.0%)	8/12 (66.7%)	5/11 (45.5%)
Poly-3 adjusted incidence	1/12.0 (8.3%)	5/9.7 (51.5%)	5/12.0 (41.7%)	5/12.0 (41.7%)	2/12.0 (16.7%)	3/12.0 (25.0%)	4/10.0 (40.0%)	8/11.8 (68.0%)	5/11.0 (45.5%)
Terminal incidence	1/12 (8.3%)	5/7 (71.4%)	5/12 (41.7%)	5/12 (41.7%)	2/12 (16.7%)	3/12 (25.0%)	4/10 (40.0%)	8/11 (72.7%)	5/11 (45.5%)
Lesion onset (days)	94	94	94	94	94	94	94	94	94
Poly-3 P value		**0.029**	**0.046**	0.654	0.186N	0.337N	0.633N	0.191	0.590
Average severity score	4.0	3.0	2.2	2.0	2.5	2.3	3.0	2.5	3.0

[a] Pairwise comparison tests of incidences are made to control cream groups. P values are based on one-sided tests. Significant P values ($P \leq 0.05$) appear in bold-faced type. Negative P values are appended with "**N**". P values for the control cream group represent dose trend effects for incidence with increasing doses of retinyl palmitate.

TABLE I23
Skin Acanthosis in Female Mice on the MED Study[a]

Treatment	Skin – Site of Application				Skin – Untreated			
	No Cream	Control Cream	2.0% Retinyl Palmitate	10.0% Retinyl Palmitate	No Cream	Control Cream	2.0% Retinyl Palmitate	10.0% Retinyl Palmitate
0.00 mJ•CIE/cm^2								
Overall incidence	0/6 (0.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)	0/6 (0.0%)	0/6 (0.0%)	6/6 (100.0%)	5/5 (100.0%)
Poly-3 adjusted incidence	0/6.0 (0.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)	0/6.0 (0.0%)	0/6.0 (0.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)
Terminal incidence	0/6 (0.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)	0/6 (0.0%)	0/6 (0.0%)	6/6 (100.0%)	5/5 (100.0%)
Lesion onset (days)	—	95	95	95	—	—	95	95
Poly-3 p-value	—	—	—	—	—	**<0.001**	**<0.002**	**<0.003**
Average severity score	—	1.8	3.0	3.8	—	—	1.5	1.8
60 mJ•CIE/cm^2								
Overall incidence	1/6 (16.7%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)	0/6 (0.0%)	0/6 (0.0%)	6/6 (100.0%)	5/5 (100.0%)
Poly-3 adjusted incidence	1/6.0 (16.7%)	6/6.0 (100.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)	0/6.0 (0.0%)	0/6.0 (0.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)
Terminal incidence	1/6 (16.7%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)	0/6 (0.0%)	0/6 (0.0%)	6/6 (100.0%)	5/5 (100.0%)
Lesion onset (days)	95	95	95	95	—	—	95	95
Poly-3 P value	**<0.001**	—	—	—	—	**<0.001**	**<0.002**	**<0.003**
Average severity score	1.0	2.0	3.0	3.8	—	—	1.2	2.0
100 mJ•CIE/cm^2								
Overall incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	0/6 (0.0%)	0/6 (0.0%)	6/6 (100.0%)	6/6 (100.0%)
Poly-3 adjusted incidence	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	0/6.0 (0.0%)	0/6.0 (0.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)
Terminal incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	0/6 (0.0%)	0/6 (0.0%)	6/6 (100.0%)	6/6 (100.0%)
Lesion onset (days)	95	95	95	95	—	—	95	95
Poly-3 P value	—	—	—	—	—	**<0.001**	**<0.002**	**<0.002**
Average severity score	1.0	2.2	3.3	4.0	—	—	1.5	1.8
140 mJ•CIE/cm^2								
Overall incidence	5/6 (83.3%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	0/6 (0.0%)	3/6 (50.0%)	6/6 (100.0%)	6/6 (100.0%)
Poly-3 adjusted incidence	5/6.0 (83.3%)	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	0/6.0 (0.0%)	3/6.0 (50.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)
Terminal incidence	5/6 (83.3%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	0/6 (0.0%)	3/6 (50.0%)	6/6 (100.0%)	6/6 (100.0%)
Lesion onset (days)	95	95	95	95	—	95	95	95
Poly-3 P value	0.500	—	—	—	0.068	0.084	0.068	0.068
Average severity score	1.0	2.0	3.5	4.0	—	1.0	1.7	2.0

TABLE I23
Skin Acanthosis in Female Mice on the MED Study

Treatment	Skin – Site of Application				Skin – Untreated			
	No Cream	Control Cream	2.0% Retinyl Palmitate	10.0% Retinyl Palmitate	No Cream	Control Cream	2.0% Retinyl Palmitate	10.0% Retinyl Palmitate
180 mJ•CIE/cm^2								
Overall incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	1/6 (16.7%)	1/6 (16.7%)	6/6 (100.0%)	6/6 (100.0%)
Poly-3 adjusted incidence	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	1/6.0 (16.7%)	1/6.0 (16.7%)	6/6.0 (100.0%)	6/6.0 (100.0%)
Terminal incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	1/6 (16.7%)	1/6 (16.7%)	6/6 (100.0%)	6/6 (100.0%)
Lesion onset (days)	95	95	95	95	95	95	95	95
Poly-3 P value	—	—	—	—	0.760	**<0.001**	**<0.001**	**<0.001**
Average severity score	1.0	2.0	3.5	4.0	1.0	1.0	1.3	2.0
220 mJ•CIE/cm^2								
Overall incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)	2/6 (33.3%)	2/6 (33.3%)	6/6 (100.0%)	5/5 (100.0%)
Poly-3 adjusted incidence	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)	2/6.0 (33.3%)	2/6.0 (33.3%)	6/6.0 (100.0%)	5/5.0 (100.0%)
Terminal incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)	2/6 (33.3%)	2/6 (33.3%)	6/6 (100.0%)	5/5 (100.0%)
Lesion onset (days)	95	95	95	95	95	95	95	95
Poly-3 P value	—	—	—	—	0.712	**0.023**	**0.009**	**0.019**
Average severity score	1.2	2.0	3.2	3.8	1.0	1.0	1.0	2.0
260 mJ•CIE/cm^2								
Overall incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)	2/6 (33.3%)	2/6 (33.3%)	6/6 (100.0%)	5/5 (100.0%)
Poly-3 adjusted incidence	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)	2/6.0 (33.3%)	2/6.0 (33.3%)	6/6.0 (100.0%)	5/5.0 (100.0%)
Terminal incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)	2/6 (33.3%)	2/6 (33.3%)	6/6 (100.0%)	5/5 (100.0%)
Lesion onset (days)	95	95	95	95	95	95	95	95
Poly-3 P value	—	—	—	—	0.712	**0.023**	**0.009**	**0.019**
Average severity score	1.3	2.2	3.5	4.0	1.0	1.0	1.2	2.0

[a] Pairwise comparison tests of incidences are made to control cream groups. P values are based on one-sided tests. Significant P values ($P \leq 0.05$) appear in bold-faced type. P values for the control cream group represent dose trend effects for incidence with increasing doses of retinyl palmitate.

TABLE I24
Chronic Active Inflammation of the Dermis in Female Mice on the MED Study[a]

Treatment	Skin – Site of Application				Skin – Untreated			
	No Cream	Control Cream	2.0% Retinyl Palmitate	10.0% Retinyl Palmitate	No Cream	Control Cream	2.0% Retinyl Palmitate	10.0% Retinyl Palmitate
0.00 mJ•CIE/cm^2								
Overall incidence	1/6 (16.7%)	0/6 (0.0%)	6/6 (100.0%)	5/5 (100.0%)				
Poly-3 adjusted incidence	1/6.0 (16.7%)	0/6.0 (0.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)				
Terminal incidence	1/6 (16.7%)	0/6 (0.0%)	6/6 (100.0%)	5/5 (100.0%)				
Lesion onset (days)	95	---	95	95				
Poly-3 P value	0.500N	**<0.001**	**<0.002**	**<0.003**				
Average severity score	1.0	—	2.0	3.4				
60 mJ•CIE/cm^2								
Overall incidence	0/6 (0.0%)	0/6 (0.0%)	6/6 (100.0%)	5/5 (100.0%)				
Poly-3 adjusted incidence	0/6.0 (0.0%)	0/6.0 (0.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)				
Terminal incidence	0/6 (0.0%)	0/6 (0.0%)	6/6 (100.0%)	5/5 (100.0%)				
Lesion onset (days)	—	—	95	95				
Poly-3 P value	—	**<0.001**	**<0.002**	**<0.003**				
Average severity score	—	—	2.0	3.4				
100 mJ•CIE/cm^2								
Overall incidence	4/6 (66.7%)	3/6 (50.0%)	6/6 (100.0%)	6/6 (100.0%)	0/6 (0.0%)	0/6 (0.0%)	0/6 (0.0%)	1/6 (16.7%)
Poly-3 adjusted incidence	4/6.0 (66.7%)	3/6.0 (50.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	0/6.0 (0.0%)	0/6.0 (0.0%)	0/6.0 (0.0%)	1/6.0 (16.7%)
Terminal incidence	4/6 (66.7%)	3/6 (50.0%)	6/6 (100.0%)	6/6 (100.0%)	0/6 (0.0%)	0/6 (0.0%)	0/6 (0.0%)	1/6 (16.7%)
Lesion onset (days)	95	95	95	95	—	—	—	95
Poly-3 P value	0.500N	0.084	0.068	0.068	—	0.322	—	0.500
Average severity score	1.3	1.3	2.3	4.0	—	—	—	1.0
140 mJ•CIE/cm^2								
Overall incidence	2/6 (33.3%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)				
Poly-3 adjusted incidence	2/6.0 (33.3%)	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)				
Terminal incidence	2/6 (33.3%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)				
Lesion onset (days)	95	95	95	95				
Poly-3 P value	**0.009**	—	—	—				
Average severity score	1.0	1.2	2.8	3.3				

