NTP TECHNICAL REPORT

ON THE

PHOTOCARCINOGENESIS

STUDY OF GLYCOLIC ACID AND SALICYLIC ACID

(CAS NOS. 79-14-1 and 69-72-7)

IN SKH-1 MICE

(SIMULATED SOLAR LIGHT
AND TOPICAL APPLICATION STUDY)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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The photocarcinogenesis study of glycolic acid and salicylic acid was conducted at the FDA's National Center for Toxicological Research under an interagency agreement between the FDA and the NIEHS. The study was designed and monitored by a Toxicology Study Selection and Review Committee composed of representatives from the NCTR and other FDA product centers, NIEHS, and other *ad hoc* members from other government 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 information for hazard identification and risk assessment.

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CONTENTS

SUMMARY

Background

Glycolic acid and salicylic acid are two of the more commonly used active ingredients of skin peels and are used in cosmetics to treat photoaged skin. We studied the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing glycolic acid or salicylic acid.

Methods

We applied creams containing 4% or 10% glycolic acid, or 2% or 4% salicylic acid, to groups of 18 male and 18 female hairless mice in the mornings; other groups received creams containing no acids. Additional groups of 36 male and 36 female mice were not exposed to cream. In the afternoon, groups of animals were exposed to one of three strengths of synthetic solar light for four hours. Other groups were not exposed to light and were control groups. In total, there were 38 groups of mice (18 male and 18 female, or 36 male and 36 female), each receiving one combination of cream and light exposure level. The treatment and exposures were performed five days per week for 40 weeks, during which time the animals were monitored for development of skin cancers.

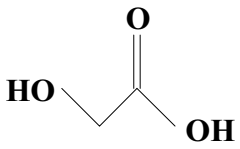
Results

Greater strengths of light increased the incidences of skin cancers in mice not given a cream or a cream with no acid included. Creams containing glycolic acid had no effect on this effect of the simulated solar light. Creams containing salicylic acid did decrease the incidence of skin tumors in mice receiving the lower of the two light intensities.

Conclusions

We conclude that glycolic acid did not affect the photocarcinogenesis of simulated solar light, and salicylic acid did have some protective effect against the photocarcinogenicity of light at lower intensities.

ABSTRACT

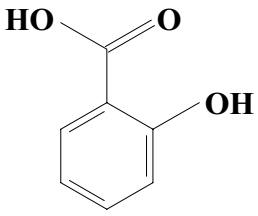


GLYCOLIC ACID

CAS No. 79-14-1

Chemical Formula: $C_2H_4O_3$ Molecular Weight: 76.05

Synonyms: Hydroxyacetic acid; hydroxyethanoic acid
Trade names: Glypure 70, Glypure 99



SALICYLIC ACID

CAS No. 69-72-7

Chemical Formula: $C_7H_6O_3$ Molecular Weight: 138.12

Synonym: 2-Hydroxybenzoic acid

Acidic solutions have been used for decades to treat a variety of skin conditions. Many of these solutions consist of organic acids with a hydroxy group on a carbon adjacent to the carbonyl carbon and are referred to as alpha-hydroxy acids (AHA). Organic acids with hydroxy groups on the second carbon from the carbonyl carbon are referred to as beta-hydroxy acids (BHA). Both AHA and BHA are used to treat various skin conditions. One of the most widely used AHA is glycolic acid, while salicylic acid is a commonly used BHA.

Chemical peels containing 20% to 70% glycolic acid have been used by dermatologists to treat ichthyosis, acne, xerosis, actinic keratosis, seborrheic keratoses, warts, and psoriasis. AHA have recently been used to treat photoaged skin and are now included in many commercially available cosmetic skin treatments. When used in a formulation for a chemical peel, topical treatment of skin with AHA and BHA can result in removal of the stratum corneum, alteration of the skin's histology, and increased cell proliferation in the basal layer of the epidermis.

Since AHA and BHA are used to correct photoaged skin, and since exposure to sunlight of skin treated with AHA or BHA is likely, studies were designed to determine the effects of topical application of creams containing AHA (0%, 4%, or 10% glycolic acid, pH 3.5) or BHA (0%, 2%, or 4% salicylic acid, pH 4.0) on the photocarcinogenesis of simulated solar radiation using a filtered 6.5 kW xenon arc light source [simulated solar light (SSL)]. Male and female Crl:SKH-1 (hr^{-}/hr^{-}) hairless mice were exposed to glycolic acid or salicylic acid alone or in combination with SSL for 40 weeks, and the mice were followed for an additional 12 weeks.

1-Year Study in Mice

Groups of 36 male and 36 female mice were exposed to 0.0, 0.3, 0.6, or 0.9 minimal erythema dose (MED) of SSL during the afternoon (1200 to 1600 hours) 5 days per week for 40 weeks. Groups of 18 male and 18 female mice were treated in the morning (0800 to 1100 hours) with 2 mg/cm^2 control cream, 4% glycolic acid cream, 10% glycolic acid cream, 2% salicylic acid cream, or 4% salicylic acid cream on the dorsal skin, and in the afternoon (1200 to 1600 hours) with 0.3 MED of SSL 5 days per week for 40 weeks. Additional groups of 18 male and 18 female mice were treated in the morning (0800 to 1100 hours) with 2 mg/cm^2 control cream, 4% glycolic acid cream, 10% glycolic acid cream, 2% salicylic acid cream, or 4% salicylic acid cream on the dorsal skin, and in the afternoon (1200 to 1600 hours) with 0.6 MED of SSL 5 days per week for 40 weeks. All mice were held an additional 12 weeks following the end of treatment.

There were no effects of SSL exposure or topical treatment on the body weights of the mice. Increasing doses of SSL resulted in an SSL-dose trend in survival, with the greatest dose of SSL causing the earliest removal. This effect was present in both the untreated and control cream treated mice. The only consistent effect of glycolic acid on survival was a dose-dependent increase in survival of females at 0.3 MED SSL. Survival was increased in mice exposed to 0.6 MED of SSL and treated with 2% and 4% salicylic acid compared to mice treated with 0.6 MED and treated only with the vehicle. This effect was not observed in the mice treated with 0.0 and 0.3 MED of SSL and salicylic acid compared to the control groups.

The mean or median time to first skin tumor of at least 1 mm decreased with increasing SSL exposure concentration in mice that were not treated with cream. Addition of the control cream resulted in a decrease in the time to tumor at 0.3 and 0.6 MED of SSL in male and female mice. The addition of glycolic acid (4% or 10%) did not affect the time to tumor in male or female mice at either SSL dose when compared to mice receiving the control cream. When compared to mice receiving control cream, the inclusion of 4% salicylic acid in the cream increased the time to tumor for male mice receiving 0.3 or 0.6 MED of SSL and female mice receiving 0.3 MED of SSL. The results indicate that inclusion of glycolic acid in the topical cream had no effect on the time required to induce tumors by SSL; however, inclusion of salicylic acid at 4% in the cream was photoprotective, increasing the time required to achieve median tumor incidence at a corresponding dose of SSL and control cream.

The skin tumors induced by SSL in mice were squamous cell papilloma, carcinoma *in situ*, and squamous cell carcinoma. Except for papilloma in male mice, the tumors were induced in a dose-dependent manner by SSL in male and female mice. In male and female mice treated with control cream, the exposure to SSL caused significant increases in the incidences of carcinoma *in situ*, squamous cell carcinoma, and the combined incidence of carcinoma *in situ* and squamous cell carcinoma. When male or female mice were exposed to 0.3 or 0.6 MED SSL, the inclusion of 4% or 10% glycolic acid did not affect the induction of skin neoplasms over the incidence detected when the control cream was used, with the single exception of a glycolic acid dose-trend in squamous cell carcinoma incidence in male mice receiving 0.3 MED SSL.

The inclusion of salicylic acid in the cream that was topically applied to female mice did not affect squamous cell papilloma formation at either SSL dose. The incidence of carcinoma *in situ* was decreased in male

and female mice at 0.3 MED SSL when treated with 4% salicylic acid. A salicylic acid dose-trend was also observed in both sexes at 0.3 MED SSL.

CONCLUSIONS

These experiments investigated the impact of topical application of a cosmetic formulation containing 4% or 10% glycolic acid (pH 3.5) or 2% or 4% salicylic acid (pH 4) on the photocarcinogenesis of filtered 6.5 kW xenon arc simulated solar light (SSL) in SKH-1 hairless mice. Taking into consideration the survival data, time to tumor data, and the pathology results, glycolic acid did not alter the photocarcinogenesis of SSL, and salicylic acid was photoprotective, reducing the carcinogenicity of 0.3 MED SSL.

Summary of the 1-Year Photocarcinogenesis Study of Glycolic Acid and Salicylic Acid

	Glycolic Acid SKH-1 Male Mice	Glycolic Acid SKH-1 Female Mice	Salicylic Acid SKH-1 Male Mice	Salicylic Acid SKH-1 Female Mice
Dose Concentrations	0.0 MED SSL control cream 4% glycolic acid cream 10% glycolic acid cream 0.3 MED SSL control cream 4% glycolic acid cream 10% glycolic acid cream 0.6 MED SSL control cream 4% glycolic acid cream 10% glycolic acid cream	0.0 MED SSL control cream 4% glycolic acid cream 10% glycolic acid cream 0.3 MED SSL control cream 4% glycolic acid cream 10% glycolic acid cream 0.6 MED SSL control cream 4% glycolic acid cream 10% glycolic acid cream	0.0 MED SSL control cream 2% salicylic acid cream 4% salicylic acid cream 0.3 MED SSL control cream 2% salicylic acid cream 4% salicylic acid cream 0.6 MED SSL control cream 2% salicylic acid cream 4% salicylic acid cream	0.0 MED SSL control cream 2% salicylic acid cream 4% salicylic acid cream 0.3 MED SSL control cream 2% salicylic acid cream 4% salicylic acid cream 0.6 MED SSL control cream 2% salicylic acid cream 4% salicylic acid cream
Body weights	Exposed groups similar to the control group	Exposed groups similar to the control group	Exposed groups similar to the control group	Exposed groups similar to the control group
Survival rates	0.0 MED SSL 16/18, 15/18, 17/18 0.3 MED SSL 14/18, 14/18, 11/18 0.6 MED SSL 0/18, 0/18, 0/18	0.0 MED SSL 15/18, 17/18, 17/18 0.3 MED SSL 12/18, 12/18, 16/18 0.6 MED SSL 1/18, 1/18, 1/18	0.0 MED SSL 16/18, 17/18, 17/18 0.3 MED SSL 14/18, 12/18, 15/18 0.6 MED SSL 0/18, 2/18, 1/18	0.0 MED SSL 15/18, 17/18, 14/18 0.3 MED SSL 12/18, 14/18, 15/18 0.6 MED SSL 1/18, 6/18, 8/18
Photococarcinogenesis increased incidences	None	None	None	None
Photococarcinogenesis decreased incidences	None	None	Skin: carcinoma *in situ* 0.0 MED SSL 0/18, 0/18, 0/18 0.3 MED SSL 9/18, 4/18, 1/18 0.6 MED SSL 13/18, 15/18, 13/18 Skin: carcinoma *in situ* or squamous cell carcinoma 0.0 MED SSL 0/18, 0/18, 0/18 0.3 MED SSL 10/18, 4/18, 2/18 0.6 MED SSL 18/18, 17/18, 17/18	Skin: carcinoma *in situ* 0.0 MED SSL 0/18, 0/18, 0/18 0.3 MED SSL 8/18, 4/18, 0/17 0.6 MED SSL 14/18, 11/18, 11/18 Skin: carcinoma *in situ* or squamous cell carcinoma 0.0 MED SSL 0/18, 0/18, 0/18 0.3 MED SSL 8/18, 7/18, 2/17 0.6 MED SSL 17/18, 17/18, 14/18

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on photocarcinogenesis of glycolic acid and salicylic acid on September 27, 2005, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee 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 TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On September 27, 2005, the draft Technical Report on the photocarcinogenesis study of glycolic and salicylic acids received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. P.C. Howard, National Center for Toxicological Research (NCTR), described the NCTR's program for phototoxicity and photococarcinogenicity studies and their facilities for exposure to simulated solar light (SSL). Dr. Howard then described the rationale, design, and results for two studies to test the effects of an alpha hydroxy acid (glycolic acid) and a beta hydroxy acid (salicylic acid) on the photocarcinogenicity of simulated solar light. The proposed conclusions were: glycolic acid did not alter the photocarcinogenesis of SSL, and salicylic acid was photoprotective, reducing the carcinogenicity of 0.3 MED SSL.

Dr. Roberts, the first principal reviewer, did not have scientific criticisms. He suggested adding more description of the animal exposure procedures and the survival analysis. He also suggested that data on tumor multiplicity shown in the opening presentation be included in the report.

Dr. Soper, the second principal reviewer, noted that the Poly-3 statistical test did not require lethality assumptions. He also thought inclusion of the tumor multiplicity data would be helpful and asked if the tumor incidence in the 10% group might be a false positive.

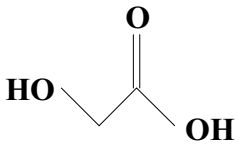
Dr. Birt, the third principal reviewer, noted the higher incidences of tumors in animals exposed to SSL and receiving the control cream alone and wondered if this may be related to higher observed incidences of skin cancers.

Dr. Howard agreed to augment the description of methodology. Regarding cause of animal removal, he said the majority were due to observation of large tumors. Regarding the effect of the control cream, Dr. Howard noted that a large variety of cream formulations are used for various preparations. In a review of 12 coded formulations studied by Argus Laboratories, some enhanced and some protected against photocarcinogenicity. Dr. Howard explained that the principal effect of creams was to affect the optical scattering and absorption properties of the skin itself.

Dr. J.R. Bucher, NIEHS, indicated that the added tumor multiplicity data had been developed more recently and would not be part of the report conclusions to be determined at this review but could be presented as an appendix in this report or in a separate publication. Dr. Roberts thought the data were important enough to warrant inclusion and did not contradict the conclusions from the tumor incidence data. Dr. C.J. Portier proposed that the P values for the tumor multiplicity be included in the appendix tables but not in the results tables in the text (Appendix H).

Dr. Roberts moved, and Dr. Birt seconded, that the conclusions be accepted as written. The motion was accepted unanimously with six votes.

INTRODUCTION

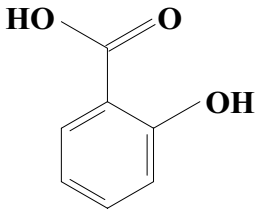


GLYCOLIC ACID

CAS No. 79-14-1

Chemical Formula: $C_2H_4O_3$ Molecular Weight: 76.05

Synonyms: Hydroxyacetic acid; hydroxyethanoic acid
Trade names: Glypure 70, Glypure 99



SALICYLIC ACID

CAS No. 69-72-7

Chemical Formula: $C_7H_6O_3$ Molecular Weight: 138.12

Synonym: 2-Hydroxybenzoic acid

Chemical and Physical Properties

Glycolic acid is an organic acid, where the hydroxyl group is on the carbon atom adjacent to the carbonyl carbon (i.e., alpha hydroxy acid, AHA). Glycolic acid can be obtained as colorless, odorless, and somewhat hygroscopic crystals. It is typically available as a 70% aqueous solution.

Salicylic acid is an organic acid, where the hydroxyl group is two carbons removed from the carbonyl carbon (i.e., beta hydroxy acid, BHA). Salicylic acid can be obtained as crystals with a melting point between 157° and 159° C or as a powder. Salicyclic acid is soluble in water (0.016 M) and very soluble in alcohol, acetone, and ether.

The Cosmetic Ingredient Review (CIR) panel has published extensive reviews of the chemical and toxicological properties of glycolic acid and salicylic acid and their corresponding salts (Andersen, 1998, 2003).

Production, Use, and Human Exposure

Glycolic Acid

Glycolic acid can be produced by several methods including bubbling of carbon monoxide through formaldehyde (Elson, 1993), dehalogenation of monochloroacetic acid with sodium hydroxide, or electrolytic reduction of oxalic acid (Andersen, 1998). Glycolic acid is available as a technical grade 70% solution or as purified 70% (Glypure 70) or 99% (Glypure 99) solutions. Glycolic acid is also available as ammonium, calcium, sodium, and potassium salts; however, this Technical Report focuses on the free acid.

The use of topical acids to improve the esthetics of skin dates back to ancient Egypt, where women bathed in soured milk (lactic acid) to improve their appearance (Brody, 1992). There are several historical accounts of the development of chemical peels for skin conditions (Eller and Wolff, 1941; Brody, 1992), and these highlight the development of peels starting in the 1880s, with the topical use of salicylic acid, resorcinol, phenol, and trichloroacetic acid, and their use in the early 1900s in facial salons. Starting in the 1970s, phenol and trichloroacetic acid became increasingly popular as the principal ingredients in face peels.

Glycolic acid is primarily used in health care products as an additive to topically applied cosmetic formulations, primarily as a topical exfoliant. Chemical peels containing 20% to 70% glycolic acid have been used by dermatologists to correct a number of skin disorders including ichythyosis, acne, xerosis, actinic keratosis, seborrheic keratosis, warts, and psoriasis (Van Scott and Yu, 1984, 1989; Sexton and Rubin, 1994; Murad *et al.*, 1995). Human exposure also occurs through personal selection of over-the-counter (OTC) topical products that contain up to 13% glycolic acid (Andersen, 1998).

Glycolic acid and lactic acid are the two most widely used AHAs in cosmetic products. The AHAs serve as pH buffers in the cosmetics, adjusting the pH of the skin where the products are applied (Wenninger and McEwen, 1995). The pH of cosmetic products varies, with a range of 0.2 to 4.4 for professional products and 2.4 to 8.0 for commercial products (Andersen, 1998).

There are no complete market analyses of the use of formulations containing glycolic acid. The Food and Drug Administration reported that glycolic acid was available in 42 cosmetic formulations in 1997, with the largest use being in moisturizing, cleansing, and face and neck preparations (Andersen, 1998). The CIR panel (Andersen, 1998) has reported that the concentrations of glycolic acid in cosmetic preparations varies greatly. Moisturizing and cleansing preparations contained less than 10% glycolic acid; face and neck products contained up to 13% glycolic acid. The products with the highest concentration of glycolic acid were "skin care preparations" with less than 20% glycolic acid and "skin peeling agents" with 2% to 19% glycolic acid.

Salicylic Acid

Salicylic acid is produced by the reaction of carbon dioxide with sodium phenolate to form sodium salicylate, which is converted to salicylic acid with mineral acid (*Remmington's*, 1990; Andersen, 2003). Salicylic acid is also available from the bark of willow trees (Lin and Nakatsui, 1998). Salicylic acid is also available as ammonium, calcium, sodium, and potassium salts; however, this Technical Report focuses on the free acid.

Salicylic acid was reportedly used in 107 cosmetic formulations in 1998, with the largest use being in skin cleansing products, shampoos, moisturizing preparations, and hair grooming aids (Andersen, 1998). In general, the concentrations of salicylic acid in these commercial products did not exceed 3%. Other applications of salicylic acid that may constitute a more acute use but higher level of exposure include OTC acne preparations (2% to 5%), OTC wart remover (5% to 40%, depending on vehicle), OTC corn or callus remover (12% to 40%, depending on vehicle), and dandruff, seborrheic dermatitis, and psoriasis controls (3%).

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

Glycolic Acid

The pKa of glycolic acid is 3.83 at 25° C (Rosan, 1994). The bioavailability of glycolic acid depends on the

availability of free acid (Andersen, 1998) and, as a result, the pH of the topical formulation. In addition, the bioavailability of glycolic acid is influenced by the vehicle used in a given formulation. Ohta *et al.* (1996) applied 40 mg/mL solutions (4% w/w) of ^{14}C-glycolic acid in several formulations, including an aqueous solution, a solution containing 30% propylene glycol, an oil-in-water emulsion, a water-in-oil emulsion, and two nonionic liposomal formulations containing cholesterol, polyoxyethylene-10-stearyl ether, and either glyceryl dilaurate or distearate. The formulations were applied at a dose of 25 mg to 4 cm^2 (6.25 mg/cm^2) to skin of anesthetized SKH-1 hairless mice. Glycolic acid penetrated the stratum corneum into the living tissue. At 4 hours, 0.96% of the applied glycolic acid from the aqueous preparation penetrated into the viable skin, while 2.02% of the glycolic acid penetrated into the skin from the dilauryl-based liposomal formula. The other formulas had the following penetrations in 4 hours: propylene glycol, 0.51%; oil-in-water, 0.98%; water-in-oil, 0.66%; distearyl-based liposomes, 1.15%.

The absorption of topically applied ^{14}C-glycolic acid has been determined in SKH-1 mice (Ohta *et al.* 1996). The amount of glycolic acid recovered from the stratum corneum surface depended on the vehicle. Glycolic acid penetrated the epidermal and dermal skin tissue and was detected in the urine in an amount that was generally increased with time and was related to the amount absorbed into the skin. Some glycolic acid (1% to 2%) was recovered from the liver, and the authors proposed that glycolic acid undergoes metabolic conversion once absorbed.

When ^{14}C-glycolic acid in a cream formulation was applied topically to pig skin at a dose of 5 mg/0.79 cm^2, 3.1% of the dose penetrated the skin (Andersen, 1998).

Salicylic Acid

The effects of pH and concentration on the absorption of salicylic acid from ointments have been examined in numerous studies using guinea pigs, New Zealand white rabbits, Sprague-Dawley rats, Wistar rats, and female rhesus monkeys. These studies have been reviewed in Andersen (2003). Salicylic acid is absorbed through the skin. The absorption is dependent on the pH of the vehicle, with maximum absorption at acidic (pH < 4) and alkaline (pH > 8) conditions. The absorption of salicylic acid is also dependent on the hydrophobicity of the vehicle (ointment).

Humans

Glycolic Acid

Kraeling and Bronaugh (1997) examined the absorption of ^{14}C-glycolic acid in human abdominal skin *in vitro* using a diffusion cell method. A 5% (w/w) glycolic acid solution was prepared at pH 3 or pH 7 in two different oil-in-water emulsions and applied to the skin at 3 mg/cm^2. With one of the oil-in-water emulsions, 27.2% ± 3.3% of the glycolic acid applied at pH 3 penetrated the skin in 24 hours, while only 3.5% ± 0.9% penetrated when applied at pH 7. The glycolic acid penetrated the viable epidermis and dermis and was detected in receptor fluid below the skin. The second oil-in-water emulsion, containing 1% ionic lauryl sulfate, increased the absorption at pH 3 to 34.8% ± 3.9%, while the penetration at pH 7 decreased to 2.3% ± 0.8% of the applied dose. These results suggest that the penetration of glycolic acid into the skin of humans is dependent on both the pH and the composition of the emulsion.

Salicylic Acid

The absorption of salicylic acid across human skin *in vivo* has been recently reviewed (Andersen, 2003). Salicylic acid penetrates the skin of humans, and this penetration is affected by the dose of salicylic acid in the cream, the cream base, the pH of the cream, and the nature of any excipients in the cream. For instance, repeated application of 6% salicylic acid in a propylene glycol/alcohol gel to patients with active psoriasis resulted in absorption of 63% to 82% of the applied salicylic acid (Taylor and Halprin, 1975). The topical application of 2% salicylic acid in another study (Davis *et al.*, 1997) resulted in greater absorption of salicylic acid from a water/alcohol vehicle than from a water/cosmetic excipient mixture.

TOXICITY

Experimental Animals

Glycolic Acid

The toxicity of orally administered glycolic acid, while not directly pertinent to this document, has been studied. Oral administration of glycolic acid (5% solution) has an LD_{50} of 1,950 mg/kg for rats and 1,920 mg/kg for guinea pigs (Smyth *et al.*, 1941). In rats, oral administration of 3,500 mg/kg of 70% glycolic acid caused the death of 8 of 10 rats, while a dose of 350 mg/kg caused

no mortality (Andersen, 1998). In separate studies, oral administration of a 20% solution had an LD_{50} of 1,600 to 3,200 mg/kg in rats (Patty, 1963; Andersen, 1998). The LD_{50} for glycolic acid in mice was reported as 2,000 mg/kg (Perier *et al.*, 1988).

Glycolic acid is metabolized to oxalic acid. The feeding of diets containing high amounts of glycolic acid (3% w/w) for a short term (3 to 4 weeks) led to the formation of calculi (calcium oxalate) in the ureters, urinary bladder, and renal tubules (Andersen, 1998). Longer feeding studies (31 to 35 weeks) with male and female albino rats and 1% to 2% glycolic acid led to decreased weight gain, increased renal oxalate, and nephrotoxicity.

The LD_{50} for oral administration of salicylic acid has been determined in several studies. In one study, the LD_{50} was 891 mg/kg for rats and 480 mg/kg for mice (Andersen, 2003). Administration of salicylic acid in gum arabic increased the dose tolerance to LD_{50}s of 1,580 and 1,250 mg/kg in male and female rats, respectively (Andersen, 2003).

There have been several reports regarding the dermal toxicity of salicylic acid. Application of an occlusive patch of salicylic acid to the clipped skin of rats resulted in no deaths and an LD_{50} of > 2 g/kg (Bomhard, 1996). Topical application of salicylic acid had a positive result in the local lymph node assay for sensitization (Gerberick *et al.*, 1992); however, in a study with female albino ICR mice, salicylic acid was not a contact photosensitizer using UVA light (Miyachi and Takigawa, 1983).

Humans

Glycolic Acid

Van Scott and Yu (1984) studied the effect of topical AHA on hyperkeratinization in humans. Glycolic acid is not a true keratolytic compound that results in disaggregation of corneocytes at the upper strateum corneum; rather, it appears to exert its influence on lower, newly forming levels of the strateum corneum. Van Scott and Yu (1984) hypothesized that the effects of AHA are through inhibition of phosphotransferases and kinases, which increase the cohesion between corneocytes of the strateum corneum.

Ditre *et al.* (1996) investigated the effects of 25% solutions of glycolic acid, lactic acid, or citric acid on photoaged human skin. The forearms of patients were treated for 6 months with cream either with or without the acids. The use of the AHA reversed the effects of photoaging, increasing the skin bi-fold thickness by 25% from a mean of 11.5 mm to 14.3 mm. This increase in thickness following AHA treatment was accompanied by a reversal of basal cell atypia, improved dispersion of melanin pigmentation, and more uniform basal keratinocyte nuclei. The authors demonstrated that the increased skin thickness was accompanied by increased glycosaminoglycans and collagen, but not necessarily by increased edema. Griffin *et al.* (1996) reported these treatments resulted in increased factor XIIIA transglutaminase levels in dermal dendrocytes and mast cell degranulation.

Salicylic Acid

In general, salicylic acid is a keratolytic chemical, with the rapidity of effect being concentration dependent (Andersen, 2003). Application of salicylic acid creams typically results in thinner stratum corneum but no change in the epidermis thickness or labeling index. The changes in the skin result in increased transepidermal water loss.

A 2% salicylic acid gel was applied (200 mg total) to the backs of 27 subjects three times per week for 2 weeks, and the conclusion was that salicylic acid produced minimal cumulative irritation (Andersen, 2003). In a separate study, the application of a 1.5% salicylic acid cream (pH 2.75) to 27 subjects 5 days per week for 3 weeks resulted in slight irritation to the skin (Andersen, 2003). In studies where 0.2% or 1.5% salicylic acid solutions were applied in occlusive or semiocclusive patches for 21 days, it was concluded that salicylic acid was nonirritating. In multiple studies, salicylic acid was not shown to be a sensitizer (Andersen, 2003).

CARCINOGENICITY

There are no reports on the carcinogenicity of topically applied glycolic acid or salicylic acid in experimental animals, and no epidemiology studies of glycolic acid or salicylic acid in humans were found in a review of the literature.

PHOTOCARCINOGENICITY

Experimental Animals

Glycolic Acid

Hong *et al.* (2001) reported that glycolic acid had an inhibitory effect on ultraviolet (UV) light induced skin

carcinogenesis in SKH-1 hairless mice. Female mice (15/group) were treated 5 days per week with UV radiation from a combination of UVA- and UVB-emitting fluorescent lamps, which resulted in an initial dose of 11.4 J/cm^2 UVA and 40 mJ/cm^2 UVB. The dose of light was incrementally increased over the course of the study. Immediately after irradiation, a skin area (1.5 × 2.5 cm) was treated twice each week with glycolic acid in polyethylene glycol at a dose of 8 mg/cm^2. After 9 weeks, the animals receiving UV radiation alone or with glycolic acid had reduced body weights (approximate 7% decrease) compared to control animals. With UV radiation alone, tumors first appeared after 9 weeks; by 20 weeks, 100% of the mice had tumors. The effect of the twice weekly treatment with glycolic acid was to decrease the effect of the UV light, resulting in a doubling of the time required to develop tumors, a decrease in the incidence of large (greater than 2 mm) tumors, and a decrease in the average number of tumors on the mice. The reduction in tumor formation was accompanied by a reduction in skin cyclin dependent kinases 2 and 4, proliferating cell nuclear antigen (PCNA), and *jun* N-terminal kinase. The study, as designed, supported the authors' conclusions that postirradiation treatment with glycolic acid may reduce skin cancer incidence.

Salicylic Acid

There is a single report on the photocarcinogenicity of salicylic acid (Bair *et al.*, 2002), which was published subsequent to the start of these studies. Sodium salicylate (10 or 40 µmol) was dissolved in 75 µL of Vanicream® (pH not specified) and applied to the skin of SKH-1 mice 1 hour prior to irradiation. The mice were irradiated three times per week with FS-40 UVB fluorescent lamps, starting at a dose of 1.5 kJ/m^2 and increasing weekly by 1.5 kJ/m^2, until the final dose of 9.0 kJ/m^2 was reached. The topical application of sodium salicylate decreased the carcinogenicity of the UVB light, resulting in fewer mice with skin tumors and fewer tumors per mouse (i.e., multiplicity) when compared to the Vanicream® control. The reduction of tumors, coupled with a reduction of pyrimidine dimer formation in the skin of salicylate treated mice, led the authors to conclude that salicylate was acting as a sunscreen and reducing the amount of UVB reaching the epidermal tissue.

Study Rationale

The Center for Food Safety and Applied Nutrition nominated topically applied AHA to the National Toxicology Program for carcinogenicity testing. After a review of the nomination and consideration of the use of these products in the marketplace, it was determined that the most representative AHA was glycolic acid, and that the effect of topical application of glycolic acid on the carcinogenesis of simulated solar light would be the most appropriate test model. In addition, the study was designed to include a representative BHA, and salicylic acid was chosen as the BHA to use in the study.

The hypothesis was that topical application of creams containing glycolic or salicylic acid would enhance the photocarcinogenicity of light containing UVB radiation due to increased cell proliferation in the epidermal basal layer. This hypothesis was proposed prior to the publication of the studies by Hong *et al.* (2001) and Bair *et al.* (2002).

The hypothesis was supported by the studies of Sams *et al.* (2001) in which 4% and 10% glycolic acid increased proliferation (i.e., labeling index) in the epidermal basal cells in treated mice, with maximum proliferation 12 to 16 hours posttreatment. The inclusion of salicylic acid up to 8% in cream induced a linear increase in epidermal basal cell proliferation.

Glycolic acid is included in a wide variety of cosmetics. The CIR panel (Andersen, 1998) recommended that glycolic acid not exceed 10% in cosmetic formulations at a pH not lower than 3.5. Based on this information, FDA market surveys (referenced in Andersen, 1998), and the results of Sams *et al.* (2001), the NTP Toxicology Study Selection and Review Committee approved the recommendation of glycolic acid concentrations of 4% and 10% at pH 3.5 for this study. The glycolic acid was to be incorporated into a cream representative of cosmetic creams on the market.

Salicylic acid is used in a variety of cosmetic products at concentrations as high as 3% (Andersen, 2003). The concentrations of salicylic acid to be used in the study, 2% and 4% at a pH of 4, were approved by the NTP Toxicology Study Selection and Review Committee based on consideration of published studies on the effects of salicylic acid and unpublished market analyses on the concentration and pH of cosmetic products containing salicylic acid. The salicylic acid was to be incorporated into a cream representative of cosmetic creams on the market.

The study design also took into consideration the doses of light used in traditional photocarcinogenesis studies.

The study animals included male and female mice because there was no available information regarding sex differences in response to glycolic or salicylic acid. Due to animal room limitations and a desire for two dose groups per chemical, an unbalanced study design was employed consisting of 36 mice per sex in groups exposed to simulated solar light only and 18 mice per sex in groups treated topically with creams containing glycolic or salicylic acid or no hydroxy acid.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Glycolic Acid and Salicylic Acid Creams

Glycolic and salicylic acid creams were obtained from Cosmetech Laboratories, Inc. (Fairfield, NJ); glycolic acid creams 4% (by weight) in lot CLI 10220/5 and 10% (by weight) in lot CLI 10220/9 and salicylic acid creams 2% (by weight) in lot CLI 10220/16 and 4% (by weight) in lot CLI 10220/10 were used in the 1-year dermal study. Determination of the glycolic acid and salicylic acid concentrations and pH of the creams was performed by the study laboratory at the National Center for Toxicological Research (Jefferson, AR) (Appendix C). Reports on analyses performed in support of the study of the effect of glycolic acid and salicylic acid on the photocarcinogenicity of simulated solar light are on file at the National Center for Toxicological Research (NCTR).

The concentrations of glycolic and salicylic acid creams were determined using high performance liquid chromatography (HPLC), and the pH of the creams were determined using a pH meter.

Initial analyses of the glycolic acid creams indicated a mean of 3.90% and 10.04% glycolic acid in the 4% and 10% glycolic acid stock creams, respectively, and a mean pH of 3.5 (Tables C1 and C2); initial analyses of the salicylic acid creams indicated a mean of 2.20% and 4.65% salicylic acid in the 2% and 4% salicylic acid stock creams, respectively, and a mean pH of 3.9 (Tables C3 and C4).

To ensure stability, the bulk cream containers were capped, sealed with Parafilm® and tape, and stored protected from light at room temperature.

Control Cream

Control cream was obtained from Cosmetech Laboratories, Inc., in one lot (CLI 10220/4), which was used in the 1-year dermal studies. The composition of the control cream was identical to the creams containing glycolic and salicylic acid with the exception of the glycolic acid, salicylic acid, and water required for final dilution. The study laboratory determined that the mean pH of the control cream at receipt was 3.61 and confirmed the absence of glycolic acid and salicylic acid in the control cream using HPLC. The composition of the control cream as reported on the manufacturer's batch sheet was (percent by weight): deionized water (70.02%), 96% glycerin (3.25%), 2% Keltrol T solution (8.00%), Veegum ultra (1.20%), cetearyl alcohol (2.50%), Eutanol G (4.00%), dimethicone DC 200-100 (0.80%), Lipomulse 165 (2.40%), Brij 721 (Steareth-21) (2.40%), Lipowax D (4.00%), Germaben II (1.00%), and a 10% solution of 85% phosphoric acid (0.43%, q.s. pH to 3.5). The pH of the bulk cream was monitored once during the 1-year study by the study laboratory; no change in pH was detected.

DISPENSATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations were dispensed approximately once a month. Stock creams were either mixed with a metal spatula or shaken vigorously, then aliquots of approximately 100 g were weighed into 8 ounce plastic straight sided jars, capped, sealed with tape, and stored at room temperature (Table C5).

Analyses of the bulk formulations were conducted approximately once a month by the study laboratory using HPLC and pH measurement. Of the glycolic acid samples analyzed, all 12 of the 4% creams and all 12 of the 10% creams were within 10% of target concentrations (Table C1); 24 of 27 pH determinations were within 10% of target (Table C2). Of the salicylic acid samples analyzed, all 12 of the 2% creams and 9 of 12 of the 4% creams were within 10% of target concentrations (Table C3); 21 of 26 pH determinations were within 10% of target concentrations (Table C4).

LIGHT SOURCE AND DOSIMETRY

The photocarcinogenesis study was based on the experimental design used at Argus Research Laboratories, Horsham, PA. SKH-1 hairless mice were exposed

horizontally to light emitted from a 6.5-kW long-arc xenon arc light source (Atlas Electric Devices Co., Chicago, IL) and filtered through 0.6 mm thick Schott WG-320 glass filters (Schott Glass Technologies, Southbridge, MA). In this study, mice were exposed to 0, 0.3, 0.6, or 0.9 minimal erythema dose (MED) of filtered simulated solar light (SSL) as determined using a Solar Light PMA2101 dosimeter (Solar Light Co., Inc., Glenside, PA).

The actual measure of the dose of light in these studies was based on the recommendations of the Commission Internationale de l'Eclairage convention (CIE, 1987, 1998), where the irradiation from the light source was quantified as erythemally effective radiation. This value is determined by measuring the irradiance from the SSL (mW/cm^2) and multiplying it by the human erythema action spectrum to obtain a weighted irradiance value ($mW•CIE/cm^2$). Since exposure to 1 $mW•CIE/cm^2$ for 1 second equals 1 $mJ•CIE/cm^2$, the weighted irradiance from the SSL is multiplied by the length of exposure (seconds) to calculate the exposure dose [$mJ•CIE/cm^2$; where 10 $mJ•CIE/cm^2$ equals 1 standard erythema dose (SED; CIE, 1998)]. Using this approach and a Solar Light PMA2101 dosimeter, we determined that 0.3, 0.6, and 0.9 MED of SSL, recommended and used at Argus Laboratories, were equivalent to 6.85, 13.70, and 20.55 $mJ•CIE/cm^2$. All dosimetry was conducted based on measurements as $mJ•CIE/cm^2$; however, in this Technical Report, doses of light are referred to as 0, 0.3, 0.6, and 0.9 MED as defined in the protocol. Additional information regarding the spectrum of SSL and doses of light is provided in Appendixes D and E.

1-YEAR STUDY

Study Design

Groups of 36 male and 36 female mice were exposed to 0.0, 0.3, 0.6, or 0.9 MED SSL light during the afternoon (1200 to 1600 hours) 5 days per week for 40 weeks (Table 1). Groups of 18 male and 18 female mice were treated in the morning (0800 to 1100 hours) with 2 mg/cm^2 control cream, 4% glycolic acid cream, 10% glycolic acid cream, 2% salicylic acid cream, or 4% salicylic acid cream on the dorsal skin and in the afternoon (1200 to 1600 hours) with 0.3 MED SSL 5 days per week for 40 weeks. Additional groups of 18 male and 18 female mice were treated in the morning (0800 to 1100 hours) with 2 mg/cm^2 control cream, 4% glycolic acid cream, 10% glycolic acid cream, 2% salicylic acid cream, or 4% salicylic acid cream on the dorsal skin, and in the afternoon (1200 to 1600 hours) with 0.6 MED SSL 5 days per week for 40 weeks. All mice were held an additional 12 weeks following the end of treatment. The mice were housed in stainless steel racks that allowed horizontal exposure to the SSL light source. The racks were placed around

TABLE 1
Level of Exposure to Simulated Solar Light in Mice in the 1-Year Study[a]

Cream Application	No Light (0.0 MED/day)	Low Dose (0.3 MED/day)	Medium Dose (0.6 MED/day)	High Dose (0.9 MED/day)
None	36 males	36 males	36 males	36 males
	36 females	36 females	36 females	36 females
Control cream, pH 7	18 males	18 males	18 males	
	18 females	18 females	18 female	
Cream, 4% glycolic acid, pH 3.5	18 males	18 males	18 males	
	18 females	18 females	18 females	
Cream, 10% glycolic acid, pH 3.5	18 males	18 males	18 males	
	18 females	18 females	18 females	
Cream, 2% salicylic acid, pH 4	18 males	18 males	18 males	
	18 females	18 females	18 females	
Cream, 4% salicylic acid, pH 4	18 males	18 males	18 males	
	18 females	18 females	18 females	

[a] Mice were treated 5 days/week with cream and/or simulated solar light.

the light source with the front of the animal cage being approximately 2 meters from the light source. The duration of exposure was based on the dose of SSL. The mice were volumetrically dosed with the cream, and the cream was dispersed using a gloved fingertip circulating the cream for less than 30 seconds in the dosed area (dorsal back, from base of neck to base of tail, midpoint on the flanks).

Source and Specification of Animals

Male and female Crl:SKH-1 (hr^{-}/hr^{-}) hairless mice were obtained from Charles River Laboratories (Portage, MI) for use in the 1-year study. On receipt, the mice were 5 weeks old. Mice were quarantined for 2 weeks then acclimated for 1 week to individual housing before the beginning of the studies. Six male and six female mice were randomly selected for parasite evaluation and gross observation of disease. Mice were approximately 8 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NCTR Sentinel Animal Program (Appendix G).

Animal Maintenance

Mice were housed individually in Lenderking EXP355-72 animal racks. The mice were individually housed in a compartment, with six compartments per cage, six cages per column, and two columns per rack. Feed and water were available *ad libitum*. 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 once weekly. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix F.

Clinical Examinations and Pathology

The mice were weighed and examined weekly for the presence of skin lesions consistent with the development of skin tumors. The size of each lesion was determined using calipers, and the size and location were recorded in the NCTR Multi-Gen Animal Tracking Database. Other clinical observations were also recorded. Mice were removed from the study when the diameter of any skin lesion reached 10 mm, when significant merging of lesions occurred, or when the health or welfare of the mouse was inconsistent with continuation on the study. As a result, the survival index reflects tumor growth to 10 mm in addition to morbidity and mortality.

Necropsies and microscopic examinations were performed on all mice. After euthanasia, but prior to initiation of necropsy, digital photographs were taken of all mice with the exception of 63 mice that died early. Skin lesions were numbered on the photographs to facilitate the gross-to-microscopic correlation. At necropsy, gross skin lesions, tissue masses, skin tumors, spleen, lungs, and the right femur were examined. Tumors were removed, fixed, and preserved in 10% neutral buffered formalin. At the discretion of the Study Pathologist or Principal Investigator, samples of skin tumors from sacrificed and moribund animals were frozen in liquid nitrogen. Additional samples of normal skin were removed from the dorsal surfaces of the front and rear of the left and right shoulders, and from abdominal and thoracic ventral areas. Samples were preserved in 10% neutral buffered formalin. Fixed tissues were trimmed, mounted in paraffin-plastic polymer blocks, sectioned at 5 µm, and stained with hematoxylin and eosin.

Microscopic evaluations were completed by the study pathologist, and the pathology data were entered into the NCTR Micropath Data Collection System. The slides, paraffin blocks, and residual wet tissues were stored in the NCTR Pathology archives. An internal peer review was conducted in which all neoplasms not located in the skin were reviewed and 10% of each dose group (with the exception of the 4% glycolic acid and 2% salicylic acid groups) were completely reviewed by a quality control pathologist. The quality control pathologist evaluated the gross individual animal necropsy records, the gross/microscopic correlation, and the histopathology of each case, and concurrence was documented. In the case of nonconcurrence, the quality control pathologist consulted with the study pathologist to attempt resolution of differences. Unresolved issues were decided by the NCTR pathology staff. The wet tissues, blocks, slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal necropsy records and pathology tables were compared for accuracy; the slide and tissue counts were verified, and the histotechnique was evaluated. A quality assessment pathologist evaluated all diagnoses for proliferative lesions involving the site of application for the first 50% of the males and females in all exposure groups. Additionally, all

diagnoses from the first 16.7% of male and female mice from the 0.0 and 0.6 MED groups were reviewed.

The number of tumors (of at least 1 mm) per animal at a given week were extracted from the Multi-Gen Animal Tracking Database. Statistical analyses of these occurrences were conducted as described in the next section. As part of the pathology evaluation of the tumors, multiplicity for neoplastic lesions was determined by examining each gross lesion and classifying it appropriately. The total number of neoplastic lesions of each type (squamous cell papilloma, carcinoma *in situ*, and squamous cell carcinoma) was counted and summarized for each neoplasm type as the total number present: 1, 2, 3, 4, 5, or greater than 5.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the study and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the study and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the study pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the study pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

TABLE 2
Experimental Design and Materials and Methods in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid

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

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

Animal Source
Charles River Laboratories (Portage, MI)

Time Held Before Study
2 weeks quarantine, plus 1 week acclimation

Average Age When Study Began
8 weeks

Date of First Exposure
July 17 and 24, 2000, and August 14 and 21, 2000

Duration of Exposure
52 weeks (40 weeks exposure; 12 weeks held prior to terminal sacrifice the following week)

Date of Last Exposure
April 20 and 27, 2001, and May 18 and 25, 2001

Necropsy Dates
Weeks of July 16 and 23, 2001, and August 13 and 20, 2001

Average Age at Necropsy
61 weeks

Size of Study Groups
0.0 MED light dose, no cream - 36 males, 36 females
0.0 MED light dose, control cream - 18 males, 18 females
0.0 MED light dose, 4% glycolic acid cream - 18 males, 18 females
0.0 MED light dose, 10% glycolic acid cream - 18 males, 18 females
0.0 MED light dose, 2% salicylic acid cream - 18 males, 18 females
0.0 MED light dose, 4% salicylic acid cream - 18 males, 18 females
0.3 MED light dose, no cream - 36 males, 36 females
0.3 MED light dose, control cream - 18 males, 18 females
0.3 MED light dose, 4% glycolic acid cream - 18 males, 18 females
0.3 MED light dose, 10% glycolic acid cream - 18 males, 18 females
0.3 MED light dose, 2% salicylic acid cream - 18 males, 18 females
0.3 MED light dose, 4% salicylic acid cream - 18 males, 18 females
0.6 MED light dose, no cream - 36 males, 36 females
0.6 MED light dose, control cream - 18 males, 18 females
0.6 MED light dose, 4% glycolic acid cream - 18 males, 18 females
0.6 MED light dose, 10% glycolic acid cream - 18 males, 18 females
0.6 MED light dose, 2% salicylic acid cream - 18 males, 18 females
0.6 MED light dose, 4% salicylic acid cream - 18 males, 18 females
0.9 MED light dose, no cream - 36 males, 36 females

TABLE 2
Experimental Design and Materials and Methods in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid

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

Animals per Cage
1

Method of Animal Identification
Tail tattoo

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

Water
Millipore-filtered water (Jefferson municipal supply) then UV-light sterilized prior to delivery to automatic sipper valves located in each cage (Edstrom Industries, Waterford, WI). Water was available *ad libitum* except during light exposure.

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

Animal Room Environment
Temperature: 25° ± 2° C
Relative humidity: 50% ± 20%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Exposure Concentrations
None, control cream, 4% or 10% glycolic acid, or 2% or 4% salicylic acid with 0.0, 0.3, 0.6, or 0.9 MED/day

Type and Frequency of Observation
Observed twice daily; animals were weighed initially, once weekly, and at the end of the study; clinical findings and skin lesions were recorded weekly.

Method of Sacrifice
Asphyxiation with carbon dioxide

Necropsy
Necropsies were performed on all animals.

Histopathology
Limited histopathology was performed on all animals including those that died during the study or were removed early. In addition to gross lesions and tissue masses, the following tissues were examined: skin (6 sections), skin tumors, spleen, lungs, and right femur (bone marrow).

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Body Weight Analyses

Analyses of mouse body weights during the study were separated into three separate tests: effect of SSL exposure on mice not treated with cream; effect of glycolic acid concentration on body weights in SSL-exposed (0.0, 0.3, and 0.6 MED SSL) mice; and effect of salicylic acid concentration on body weights in SSL-exposed mice. Statistical significance was considered when $P \leq 0.05$.

A repeated measures model with a heterogeneous autoregressive covariance structure was used to assess differences in body weights during the course of the study. The analysis employed body weights obtained every fourth week from weeks 0 to 52.

For the comparison of SSL effects in mice that were not treated with creams, the design was a one-way repeated measures model with light exposure as the fixed effect and time as the repeated measures variable. Testing for the linear dose trend was accomplished using contrasts. Dunnett's tests on SSL dose were calculated for each time. These tests compare each SSL dose with the no-SSL dose and are adjusted for the fact that several comparisons are occurring concurrently.

For the determination of the effect of glycolic acid on body weights, the design within each sex was a two-way repeated measures model with skin cream dose and SSL exposure as the two-way portion and time as the repeated measures variable. Two *ad hoc* tests were performed. First, Dunnett's (1955) tests on glycolic acid dose were calculated for each SSL dose and time. These tests compared the control cream with each of the doses of glycolic acid (4% or 10%) and made adjustments for the fact that several comparisons by exposure and week were occurring simultaneously. Second, independent t-tests on SSL dose were conducted by glycolic acid dose and time. These tests make all pairwise comparisons of the different exposures; these P values are unadjusted for multiple comparisons.

The effects of inclusion of salicylic acid in the skin cream were analyzed in an identical manner to that of glycolic acid.