TABLE I24
Chronic Active Inflammation of the Dermis in Female Mice on the MED Study

Treatment	Skin – Site of Application				Skin – Untreated			
	No Cream	Control Cream	2.0% Retinyl Palmitate	10.0% Retinyl Palmitate	No Cream	Control Cream	2.0% Retinyl Palmitate	10.0% Retinyl Palmitate
180 mJ•CIE/cm^2								
Overall incidence	6/6 (100%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	1/6 (16.7)	0/6 (0.0%)	0/6 (0.0%)	0/6 (0.0%)
Poly-3 adjusted incidence	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	1/6.0 (16.7%)	0/6.0 (0.0%)	0/6.0 (0.0%)	0/6.0 (0.0%)
Terminal incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	1/6 (16.7)	0/6 (0.0%)	0/6 (0.0%)	0/6 (0.0%)
Lesion onset (days)	95	95	95	95	95	—	—	—
Poly-3 P value	—	—	—	—	0.500N	—	—	—
Average severity score	1.7	2.0	2.3	3.3	1.0	—	—	—
220 mJ•CIE/cm^2								
Overall incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)				
Poly-3 adjusted incidence	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)				
Terminal incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)				
Lesion onset (days)	95	95	95	95				
Poly-3 P value	—	—	—	—				
Average severity score	1.8	2.0	2.3	3.6				
260 mJ•CIE/cm^2								
Overall incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)	1/6 (16.7%)	0/6 (0.0%)	0/6 (0.0%)	0/5 (0.0%)
Poly-3 adjusted incidence	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)	1/6.0 (16.7%)	0/6.0 (0.0%)	0/6.0 (0.0%)	0/5.0 (0.0%)
Terminal incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)	1/6 (16.7%)	0/6 (0.0%)	0/6 (0.0%)	0/5 (0.0%)
Lesion onset (days)	95	95	95	95	95	—	—	—
Poly-3 P value	—	—	—	—	0.500N	—	—	—
Average severity score	1.8	1.7	2.7	3.4	1.0	—	—	—

[a] Pairwise comparison tests of incidences are made to control cream groups. P values are based on one-sided tests. Significant P values ($P \leq 0.05$) appear in bold-faced type. Negative P values are appended with "**N**". P values for the control cream group represent dose trend effects for incidence with increasing doses of retinyl palmitate.

TABLE I25
Suppurative Inflammation of the Skin in Female Mice on the MED Study[a]

Treatment	Skin – Site of Application			
	No Cream	Control Cream	2.0% Retinyl Palmitate	10.0% Retinyl Palmitate
0.00 mJ•CIE/cm^2				
Overall incidence	0/6 (0.0%)	0/6 (0.0%)	0/6 (0.0%)	3/5 (60.0%)
Poly-3 adjusted incidence	0/6.0 (0.0%)	0/6.0 (0.0%)	0/6.0 (0.0%)	3/5.0 (60.0%)
Terminal incidence	0/6 (0.0%)	0/6 (0.0%)	0/6 (0.0%)	3/5 (60.0%)
Lesion onset (days)	—	—	—	95
Poly-3 P value	—	**0.001**	—	**0.030**
Average severity score	—	—	—	2.3
60 mJ•CIE/cm^2				
Overall incidence	0/6 (0.0%)	0/6 (0.0%)	2/6 (33.3%)	5/5 (100.0%)
Poly-3 adjusted incidence	0/6.0 (0.0%)	0/6.0 (0.0%)	2/6.0 (33.3%)	5/5.0 (100.0%)
Terminal incidence	0/6 (0.0%)	0/6 (0.0%)	2/6 (33.3%)	5/5 (100.0%)
Lesion onset (days)	—	—	95	95
Poly-3 P value	—	**<0.001**	0.215	**<0.003**
Average severity score	---	—	1.0	2.4
100 mJ•CIE/cm^2				
Overall incidence	1/6 (16.7%)	0/6 (0.0%)	1/6 (16.7%)	6/6 (100.0%)
Poly-3 adjusted incidence	1/6.0 (16.7%)	0/6.0 (0.0%)	1/6.0 (16.7%)	6/6.0 (100.0%)
Terminal incidence	1/6 (16.7%)	0/6 (0.0%)	1/6 (16.7%)	6/6 (100.0%)
Lesion onset (days)	95	—	95	95
Poly-3 P value	0.500N	**<0.001**	0.500	**<0.002**
Average severity score	1.0	—	1.0	2.0
140 mJ•CIE/cm^2				
Overall incidence	0/6 (0.0%)	0/6 (0.0%)	3/6 (50.0%)	2/6 (33.3%)
Poly-3 adjusted incidence	0/6.0 (0.0%)	0/6.0 (0.0%)	3/6.0 (50.0%)	2/6.0 (33.3%)
Terminal incidence	0/6 (0.0%)	0/6 (0.0%)	3/6 (50.0%)	2/6 (33.3%)
Lesion onset (days)	—	—	95	95
Poly-3 P value	—	0.401	0.068	0.215
Average severity score	—	—	1.7	1.5
180 mJ•CIE/cm^2				
Overall incidence	0/6 (0.0%)	4/6 (66.7%)	4/6 (66.7%)	6/6 (100.0%)
Poly-3 adjusted incidence	0/6.0 (0.0%)	4/6.0 (66.7%)	4/6.0 (66.7%)	6/6.0 (100.0%)
Terminal incidence	0/6 (0.0%)	4/6 (66.7%)	4/6 (66.7%)	6/6 (100.0%)
Lesion onset (days)	—	95	95	95
Poly-3 P value	**0.009**	0.150	0.712	0.215
Average severity score	—	1.3	1.3	2.5
220 mJ•CIE/cm^2				
Overall incidence	1/6 (16.7%)	5/6 (83.3%)	4/6 (66.7%)	5/5 (100.0%)
Poly-3 adjusted incidence	1/6.0 (16.7%)	5/6.0 (83.3%)	4/6.0 (66.7%)	5/5.0 (100.0%)
Terminal incidence	1/6 (16.7%)	5/6 (83.3%)	4/6 (66.7%)	5/5 (100.0%)
Lesion onset (days)	95	95	95	95
Poly-3 P value	**0.017**	0.332	0.500N	0.536
Average severity score	1.0	1.2	2.3	2.6
260 mJ•CIE/cm^2				
Overall incidence	2/6 (33.3%)	3/6 (50.0%)	4/6 (66.7%)	5/5 (100.0%)
Poly-3 adjusted incidence	2/6.0 (33.3%)	3/6.0 (50.0%)	4/6.0 (66.7%)	5/5.0 (100.0%)
Terminal incidence	2/6 (33.3%)	3/6 (50.0%)	4/6 (66.7%)	5/5 (100.0%)
Lesion onset (days)	95	95	95	95
Poly-3 P value	0.500	0.094	0.500	0.100
Average severity score	1.0	2.7	3.0	3.0

[a] Pairwise comparison tests of incidences are made to control cream groups. P values are based on one-sided tests. Significant P values ($P \leq 0.05$) appear in bold-faced type. Negative P values are appended with "**N**". P values for the control cream group represent dose trend effects for incidence with increasing doses of retinyl palmitate.