Analysis of Time to First Tumor

The analysis of time to first tumor was based on weekly observation of each mouse for the presence of lesions consistent with tumor development. The data were analyzed using the log-rank test with Tarone's test for trend.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A3, B1, and B3 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A2 and B2) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. Tables A2 and B2 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, only to site-specific, lesion-free animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess the effect of cream doses on the neoplastic lesion prevalence within SSL-level and to assess the effect of SSL-level within cream dose level. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk

weight is the fraction of the entire study time that it survived, raised to the k^{th} power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). A value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and $B6C3F_1$ mice (Portier *et al.,* 1986). A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions is represented as 1–P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

This study involved a two-way design of SSL dose by cream dose. Since interaction was considered a possibility, a method of extending the Poly-k test was devised by recognizing that the Poly-k test can be cast as a generalized linear model with a binomial error and an identity link function. Therefore, it would be possible to run a multifactor generalized linear model using Poly-k weights, binomial error, and an identity link. However, the identity link has unfortunate characteristics for multifactors (additive probabilities do not necessarily preserve the [0,1] range). Therefore this study used Poly-3 weights, binomial errors, and a logit link function, basically a Poly-3 weighted logistic regression analysis. The fact that some cells were empty required artificially scaling cells away from zero or one. Contrasts were used to compare to test for trends and comparisons to control. P values resulting from this procedure are one sided if that may sensibly be done and the usual appending of "N" is done.

The Jonckheere-Terpstra test (Jonckheere, 1954) and Shirley's test (Shirley, 1977; Williams, 1986) were used to assess nonneoplastic lesion incidence with severity information. Since multiple nonneoplastic lesions of the same morphology were possible, the maximum severity was used. The tests presume monotonicity in the dose response and do not readily lend themselves to multifactor studies. Therefore, the data were analyzed within each SSL level testing whether nonneoplastic lesion severity/incidence was monotonically related to cream dose. The overall trend test is Jonckheere-Terpstra (Jonckheere, 1954), while Shirley's test (Shirley, 1977) was used for comparison to control cream.

Quality Assurance Methods

The 1-year study was conducted in compliance with 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. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at the NCTR. The audit findings were reviewed and assessed by NCTR staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

RESULTS

1-YEAR STUDY

Survival

The survival of the male and female mice that received only simulated solar light (SSL) is summarized in Table 3 and shown in Figure 1 for both the Cox proportional hazards analysis and log-rank analysis with Tarone's trend test. The survival of mice receiving 0.3 minimal erythema dose (MED) SSL/day versus no light was not significantly different from the corresponding control group in male or female mice. At the higher SSL exposures (0.6 and 0.9 MED), survival was decreased when compared to the survival of the mice that received no SSL. A linear trend for SSL effect was detected for both male and female mice in the groups that received SSL only.

The analyses of survival of male and female mice that received SSL and either no cream or control cream are listed in Table 4 and presented graphically in Figures 2, 3, and 4. When mice were treated with control cream, there was not a significant difference in survival between mice treated with 0.0 and 0.3 MED SSL (Table 4; Figure 2). Mice treated with control cream and 0.6 MED SSL had decreased survival compared to mice treated with control cream and 0.0 MED SSL. A positive linear trend with SSL exposure (i.e. 0.0, 0.3, and 0.6 MED SSL) was noted for both male and female mice receiving control cream (Table 4). In summary, the effects of SSL on survival of mice that received no cream (Figure 1) were replicated in the mice that were treated with the control cream (Figure 2) in that survival decreased in a dose-dependent manner with SSL.

Table 4 presents the results of the statistical analysis of survival at each SSL exposure, testing whether a difference in survival at a given SSL exposure was detected when no cream and control cream groups were compared (males, Figure 3; females, Figure 4). Survival of male and female mice that did not receive SSL was not altered by the application of control cream. The application of cream did not affect survival of male mice receiving 0.3 MED SSL. The two statistical analyses (Cox proportional hazards analysis and log-rank analysis with Tarone's trend test) (Cox, 1972; Tarone, 1975) differ in significance when comparing the no cream group to the control cream group in male mice treated with 0.6 MED SSL, and as a result, it is unclear if an effect was present (Table 4). In female mice that received 0.3 or 0.6 MED SSL, survival was decreased by the addition of control cream (Table 4).

TABLE 3
Survival (P Value) of Mice in the 1-Year Simulated Solar Light Study: Light Only

	Cox Proportional Hazards	Log-rank Analysis with Tarone's Trend Test
Male		
0.0 MED SSL vs. 0.3 MED SSL	0.720	0.627
0.0 MED SSL vs. 0.6 MED SSL	0.001	0.001
0.0 MED SSL vs. 0.9 MED SSL	0.001	0.001
SSL Linear Trend Test	0.001	0.001
Female		
0.0 MED SSL vs. 0.3 MED SSL	0.360	0.186
0.0 MED SSL vs. 0.6 MED SSL	0.001	0.001
0.0 MED SSL vs. 0.9 MED SSL	0.001	0.001
SSL Linear Trend Test	0.001	0.001

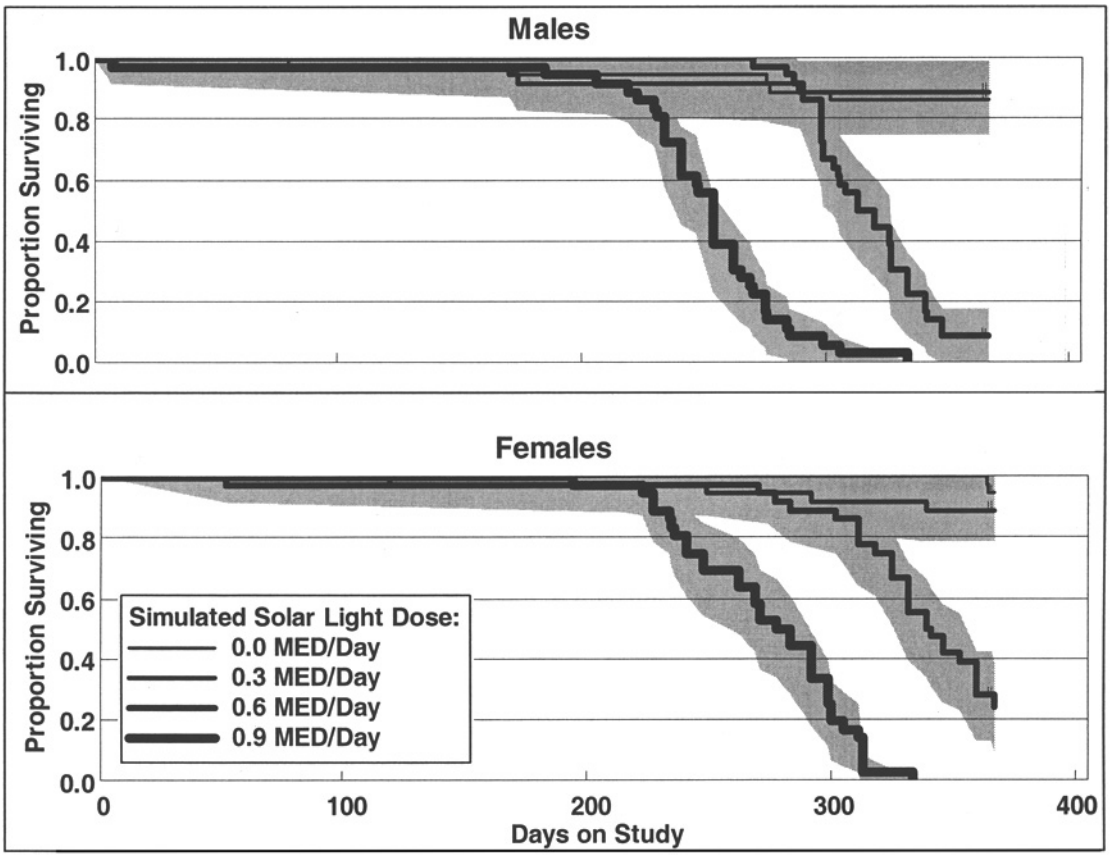


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to 0.0, 0.3, 0.6, or 0.9 MED Simulated Solar Light (Gray area equals 95% confidence range).

TABLE 4
Survival (P Value) of Mice in the 1-Year Simulated Solar Light Study: Control Cream[a]

	Cox Proportional Hazards	Log-rank Analysis with Tarone's Trend Test
Male		
Control Cream		
0.0 MED SSL vs. 0.3 MED SSL	0.192	0.217
0.0 MED SSL vs. 0.6 MED SSL	0.001	0.001
SSL Linear Trend Test	0.001	0.001
No Cream vs. Control Cream		
0.0 MED SSL	0.338N	0.412N
0.3 MED SSL	0.142	0.159
0.6 MED SSL	0.075	0.013
Female		
Control Cream		
0.0 MED SSL vs. 0.3 MED SSL	0.119	0.143
0.0 MED SSL vs. 0.6 MED SSL	0.001	0.001
SSL Linear Trend Test	0.001	0.001
No Cream vs. Control Cream		
0.0 MED SSL	0.082	0.081
0.3 MED SSL	0.021	0.020
0.6 MED SSL	0.002	0.001

[a] Increased survival in the control cream group compared to the no cream group is indicated by N.

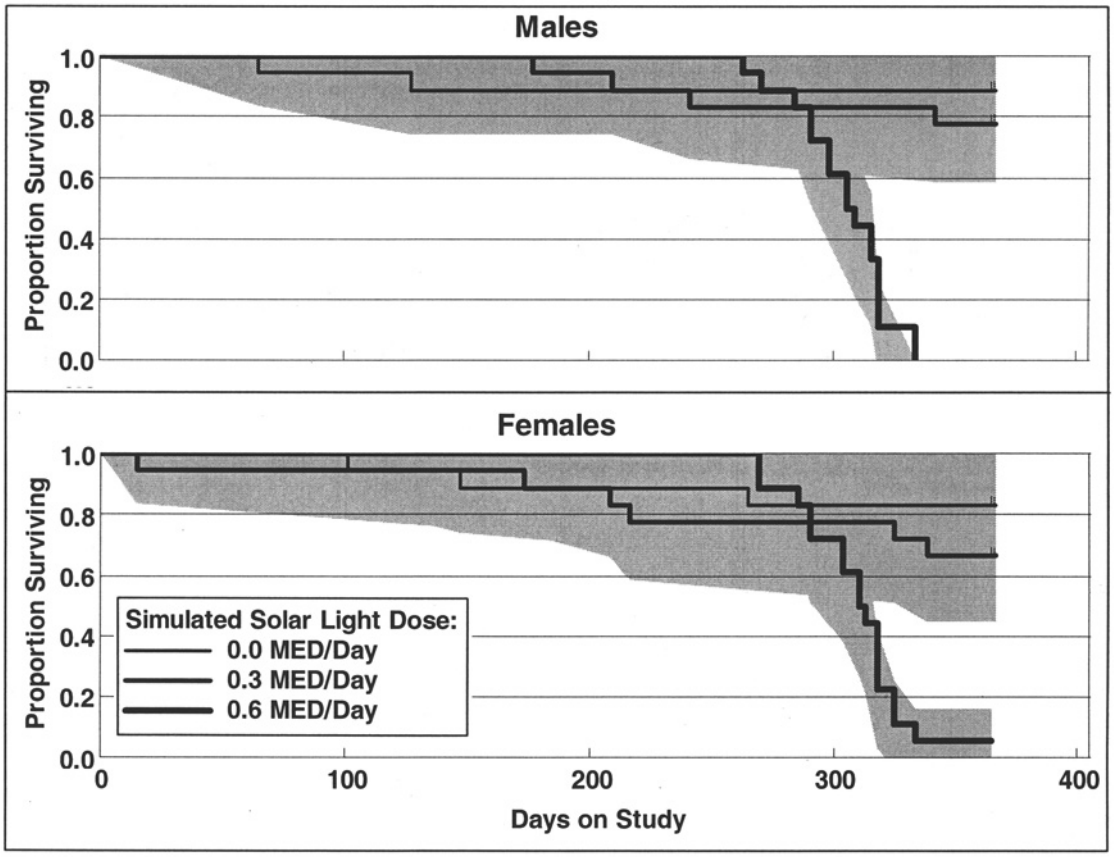


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Mice Administered Control Cream and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light (Gray area equals 95% confidence range)

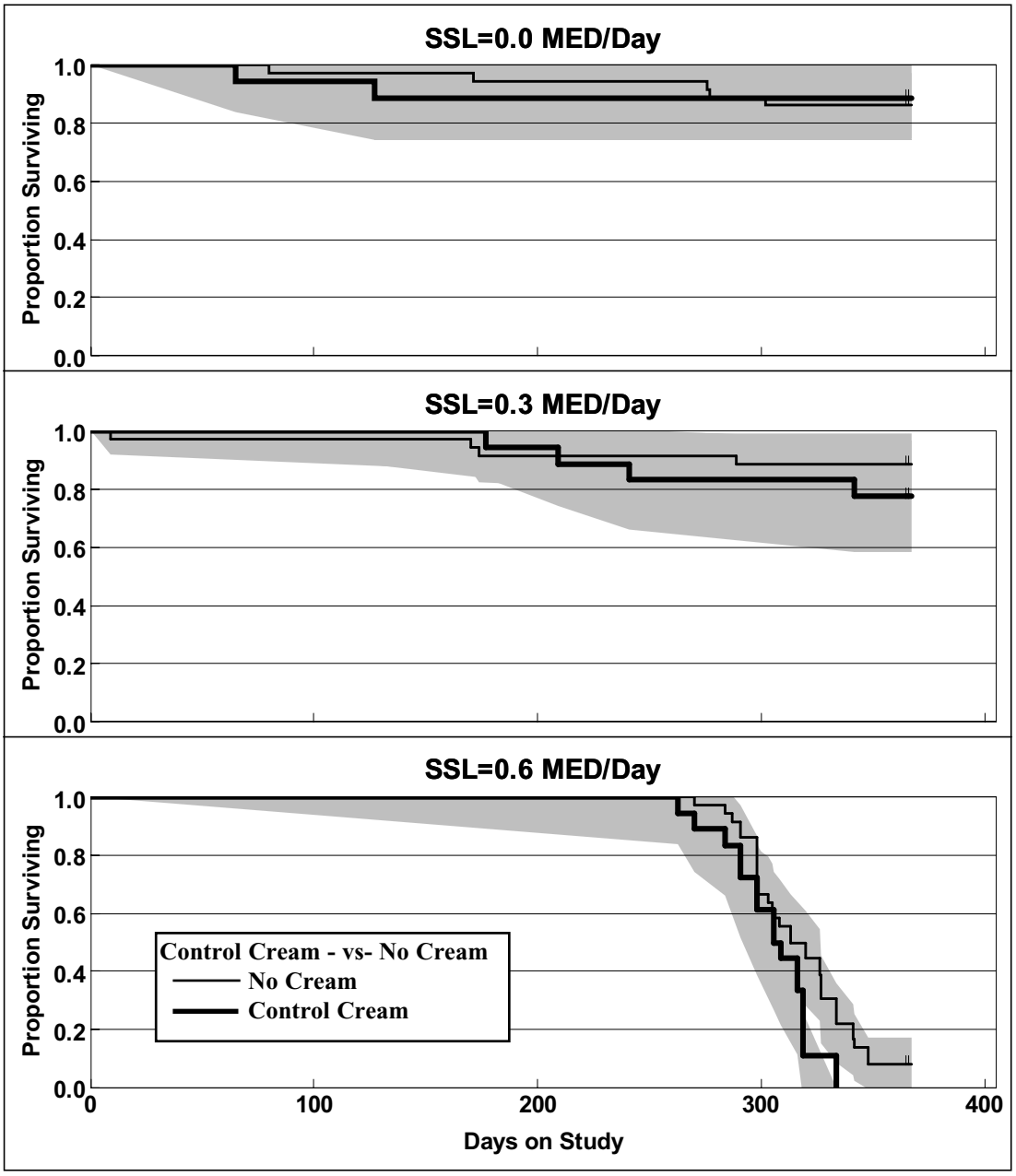


FIGURE 3
Kaplan-Meier Survival Curves for Male Mice Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light and Administered No Cream or Control Cream (Gray area equals 95% confidence range)

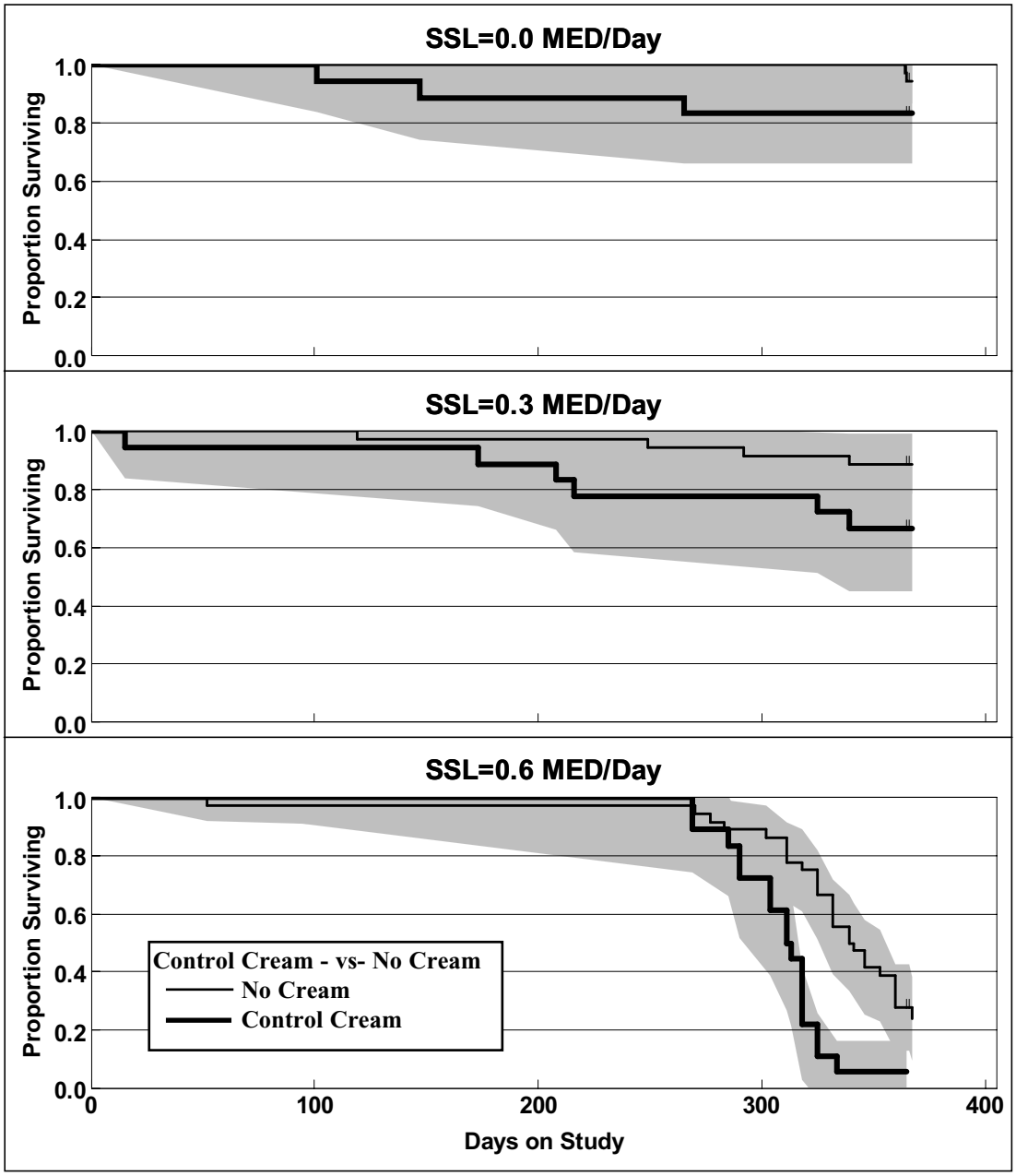


FIGURE 4
Kaplan-Meier Survival Curves for Female Mice Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light and Administered No Cream or Control Cream (Gray area equals 95% confidence range)

Survival of male and female mice that received SSL and creams containing glycolic acid is statistically summarized in Table 5 and shown in Figures 5 through 8. In male mice, a difference in survival between the 0.0 MED SSL groups and 0.3 MED SSL was detected only with cream containing 10% glycolic acid, but not with cream containing 4% glycolic acid (Table 5 and Figure 5). When cream containing 4% glycolic acid was applied to female mice, there was a significant difference in survival between the 0.0 MED SSL and 0.3 MED SSL groups. This difference between 0.0 and 0.3 MED SSL was not present when 10% glycolic acid was applied to female mice (Table 5 and Figure 6). The differences in survival between mice that received 0.0 MED SSL and those that received 0.6 MED SSL were significant regardless of the sex of the mice or the cream that was applied. This resulted in a dose-dependence of survival on SSL within each of the cream treatments.

Table 5 and Figures 7 and 8 show the analysis of the effects of doses of glycolic acid on survival at each SSL dose. In the absence of SSL, neither 4% nor 10% glycolic acid affected survival of male or female mice (Table 5 and Figures 7 and 8). In female mice exposed to 0.3 MED SSL, there was a negative dose-trend in survival (Table 5 and Figure 8). No other trends or differences were evident.

Survival of male and female mice that received SSL and creams containing salicylic acid and statistical analyses are summarized in Table 6 and shown in Figures 9 through 12. Male mice treated with 2% salicylic acid in the presence of 0.3 MED SSL had decreased survival compared to mice that were not exposed to SSL (Table 6 and Figure 9). Male and female mice exposed to 0.6 MED SSL had decreased survival compared to 0.0 MED SSL exposed mice whether they were treated with control cream, 2% salicylic acid, or 4% salicylic acid (Table 6 and Figures 9 and 10).

Male and female mice receiving either 2% or 4% salicylic acid had increased survival at 0.6 MED SSL compared to mice treated with the control cream (Table 6 and Figures 11 and 12). This difference was not significant at 0.0 or 0.3 MED SSL.

TABLE 5
Survival (P Value) of Mice in the 1-Year Simulated Solar Light Study: Glycolic Acid[a]

	Cox Proportional Hazards	Log-rank Analysis with Tarone's Trend Test
Male		
0.0 MED SSL vs. 0.3 MED SSL		
Control Cream (0% Glycolic Acid)	0.192	0.217
4% Glycolic Acid	0.346	0.347
10% Glycolic Acid	0.024	0.011
0.0 MED SSL vs. 0.6 MED SSL		
Control Cream (0% Glycolic Acid)	0.001	0.001
4% Glycolic Acid	0.001	0.001
10% Glycolic Acid	0.001	0.001
SSL Linear Trend Test		
Control Cream (0% Glycolic Acid)	0.001	0.001
4% Glycolic Acid	0.001	0.001
10% Glycolic Acid	0.001	0.001
Control Cream vs. 4% Glycolic Acid		
0.0 MED SSL	0.325	0.287N
0.3 MED SSL	0.480N	0.173
0.6 MED SSL	0.124	0.161
Control Cream vs. 10% Glycolic Acid		
0.0 MED SSL	0.270N	0.328
0.3 MED SSL	0.168	0.491N
0.6 MED SSL	0.219	0.053
Glycolic Acid Trend Test		
0.0 MED SSL	0.248N	0.272N
0.3 MED SSL	0.148	0.144
0.6 MED SSL	0.251	0.207
Female		
0.0 MED SSL vs. 0.3 MED SSL		
Control Cream (0% Glycolic Acid)	0.121	0.143
4% Glycolic Acid	0.042	0.024
10% Glycolic Acid	0.278	0.287
0.0 MED SSL vs. 0.6 MED SSL		
Control Cream (0% Glycolic Acid)	0.001	0.001
4% Glycolic Acid	0.001	0.001
10% Glycolic Acid	0.001	0.001
SSL Linear Trend Test		
Control Cream (0% Glycolic Acid)	0.001	0.001
4% Glycolic Acid	0.001	0.001
10% Glycolic Acid	0.001	0.001
Control Cream vs. 4% Glycolic Acid		
0.0 MED SSL	0.146N	0.145N
0.3 MED SSL	0.380N	0.050N
0.6 MED SSL	0.271	0.352N
Control Cream vs. 10% Glycolic Acid		
0.0 MED SSL	0.146N	0.153N
0.3 MED SSL	0.052N	0.366N
0.6 MED SSL	0.375N	0.175N
Glycolic Acid Trend Test		
0.0 MED SSL	0.172N	0.144N
0.3 MED SSL	0.050N	0.044N
0.6 MED SSL	0.398N	0.370N

[a] Increased survival in the test cream group compared to the control cream group is indicated by **N**.