TABLE I26
Epidermal Necrosis of the Skin in Female Mice on the MED Study[a]

Treatment	Skin – Site of Application			
	No Cream	Control Cream	2.0% Retinyl Palmitate	10.0% Retinyl Palmitate
0.00 mJ•CIE/cm^2				
Overall incidence	0/6 (0.0%)	0/6 (0.0%)	0/6 (0.0%)	5/5 (100.0%)
Poly-3 adjusted incidence	0/6.0 (0.0%)	0/6.0 (0.0%)	0/6.0 (0.0%)	5/5.0 (100.0%)
Terminal incidence	0/6 (0.0%)	0/6 (0.0%)	0/6 (0.0%)	5/5 (100.0%)
Lesion onset (days)	—	---	—	95
Poly-3 P value	—	**<0.001**	—	**<0.003**
Average severity score	—	—	—	2.4
60 mJ•CIE/cm^2				
Overall incidence	0/6 (0.0%)	0/6 (0.0%)	2/6 (33.3%)	5/5 (100.0%)
Poly-3 adjusted incidence	0/6.0 (0.0%)	0/6.0 (0.0%)	2/6.0 (33.3%)	5/5.0 (100.0%)
Terminal incidence	0/6 (0.0%)	0/6 (0.0%)	2/6 (33.3%)	5/5 (100.0%)
Lesion onset (days)	—	—	95	95
Poly-3 P value	—	**<0.001**	0.215	**<0.003**
Average severity score	—	—	1.5	3.2
100 mJ•CIE/cm^2				
Overall incidence	1/6 (16.7%)	0/6 (0.0%)	5/6 (83.3%)	6/6 (100.0%)
Poly-3 adjusted incidence	1/6.0 (16.7%)	0/6.0 (0.0%)	5/6.0 (83.3%)	6/6.0 (100.0%)
Terminal incidence	1/6 (16.7%)	0/6 (0.0%)	5/6 (83.3%)	6/6 (100.0%)
Lesion onset (days)	95	—	95	95
Poly-3 P value	0.500N	**<0.001**	**<0.001**	**<0.002**
Average severity score	1.0	—	1.0	3.5
140 mJ•CIE/cm^2				
Overall incidence	2/6 (33.3%)	1/6 (16.7%)	6/6 (100.0%)	6/6 (100.0%)
Poly-3 adjusted incidence	2/6.0 (33.3%)	1/6.0 (16.7%)	6/6.0 (100.0%)	6/6.0 (100.0%)
Terminal incidence	2/6 (33.3%)	1/6 (16.7%)	6/6 (100.0%)	6/6 (100.0%)
Lesion onset (days)	95	95	95	95
Poly-3 P value	0.500N	**<0.001**	**<0.001**	**<0.001**
Average severity score	1.5	1.0	1.8	2.3
180 mJ•CIE/cm^2				
Overall incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)
Poly-3 adjusted incidence	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)
Terminal incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)
Lesion onset (days)	95	95	95	95
Poly-3 P value	—	—	—	—
Average severity score	2.0	2.5	2.2	3.5
220 mJ•CIE/cm^2				
Overall incidence	5/6 (83.3%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)
Poly-3 adjusted incidence	5/6.0 (83.3%)	6/6.0 (100.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)
Terminal incidence	5/6 (83.3%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)
Lesion onset (days)	95	95	95	95
Poly-3 P value	0.500	—	—	—
Average severity score	2.6	3.3	2.7	3.6
260 mJ•CIE/cm^2				
Overall incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)
Poly-3 adjusted incidence	6/6.0 (100.0%)	6/6.0 (100.0%)	6/6.0 (100.0%)	5/5.0 (100.0%)
Terminal incidence	6/6 (100.0%)	6/6 (100.0%)	6/6 (100.0%)	5/5 (100.0%)
Lesion onset (days)	95	95	95	95
Poly-3 P value	—	—	—	—
Average severity score	3.7	3.3	3.3	3.6

[a] Pairwise comparison tests of incidences are made to control cream groups. P values are based on one-sided tests. Significant P values ($P \leq 0.05$) appear in bold-faced type. Negative P values are appended with "**N**". P values for the control cream group represent dose trend effects for incidence with increasing doses of retinyl palmitate.

APPENDIX J
RESULTS OF NO CREAM TREATMENT IN THE 1-YEAR STUDY

RESULTS OF NO CREAM TREATMENT IN THE 1-YEAR STUDY

ANIMAL SURVIVAL/REMOVAL

The disposition of mice in the 1-year SSL study is shown in Tables 4 and 5 (Results section) for male and female mice, respectively.

This analysis examined the effects of light intensity on the survival/removal of mice. The Cox hazard ratios of male and female mice that were exposed to SSL and received no cream treatment are summarized in Table J1 and graphically represented with Kaplan-Meier survival curves in Figure J1. The reference group in this analysis was the group of mice that received no cream treatment and was not exposed to SSL. As shown in Figure J1, significant SSL exposure trend effects were observed for both male and female mice (Table J1). When compared to the survival of mice that were not exposed to SSL, the survival of mice exposed to 13.70 or 20.55 mJ•CIE/cm^2 SSL was significantly lower. As indicated by the Cox hazard ratios in Table J1, male mice exposed to 13.70 or 20.55 mJ•CIE/cm^2 SSL had approximately 11- and 85-fold increases (decreased survival) in their Cox hazard ratios, respectively, compared with mice that received no SSL exposure, while the exposure of female mice to 13.70 or 20.55 mJ•CIE/cm^2 SSL resulted in approximately 43- and 244-fold increases in their hazard ratios, respectively, when compared with female mice that received no SSL exposure.

BODY WEIGHTS

Summary tables of mean body weights, percentage of mean body weights relative to control weights, survival of mice over the 52 weeks of study, and statistical tests of dose trends and control comparisons for male and female mice in the 1-year study are shown in Appendix C.

The exposure of mice to increasing levels of SSL at 6.85, 13.70, or 20.55 mJ•CIE/cm^2 had no significant dose trend effects on the mean body weights of male or female mice that received no cream treatment during the 1-year study (Tables C1 and C2). In comparison tests with mice that received no cream treatment and no exposure to SSL, there were only a few instances of significant differences in body weight means observed among the different SSL exposure groups. These differences were small (less than or equal to 2 g in males and less than or equal to 1.2 g in female mice) and not considered biologically relevant. Similarly, the exposure of female mice that received no cream treatment to the narrow-band UVA or UVB source had no apparent effects on mean body weights when compared to those of female mice exposed to 13.70 mJ•CIE/cm^2 SSL during the 1-year study (Table C3).

IN-LIFE SKIN LESION ONSET

The time-to-skin-lesion onset was computed for each animal based on digital photographs captured during the in-life phase of the 1-year study, and the data were used to generate Kaplan-Meier curves. The mean and median times for skin lesion onset (the time point in the study when 50% of the mice in a treatment group had at least one measurable skin lesion) were calculated, and probability values were determined based on Cox contrasts for skin lesion onset. The reference group for this analysis was the same sex, no cream group that was not exposed to SSL (0.00 mJ•CIE/cm^2).

The in-life Kaplan Meier curves and Cox contrasts for skin lesion onset in male and female mice that received no cream treatment and were exposed to SSL are shown in Figure J2. Significant SSL exposure-related trends in the onset of skin lesions were observed in both male and female mice that received no cream treatment. In comparison tests to the 0.00 mJ•CIE/cm^2 SSL group, the weeks of skin lesion onset were significantly decreased as the exposure levels of SSL were increased in both male and female mice (Figure J2). Mean weeks of onset were calculated as 0, 45.3, 31.7, and 22.5 weeks for the male mice and 46.0, 45.2, 33.1, and 23.1 weeks for female mice exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL, respectively.

IN-LIFE SKIN LESION INCIDENCE AND MULTIPLICITY

The P values for the Poly-3 continuity-corrected tests of in-life skin lesion incidence rates and those for the Poisson regression tests of in-life skin lesion multiplicities for mice that were administered no cream treatment but were exposed to SSL are shown in Table J2 and those for female mice administered no cream treatment but exposed to UVA or UVB are shown in Table J3. The control group in these analyses of SSL exposed mice was the group of the same sex, administered no cream, and exposed to 0.00 mJ•CIE/cm^2 SSL, while the control group for UVA or UVB exposed mice was the female group administered no cream and exposed to 13.70 mJ•CIE/cm^2 SSL.

Significant linear dose trends for SSL effects were observed in both male and female mice. In comparison tests with the control groups exposed to 0.00 mJ•CIE/cm^2 SSL, skin lesion incidence rates were significantly increased in male and female mice exposed to 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL. Similarly, significant dose trend effects for SSL level were observed in the multiplicities of in-life skin lesions, and significant Poisson probability values were observed in pairwise comparison tests of the multiplicities of in-life skin lesions in male and female mice exposed to SSL and compared with mice that received no SSL exposure.

There was a significant difference in the Poly-3 comparison test for incidence between female mice exposed to UVA and those exposed to 13.70 mJ•CIE/cm^2 SSL. Female mice exposed to UVA had an observed incidence rate of in-life skin lesions of 6.0% compared to 97.0% in the control group. The incidence rates in female mice exposed to UVB did not differ from those of the control group, as both groups approached 100% incidence rates.

The results of the Poisson regression tests for multiplicities of in-life detected skin lesions showed significant differences between both UVA and UVB when compared with similarly treated female mice exposed to 13.70 mJ•CIE/cm^2 SSL (Table J3). In no cream treatment groups, mice exposed to UVA had significantly fewer skin lesions and mice exposed to UVB had significantly more skin lesions than the control group exposed to 13.70 mJ•CIE/cm^2 SSL.