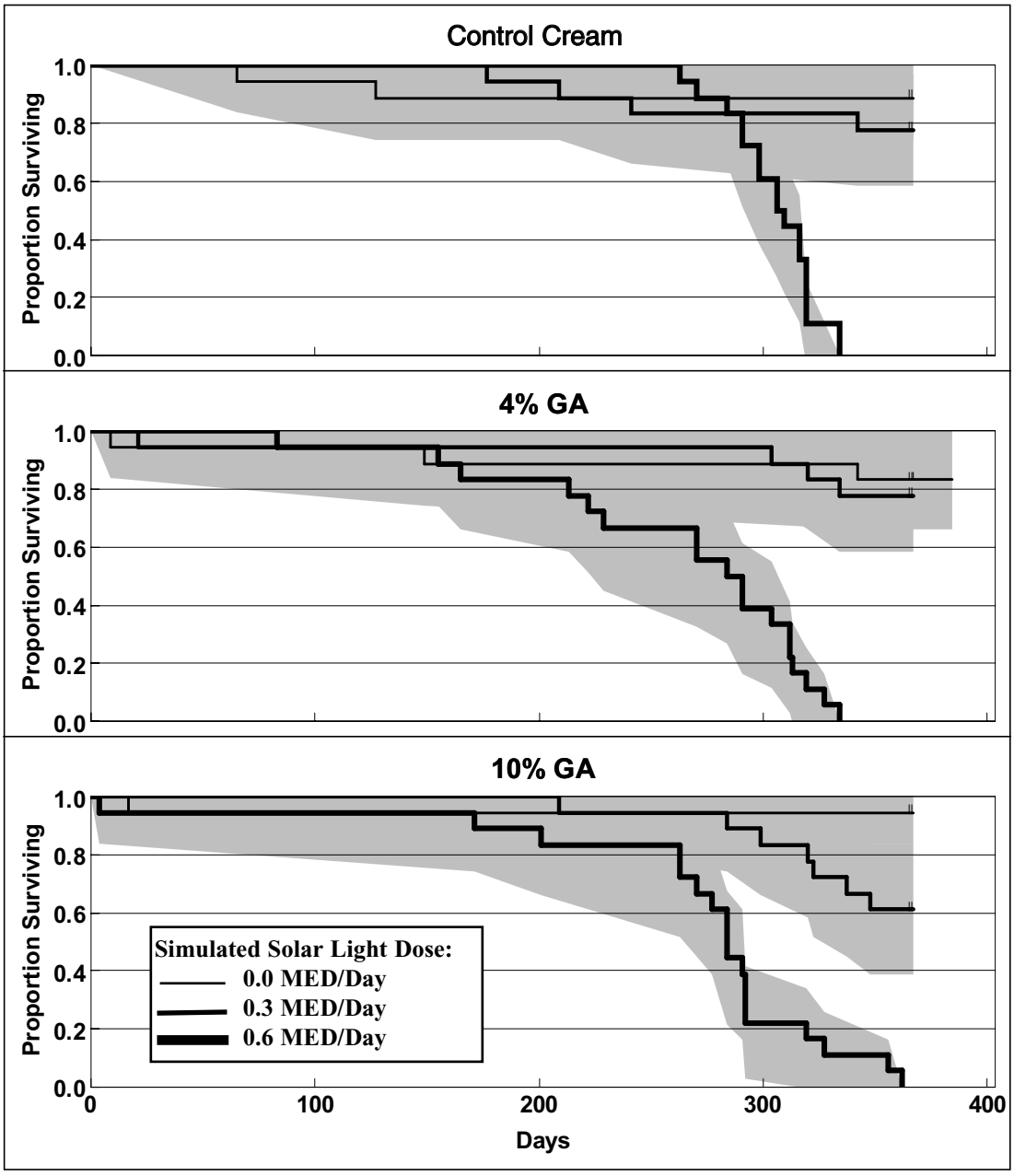


FIGURE 5
Kaplan-Meier Survival Curves for Male Mice Administered a Fixed Amount of Glycolic Acid and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light (Gray area equals 95% confidence range)

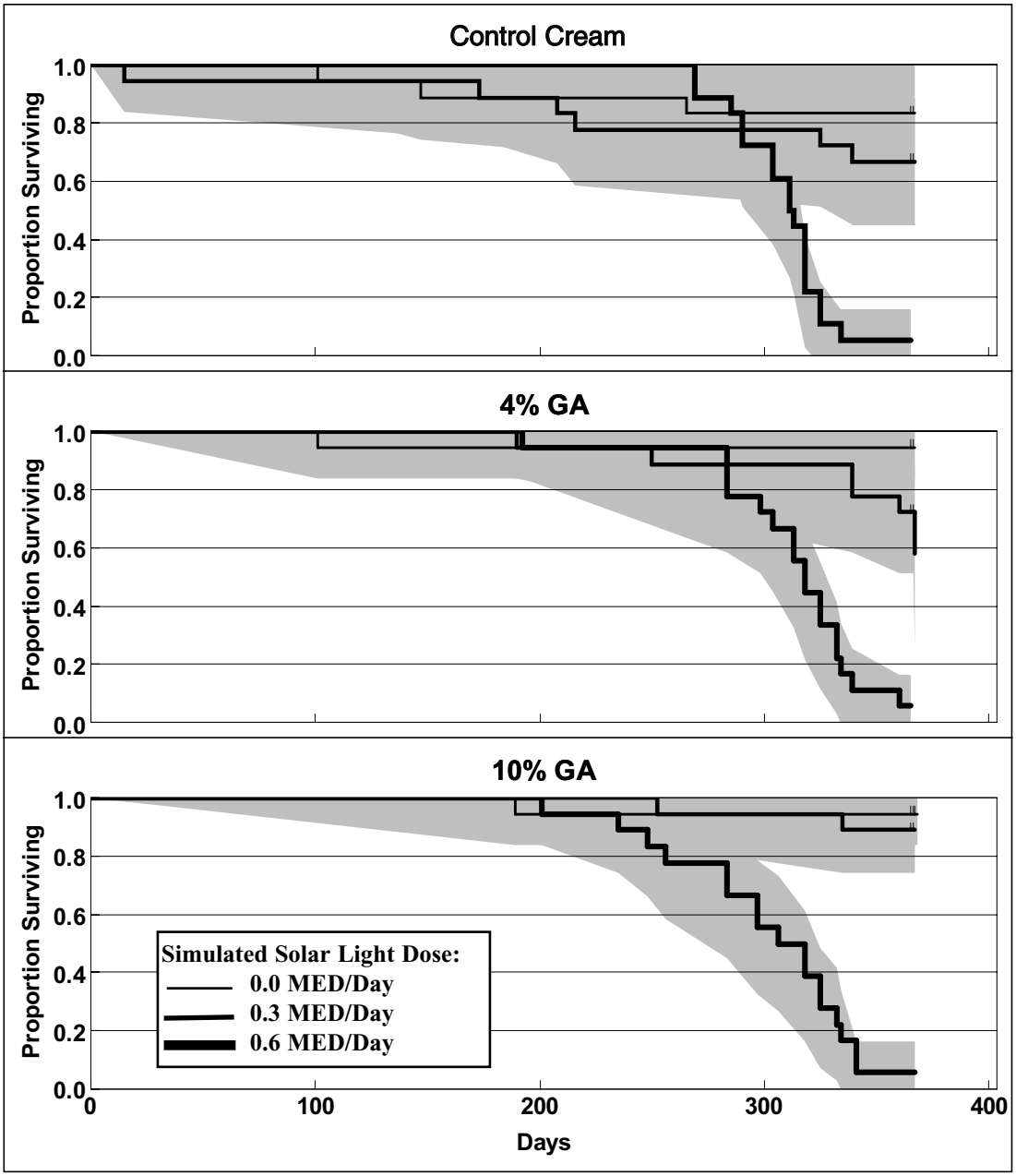


FIGURE 6
Kaplan-Meier Survival Curves for Female Mice Administered a Fixed Amount of Glycolic Acid and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light (Gray area equals 95% confidence range)

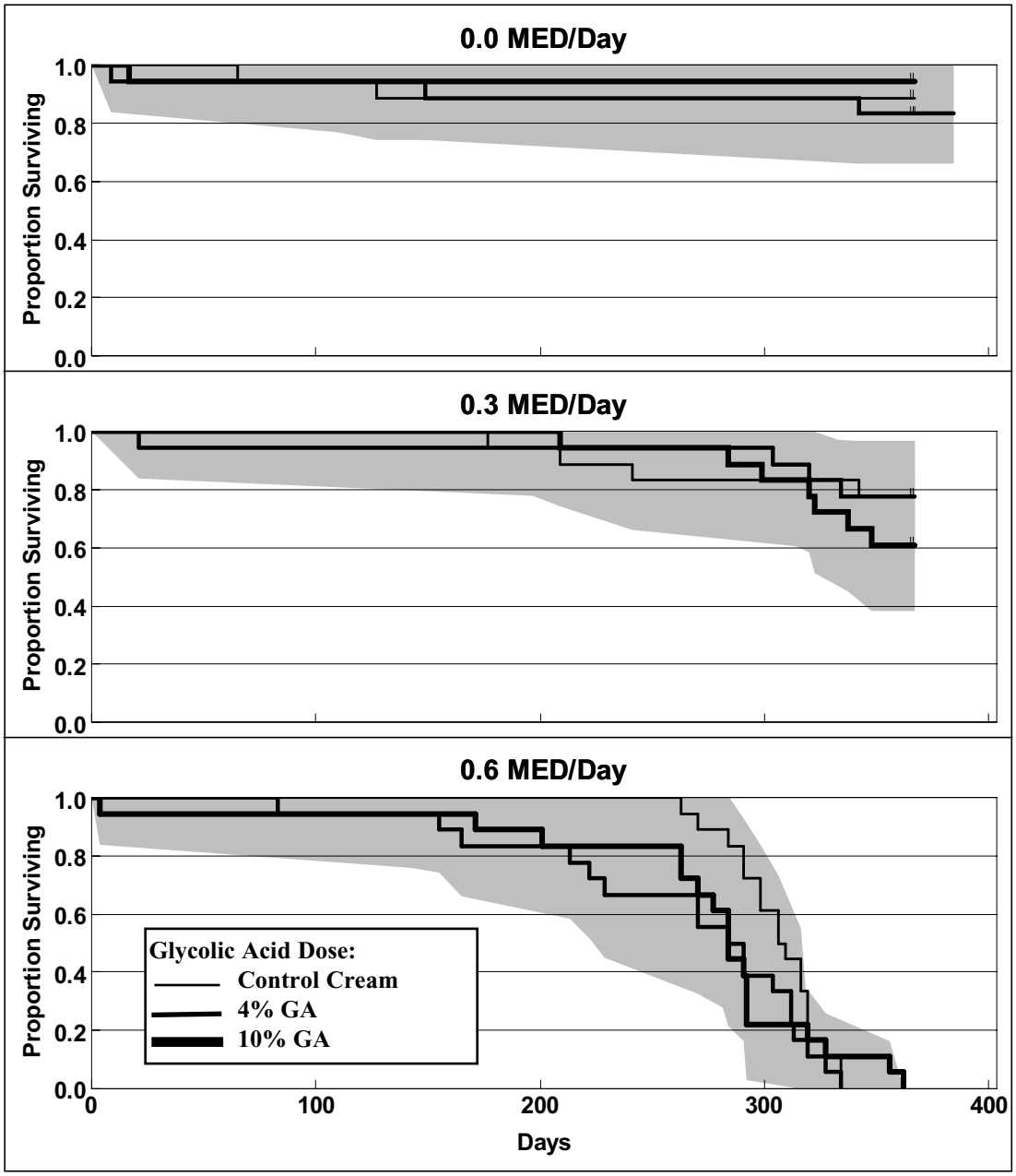


FIGURE 7
Kaplan-Meier Survival Curves for Male Mice Exposed to a Fixed Amount of Simulated Solar Light and Administered Control Cream, 4%, or 10% Glycolic Acid (Gray area equals 95% confidence range)

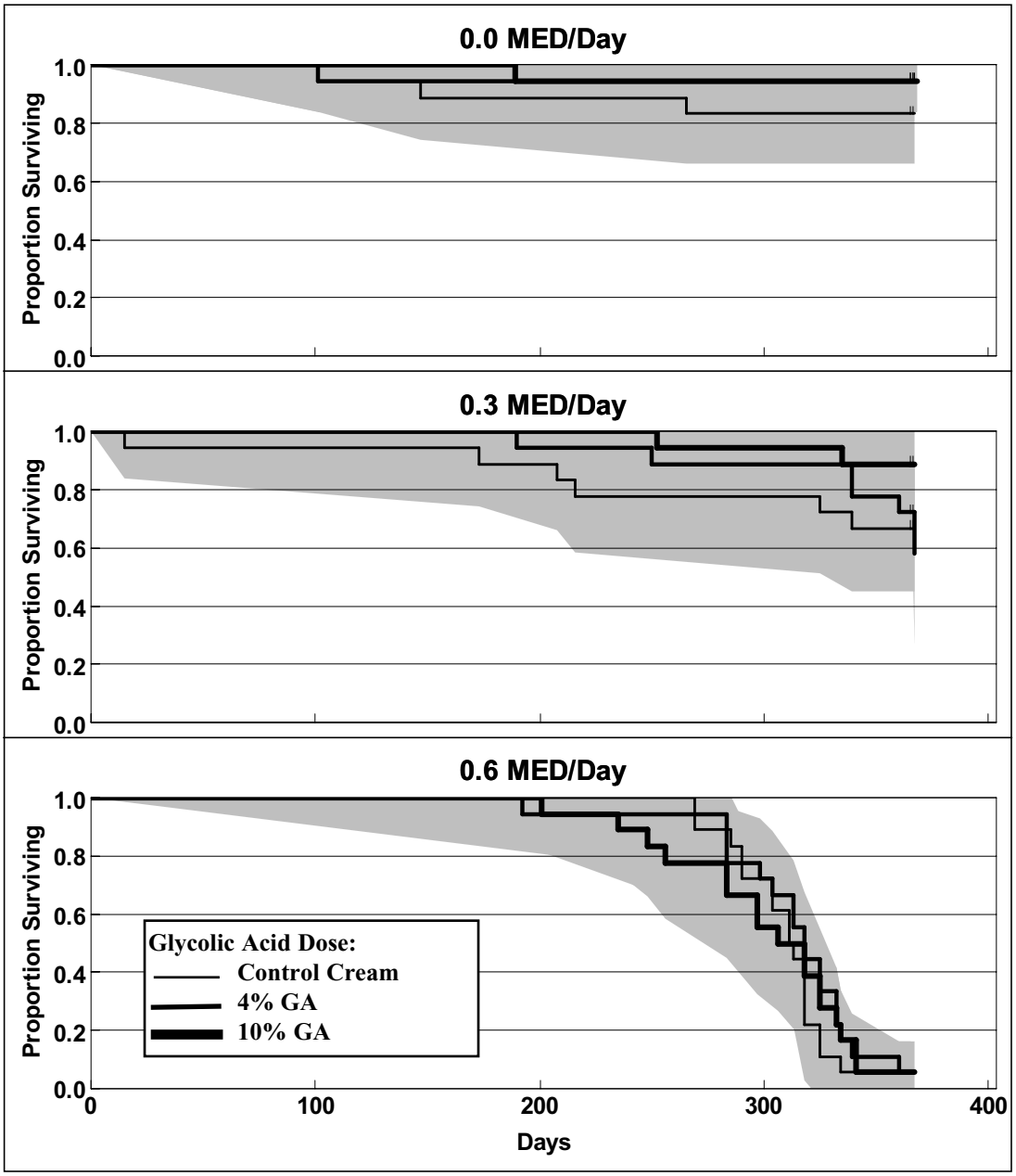


FIGURE 8
Kaplan-Meier Survival Curves for Female Mice Exposed to a Fixed Amount of Simulated Solar Light and Administered Control Cream, 4%, or 10% Glycolic Acid (Gray area equals 95% confidence range)

TABLE 6
Survival (P Value) of Mice in the 1-Year Simulated Solar Light Study: Salicylic Acid[a]

	Cox Proportional Hazards	Log-rank Analysis with Tarone's Trend Test
Male		
0.0 MED SSL vs. 0.3 MED SSL		
Control Cream (0% Salicylic Acid)	0.188	0.217
2% Salicylic Acid	0.031	0.019
4% Salicylic Acid	0.165	0.160
0.0 MED SSL vs. 0.6 MED SSL		
Control Cream (0% Salicylic Acid)	0.001	0.001
2% Salicylic Acid	0.001	0.001
4% Salicylic Acid	0.001	0.001
SSL Linear Trend Test		
Control Cream (0% Salicylic Acid)	0.001	0.001
2% Salicylic Acid	0.001	0.001
4% Salicylic Acid	0.001	0.001
Control Cream vs. 2% Salicylic Acid		
0.0 MED SSL	0.268N	0.265N
0.3 MED SSL	0.222	0.228
0.6 MED SSL	0.030N	0.005N
Control Cream vs. 4% Salicylic Acid		
0.0 MED SSL	0.269N	0.265N
0.3 MED SSL	0.301N	0.310N
0.6 MED SSL	0.011N	0.001N
Salicylic Acid Trend Test		
0.0 MED SSL	0.269N	0.253N
0.3 MED SSL	0.301N	0.322N
0.6 MED SSL	0.011N	0.001N
Female		
0.0 MED SSL vs. 0.3 MED SSL		
Control Cream (0% Salicylic Acid)	0.133	0.143
2% Salicylic Acid	0.085	0.081
4% Salicylic Acid	0.380N	0.383N
0.0 MED SSL vs. 0.6 MED SSL		
Control Cream (0% Salicylic Acid)	0.001	0.001
2% Salicylic Acid	0.004	0.001
4% Salicylic Acid	0.035	0.022
SSL Linear Trend Test		
Control Cream (0% Salicylic Acid)	0.001	0.001
2% Salicylic Acid	0.004	0.001
4% Salicylic Acid	0.035	0.019
Control Cream vs. 2% Salicylic Acid		
0.0 MED SSL	0.148N	0.152N
0.3 MED SSL	0.238N	0.246N
0.6 MED SSL	0.029N	0.004N
Control Cream vs. 4% Salicylic Acid		
0.0 MED SSL	0.377	0.366
0.3 MED SSL	0.135N	0.158N
0.6 MED SSL	0.008N	0.001N
Salicylic Acid Trend Test		
0.0 MED SSL	0.377	0.344
0.3 MED SSL	0.135N	0.149N
0.6 MED SSL	0.008N	0.001N

[a] Increased survival in the test cream group compared to the control cream group is indicated by **N**.

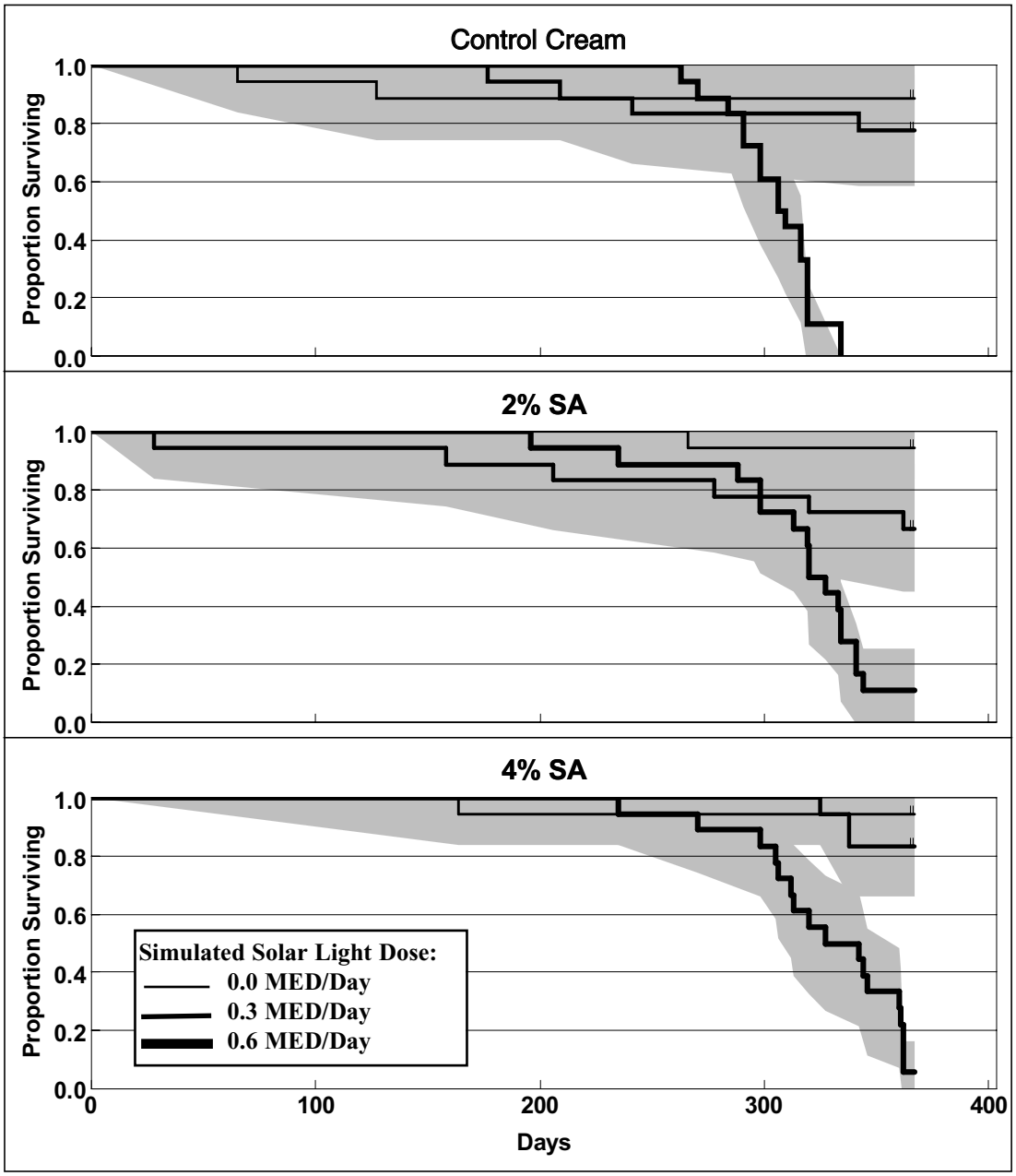


FIGURE 9
Kaplan-Meier Survival Curves for Male Mice Administered a Fixed Amount of Salicylic Acid and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light (Gray area equals 95% confidence range)

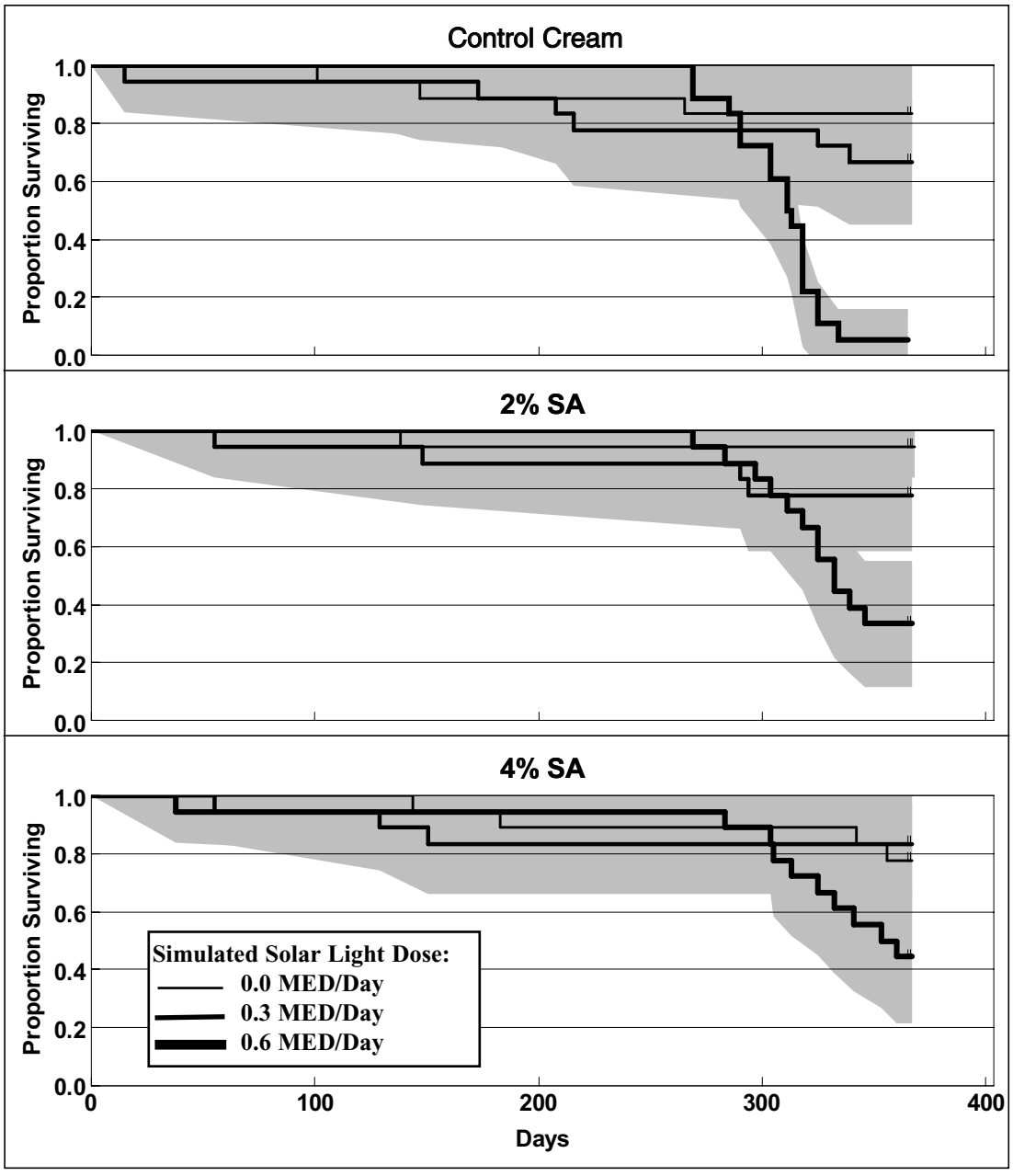


FIGURE 10
Kaplan-Meier Survival Curves for Female Mice Administered a Fixed Amount of Salicylic Acid and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light (Gray area equals 95% confidence range)