SKIN NEOPLASMS

This section describes the statistically significant changes in incidences of neoplasms that occurred in the study. The skin at the site of application of the creams (coincident with SSL exposure) was the target tissue of the study. Summaries of the incidences of neoplasms and statistical analysis of primary neoplasms are presented in Appendix A for male mice and Appendix B for female mice. Descriptions of the neoplasms discussed in this appendix appear in the Results section of this Technical Report.

The incidences and multiplicities of squamous cell neoplasms of the skin that were microscopically detected at the site of application in male and female mice that received no cream treatment are shown in Table J4. The control group for these analyses was the same sex group of mice that received no cream treatment and no exposure to SSL. The site of application was the area of dorsal skin that was exposed to SSL and extended from the nape of the neck to the base of the tail and midway along both sides of the animal.

The results of the Poly-3 tests for incidences showed that the incidences of squamous cell papilloma, squamous cell carcinoma *in situ*, and squamous cell carcinoma, when considered separately or in combination with other squamous cell neoplasms, were highly dependent on exposure to SSL, and significant SSL exposure-related trends were observed in male and female mice that received no cream treatment (Table J4). In pairwise comparison tests with the no cream group that received no SSL exposure, male mice exposed to SSL at levels of 13.70 and 20.55 mJ•CIE/cm^2, but not those exposed at the level of 6.85 mJ•CIE/cm^2, had significantly higher incidences of squamous cell papilloma, squamous cell carcinoma *in situ*, and squamous cell carcinoma, when considered separately or in combinations. Significantly increased incidences of squamous cell papilloma and of the combination of squamous cell papilloma, squamous cell carcinoma *in situ* and/or squamous cell carcinoma were observed in female mice exposed to 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL when compared to female mice exposed to 0.00 mJ•CIE/cm^2 SSL.

Significantly increased incidences of squamous cell carcinoma *in situ*, squamous cell carcinoma, and the combination of squamous cell carcinoma *in situ* and/or squamous cell carcinoma were also observed in female mice

exposed to 13.70 or 20.55 mJ•CIE/cm^2 SSL when compared to the 0.00 mJ•CIE/cm^2 SSL group. No keratoacanthomas were observed in male or female mice in the no cream groups.

The results of the Poisson regression trend analyses of skin neoplasm multiplicities in male and female mice that received no cream treatment are also shown in Table J4, and represented graphically in Figure J4. Significant SSL trends were observed in the multiplicities of squamous cell papilloma, squamous cell carcinoma *in situ*, and squamous cell carcinoma, when considered separately or in combinations. In pairwise comparison tests with mice that received no SSL exposure, significantly higher multiplicities of squamous cell papilloma, squamous cell carcinoma *in situ*, squamous cell carcinoma, and combinations of squamous cell neoplasms were observed in male and female mice exposed to SSL at levels of 13.70 or 20.55 mJ•CIE/cm^2, and significantly higher values were also observed in the multiplicities of the combination of all squamous cell neoplasms (papilloma, carcinoma *in situ*, or carcinoma) in male and female mice exposed to SSL at the level of 6.85 mJ•CIE/cm^2.

NONNEOPLASTIC SKIN LESIONS

This section describes biologically noteworthy histopathology changes in nonneoplastic lesions that occurred in the study. The skin at the site of application of the creams (coincident with the site of SSL exposure) was the target tissue of the study. Summaries of the incidences of nonneoplastic lesions are presented in Appendix A for male mice and Appendix B for female mice. Descriptions of the nonneoplastic lesions discussed in this appendix appear in the Results section of this Technical Report.

The incidences and multiplicities of nonneoplastic skin lesions at the site of application in male and female mice that received no cream treatment are shown in Table J5. Significant SSL-related trends were observed in the incidences of squamous cell hyperplasia, focal atypical squamous hyperplasia, inflammation of the dermis, and necrosis of the epidermis in male mice. There were no incidences of these nonneoplastic skin lesions in the group of male mice that were not exposed to SSL. In pairwise comparison tests with the reference group exposed to 0.00 mJ•CIE/cm^2 SSL, significantly increased incidences of squamous cell hyperplasia, focal atypical squamous hyperplasia, and inflammation of the dermis were observed in male mice that were exposed to 13.70 or 20.55 mJ•CIE/cm^2 SSL. Male mice that were exposed to 6.85 mJ•CIE/cm^2 SSL also had a significantly increased incidence of focal atypical squamous hyperplasia. The multiplicities of focal atypical squamous hyperplasia showed a significant SSL exposure-related increased trend, and in pairwise comparisons with the group of male mice that received 0.00 mJ•CIE/cm^2 SSL, significant P values were found at the 6.85, 13.70, and 20.55 mJ•CIE/cm^2 levels of SSL.

In female mice that received no cream treatment, significant SSL-related trends were observed in the incidences of squamous cell hyperplasia, focal atypical squamous hyperplasia, inflammation of the dermis, and ulceration of the epidermis (Table J5). For the most part, these nonneoplastic skin lesions did not occur in female mice that were not exposed to SSL and received no cream treatment. In pairwise comparison tests with the group that received 0.00 mJ•CIE/cm^2 SSL, significantly increased incidences were observed for squamous cell hyperplasia and focal atypical squamous hyperplasia in female mice exposed to SSL levels of 6.85, 13.70, and 20.55 mJ•CIE/cm^2. Significantly increased incidences (6- to 10-fold increases) of inflammation of the dermis were observed in female mice exposed to SSL at levels of 13.70 and 20.55 mJ•CIE/cm^2 when compared with mice that received no exposure to SSL. Significantly increased incidences of inflammation and ulceration of the epidermis were also observed in female mice exposed to SSL at 20.55 mJ•CIE/cm^2 when compared with female mice that received no exposure to SSL. As observed in male mice, the multiplicities of focal atypical squamous hyperplasia showed a significant SSL-exposure-related increased trend, and in pairwise comparisons with female mice that received no SSL exposure, significantly higher multiplicities were observed at the 6.85, 13.70, and 20.55 mJ•CIE/cm^2 levels of SSL.

TABLE J1
Cox Hazard Ratios for Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	Hazard Ratio (SSL compared to No SSL)	Lower Confidence Limit	Upper Confidence Limit	P Value[a]
Male				
0.00 mJ•CIE/cm^2				**<0.001**
6.85 mJ•CIE/cm^2	1.58	0.61	4.07	0.346
13.70 mJ•CIE/cm^2	11.25	4.93	25.66	**<0.001**
20.55 mJ•CIE/cm^2	84.84	36.18	198.94	**<0.001**
Female				
0.00 mJ•CIE/cm^2				**<0.001**
6.85 mJ•CIE/cm^2	3.19	0.64	15.81	0.155
13.70 mJ•CIE/cm^2	43.37	10.37	181.38	**<0.001**
20.55 mJ•CIE/cm^2	243.83	57.62	1,031.78	**<0.001**

[a] Tests formed by suitable contrasts with the 0.00 mJ•CIE/cm^2 group, which was assigned a Cox hazard ratio of 1.00. Significant P values appear in bold-faced type. P values for the 0.00 mJ•CIE/cm^2 group represent linear trend results.

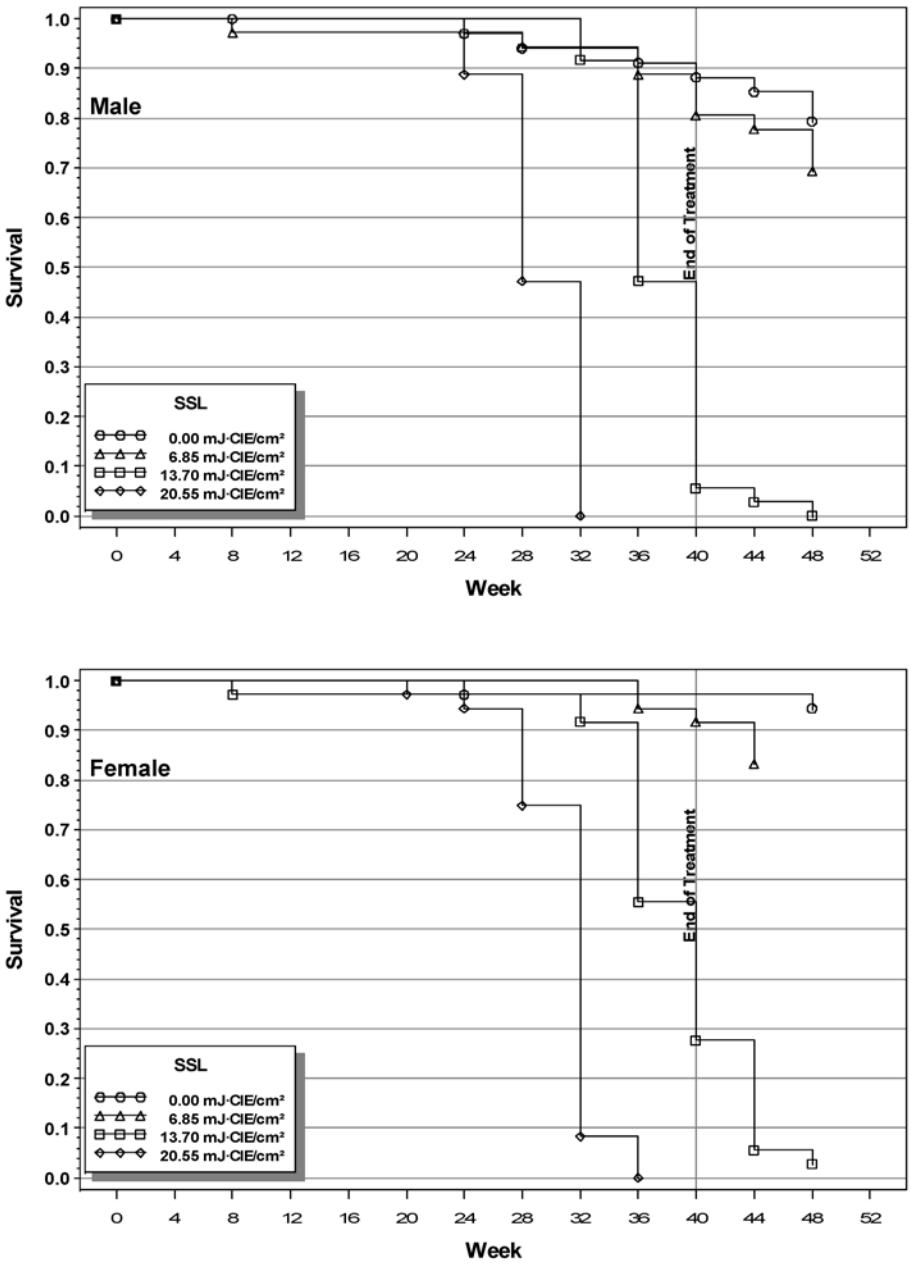
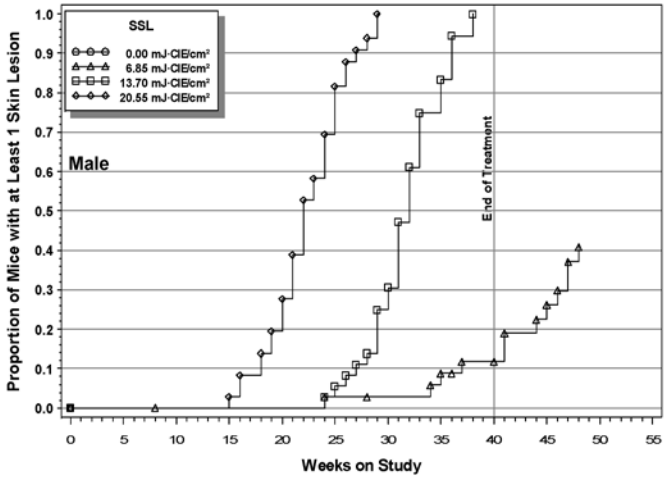


FIGURE J1
Kaplan-Meier Survival Curves for Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Treatment	Mean Wk of Onset	Median Wk. of Onset	P Value
SSL = 0.00	-	Q_{50} = -	< **0.001**
SSL = 6.85	45.3	Q_{50} = -	**0.013**
SSL = 13.70	31.7	Q_{50} = 32.0	< **0.001**
SSL = 20.55	22.5	Q_{50} = 22.0	< **0.001**



Treatment	Mean Wk of Onset	Median Wk. of Onset	P Value
SSL = 0.00	46.0	Q_{50} = -	< **0.001**
SSL = 6.85	45.2	Q_{50} = 49.0	**0.001**
SSL = 13.70	33.1	Q_{50} = 33.0	< **0.001**
SSL = 20.55	23.1	Q_{50} = 23.0	< **0.001**

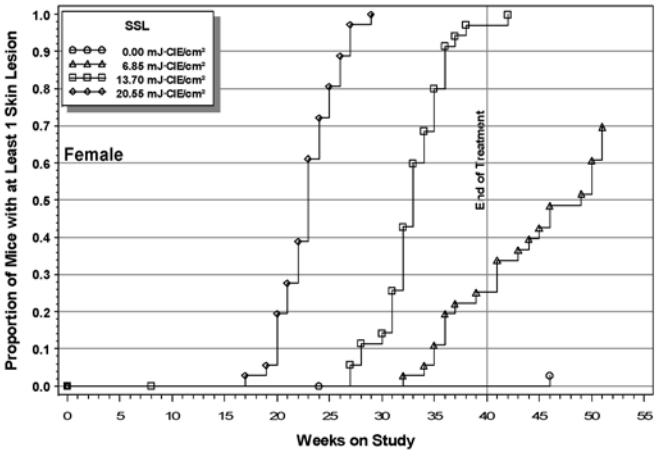


FIGURE J2
Kaplan-Meier Curves and Cox Contrasts for In-life Skin Lesion Onset in Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate
(Median values are Kaplan-Meier estimates. Dashed entries were not estimable. P values are based on the Cox proportional hazards model. P values for the 0.00 mJ•CIE/cm^2 SSL groups represent linear trend results; P values for the remaining groups represent pairwise comparisons to the 0.00 mJ•CIE/cm^2 SSL group.).

TABLE J2
Incidences and Multiplicities of Skin Lesions Detected In-life at the Site of Application in Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Male				
Observed rate[a]	0/36 (0.0%)	12/36 (33.0%)	36/36 (100.0%)	35/36 (97.0%)
Adjusted rate[b]	0/30.8 (0.0%)	12/31.0 (38.6%)	36/36.0 (100.0%)	35/35.1 (99.7%)
First incidence (weeks)	—[d]	24	24	15
Incidence test results[c]	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM[e]	0.0 ± 0.0	1.0 ± 2.0	5.2 ± 2.1	9.0 ± 3.6
Overall LS mean[f] lesion multiplicity ± SEM	0.0 ± 0.1	1.2 ± 0.2	7.0 ± 0.5	15.6 ± 0.9
Multiplicity test results[g]	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**
Female				
Observed rate	1/36 (3.0%)	24/36 (67.0%)	35/36 (97.0%)	36/36 (100.0%)
Adjusted rate	1/35.0 (2.9%)	24/35 (68.5%)	35/35 (100.0%)	36/36.0 (100.0%)
First incidence (weeks)	46	32	27	17
Incidence test results	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.0 ± 0.2	1.3 ± 1.5	5.8 ± 2.9	5.5 ± 2.6
Overall LS mean lesion multiplicity ± SEM	0.0 ± 0.1	1.4 ± 0.2	7.7 ± 0.5	9.1 ± 0.7
Multiplicity test results	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**

[a] Number of lesion-bearing animals/number of animals with skin observed
[b] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[c] P values are based on a two-sided continuity-corrected Poly-3 test. P values in the control group (0.00 mJ•CIE/cm^2) column are for the linear trend test; otherwise, P values represent pairwise comparisons to the control group. Significant P values appear in bold-faced type.
[d] Not applicable; no lesions observed.
[e] Standard error of the mean (SEM) is approximated based on an additive error structure.
[f] Least square (LS) means are estimated as lesions per animal per year.
[g] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal). P values in the control group column are for the linear trend test; otherwise, P values represent pairwise comparisons to the control group. Significant P values appear in bold-faced type.

TABLE J3
Incidences and Multiplicities of Skin Lesions Detected In-life at the Site of Application in Female Mice Administered No Cream and Exposed to 13.70 mJ•CIE/cm^2 SSL, UVA, or UVB in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	13.70 mJ•CIE/cm^2	UVA	UVB
Observed rate[a]	35/36 (97.0%)	2/36 (6.0%)	36/36 (100.0%)
Adjusted rate[b]	35/35.0 (100.0%)	2/31.7 (6.3%)	36/36.0 (100.0%)
First incidence (weeks)	27	27	22
Incidence test results[c]		**P<0.001**	P=1.000
Observed mean lesion multiplicity ± SEM[d]	5.8 ± 2.9	0.1 ± 0.2	8.7 ± 4.2
Overall LS mean[e] lesion multiplicity ± SEM	7.7 ± 0.5	0.1 ± 0.1	12.1 ± 0.7
Multiplicity test results[f]		**P<0.001**	**P<0.001**

[a] Number of lesion-bearing animals/number of animals with skin observed
[b] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.
[c] P values are based on a two-sided continuity-corrected Poly-3 test and represent pairwise comparisons to the 13.70 mJ•CIE/cm^2 SSL group. Significant P values appear in bold-faced type.
[d] Standard error of the mean (SEM) is approximated based on an additive error structure.
[e] Least square (LS) means are estimated as lesions per animal per year.
[f] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal) and represent pairwise comparisons to 13.70 mJ•CIE/cm^2 SSL group. Significant P values appear in bold-faced type.