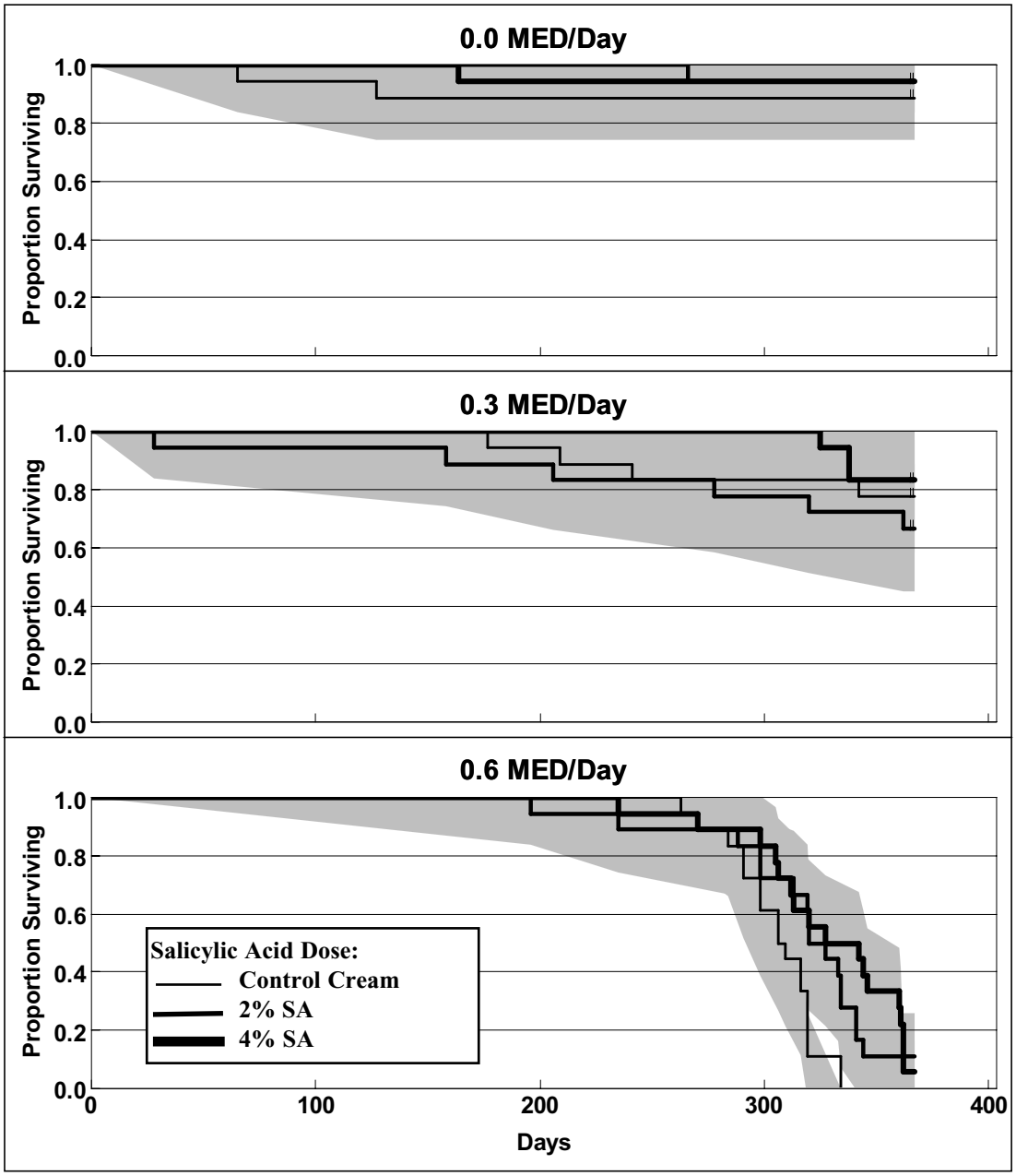


FIGURE 11
Kaplan-Meier Survival Curves for Male Mice Exposed to a Fixed Amount of Simulated Solar Light and Administered Control Cream, 2%, or 4% Salicylic Acid (Gray area equals 95% confidence range)

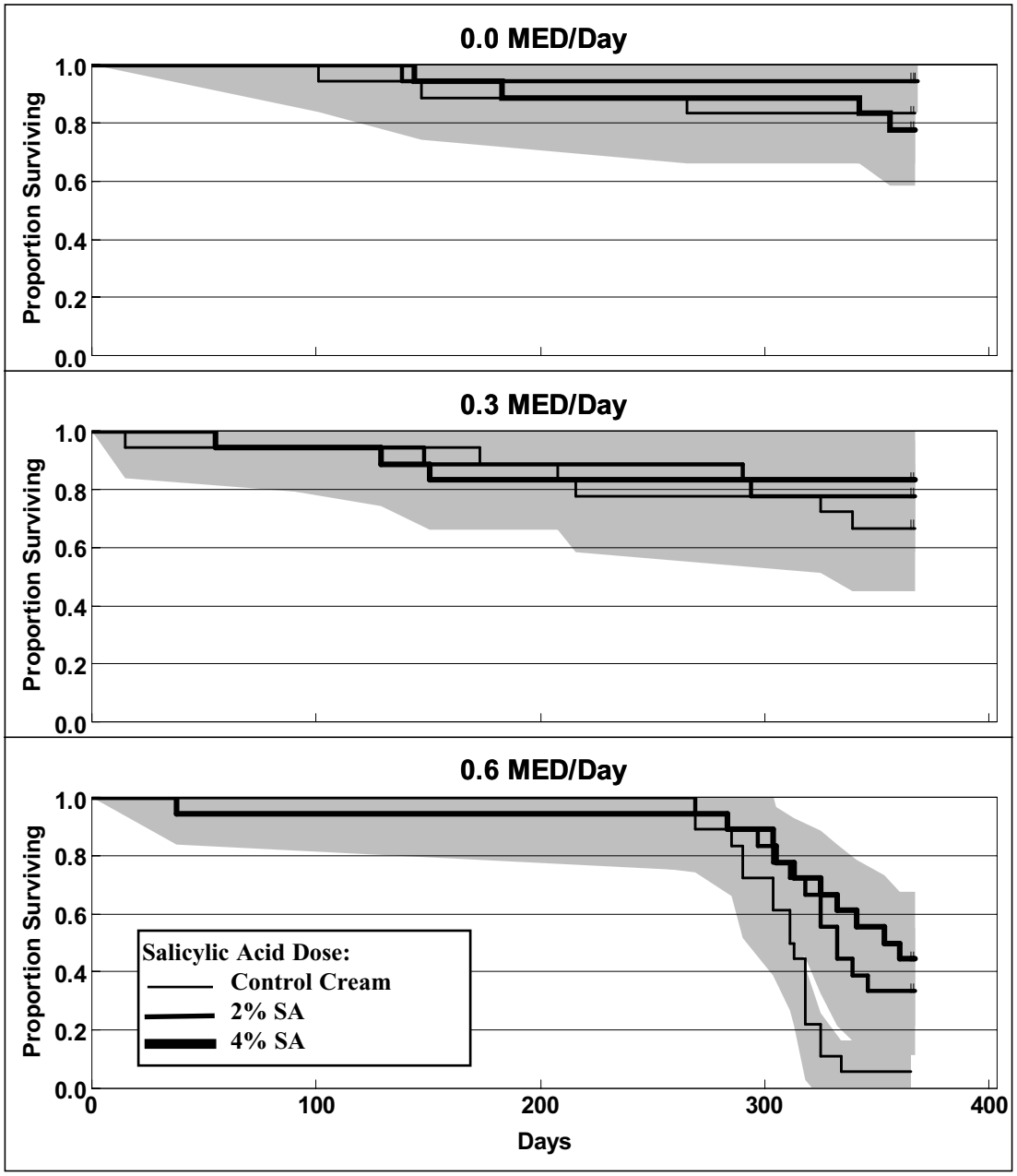


FIGURE 12
Kaplan-Meier Survival Curves for Female Mice Exposed to a Fixed Amount of Simulated Solar Light and Administered Control Cream, 2%, or 4% Salicylic Acid (Gray area equals 95% confidence range)

Body Weights and Clinical Findings

The analyses of the body weights were separated into three tests: effect of SSL exposure level on mice not treated with cream, effect of glycolic acid concentration in SSL-exposed mice, and effect of salicylic acid concentration in SSL-exposed mice. The mean body weights and survival are shown in Tables 7, 8, and 10 for males and Tables 7, 9, and 11 for females. Mean body weights of treated male and female mice were similar to controls.

TABLE 7
Mean Body Weights and Survival of Mice in the 1-Year Simulated Solar Light Study: Light Only

Weeks on Study	0.0 MED/ No Cream		0.3 MED/ No Cream			0.6 MED/ No Cream			0.9 MED/ No Cream		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
Male											
0	31.5	36	30.5	97	36	31.6	100	36	31.0	98	36
4	33.4	36	33.7	101	35	33.9	102	36	32.5	97	35
8	33.4	36	34.6	104	35	35.1	105	36	33.7	101	35
12	34.3	35	35.1	102	35	35.4	103	36	33.8	99	35
16	34.9	35	35.6	102	35	35.6	102	36	34.5	99	35
20	34.9	35	35.9	103	35	36.0	103	36	35.2	101	35
24	34.7	34	35.7	103	34	35.9	103	36	35.2	101	35
28	35.4	34	35.9	101	33	36.5	103	36	36.1	102	34
32	36.0	34	36.1	100	33	36.6	102	36	35.7	99	31
36	36.0	34	36.8	102	33	36.7	102	36	36.2	101	14
40	36.2	32	36.7	101	33	37.1	102	35	36.1	100	4
44	36.1	31	36.7	102	32	37.9	105	20	34.7	96	1
48	36.5	31	36.4	100	32	37.4	102	8			0
52	38.4	12			0			0			0
Mean	35.1		35.4	101		35.8	102		34.6	99	
Female											
0	24.7	36	24.4	99	36	24.4	99	36	24.1	98	36
4	25.9	36	26.9	104	36	26.0	100	36	26.5	102	36
8	27.3	36	27.9	102	36	27.6	101	35	26.6	97	36
12	28.4	36	28.6	101	36	28.0	99	35	27.6	97	36
16	29.0	36	28.7	99	36	28.4	98	35	29.1	100	36
20	29.3	36	29.5	101	35	28.7	98	35	29.4	100	36
24	29.6	36	29.6	100	35	29.5	100	35	29.6	100	36
28	30.0	36	30.0	100	35	29.8	99	35	30.5	102	35
32	30.2	36	30.2	100	35	30.2	100	35	31.5	104	32
36	30.6	36	30.9	101	34	31.1	102	35	31.4	103	25
40	30.9	36	30.9	100	34	31.1	101	33	31.6	102	16
44	31.4	36	31.4	100	33	31.3	100	31	31.0	99	5
48	31.8	30	31.7	100	33	32.3	102	20			0
52	32.7	23	32.3	99	20	32.4	99	6			0
Mean	29.4		29.5	100		29.3	100		29.1	100	

TABLE 8
Mean Body Weights and Survival of Male Mice in the 1-Year Simulated Solar Light Study: Glycolic Acid

Weeks on Study	Control Cream Av. Wt. (g)	Control Cream No. of Survivors	4% Glycolic Acid Cream Av. Wt. (g)	4% Glycolic Acid Cream Wt. (% of controls)[a]	4% Glycolic Acid Cream No. of Survivors	10% Glycolic Acid Cream Av. Wt. (g)	10% Glycolic Acid Cream Wt. (% of controls)[a]	10% Glycolic Acid Cream No. of Survivors
0.0 MED SSL								
0	29.8	18	29.7	100	18	30.2	101	18
4	31.0	18	30.5	98	17	33.3	107	17
8	33.4	18	33.2	99	17	33.4	100	17
12	33.1	17	33.7	102	17	34.2	103	17
16	35.3	17	35.0	99	17	35.7	101	17
20	35.4	16	34.5	98	17	35.7	101	17
24	35.0	16	35.2	101	16	36.5	104	17
28	35.4	16	35.8	101	16	37.0	105	17
32	36.0	16	36.4	101	16	37.4	104	17
36	36.6	16	36.6	100	16	38.0	104	17
40	36.6	16	36.3	101	16	37.5	103	17
44	36.4	16	36.6	101	16	37.4	103	17
48	37.1	16	36.1	97	16	37.5	101	17
52	35.8	4	37.3	104	7	37.2	104	4
Mean	34.8		34.8	100		35.8	103	
0.3 MED SSL								
0	30.9	18	31.0	100	18	31.7	103	18
4	33.4	18	32.8	98	17	34.1	102	18
8	34.8	18	34.4	99	17	35.5	102	18
12	35.8	18	35.4	99	17	36.1	101	18
16	36.3	18	36.3	100	17	36.9	102	18
20	36.7	18	36.7	100	17	37.1	101	18
24	37.0	18	37.1	100	17	37.1	100	18
28	37.1	17	37.0	100	17	37.2	100	18
32	38.0	16	37.4	98	17	38.0	100	17
36	38.0	15	38.4	101	17	38.0	100	17
40	37.8	15	38.1	101	17	36.7	97	17
44	37.7	15	37.2	99	16	37.2	99	15
48	38.1	15	37.3	98	14	37.8	99	12
52		0			0			0
Mean	36.3		36.1	99		36.4	100	
0.6 MED SSL								
0	30.1	18	31.4	104	18	30.9	103	17
4	33.1	18	34.3	104	18	33.6	102	17
8	34.0	18	34.1	100	18	35.5	104	17
12	35.5	18	34.9	98	17	35.0	99	17
16	36.4	18	36.9	101	17	36.7	101	17
20	36.3	18	36.9	102	17	37.0	102	17
24	36.8	18	37.5	102	15	36.2	98	16
28	36.5	18	37.7	103	15	36.8	101	16
32	37.6	18	38.5	102	13	37.2	99	15
36	38.6	18	38.6	100	12	37.7	98	15
40	37.9	16	37.1	98	10	37.7	100	11
44	39.3	8	37.8	96	6	35.9	91	4
48	25.7	2			0			0
52		0			0			0
Mean	35.2		36.3	103		35.9	102	

[a] Compared to the control cream group at the same SSL exposure concentration

TABLE 9
Mean Body Weights and Survival of Female Mice in the 1-Year Simulated Solar Light Study: Glycolic Acid

Weeks on Study	Control Cream Av. Wt. (g)	Control Cream No. of Survivors	4% Glycolic Acid Cream Av. Wt. (g)	4% Glycolic Acid Cream Wt. (% of controls)[a]	4% Glycolic Acid Cream No. of Survivors	10% Glycolic Acid Cream Av. Wt. (g)	10% Glycolic Acid Cream Wt. (% of controls)[a]	10% Glycolic Acid Cream No. of Survivors
0.0 MED SSL								
0	23.9	18	24.0	100	18	23.6	99	18
4	26.2	18	25.0	95	18	25.7	98	18
8	27.8	18	27.7	100	18	27.1	98	18
12	28.6	18	28.3	99	18	27.6	97	18
16	28.8	17	28.9	100	17	28.6	99	18
20	29.6	17	29.5	100	17	28.9	98	18
24	29.8	16	29.6	99	17	29.0	97	18
28	29.8	16	28.6	96	17	29.1	98	17
32	29.8	16	29.8	100	17	29.3	98	17
36	30.6	16	30.3	99	17	30.0	98	17
40	30.7	15	30.5	99	17	30.4	99	17
44	30.7	15	31.0	101	17	30.7	100	17
48	31.0	15	30.9	100	17	31.0	100	17
52	31.1	11	32.1	103	11	31.9	103	12
Mean	29.2		29.0	99		28.8	99	
0.3 MED SSL								
0	24.0	18	23.9	100	18	24.2	101	18
4	25.9	17	26.7	103	18	26.4	102	18
8	27.3	17	27.7	102	18	28.2	103	18
12	28.1	17	28.6	102	18	28.8	103	18
16	28.4	17	29.0	102	18	29.5	104	18
20	29.0	17	29.4	101	18	29.9	103	18
24	29.3	17	29.8	102	18	30.0	102	18
28	29.3	16	29.7	101	17	30.1	103	18
32	30.0	14	30.1	100	17	30.9	103	18
36	30.1	14	30.6	102	16	30.8	102	17
40	30.3	14	31.1	103	16	31.4	104	17
44	30.3	14	30.8	102	16	31.3	103	17
48	30.8	13	31.5	102	16	30.8	100	16
52	31.5	7	33.3	106	9	31.1	99	10
Mean	28.9		29.4	102		29.5	102	
0.6 MED SSL								
0	23.5	18	24.1	103	18	23.8	101	18
4	26.1	18	26.1	100	18	26.0	100	18
8	27.3	18	27.8	102	18	27.5	101	18
12	27.7	18	28.6	103	18	28.4	103	18
16	27.3	18	28.6	105	18	28.2	103	18
20	28.6	18	28.4	99	18	29.4	103	18
24	29.2	18	30.0	103	18	29.6	101	18
28	29.5	18	30.7	104	17	30.5	103	18
32	30.4	18	31.5	104	17	31.0	102	17
36	31.4	18	31.9	102	17	32.2	103	15
40	32.5	16	32.9	102	17	32.4	100	14
44	31.9	11	32.2	101	12	32.5	102	9
48	29.7	1	28.0	95	3	33.8	114	3
52		0			0			0
Mean	28.9		29.3	101		29.6	102	

[a] Compared to the control cream group at the same SSL exposure concentration

TABLE 10
Mean Body Weights and Survival of Male Mice in the 1-Year Simulated Solar Light Study: Salicylic Acid

Weeks on Study	Control Cream		2% Salicylic Acid Cream			4% Salicylic Acid Cream		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)[a]	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)[a]	No. of Survivors
0.0 MED SSL								
0	29.8	18	31.0	104	18	29.3	98	18
4	31.0	18	33.6	108	18	32.3	104	18
8	33.4	18	35.1	105	18	33.3	100	18
12	33.1	17	35.7	108	18	34.4	104	18
16	35.3	17	36.5	103	18	34.7	98	18
20	35.4	16	36.5	103	18	34.8	99	18
24	35.0	16	36.0	103	18	34.4	98	17
28	35.4	16	37.0	105	18	35.5	100	17
32	36.0	16	37.9	105	18	35.6	99	17
36	36.6	16	37.6	103	18	36.1	99	17
40	36.6	16	38.0	104	17	35.9	98	17
44	36.4	16	37.8	104	17	36.0	99	17
48	37.1	16	38.2	103	17	35.7	96	17
52	35.8	4	40.4	113	6	35.5	99	4
Mean	34.8		36.5	105		34.5	99	
0.3 MED SSL								
0	30.9	18	30.5	99	18	31.0	100	18
4	33.4	18	33.0	99	17	32.2	96	18
8	34.8	18	34.3	99	17	33.6	97	18
12	35.8	18	35.9	100	17	34.6	97	18
16	36.3	18	36.4	100	17	35.3	97	18
20	36.7	18	36.6	100	17	35.7	97	18
24	37.0	18	36.7	99	16	35.7	97	18
28	37.1	17	37.2	100	16	36.1	97	18
32	38.0	16	37.8	100	15	36.8	97	18
36	38.0	15	38.3	101	15	37.0	97	18
40	37.8	15	38.1	101	14	36.7	97	18
44	37.7	15	37.9	101	14	36.5	97	18
48	38.1	15	37.9	100	13	36.8	97	15
52		0			0			0
Mean	36.3		36.2	100		35.2	97	
0.6 MED SSL								
0	30.1	18	30.9	103	18	30.9	103	18
4	33.1	18	33.8	102	18	33.3	101	18
8	34.0	18	35.1	103	18	33.8	99	18
12	35.5	18	35.8	101	18	35.0	99	18
16	36.4	18	36.2	100	18	35.4	97	18
20	36.3	18	37.1	102	18	36.1	100	18
24	36.8	18	37.0	101	18	36.7	100	18
28	36.5	18	37.0	101	17	36.0	99	18
32	37.6	18	38.1	101	17	37.4	100	18
36	38.6	18	37.8	98	16	37.2	96	17
40	37.9	16	38.0	100	16	36.8	97	16
44	39.3	8	37.5	95	13	37.4	95	13
48		0	40.4		5	36.9		9
52		0			0			0
Mean	36.0		36.5	101		35.6	99	

[a] Compared to the control cream group at the same SSL exposure concentration

TABLE 11
Mean Body Weights and Survival of Female Mice in the 1-Year Simulated Solar Light Study: Salicylic Acid

Weeks on Study	Control Cream		2% Salicylic Acid Cream			4% Salicylic Acid Cream		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)[a]	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)[a]	No. of Survivors
0.0 MED SSL								
0	23.9	18	24.5	103	18	23.8	100	18
4	26.2	18	25.9	99	18	26.4	101	18
8	27.8	18	27.3	98	18	27.3	98	18
12	28.6	18	28.0	98	18	28.9	101	18
16	28.8	17	28.5	99	18	29.3	102	18
20	29.6	17	29.1	98	17	29.6	100	18
24	29.8	16	28.5	96	17	29.9	100	17
28	29.8	16	29.5	99	17	30.7	103	16
32	29.8	16	30.0	101	17	31.2	105	16
36	30.6	16	30.4	99	17	32.1	105	16
40	30.7	15	30.2	98	17	31.7	103	16
44	30.7	15	30.2	98	17	32.4	106	16
48	31.0	15	30.6	99	17	32.5	105	16
52	31.1	11	30.9	99	11	32.0	103	10
Mean	29.2		28.8	99		29.8	103	
0.3 MED SSL								
0	24.0	18	24.1	100	18	24.7	103	18
4	25.9	17	26.9	104	18	26.2	101	18
8	27.3	17	27.6	101	17	27.3	100	17
12	28.1	17	28.1	100	17	28.1	100	17
16	28.4	17	28.8	101	17	28.6	101	17
20	29.0	17	29.1	100	17	29.1	100	16
24	29.3	17	29.1	99	16	28.9	99	15
28	29.3	16	29.9	102	16	29.5	101	15
32	30.0	14	30.2	101	16	30.2	101	15
36	30.1	14	30.6	102	16	30.3	101	15
40	30.3	14	30.9	102	16	30.6	101	15
44	30.3	14	31.6	104	14	30.9	102	15
48	30.8	13	31.6	103	14	31.1	101	15
52	31.5	7	32.1	102	10	31.9	101	9
Mean	28.9		29.3	101		29.1	101	
0.6 MED SSL								
0	23.5	18	23.4	100	18	24.0	102	18
4	26.1	18	26.1	100	18	26.2	100	18
8	27.3	18	27.4	100	18	27.2	100	17
12	27.7	18	28.2	102	18	28.3	102	17
16	27.3	18	28.2	103	18	28.9	106	17
20	28.6	18	29.1	102	18	29.1	102	17
24	29.2	18	29.4	101	18	29.6	101	17
28	29.5	18	30.0	102	18	30.0	102	17
32	30.4	18	30.6	101	18	30.5	100	17
36	31.4	18	30.7	98	18	31.4	100	17
40	32.5	16	31.5	97	17	31.6	97	17
44	31.9	11	32.1	101	14	32.0	100	14
48	29.7	1	32.8	110	8	32.9	111	11
52		0	32.4		2	29.7		1
Mean	28.9		29.4	101		29.4	102	

[a] Compared to the control cream group at the same SSL exposure concentration

The occurrence of skin lesions that are consistent with formation and progression to skin tumors was recorded in the NCTR Multi-Gen Animal Tracking Database. The incidences of the lesions of at least 1 mm were analyzed using log-rank and Tarone's trend tests (Table 12) to determine if differences in onset of lesions of at least 1 mm occurred between groups and are plotted as Kaplan-Meier distributions in Figures 13 through 23.