TABLE J4
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Male				
Squamous Cell Papilloma				
Overall rate[a]	1/34 (2.9%)	6/35 (17.1%)	23/36 (63.9%)	22/36 (61.1%)
Adjusted rate[b]	1/30.8 (3.2%)	6/30.7 (19.6%)	23/28.5 (80.7%)	22/24.7 (88.9%)
Terminal rate[c]	1/27 (3.7%)	5/25 (20.0%)	0/0	0/0
First incidence (days)	368	354	246	193
Incidence test results[d]	**P<0.001**	P=0.100	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM[e]	0.03 ± 0.03	0.34 ± 0.17	1.22 ± 0.24	1.64 ± 0.30
LS adjusted mean[f] lesion multiplicity ± SEM	0.05 ± 0.13	0.39 ± 0.17	1.76 ± 0.29	3.07 ± 0.41
Multiplicity test results[g]	**P<0.001**	P=0.104	**P<0.001**	**P<0.001**
Squamous Cell Carcinoma *in situ*				
Overall rate	0/34 (0.0%)	1/35 (2.9%)	14/36 (38.9%)	25/36 (69.4%)
Adjusted rate	0/30.8 (0.0%)	1/30.7 (3.3%)	14/23.8 (58.8%)	25/27.4 (91.2%)
Terminal rate	0/27 (0.0%)	0/25 (0.0%)	0/0	0/0
First incidence (days)	—[h]	347	262	192
Incidence test results	**P<0.001**	P=0.999	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.03 ± 0.03	0.64± 0.17	2.11 ± 0.38
LS adjusted mean lesion multiplicity ± SEM	0.02 ± 0.13	0.06 ± 0.13	1.00 ± 0.23	3.86 ± 0.45
Multiplicity test results	**P<0.001**	P=0.820	**P<0.001**	**P<0.001**
Squamous Cell Carcinoma				
Overall rate	0/34 (0.0%)	2/35 (5.7%)	27/36 (75.0%)	28/36 (77.8%)
Adjusted rate	0/30.8 (0.0%)	2/30.7 (6.5%)	27/31.0 (87.1%)	28/29.6 (94.7%)
Terminal rate	0/27 (0.0%)	1/25 (4.0%)	0/0	0/0
First incidence (days)	—	354	243	192
Incidence test results	**P<0.001**	P=0.235	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.06 ± 0.04	1.33 ± 0.20	2.31 ± 0.33
LS adjusted mean lesion multiplicity ± SEM	0.02 ± 0.13	0.09 ± 0.14	1.91 ± 0.30	4.18 ± 0.47
Multiplicity test results	**P<0.001**	P=0.470	**P<0.001**	**P<0.001**
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma				
Overall rate	0/34 (0.0%)	3/35 (8.6%)	30/36 (83.3%)	31/36 (86.1%)
Adjusted rate	0/30.8 (0.0%)	3/30.8 (9.7%)	30/32.8 (91.5%)	31/32.0 (96.9%)
Terminal rate	0/27 (0.0%)	1/25 (4.0%)	0/0	0/0
First incidence (days)	—	347	243	192
Incidence test results	**P<0.001**	P=0.232	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.09 ± 0.05	1.97 ± 0.29	4.42 ± 0.63
LS adjusted mean lesion multiplicity ± SEM	0.02 ± 0.13	0.12 ± 0.14	2.75 ± 0.34	7.71 ± 0.62
Multiplicity test results	**P<0.001**	P=0.585	**P<0.001**	**P<0.001**

TABLE J4
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Male (continued)				
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma				
Overall rate	1/34 (2.9%)	7/35 (20.0%)	36/36 (100.0%)	34/36 (94.4%)
Adjusted rate	1/30.8 (3.2%)	7/30.8 (22.7%)	36/36.0 (100.0%)	34/34.2 (99.4%)
Terminal rate	1/27 (3.7%)	5/25 (20.0%)	0/0	0/0
First incidence (days)	368	347	243	192
Incidence test results	**P<0.001**	P=0.052	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.03 ± 0.03	0.43 ± 0.19	3.19 ± 0.34	6.06 ± 0.79
LS adjusted mean lesion multiplicity ± SEM	0.05 ± 0.13	0.49 ± 0.17	4.35 ± 0.42	10.44 ± 0.71
Multiplicity test results	**P<0.001**	**P=0.047**	**P<0.001**	**P<0.001**
Female				
Squamous Cell Papilloma				
Overall rate	1/36 (2.8%)	13/36 (36.1%)	29/36 (80.6%)	23/36 (63.9%)
Adjusted rate	1/35.0 (2.9%)	13/34.6 (37.6%)	29/31.8 (91.2%)	23/26.1 (88.1%)
Terminal rate	1/34 (2.9%)	10/30 (33.3%)	1/1 (100.0%)	0/0
First incidence (days)	367	260	256	187
Incidence test results	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.03 ± 0.03	0.47 ± 0.13	2.14 ± 0.34	1.94 ± 0.42
LS adjusted mean lesion multiplicity ± SEM	0.03 ± 0.12	0.50 ± 0.17	2.90 ± 0.35	3.36 ± 0.41
Multiplicity test results	**P<0.001**	**P=0.028**	**P<0.001**	**P<0.001**
Squamous Cell Carcinoma *in situ*				
Overall rate	0/36 (0.0%)	2/36 (5.6%)	18/36 (50.0%)	22/36 (61.1%)
Adjusted rate	0/35.0 (0.0%)	2/33.3 (6.0%)	18/26.5 (68.0%)	22/25.4 (86.7%)
Terminal rate	0/34 (0.0%)	2/30 (6.7%)	1/1 (100.0%)	0/0
First incidence (days)	—	367	256	187
Incidence test results	**P<0.001**	P=0.451	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.08 ± 0.06	0.97 ± 0.22	1.28 ± 0.23
LS adjusted mean lesion multiplicity ± SEM	0.01 ± 0.12	0.10 ± 0.13	1.40 ± 0.26	2.31 ± 0.35
Multiplicity test results	**P<0.001**	P=0.597	**P<0.001**	**P<0.001**
Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	1/36 (2.8%)	24/36 (66.7%)	26/36 (72.2%)
Adjusted rate	0/35.0 (0.0%)	1/33.8 (3.0%)	24/29.0 (82.7%)	26/28.4 (91.5%)
Terminal rate	0/34 (0.0%)	0/30 (0.0%)	1/1 (100.0%)	0/0
First incidence (days)	—	299	235	166
Incidence test results	**P<0.001**	P=0.986	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.03 ± 0.03	0.94 ± 0.16	1.42 ± 0.21
LS adjusted mean lesion multiplicity ± SEM	0.01 ± 0.12	0.04 ± 0.13	1.36 ± 0.26	2.52 ± 0.37
Multiplicity test results	**P<0.001**	P=0.832	**P<0.001**	**P<0.001**

TABLE J4
Incidences and Multiplicities of Skin Neoplasms at the Site of Application in Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Female (continued)				
Squamous Cell Carcinoma *in situ* and/or Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	3/36 (8.3%)	31/36 (86.1%)	30/36 (83.3%)
Adjusted rate	0/35.0 (0.0%)	3/33.8 (8.9%)	31/33.2 (93.4%)	30/31.5 (95.3%)
Terminal rate	0/34 (0.0%)	2/30 (6.7%)	1/1 (100.0%)	0/0
First incidence (days)	—	299	235	166
Incidence test results	**P<0.001**	P=0.221	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.11 ± 0.07	1.92 ± 0.22	2.69 ± 0.35
LS adjusted mean lesion multiplicity ± SEM	0.01 ± 0.12	0.13 ± 0.13	2.62 ± 0.33	4.54 ± 0.47
Multiplicity test results	**P<0.001**	P=0.496	**P<0.001**	**P<0.001**
Squamous Cell Papilloma, Squamous Cell Carcinoma *in situ*, and/or Squamous Cell Carcinoma				
Overall rate	1/36 (2.8%)	16/36 (44.4%)	34/36 (94.4%)	33/36 (91.7%)
Adjusted rate	1/35.0 (2.9%)	16/35.0 (45.7%)	34/34.7 (98.1%)	33/33.8 (97.7%)
Terminal rate	1/34 (2.9%)	12/30 (40.0%)	1/1 (100.0%)	0/0
First incidence (days)	367	260	235	166
Incidence test results	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.03 ± 0.03	0.58 ± 0.13	4.06 ± 0.49	4.64 ± 0.56
LS adjusted mean lesion multiplicity± SEM	0.03 ± 0.12	0.61 ± 0.18	5.38 ± 0.46	7.61 ± 0.60
Multiplicity test results	**P<0.001**	**P=0.009**	**P<0.001**	**P<0.001**