The empirical Kaplan-Meier distributions of occurrence of skin lesions of at least 1 mm in male and female mice that received SSL only (0.0, 0.3, 0.6, or 0.9 MED) are shown in Figure 13. In male mice, a dose response was apparent with median time to tumor of greater than 53 weeks for 0.3 MED SSL, 35.5 weeks for 0.6 MED SSL, and 24 weeks for 0.9 MED SSL (Table 12). Similarly, in female mice, the median time to tumor decreased from greater than 53 weeks with 0.3 MED, to 33 weeks with 0.6 MED, and 24 weeks with 0.9 MED SSL.

The effect of topical application of control cream on the incidences of skin lesions in male mice exposed to SSL is shown in Figure 14. Increasing the dose of SSL resulted in decreased time to tumor in male mice treated with control cream (Table 12; Figure 14). Treatment with cream also resulted in a significant decrease in time to tumor in male mice exposed to 0.3 or 0.6 MED SSL compared to male mice not treated with cream (Table 12; Figure 14). This effect did not occur in mice receiving 0.0 MED SSL.

Figures 15 and 16 show the effects of topical application of glycolic acid on the SSL-induced skin tumor incidence in male mice. There was an SSL dose-response in time to tumor in the male mice within each of the treatment groups (control cream; 4% glycolic acid; and 10% glycolic acid; Table 12; Figure 15). The effect of glycolic acid dose on the induction of skin tumors at each exposure concentration of SSL is shown in Figure 16, and while neither the 4% nor 10% gylcolic acid group was different than the control groups, there was a glycolic acid trend effect at 0.3 MED SSL but not at 0.6 MED SSL (Table 12). Analysis of the tumor multiplicity (Appendix H) revealed that glycolic acid did not have a dose-trend effect on tumor multiplicity at 0.3 or 0.6 MED SSL, and significance was only seen in the 4% glycolic acid at 0.3 MED SSL group. Overall, the data suggest a lack of consistent effect of glycolic acid in male mice.

The effect of application of salicylic acid on the onset of tumors in male mice is shown in Figures 17 and 18. The induction of tumors was SSL dose-dependent in each of the salicylic acid treatment groups (Table 12; Figure 18), with an increase in SSL resulting in a decrease in time to tumor. The application of salicylic acid resulted in a significant dose-dependent increase in time to tumor in male mice exposed to 0.3 or 0.6 MED SSL (Table 12; Figure 17), with the difference at 4% salicylic acid being significant. There was a salicylic acid trend effect at 0.3 and 0.6 MED SSL (Table 12). This effect did not occur in male mice exposed to 0.0 MED SSL. Analysis of the tumor multiplicity in male mice treated with salicylic acid (Appendix H) revealed that 2% and 4% salicylic acid decreased tumor multiplicity at 0.3 MED SSL, but did not affect multiplicity at 0.6 MED SSL. A negative dose-trend was present at 0.3 MED SSL

The effect of the topical application of control cream on the occurrence of skin lesions in female mice exposed to SSL is shown in Figure 19. At 0.3 MED SSL, the application of control cream decreased the time for onset of lesions of at least 1 mm in female mice (Table 12) from greater than 53 weeks to 38 weeks. At 0.6 MED SSL, a similar trend occurred with the control cream significantly reducing the median onset of time to tumor from 33 weeks to 28 weeks, a difference that was significant.

Figures 20 and 21 show the effects of topical application of glycolic acid on the occurrence of skin lesions in female mice. The median time to tumor incidence was not significantly affected by 4% or 10% glycolic acid at either 0.3 or 0.6 MED SSL. At both doses of glycolic acid, increasing SSL level resulted in a decreased time to tumor occurrence in female mice. Glycolic acid did not affect the tumor multiplicity in female mice exposed to 0.3 or 0.6 MED SSL (Appendix H).

The incidences of lesions of at least 1 mm in female mice treated with control cream or creams containing 2% or 4% salicylic acid are shown in Figures 22 and 23, and the results of the statistical analyses are summarized in Table 12. In female mice exposed to 0.3 MED SSL, the application of salicylic acid resulted in a significant dose-related increase in the median time to tumor, with the increase being significant at 4% salicylic acid. This led to a salicylic acid dose trend in the 0.3 MED SSL dosed female mice; this effect was not observed at 0.6 MED SSL. Salicyclic acid at 4% decreased tumor multiplicity in female mice at 0.3 and 0.6 MED SSL, and a negative dose-trend was indicated for salicylic acid effects at 0.3 and 0.6 MED SSL (Appendix H).

TABLE 12
Time to Skin Tumor Analysis for Mice Receiving Simulated Solar Light

	Group Mean Time to Tumor of at least 1 mm (weeks)	P Value	Group Median Time to Tumor of at least 1 mm (weeks) [95% confidence interval]
Male			
0.3 MED SSL			
No Cream	48.6 ± 1.3		> 53.0 [>53.0 to >53.0]
Control Cream	34.9 ± 2.0	P=0.001[a]	36.0 [29.0 to 41.0]
4% Glycolic Acid	36.6 ± 1.3	P=0.467N[b]	37.0 [33.0 to 39.0]
10% Glycolic Acid	31.8 ± 1.4	P=0.061[b]	30.5 [27.0 to 37.0]
Glycolic Acid Trend		P=0.034	
2% Salicylic Acid	33.4 ± 2.1	P=0.126N[b]	39.0 [26.0 to >53.0]
4% Salicylic Acid	41.1 ± 3.0	P=0.003N[b]	50.0 [35.0 to >53.0]
Salicylic Acid Trend		P=0.008N	
0.6 MED SSL			
No Cream	34.8 ± 1.0		35.5 [32.0 to 37.0]
Control Cream	26.1 ± 1.0	P=0.001[a]	26.0 [23.0 to 28.0]
4% Glycolic Acid	24.5 ± 0.7	P=0.067[b]	24.0 [24.0 to 26.0]
10% Glycolic Acid	26.3 ± 1.0	P=0.405N[b]	26.0 [24.0 to 27.0]
Glycolic Acid Trend		P=0.357N	
2% Salicylic Acid	26.7 ± 1.0	P=0.335N[b]	26.5 [24.0 to 29.0]
4% Salicylic Acid	30.3 ± 1.5	P=0.008N[b]	30.0 [27.0 to 33.0]
Salicylic Acid Trend		P=0.005N	
0.9 MED SSL			
No Cream	24.4 ± 0.4		24.0 [23.0 to 25.0]
Female			
0.3 MED SSL			
No Cream	48.2 ± 1.3		>53.0 [>47.0 to >53.0]
Control Cream	37.2 ± 2.3	P=0.001[a]	38.0 [30.0 to 46.0]
4% Glycolic Acid	37.8 ± 2.3	P=0.373[b]	38.0 [35.0 to 37.0]
10% Glycolic Acid	44.2 ± 1.7	P=0.085N[b]	47.0 [37.0 to 48.0]
Glycolic Acid Trend		P=0.074N	
2% Salicylic Acid	41.5 ± 2.2	P=0.128N[b]	43.0 [38.0 to 50.0]
4% Salicylic Acid	48.9 ± 1.6	P=0.002N[b]	53.0 [43.0 to >53.0]
Salicylic Acid Trend		P=0.001N	
0.6 MED SSL			
No Cream	33.7 ± 0.9		33.0 [33.0 to 37.0]
Control Cream	28.7 ± 1.5	P=0.005[a]	28.0 [23.0 to 34.0]
4% Glycolic Acid	27.6 ± 1.4	P=0.393[b]	25.5 [23.0 to 29.0]
10% Glycolic Acid	28.1 ± 1.1	P=0.208[b]	27.5 [26.0 to 29.0]
Glycolic Acid Trend		P=0.265	
2% Salicylic Acid	31.1 ± 1.3	P=0.254N[b]	32.5 [28.0 to 34.0]
4% Salicylic Acid	32.1 ± 1.5	P=0.102N[b]	32.0 [27.0 to 36.0]
Salicylic Acid Trend		P=0.104N	
0.9 MED SSL			
No Cream	25.0 ± 0.4		24.0 [24.0 to 26.0]

[a] Comparison of No Cream to Control Cream
[b] Comparison to Control Cream. Increased time to tumor in the test cream group compared to the control cream group is indicated by **N**.

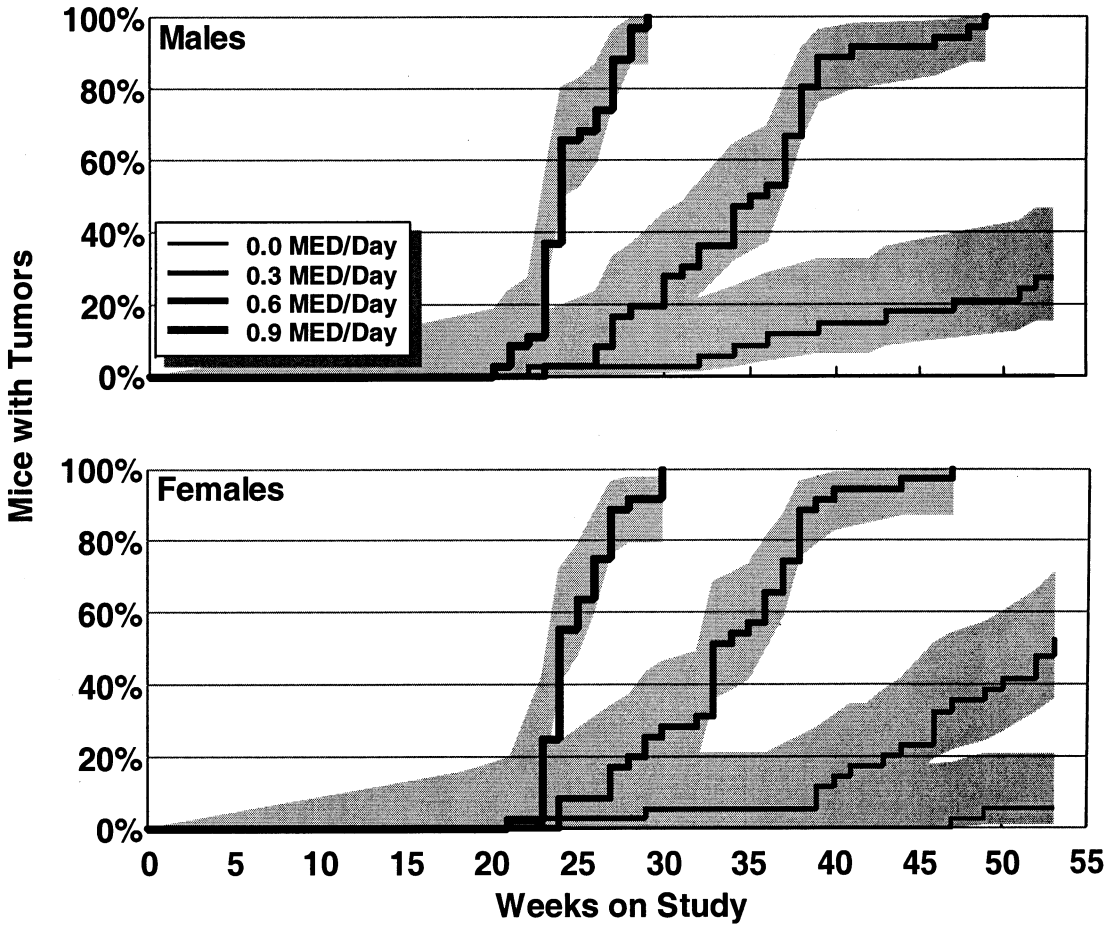


FIGURE 13
Time to Development of at Least 1 mm Skin Tumors in Mice Not Treated with Cream and Exposed to 0.0, 0.3, 0.6, or 0.9 MED Simulated Solar Light
(Gray area equals 95% confidence range)

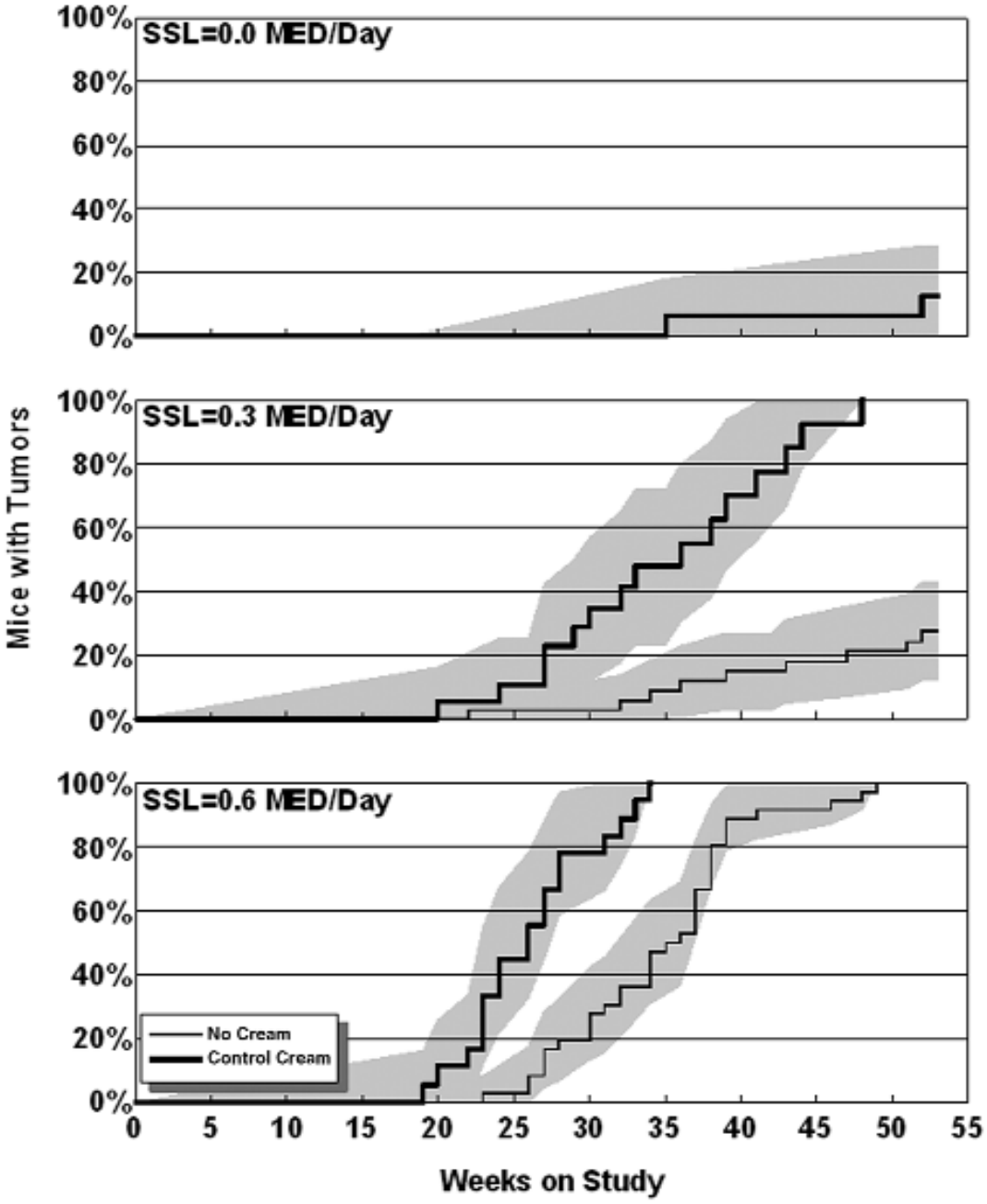


FIGURE 14
Time to Development of at Least 1 mm Skin Tumors in Male Mice Administered No Cream or Control Cream and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light
(Gray area equals 95% confidence range)

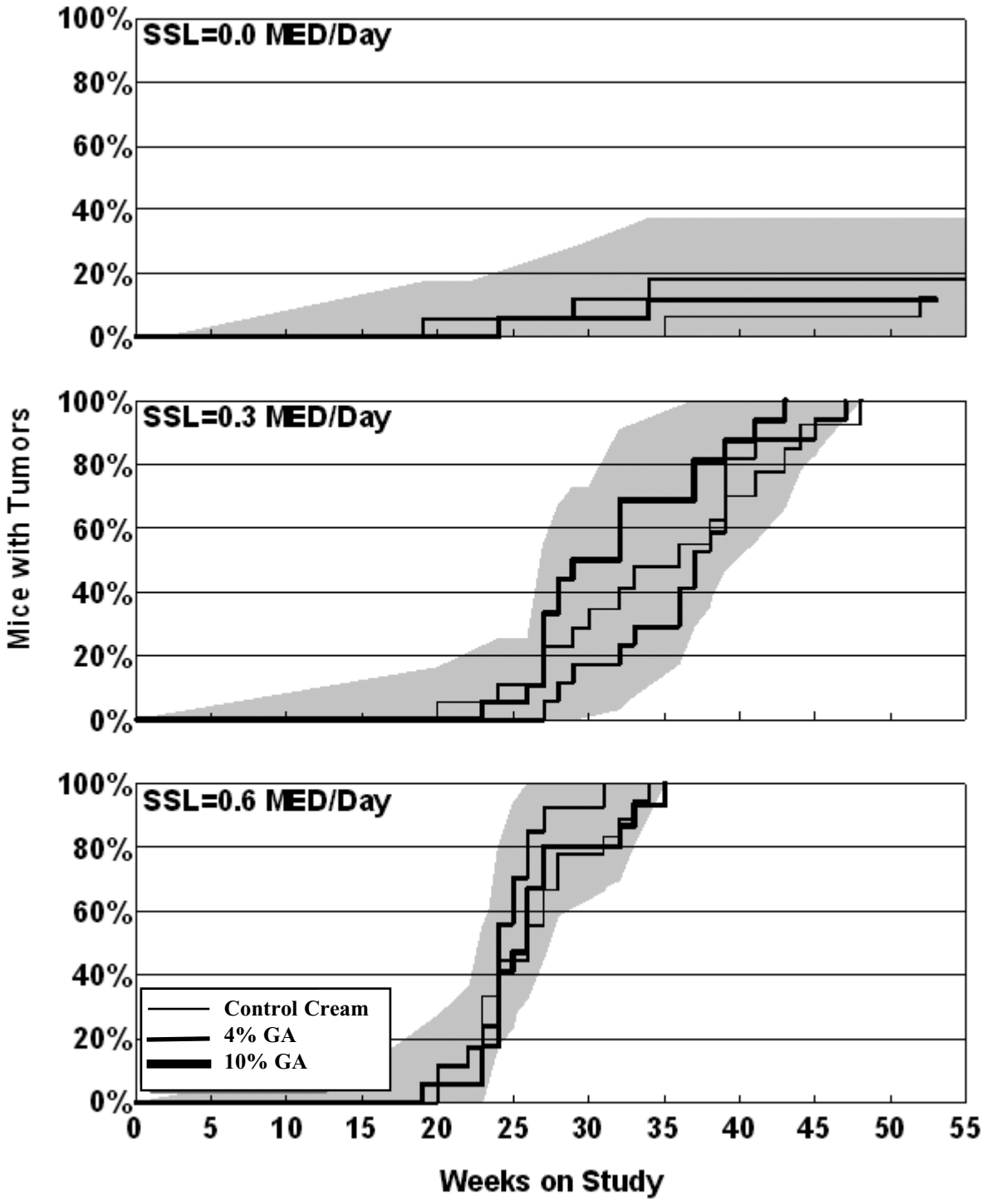


FIGURE 15
Time to Development of at Least 1 mm Skin Tumors in Male Mice Exposed to a Fixed Amount of Simulated Solar Light and Administered Control Cream, 4%, or 10% Glycolic Acid
(Gray area equals 95% confidence range)

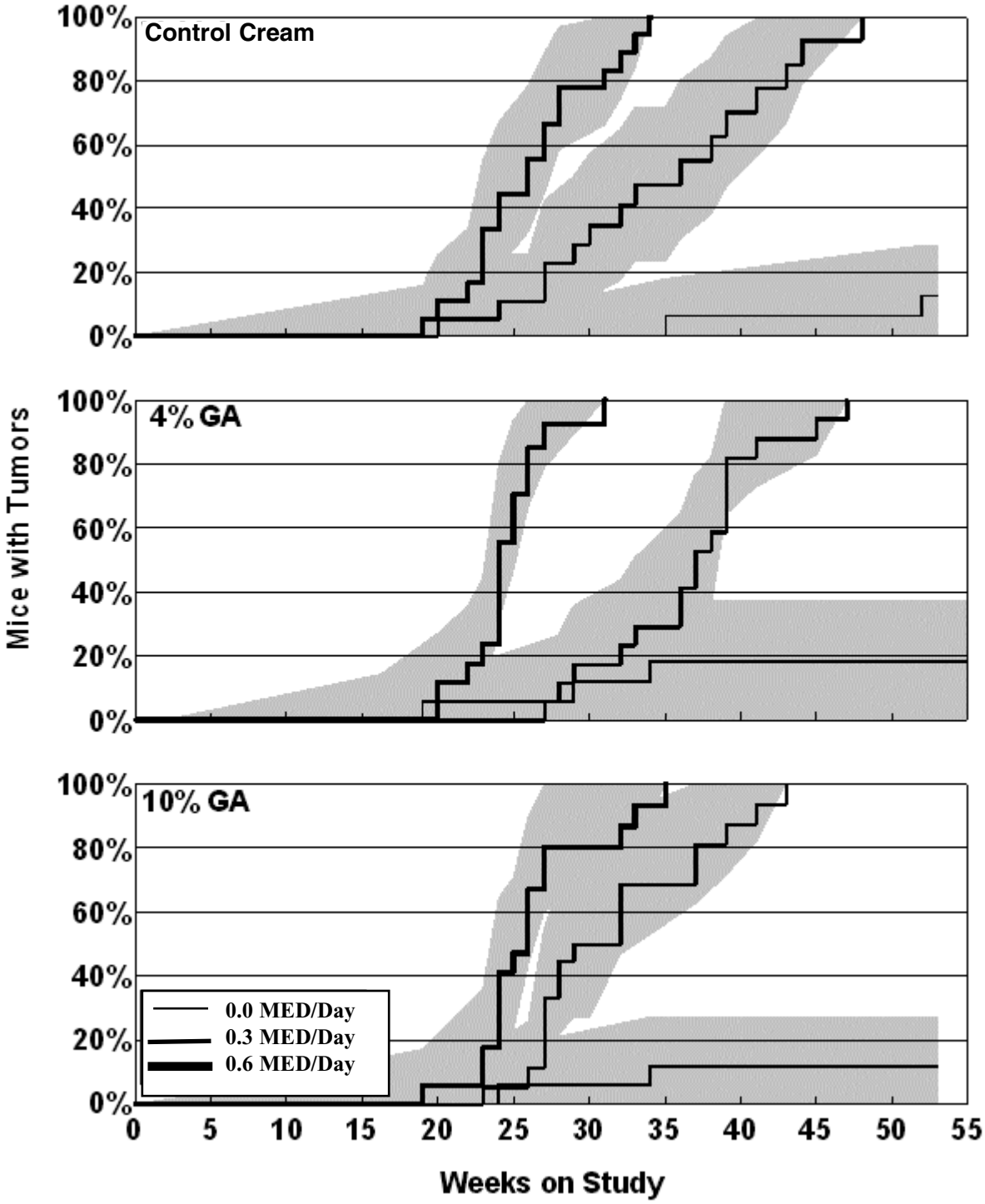


FIGURE 16
Time to Development of at Least 1 mm Skin Tumors in Male Mice Administered a Fixed Amount of Glycolic Acid and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light
(Gray area equals 95% confidence range)