[a] Number of neoplasm-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are based on a two-sided, continuity-corrected Poly-3 test. P values in the control group (0.00 mJ•CIE/cm^2) column are for the linear trend test; otherwise, P values represent pairwise comparisons to the control group. Significant P values appear in bold-faced type.
[e] Standard error of the mean (SEM) is approximated based on an additive error structure.
[f] Least square (LS) means are estimated as neoplasms per animal per year.
[g] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal). P values in the control group column are for the linear trend test; otherwise, P values represent pairwise comparisons to the control group. Significant P values appear in bold-faced type.
[h] Not applicable; no neoplasms in animal group

Male	Trend	Female	Trend
Carcinoma	< **0.001**	Carcinoma	**< 0.001**
Carcinoma *in Situ*	< **0.001**	Carcinoma *in Situ*	**< 0.001**
Papilloma	< **0.001**	Papilloma	**< 0.001**
Carcinoma or Carcinoma *in Situ*	< **0.001**	Carcinoma or Carcinoma *in Situ*	**< 0.001**
All Squamous Neoplasms	**< 0.001**	All Squamous Neoplasms	**< 0.001**

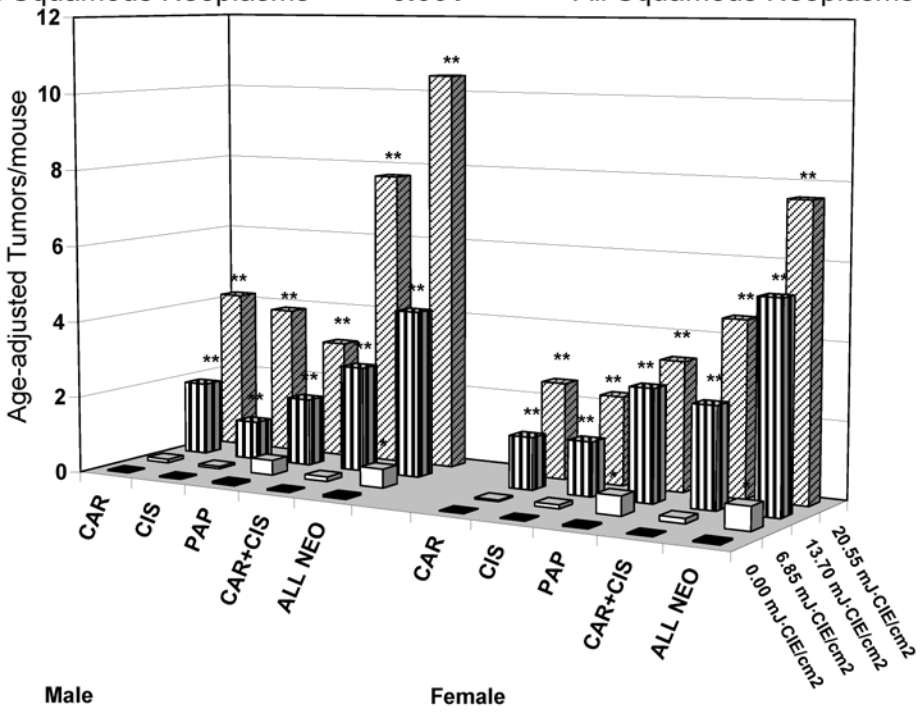


FIGURE J3
Comparisons of the Effects of SSL Exposure on the Multiplicity of Squamous Cell Neoplasms in No Cream Male and Female Mice in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

Asterisks above chart bars denote significant pairwise comparisons with the 0.00 mJ•CIE cm^2 SSL group (*, P≤0.05; **, P<0.001). Significant P values for SSL exposure-related trends are bolded.
PAP = papilloma; CIS = carcinoma *in situ*; CAR = carcinoma; ALL NEO = PAP + CIS + CAR

TABLE J5
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Male				
Cyst Epithelial Inclusion				
Overall rate[a]	3/34 (8.8%)	4/35 (11.4%)	3/36 (8.3%)	0/36 (0.0%)
Adjusted rate[b]	3/30.8 (9.7%)	4/30.7 (13.0%)	3/17.6 (17.1%)	0/7.8 (0.0%)
Terminal rate[c]	3/27 (11.1%)	3/25 (12.0%)	0/0	0/0
First incidence (days)	368	347	246	—[e]
Incidence test results[d]	P=0.908	P=0.997	P=0.788	P=0.914
Squamous Cell Hyperplasia				
Overall rate	0/34 (0.0%)	4/35 (11.4%)	26/36 (72.2%)	18/36 (50.0%)
Adjusted rate	0/30.8 (0.0%)	4/30.7 (13.0%)	26/30.7 (84.7%)	18/21.7 (82.9%)
Terminal rate	0/27 (0.0%)	3/25 (12.0%)	0/0	0/0
First incidence (days)	—	354	243	171
Incidence test results	**P<0.001**	P=0.113	**P<0.001**	**P<0.001**
Focal Atypical Squamous Hyperplasia				
Overall rate	0/34 (0.0%)	9/35 (25.7%)	32/36 (88.9%)	30/36 (83.3%)
Adjusted rate	0/30.8 (0.0%)	9/30.7 (29.4%)	32/33.5 (95.6%)	30/31.1 (96.5%)
Terminal rate	0/27 (0.0%)	8/25 (32.0%)	0/0	0/0
First incidence (days)	—	354	250	192
Incidence test results	**P<0.001**	**P=0.002**	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM[f]	0.00 ± 0.00	0.60 ± 0.23	4.22 ± 0.54	3.78 ± 0.46
LS adjusted mean[g] lesion multiplicity ± SEM	0.02 ± 0.13	0.67 ± 0.19	5.70 ± 0.48	6.64 ± 0.58
Multiplicity test results[h]	**P<0.001**	**P=0.005**	**P<0.001**	**P<0.001**
Inflammation of the Dermis				
Overall rate	0/34 (0.0%)	3/35 (8.6%)	5/36 (13.9%)	8/36 (22.2%)
Adjusted rate	0/30.8 (0.0%)	3/30.5 (9.8%)	5/18.3 (27.3%)	8/14.0 (57.0%)
Terminal rate	0/27 (0.0%)	3/25 (12.0%)	0/0	0/0
First incidence (days)	—	368	250	171
Incidence test results	**P<0.001**	P=0.229	**P=0.011**	**P<0.001**
Inflammation of the Epidermis				
Overall rate	0/34 (0.0%)	1/35 (2.9%)	1/36 (2.8%)	1/36 (2.8%)
Adjusted rate	0/30.8 (0.0%)	1/30.5 (3.3%)	1/16.0 (6.2%)	1/8.6 (11.6%)
Terminal rate	0/27 (0.0%)	1/25 (4.0%)	0/0	0/0
First incidence (days)	—	368	339	213
Incidence test results	P=0.325	P=0.997	P=0.762	P=0.621
Necrosis of the Epidermis				
Overall rate	0/34 (0.0%)	1/35 (2.9%)	3/36 (8.3%)	2/36 (5.6%)
Adjusted rate	0/30.8 (0.0%)	1/30.7 (3.3%)	3/17.2 (17.4%)	2/9.4 (21.3%)
Terminal rate	0/27 (0.0%)	0/25 (0.0%)	0/0	0/0
First incidence (days)	—	354	264	171
Incidence test results	**P=0.036**	P=0.998	P=0.094	P=0.180

TABLE J5
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Male (continued)				
Ulceration of the Epidermis				
Overall rate	0/34 (0.0%)	1/35 (2.9%)	1/36 (2.8%)	1/36 (2.8%)
Adjusted rate	0/30.8 (0.0%)	1/30.5 (3.3%)	1/16.0 (6.2%)	1/8.6 (11.6%)
Terminal rate	0/27 (0.0%)	1/25 (4.0%)	0/0	0/0
First incidence (days)	—	368	339	213
Incidence test results	P=0.325	P=0.997	P=0.762	P=0.621
Female				
Cyst Epithelial Inclusion				
Overall rate	2/36 (5.6%)	4/36 (11.1%)	2/36 (5.6%)	2/36 (5.6%)
Adjusted rate	2/35.0 (5.7%)	4/33.3 (12.0%)	2/17.7 (11.3%)	2/10.6 (18.9%)
Terminal rate	2/34 (5.9%)	4/30 (13.3%)	1/1 (100.0%)	0/0
First incidence (days)	367	367	346	235
Incidence test results	P=0.387	P=0.626	P=0.879	P=0.598
Squamous Cell Hyperplasia				
Overall rate	1/36 (2.8%)	11/36 (30.6%)	28/36 (77.8%)	28/36 (77.8%)
Adjusted rate	1/35.0 (2.9%)	11/34.0 (32.4%)	28/31.4 (89.3%)	28/29.8 (94.0%)
Terminal rate	1/34 (2.9%)	9/30 (30.0%)	1/1 (100.0%)	0/0
First incidence (days)	367	320	235	166
Incidence test results	**P<0.001**	**P=0.002**	**P<0.001**	**P<0.001**
Focal Atypical Squamous Hyperplasia				
Overall rate	0/36 (0.0%)	16/36 (44.4%)	33/36 (91.7%)	35/36 (97.2%)
Adjusted rate	0/35.0 (0.0%)	16/33.9 (47.2%)	33/33.8 (97.6%)	35/35.3 (99.2%)
Terminal rate	0/34 (0.0%)	14/30 (46.7%)	1/1 (100.0%)	0/0
First incidence (days)	—	320	235	166
Incidence test results	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**
Observed mean lesion multiplicity ± SEM	0.00 ± 0.00	0.78 ± 0.20	4.75 ± 0.57	3.78 ± 0.57
LS adjusted mean lesion multiplicity ± SEM	0.01 ± 0.12	0.81 ± 0.19	6.27 ± 0.49	6.25 ± 0.54
Multiplicity test results	**P<0.001**	**P=0.001**	**P<0.001**	**P<0.001**
Inflammation of the Dermis				
Overall rate	2/36 (5.6%)	1/36 (2.8%)	12/36 (33.3%)	21/36 (58.3%)
Adjusted rate	2/35.0 (5.7%)	1/33.3 (3.0%)	12/23.5 (51.1%)	21/24.7 (85.2%)
Terminal rate	2/34 (5.9%)	1/30 (3.3%)	0/1 (0.0%)	0/0
First incidence (days)	367	367	256	166
Incidence test results	**P<0.001**	P=1.000	**P<0.001**	**P<0.001**
Inflammation of the Epidermis				
Overall rate	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)	3/36 (8.3%)
Adjusted rate	0/35.0 (0.0%)	0/33.3 (0.0%)	1/17.8 (5.6%)	3/11.4 (26.3%)
Terminal rate	0/34 (0.0%)	0/30 (0.0%)	0/1 (0.0%)	0/0
First incidence (days)	—	—	334	215
Incidence test results	P=0.052	—[i]	P=0.755	**P=0.050**

TABLE J5
Incidences and Multiplicities of Nonneoplastic Skin Lesions at the Site of Application in Mice Administered No Cream and Exposed to 0.00, 6.85, 13.70, or 20.55 mJ•CIE/cm^2 SSL in the 1-Year Simulated Solar Light Study of Retinoic Acid and Retinyl Palmitate

	0.00 mJ•CIE/cm^2	6.85 mJ•CIE/cm^2	13.70 mJ•CIE/cm^2	20.55 mJ•CIE/cm^2
Female (continued)				
Necrosis of the Epidermis				
Overall rate	0/36 (0.0%)	0/36 (0.0%)	2/36 (5.6%)	1/36 (2.8%)
Adjusted rate	0/35.0 (0.0%)	0/33.3 (0.0%)	2/18.2 (11.0%)	1/10.0 (10.0%)
Terminal rate	0/34 (0.0%)	0/30 (0.0%)	0/1 (0.0%)	0/0
First incidence (days)	—	—	320	166
Incidence test results	P=0.154	—	P=0.255	P=0.622
Ulceration of the Epidermis				
Overall rate	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)	4/36 (11.1%)
Adjusted rate	0/35.0 (0.0%)	0/33.3 (0.0%)	1/17.8 (5.6%)	4/12.1 (33.0%)
Terminal rate	0/34 (0.0%)	0/30 (0.0%)	0/1 (0.0%)	0/0
First incidence (days)	—	—	334	215
Incidence test results	**P=0.016**	—	P=0.755	**P=0.013**

[a] Number of lesion-bearing animals/number of animals with skin examined microscopically
[b] Poly-3 estimated lesion incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] P values are based on a two-sided, continuity-corrected Poly-3 test. P values in the control group (0.00 mJ•CIE/cm^2) column are for the linear trend test; otherwise, P values represent pairwise comparisons to the control group. Significant P values appear in bold-faced type.
[e] Not applicable; no lesions in animal group
[f] Standard error of the mean (SEM) is approximated based on an additive error structure.
[g] Least square (LS) means are estimated as lesions per animal per year.
[h] P values are based on the two-sided Poisson regression test of multiplicity (lesions per animal). P values in the control group column are for the linear trend test; otherwise, P values represent pairwise comparisons to the control group. Significant P values appear in bold-faced type.
[i] Value of statistic cannot be computed.

APPENDIX K
ASSOCIATED PUBLICATIONS

The following peer reviewed publications have been published using data or special samples obtained from the study presented in this Technical Report and other studies carried out as part of the retinoic acid and retinyl palmitate evaluation.

Cherng, S.H., Xia, Q., Blankenship, L.R., Freeman, J.P., Wamer, W.G., Howard, P.C., and Fu, P.P. (2005). Photodecomposition of retinyl palmitate in ethanol by UVA light-formation of photodecomposition products, reactive oxygen species, and lipid peroxides. *Chem. Res. Toxicol.* **18**, 129-138.

Fu, P.P., Howard, P.C., Culp, S.J., Xia, Q., Webb, P.J., Blankenship, L.R., Wamer, W.G., and Bucher, J.R. (2002). Do topically applied skin creams containing retinyl palmitate affect the photocarcinogenicity of simulated solar light? *J. Food Drug Anal.* **10**, 262-268.

Fu, P.P., Cherng, S.H., Coop, L., Xia, Q., Culp, S.J., Tolleson, W.H., Wamer, W.G., and Howard, P.C. (2003). Photoreaction, phototoxicity, and photocarcinogenicity of retinoids. *J. Environ. Sci. Health C Environ. Carcinog. Ecotoxicol. Rev.* **21**, 165-197.

Fu, P.P., Xia, Q., Boudreau, M.D., Howard, P.C., Tolleson, W.H., and Wamer, W.G. (2007). Physiological role of retinyl palmitate in the skin. *Vitam. Horm.* **75**, 223-256.

Fu, P.P., Xia, Q., Yin, J.J., Cherng, S.H., Yan, J., Mei, N., Chen, T., Boudreau, M.D., Howard, P.C., and Wamer, W.G. (2007). Photodecomposition of vitamin A and photobiological implications for the skin. *Photochem. Photobiol.* **83**, 409-424.

Mei, N., Xia, Q., Chen, L., Moore, M.M., Fu, P.P., and Chen, T. (2005). Photomutagenicity of retinyl palmitate by ultraviolet A irradiation in mouse lymphoma cells. *Toxicol. Sci.* **88**, 142-149.

Mei, N., Xia, Q., Chen, L., Moore, M.M., Chen, T., and Fu, P.P. (2006). Photomutagenicity of anhydroretinol and 5,6-epoxyretinyl palmitate in mouse lymphoma cells. *Chem. Res. Toxicol.* **19**, 1435-1440.

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Xia, Q., Yin, J.J., Cherng, S.H., Wamer, W.G., Boudreau, M., Howard, P.C., and Fu, P.P. (2006). UVA photoirradiation of retinyl palmitate – Formation of singlet oxygen and superoxide, and their role in induction of lipid peroxidation. *Toxicol. Lett.* **163**, 30-43.

Xia, Q., Yin, J.J., Wamer, W.G., Cherng, S.H., Boudreau, M.D., Howard, P.C., Yu, H., and Fu, P.P. (2006). Photoirradiation of retinyl palmitate in ethanol with ultraviolet light – Formation of photodecomposition products, reactive oxygen species, and lipid peroxides. *Int. J. Environ. Res. Public Health* **3**, 185-190.

Yan, J., Xia, Q., Cherng, S.H., Wamer, W.G., Howard, P.C., Yu, H., and Fu, P.P. (2005). Photo-induced DNA damage and photocytotoxicity of retinyl palmitate and its photodecomposition products. *Toxicol. Ind. Health* **21**, 167-175.

Yan, J., Wamer, W.G., Howard, P.C., Boudreau, M.D., and Fu, P.P. (2006). Levels of retinyl palmitate and retinol in stratum corneum, epidermis, and dermis of female SKH-1 mice topically treated with retinyl palmitate. *Toxicol. Ind. Health* **22**, 181-191.

Yan, J., Xia, Q., Webb, P., Warbritton, A.R., Wamer, W.G., Howard, P.C., Boudreau, M., and Fu, P.P. (2006). Levels of retinyl palmitate and retinol in stratum corneum, epidermis and dermis of SKH-1 mice. *Toxicol. Ind. Health* **22**, 103-112.

Yan, J., Xia, Q., Wamer, W.G., Boudreau, M.D., Warbritton, A., Howard, P.C., and Fu, P.P. (2007). Levels of retinyl palmitate and retinol in the skin of SKH-1 mice topically treated with retinyl palmitate and concomitant exposure to simulated solar light for thirteen weeks. *Toxicol. Ind. Health* **23**, 581-589.

Yin, J.J., Xia, Q., and Fu, P.P. (2007). UVA photoirradiation of anhydroretinol – Formation of singlet oxygen and superoxide. *Toxicol. Ind. Health* **23**, 625-631.

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