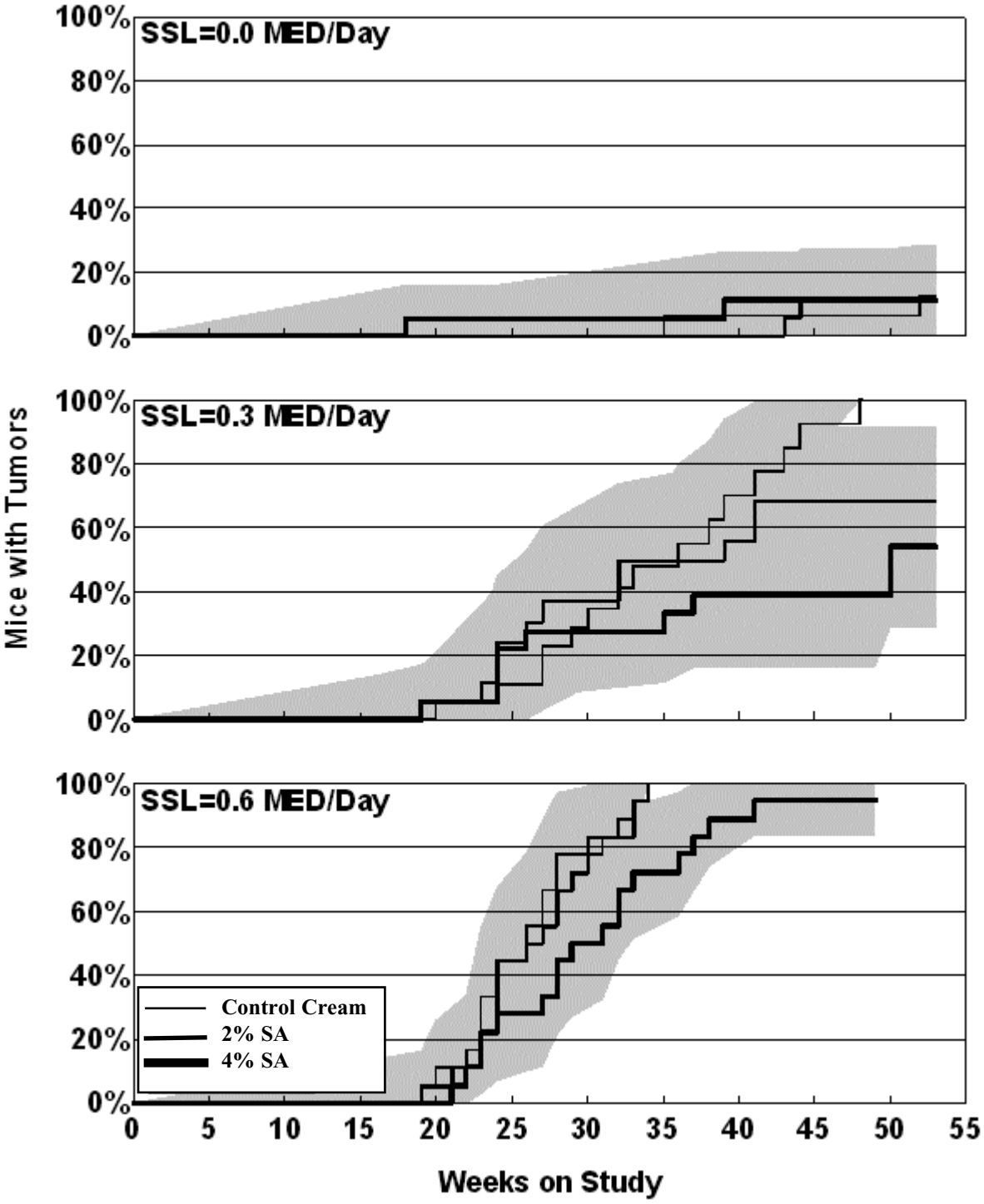


FIGURE 17
Time to Development of at Least 1 mm Skin Tumors in Male Mice Exposed to a Fixed Amount of Simulated Solar Light and Administered Control Cream, 2%, or 4% Salicylic Acid
(Gray area equals 95% confidence range)

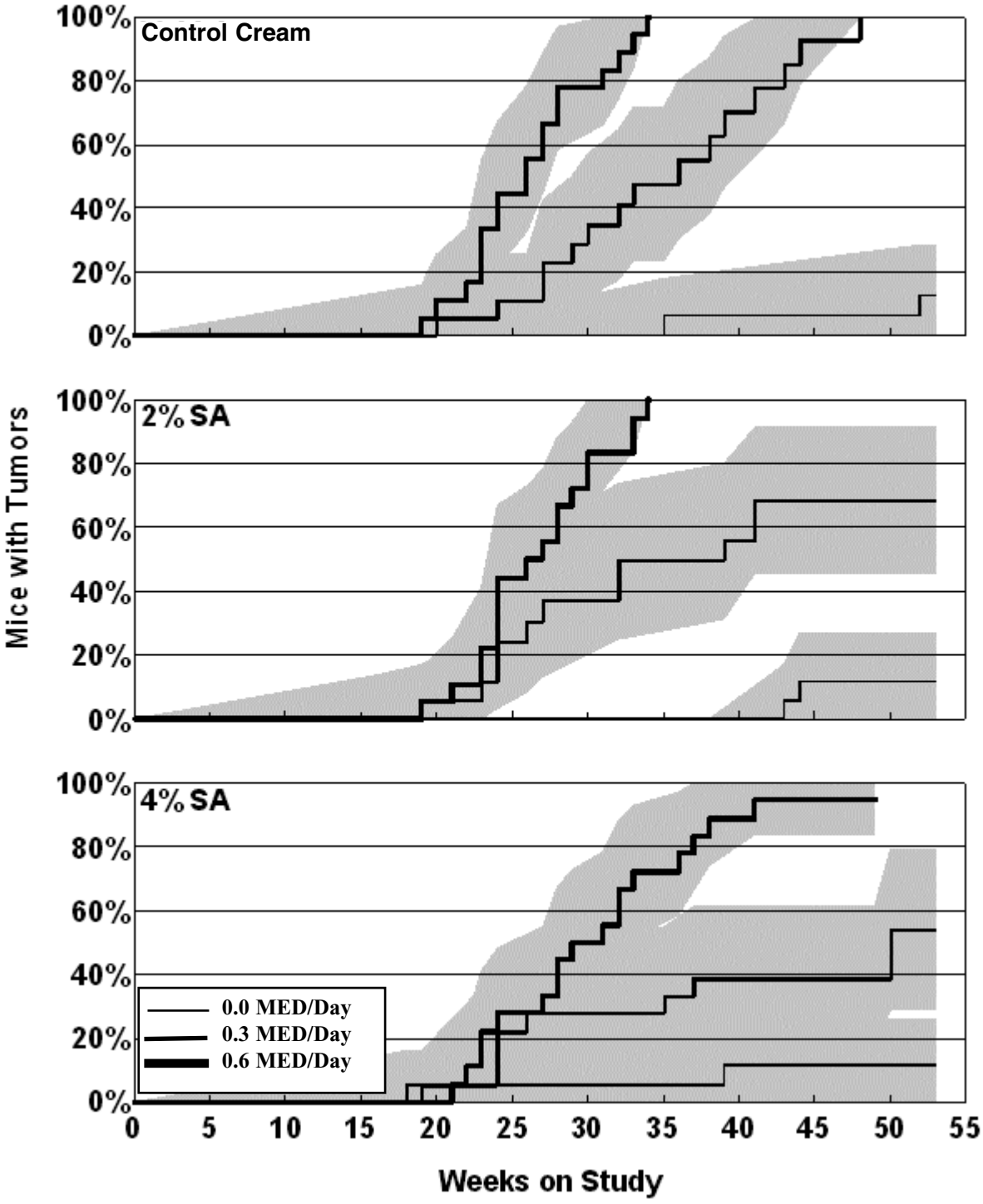


FIGURE 18
Time to Development of at Least 1 mm Skin Tumors in Male Mice Administered a Fixed Amount of Salicylic Acid and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light
(Gray area equals 95% confidence range)

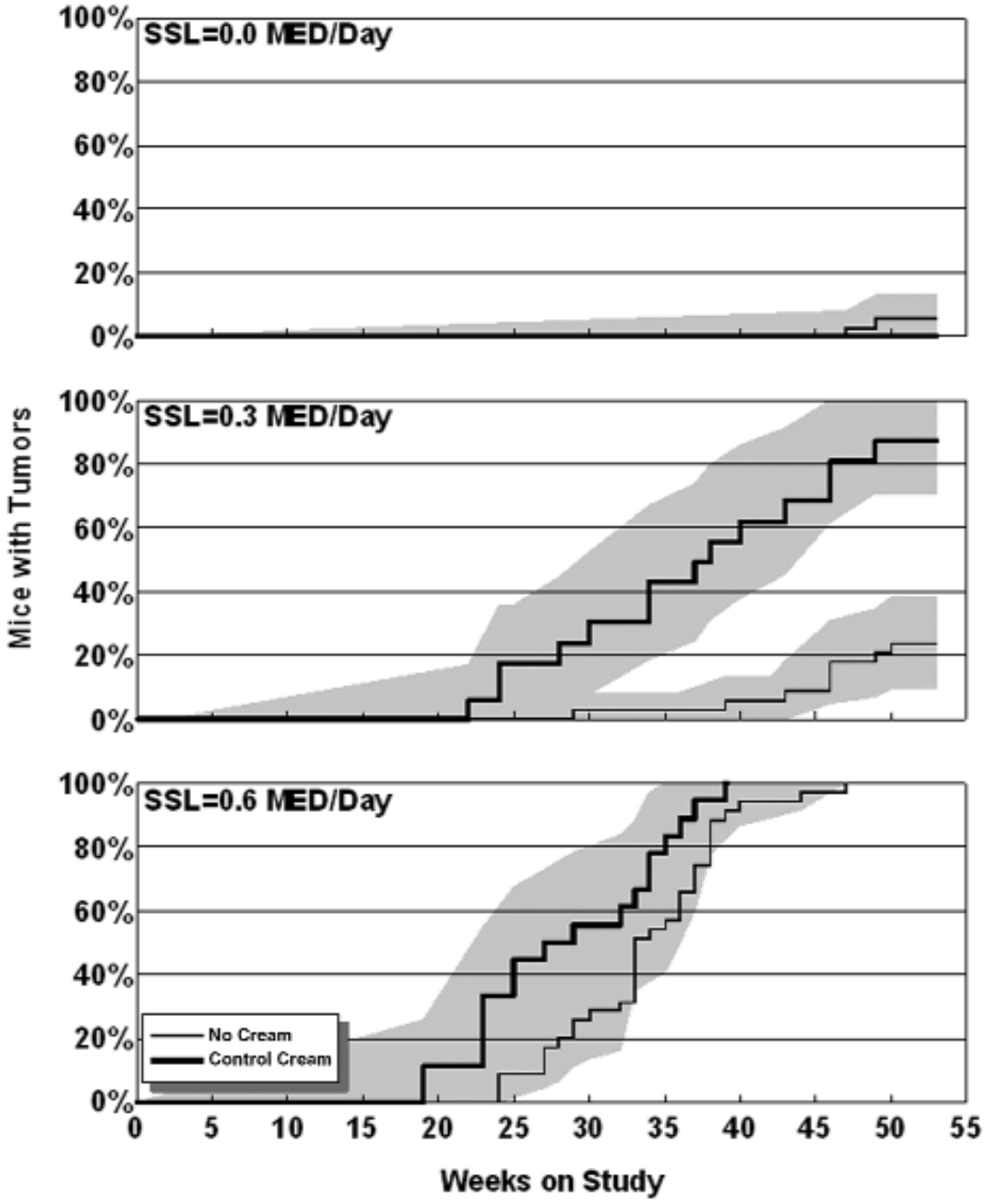


FIGURE 19
Time to Development of at Least 1 mm Skin Tumors in Female Mice Administered No Cream or Control Cream and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light
(Gray area equals 95% confidence range)

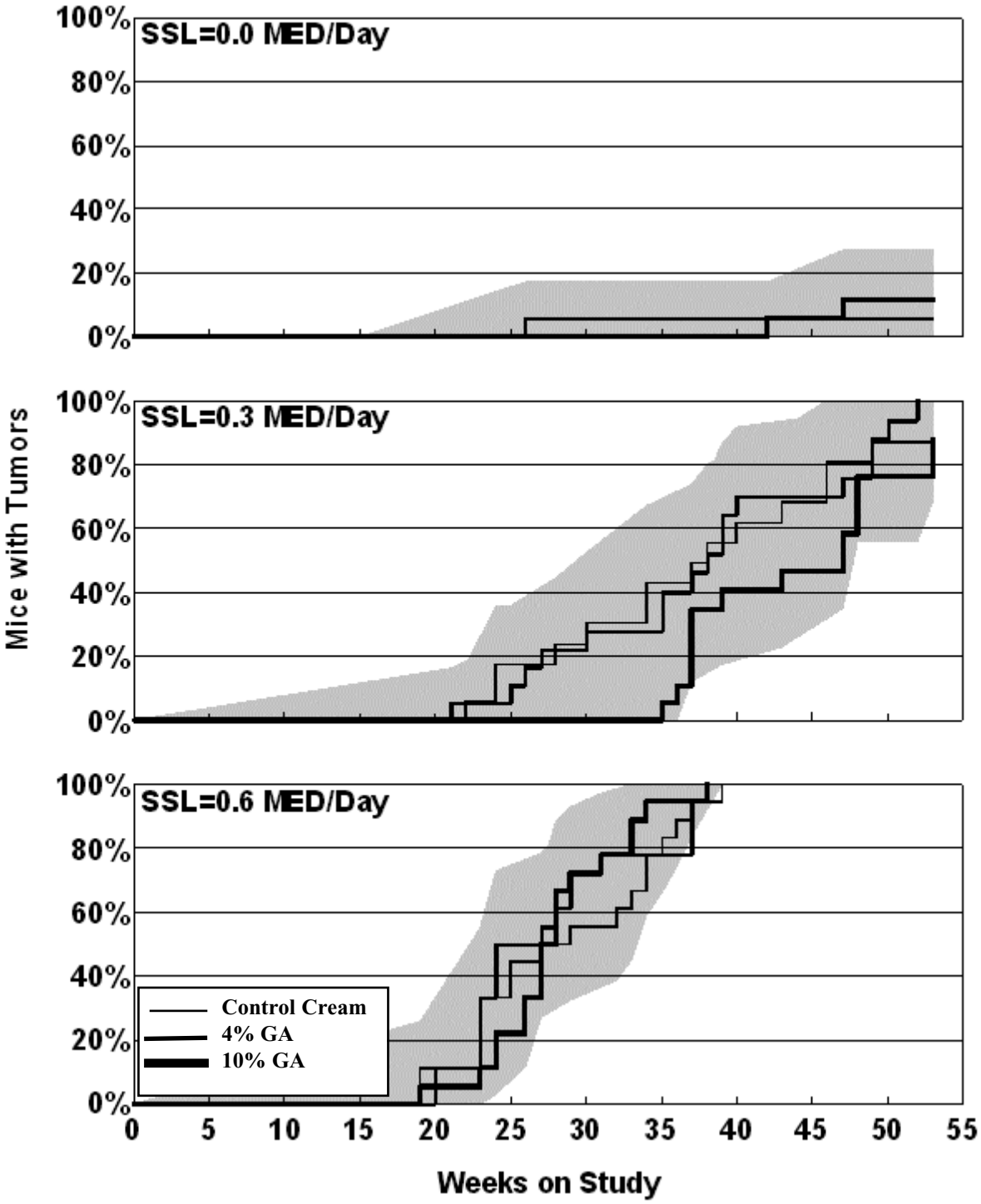


FIGURE 20
Time to Development of at Least 1 mm Skin Tumors in Female Mice Exposed to a Fixed Amount of Simulated Solar Light and Administered Control Cream, 4%, or 10% Glycolic Acid
(Gray area equals 95% confidence range)

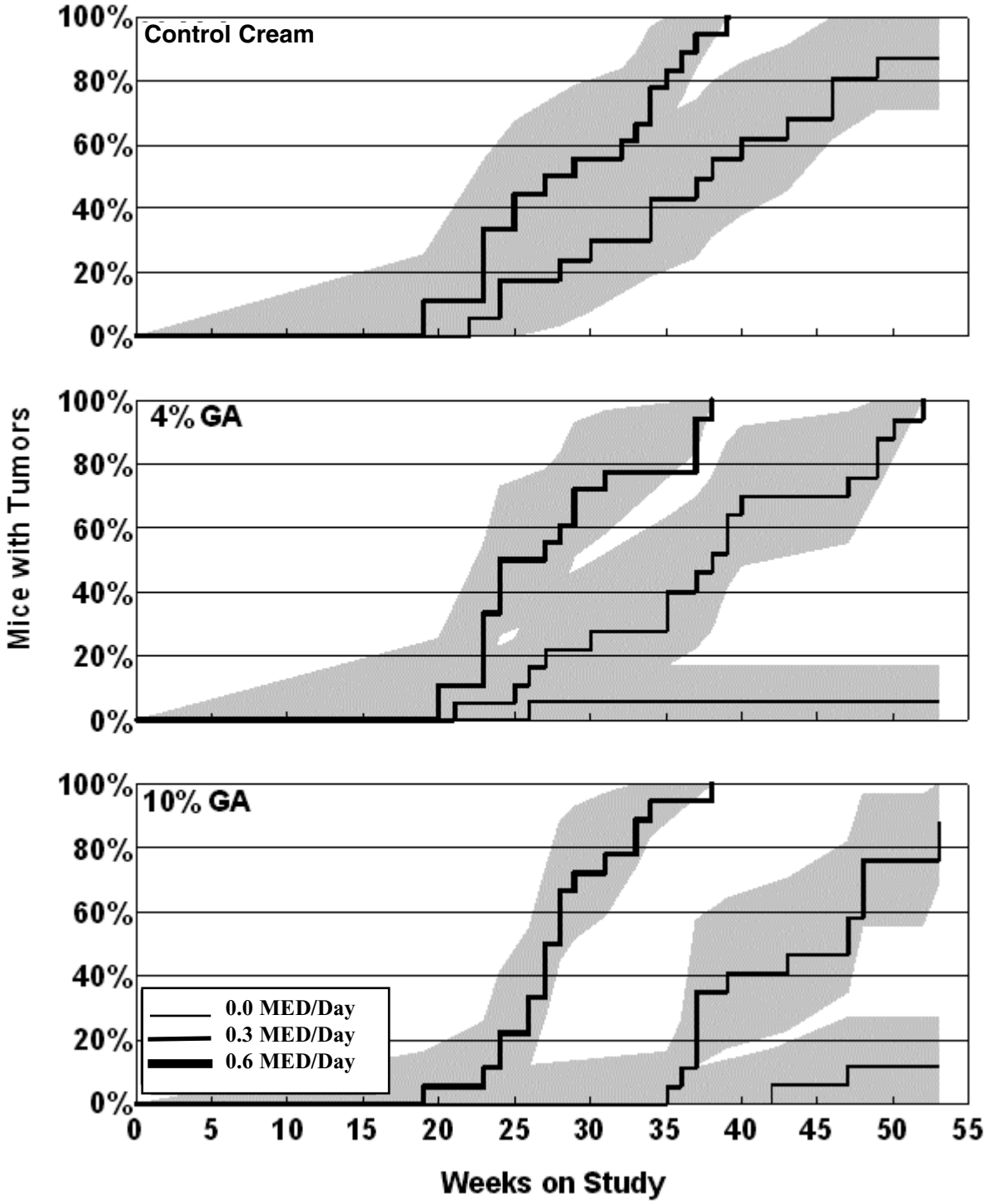


FIGURE 21
Time to Development of at Least 1 mm Skin Tumors in Female Mice Administered a Fixed Amount of Glycolic Acid and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light
(Gray area equals 95% confidence range)

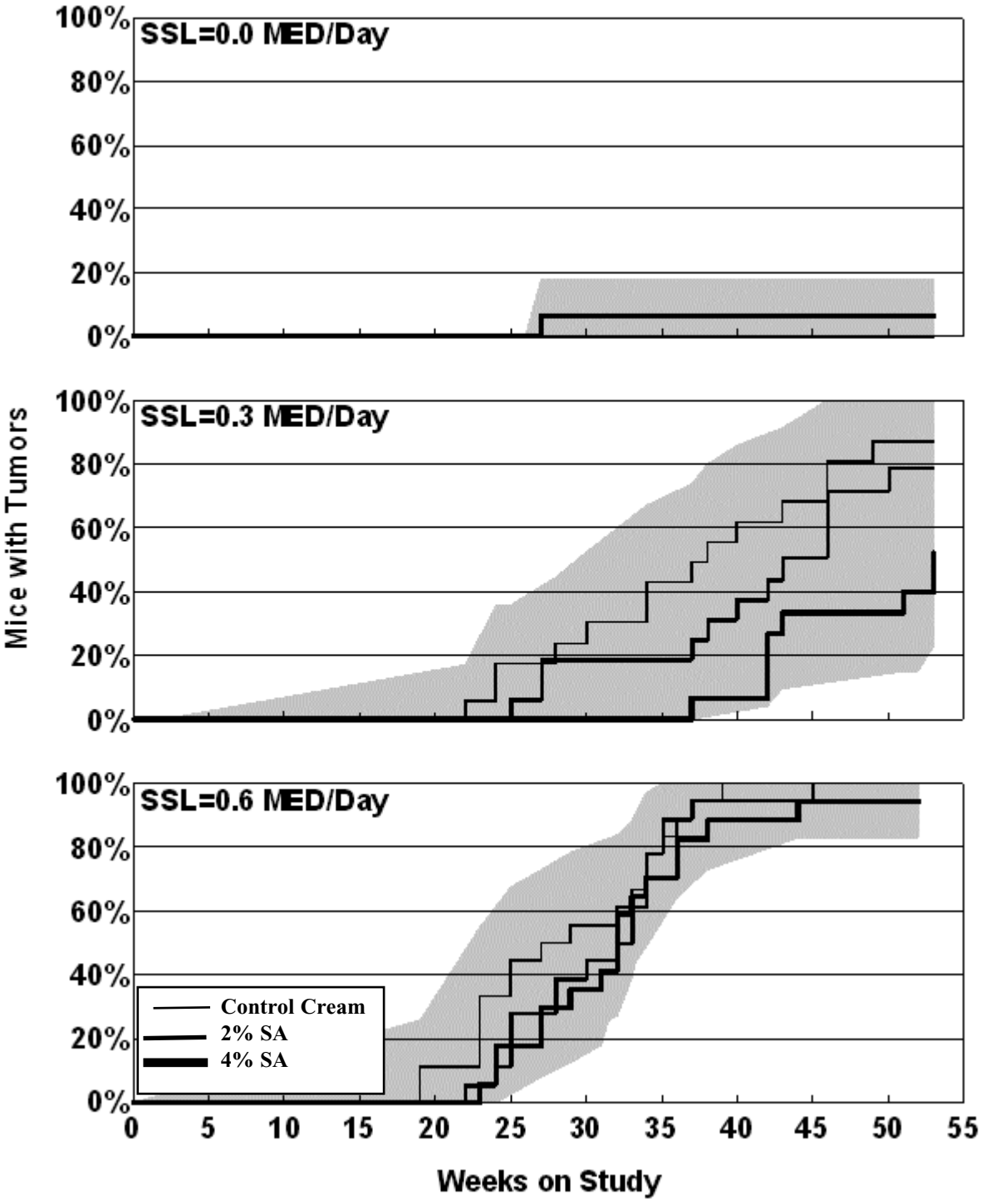


FIGURE 22
Time to Development of at Least 1 mm Skin Tumors in Female Mice Exposed to a Fixed Amount of Simulated Solar Light and Administered Control Cream, 2%, or 4% Salicylic Acid
(Gray area equals 95% confidence range)

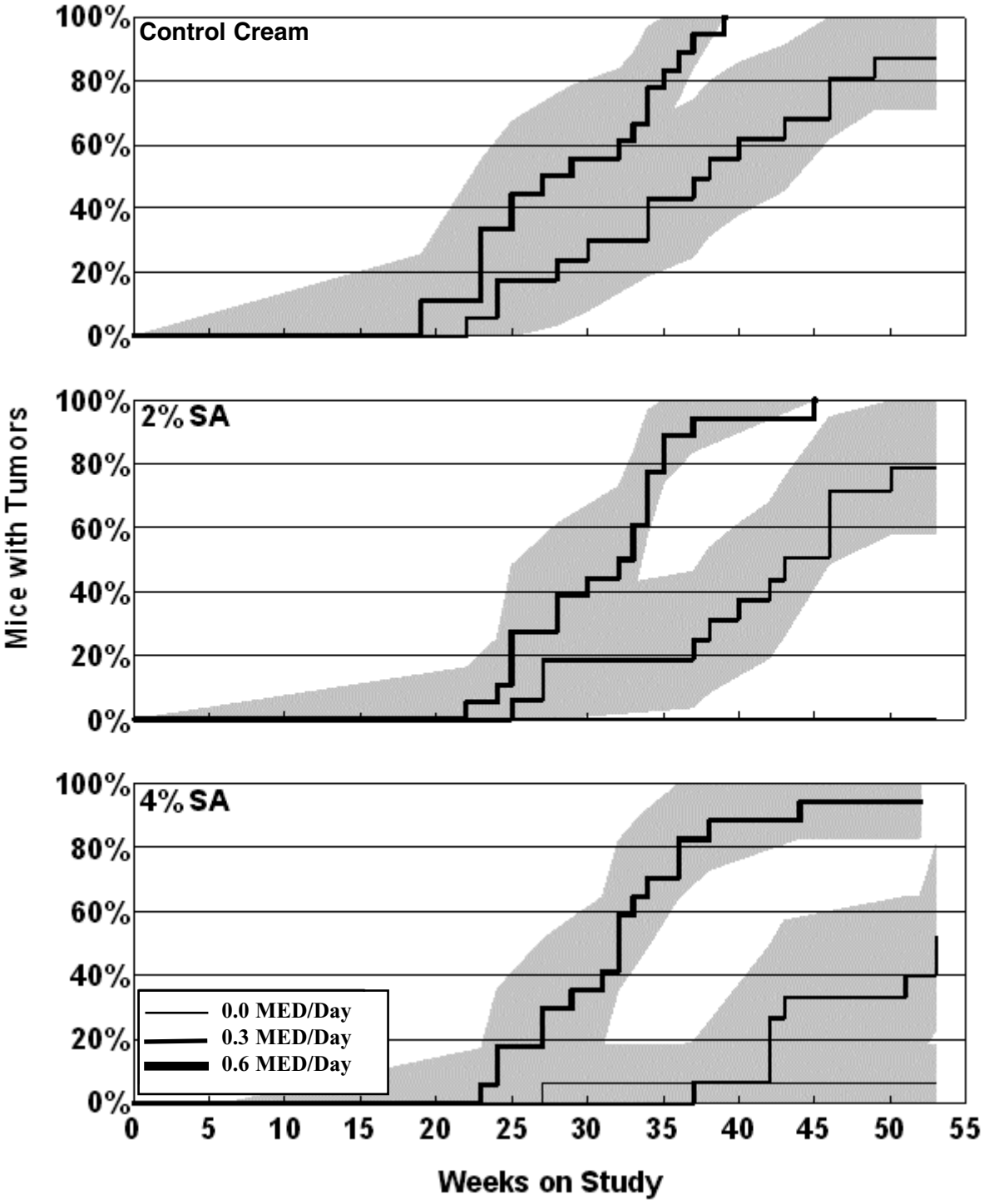


FIGURE 23
Time to Development of at Least 1 mm Skin Tumors in Female Mice Administered a Fixed Amount of Salicylic Acid and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light
(Gray area equals 95% confidence range)

Pathology and Statistical Analyses

This section describes the biologically noteworthy changes in nonneoplastic lesions or statistically significant changes in incidences of neoplastic 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 neoplasms and nonneoplastic lesions and statistical analyses of primary neoplasms are presented in Appendix A for male mice and Appendix B for female mice.

Nonneoplastic Skin Lesions

The skin of the SKH-1 hairless mouse examined in this study contained a number of unique histologic features. The epidermis usually consisted of one or two cell layers of squamous cells. In the untreated animal, hair shafts and adnexal structures, such as sebaceous glands, were either absent or atypical in location and development. Prominent cystic structures were often present in the dermis, which appeared to be remnants of hair follicles. The cysts were usually lined by squamous or cuboidal epithelium and were empty or contained small amounts of keratinized debris and occasionally fragmented hair shafts.

Acanthosis: This lesion was defined as a diffuse thickening of the epidermis. The severity of the acanthosis was graded as minimal (2 to 4 cell layers), mild (4 to 6 cell layers), moderate (6 to 9 cell layers), or marked (>9 cell layers). In all treatment groups (no cream, control cream, creams containing glycolic or salicylic acid), the incidence of acanthosis increased in a dose-dependent manner with increasing dose of SSL (Tables 13, A3a,b,c,d, and B3a,b,c,d). The application of control cream altered the incidence of acanthosis when compared to mice that were not treated with creams for males and females at 0.0 MED SSL and for females at 0.6 MED SSL. Acanthosis was absent in untreated males and females at 0.0 MED SSL and increased to 11% in males and 17% in females receiving control cream. The incidences of acanthosis at each dose of SSL with control cream were unaffected by the addition of glycolic or salicylic acid.

TABLE 13
Incidences and Severities of Acanthosis of the Skin (Site of Application) in Mice in the 1-Year Simulated Solar Light Study

	No Cream	Control Cream	4% Glycolic Acid Cream	10% Glycolic Acid Cream	2% Salicylic Acid Cream	4% Salicylic Acid Cream
Male						
0.0 MED SSL						
Minimal[a]		2/18 (11%)	2/18 (11%)	1/18 (6%)		1/18 (6%)
Mild					1/18 (6%)	
Pairwise P value[b]		P=0.0217	P=0.5000	P=0.7002	P=0.7013	P=0.8076
Acid trend P value[c]			P=0.7155		P=0.7299	
SSL trend P value[d]	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001
0.3 MED SSL						
Minimal	26/36 (72%)	12/18 (67%)	14/18 (78%)	10/18 (56%)	12/18 (67%)	3/18 (17%)
Mild	1/36 (3%)	1/18 (6%)	1/18 (6%)	2/18 (11%)		
Pairwise P value		P=0.5184	P=0.2460	P=0.4579	P=0.7181	P=0.9912
Acid trend P value			P=0.5229		P=0.9997	
SSL pairwise P value[e]	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P=0.0002	P=0.1478
0.6 MED SSL						
Minimal	23/36 (64%)	12/18 (67%)	12/18 (67%)	10/18 (56%)	9/18 (50%)	13/18 (72%)
Mild	7/36 (19%)	3/18 (17%)	4/18 (22%)	6/18 (33%)	5/18 (28%)	1/18 (6%)
Moderate			1/18 (6%)			
Pairwise P value		P=0.5646	P=0.1160	P=0.1514	P=0.3943	P=0.6974
Acid trend P value			P=0.1312		P=0.7868	
SSL pairwise P value	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001
0.9 MED SSL						
Minimal	21/35 (60%)					
Mild	7/35 (20%)					
SSL pairwise P value	P<0.0001					

TABLE 13
Incidences and Severities of Acanthosis of the Skin (Site of Application) in Mice in the 1-Year Simulated Solar Light Study

	No Cream	Control Cream	4% Glycolic Acid Cream	10% Glycolic Acid Cream	2% Salicylic Acid Cream	4% Salicylic Acid Cream
Female						
0.0 MED SSL						
Minimal		3/18 (17%)	4/18 (22%)	2/18 (11%)	5/18 (28%)	6/18 (33%)
Mild			1/18 (6%)		1/18 (6%)	1/18 (6%)
Pairwise P value		P=0.0063	P=0.1967	P=0.4755	P=0.1157	P=0.0801
Acid trend P value			P=0.6600		P=0.0686	
SSL trend P value	P<0.0001	P<0.0001	P=0.0009	P<0.0001	P=0.0014	P<0.0001
0.3 MED SSL						
Minimal	24/36 (67%)	12/18 (67%)	12/18 (67%)	11/18 (61%)	12/18 (67%)	12/17 (71%)
Mild	4/36 (11%)	3/18 (17%)	3/18 (17%)	5/18 (28%)	2/18 (11%)	2/17 (12%)
Moderate			1/18 (6%)			
Pairwise P value		P=0.2543	P=0.2659	P=0.2404	P=0.7155	P=0.7051
Acid trend P value			P=0.2019		P=0.6208	
SSL pairwise P value	P<0.0001	P<0.0001	P=0.0002	P<0.0001	P=0.0062	P=0.0071
0.6 MED SSL						
Minimal	24/36 (67%)	8/18 (44%)	15/18 (83%)	13/18 (72%)	12/18 (67%)	11/18 (61%)
Mild	9/36 (25%)	7/18 (39%)		2/18 (11%)	3/18 (17%)	6/18 (33%)
Moderate		2/18 (11%)	1/18 (6%)	2/18 (11%)		
Pairwise P value		P=0.0296	P=0.9947	P=0.9639	P=0.9868	P=0.9172
Acid trend P value			P=0.9231		P=0.8468	
SSL pairwise P value	P<0.0001	P<0.0001	P=0.0002	P<0.0001	P=0.0016	P<0.0001
0.9 MED SSL						
Minimal	23/36 (64%)					
Mild	10/36 (28%)					
Moderate	1/36 (3%)					
SSL pairwise P value	P<0.0001					

[a] Number of animals with lesion at given severity/number of animals for which skin was microscopically examined
[b] Pairwise comparison (Shirley-Williams test) value: all groups are compared to the control cream group.
[c] Trend test (Jonckheere-Terpstra test) value for control cream group and test article (glycolic or salicylic acid) groups
[d] Trend test (Jonckheere-Terpstra test) for effect of 0.0, 0.3, 0.6, 0.9 MED SSL with test groups
[e] Pairwise comparison (Shirley-Williams test) of value to test group at 0.0 MED SSL

Squamous hyperplasia: This lesion was defined as a focal nodular thickening of the epidermis, differentiating it from acanthosis (diffuse thickening of the epidermis). Squamous hyperplasia was detected grossly and was graded as minimal (2 to 4 cell layers), mild (4 to 6 cell layers), moderate (6 to 9 cell layers), or marked (>9 cell layers). The cells in the nodules were orderly, resembling normal epidermis. There were often increasing numbers of normal or abnormal mitotic figures. There were additionally dysplastic changes, including lack of cohesion or orientation, pleomorphism, nuclear atypia, and basal disorganization. Increased mitotic activity and inflammatory changes were common.

With the exception of one animal in the control cream group in the females and one animal in the 4% salicylic acid group in the males, squamous hyperplasia occurred only in the animals treated with SSL (Tables 14, A3a,b,c,d, and B3a,b,c,d). Squamous hyperplasia was induced in a dose-dependent manner by SSL in all test groups. Squamous hyperplasia in the male and female mice treated with control cream was significantly increased over the incidence in untreated mice at 0.3 and 0.6 MED SSL. The inclusion of glycolic acid or salicylic acid in the cream did not affect the incidence or severity of squamous hyperplasia at any of the SSL doses.

TABLE 14
Incidences and Severities of Squamous Hyperplasia of the Skin (Site of Application) in Mice in the 1-Year Simulated Solar Light Study

	No Cream	Control Cream	4% Glycolic Acid Cream	10% Glycolic Acid Cream	2% Salicylic Acid Cream	4% Salicylic Acid Cream
Male						
0.0 MED SSL						
Mild[a]						1/18 (6%)
Pairwise P value[b]						P=0.1310
Acid trend P value[c]						P=0.1103
SSL trend P value[d]	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001
0.3 MED SSL						
Minimal	4/36 (11%)			1/18 (6%)	1/18 (6%)	
Mild	2/36 (6%)	2/18 (11%)	7/18 (39%)	4/18 (22%)	3/18 (17%)	2/18 (11%)
Moderate	2/36 (6%)	5/18 (28%)	5/18 (28%)	5/18 (28%)	1/18 (6%)	4/18 (22%)
Marked	3/36 (8%)	3/18 (17%)	2/18 (11%)	2/18 (11%)	1/18 (6%)	1/18 (6%)
Pairwise P value		P=0.0186	P=0.3404	P=0.4826	P=0.9596	P=0.9373
Acid trend P value			P=0.5033		P=0.8827	
SSL pairwise P value[e]	P=0.0002	P=0.0001	P<0.0001	P<0.0001	P=0.0042	P=0.0069
0.6 MED SSL						
Minimal		1/18 (6%)			1/18 (6%)	1/18 (6%)
Mild	4/36 (11%)	3/18 (17%)	1/18 (6%)	1/18 (6%)	2/18 (11%)	2/18 (11%)
Moderate	6/36 (17%)	2/18 (11%)	3/18 (17%)	4/18 (22%)	1/18 (6%)	3/18 (17%)
Marked	7/36 (19%)	8/18 (44%)	7/18 (39%)	10/18 (56%)	10/18 (56%)	10/18 (56%)
Pairwise P value		P=0.0182	P=0.7094	P=0.2352	P=0.3350	P=0.2270
Acid trend P value			P=0.2031		P=0.1946	
SSL pairwise P value	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001
0.9 MED SSL						
Moderate	7/35 (20%)					
Marked	12/35 (34%)					
SSL pairwise P value	P<0.0001					

TABLE 14
Incidences and Severities of Squamous Hyperplasia of the Skin (Site of Application) in Mice in the 1-Year Simulated Solar Light Study

	No Cream	Control Cream	4% Glycolic Acid Cream	10% Glycolic Acid Cream	2% Salicylic Acid Cream	4% Salicylic Acid Cream
Female						
0.0 MED SSL						
Minimal		1/18 (6%)				
Pairwise P value	P=0.0786		P=0.8413	P=0.9420	P=0.8413	P=0.9420
Acid trend P value				P=0.8897		P=0.8897
SSL trend P value	P<0.0001	P<0.0001	P=0.0002	P<0.0001	P<0.0001	P=0.0001
0.3 MED SSL						
Minimal	3/36 (8%)		1/18 (6%)			
Mild	7/36 (19%)	4/18 (22%)	4/18 (22%)	3/18 (17%)		2/17 (12%)
Moderate	3/36 (8%)	3/18 (17%)	4/18 (22%)	6/18 (33%)	1/18 (6%)	1/17 (6%)
Marked	3/36 (8%)	5/18 (28%)	3/18 (17%)	4/18 (22%)	4/18 (22%)	3/17 (18%)
Pairwise P value		P=0.0163	P=0.6707	P=0.4568	P=0.9567	P=0.9789
Acid trend P value			P=0.3807		P=0.9484	
SSL pairwise P value	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P=0.0089	P=0.0033
0.6 MED SSL						
Mild	4/36 (11%)	2/18 (11%)	1/18 (6%)	4/18 (22%)	2/18 (11%)	5/18 (28%)
Moderate	6/36 (17%)	6/18 (33%)	5/18 (28%)	1/18 (6%)	5/18 (28%)	4/18 (22%)
Marked	10/36 (28%)	10/18 (56%)	4/18 (22%)	9/18 (50%)	8/18 (44%)	2/18 (11%)
Pairwise P value		P=0.0010	P=0.9974	P=0.9461	P=0.8570	P=0.9978
Acid trend P value			P=0.9000		P=0.9998	
SSL pairwise P value	P<0.0001	P<0.0001	P=0.0002	P<0.0001	P<0.0001	P=0.0001
0.9 MED SSL						
Mild	2/36 (6%)					
Moderate	2/36 (6%)					
Marked	8/36 (22%)					
SSL pairwise P value	P<0.0001					

[a] Number of animals with lesion at given severity/number of animals for which skin was microscopically examined
[b] Pairwise comparison (Shirley-Williams test) value: all groups are compared to the control cream group.
[c] Trend test (Jonckheere-Terpstra test) value for control cream group and test article (glycolic or salicylic acid) groups
[d] Trend test (Jonckheere-Terpstra test) for effect of 0.0, 0.3, 0.6, 0.9 MED SSL with test groups
[e] Pairwise comparison (Shirley-Williams test) of value to test group at 0.0 MED SSL

Skin Neoplasms

Squamous cell papillomas were described as focal, arborized, finger-like projections from the skin surface, consisting of a core of fibrovascular tissue contiguous with the dermis and covered by a thickened, often hyperkeratotic, stratified squamous epithelium (Plate 1). The thickness of the epithelium was variable within these lesions. The epithelial cells were orderly in arrangement, although they were often more numerous and crowded in the papilloma than in the normal epidermis (Plate 2). In most instances, papillomas were single lesions, pedunculated with the arborized projections arising from a single stalk, although sometimes they were more broad-based or sessile.

Carcinoma *in situ* referred to lesions that were grossly raised nodules ranging from one to several millimeters in size (Plate 3). Microscopically, these lesions were discrete nodules involving the squamous epithelium. In some cases, the epithelium was elevated, while in other cases, the lesions were depressions below the adjacent epidermis resulting in a cup-shaped lesion. Superficial ulceration was common in these lesions. In all of the cases of carcinoma *in situ*, the border of the tumor was sharply demarcated from the dermis. This was used as the principal feature differentiating carcinoma *in situ* from squamous cell carcinoma. The nuclei in the proliferating epithelium in carcinoma *in situ* were atypical and usually arranged in disorderly fashion (Plate 4). Mitotic figures were numerous in the tumors and in many cases were large and bizarre. Keratinization of individual cells was common, and many individual epithelial cells were dysplastic. There was often an inflammatory reaction in the underlying dermis to the carcinoma that consisted of lymphocyte, plasma cell, and polymorphonuclear leukocyte infiltration of variable severity.

Squamous cell carcinoma was defined as a nodular mass with an irregular surface that was often crateriform and ulcerated. These tumors were characterized by downward projecting sheets, nests, and anastomosing cords of neoplastic cells that extended into the dermis (Plate 5). Some tumor cells penetrated the panniculus carnosum and invaded the subcutaneous tissue. The central portion of the carcinoma was often occupied by a mass of keratin. On many occasions, concentrically arranged masses of keratin (epithelial pearls) were present in the carcinoma. The degree of differentiation was quite variable; some tumors were well differentiated, while others were very anaplastic (Plate 6). Nuclear atypia and large bizarre mitotic figures were present in the tumors. Some of the invasive squamous cell carcinomas appeared to arise within carcinoma *in situ*, suggesting there was a progression from carcinoma *in situ* to squamous cell carcinoma; however, no additional investigations were conducted to address this hypothesis.

Basal cell carcinoma was the diagnostic term used for epidermal neoplasms composed of primitive pleuripotential cells lacking intracellular bridges. Basal cells were usually small, uniform in size, and had prominent round or oval nuclei with relatively little cytoplasm. The nuclei were hyperchromatic and closely resembled those of normal basal cells in the epidermis. The tumor cells existed in a variety of growth patterns such as solid, cystic, ribbon, adenoid, or medusoid. Most often they consisted of solid sheets, lobules, or nests of cells. In several of the basal cell carcinomas, there was a mixture of patterns and the tumor cells had irregular shapes, sizes, and staining characteristics.

There were two types of analyses conducted on the tumor incidence data. The first analysis was a Poly-3 analysis. The second analysis tested for interactions among the topical creams and light groups. Since no interactions were detected, the results are not summarized in this Technical Report.

Simulated Solar Light Only

The incidences of skin neoplasms in mice exposed to SSL only are summarized in Table 15. The control for this comparison was the group that did not receive any topically applied cream or SSL. No neoplasms were detected in the skin in male mice that did not receive SSL. There were significant SSL dose-related trends for the induction of carcinoma *in situ*, squamous cell carcinoma, and the combined incidence of carcinoma *in situ* or squamous cell carcinoma. The incidences of all these lesions were significantly increased at 0.6 and 0.9 MED SSL. The combined incidence of carcinoma *in situ* or squamous cell carcinoma was also significantly increased at 0.3 MED SSL.

In female mice, positive trends with SSL were observed in the incidences of squamous cell papilloma, carcinoma *in situ*, squamous cell carcinoma, and the combined incidence of carcinoma *in situ* or squamous cell carcinoma. The incidences of these lesions were significantly increased at each SSL level with the exception of papillomas at 0.3 and 0.9 MED SSL and squamous cell carcinoma at 0.3 MED SSL.

TABLE 15
Incidences of Skin Neoplasms in Mice Exposed to 0.0, 0.3, 0.6, or 0.9 MED Simulated Solar Light

	0.0 MED SSL	0.3 MED SSL	0.6 MED SSL	0.9 MED SSL
Male				
Skin, Squamous Cell Papilloma				
Overall rate[a]	0/36 (0.0%)	3/36 (8.3%)	0/36 (0.0%)	2/35 (5.7%)
Adjusted rate[b]	0/32.5 (0.0%)	3/32.7 (9.2%)	0/24.0 (0.0%)	2/13.4 (14.9%)
Terminal rate[c]	0/31 (0.0%)	3/32 (9.4%)	0/3 (0.0%)	0/0
Poly-3 test[d]	P=0.203	P=0.117	—[e]	P=0.105
Skin, Carcinoma *in situ*				
Overall rate	0/36 (0.0%)	4/36 (11.1%)	13/36 (36.1%)	19/35 (54.3%)
Adjusted rate	0/32.5 (0.0%)	4/32.7 (12.2%)	13/27.7 (46.9%)	19/24.9 (76.4%)
Terminal rate	0/31 (0.0%)	4/32 (12.5%)	2/3 (66.7%)	0/0
Poly-3 test	P=0.001	P=0.058	P=0.001	P=0.001
Skin, Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	1/36 (2.8%)	28/36 (77.8%)	33/35 (94.3%)
Adjusted rate	0/32.5 (0.0%)	1/32.7 (3.1%)	28/33.7 (83.1%)	33/33.2 (99.4%)
Terminal rate	0/31 (0.0%)	1/32 (3.1%)	1/3 (33.3%)	0/0
Poly-3 test	P=0.001	P=0.501	P=0.001	P=0.001
Skin, Carcinoma *in situ* or Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	5/36 (13.9%)	30/36 (83.3%)	33/35 (94.3%)
Adjusted rate	0/32.5 (0.0%)	5/32.7 (15.3%)	30/33.9 (88.5%)	33/33.2 (99.4%)
Terminal rate	0/31 (0.0%)	5/32 (15.6%)	2/3 (66.7%)	0/0
Poly-3 test	P=0.001	P=0.028	P=0.001	P=0.001
Female				
Skin, Squamous Cell Papilloma				
Overall rate	1/36 (2.8%)	0/36 (0.0%)	6/36 (16.7%)	3/36 (8.3%)
Adjusted rate	1/36.0 (2.8%)	0/33.7 (0.0%)	6/29.4 (20.4%)	3/17.5 (17.1%)
Terminal rate	1/34 (2.9%)	0/32 (0.0%)	2/9 (22.2%)	0/0
Poly-3 test	P=0.006	P=0.513	P=0.027	P=0.118
Skin, Carcinoma *in situ*				
Overall rate	0/36 (0.0%)	4/36 (11.1%)	23/36 (63.9%)	18/36 (50.0%)
Adjusted rate	0/36.0 (0.0%)	4/33.7 (11.9%)	23/31.6 (72.7%)	18/25.9 (69.4%)
Terminal rate	0/34 (0.0%)	4/32 (12.5%)	6/9 (66.7%)	0/0
Poly-3 test	P=0.001	P=0.050	P=0.001	P=0.001
Skin, Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	3/36 (8.3%)	31/36 (86.1%)	35/36 (97.2%)
Adjusted rate	0/36.0 (0.0%)	3/33.7 (8.9%)	31/34.7 (89.5%)	35/35.1 (99.6%)
Terminal rate	0/34 (0.0%)	3/32 (9.4%)	7/9 (77.8%)	0/0
Poly-3 test	P=0.001	P=0.105	P=0.001	P=0.001
Skin, Carcinoma *in situ* or Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	6/36 (16.7%)	34/36 (94.4%)	35/36 (97.2%)
Adjusted rate	0/36.0 (0.0%)	6/33.7 (17.8%)	34/34.7 (98.0%)	35/35.1 (99.6%)
Terminal rate	0/34 (0.0%)	6/32 (18.8%)	9/9 (100.0%)	0/0
Poly-3 test	P=0.001	P=0.011	P=0.001	P=0.001

[a] Number of neoplasm-bearing animals/number of animals with skin microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.
[e] Value of statistic cannot be computed.

Only two skin neoplasms were induced in female mice outside the site exposed to SSL (dorsal); these were one papilloma in the 0.6 MED SSL group (Table B1c) and one carcinoma *in situ* in the 0.3 MED SSL group (Table B1b). These were not significantly increased incidences.

Control Cream

The incidences of skin neoplasms in mice administered control cream and exposed to SSL are summarized in Table 16. The statistical comparison of skin neoplasm incidences between groups not treated with cream and those treated with control cream and exposed to SSL is presented in Table 17.

Skin neoplasms did not occur in the male or female mice exposed to 0.0 MED SSL (Tables 16 and A1a). In male mice treated with control cream, exposure to SSL resulted in positive trends in the incidences of squamous cell papilloma, carcinoma *in situ*, squamous cell

TABLE 16
Incidences of Skin Neoplasms in Mice Administered Control Cream and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light

	Control Cream/ 0.0 MED SSL	Control Cream/ 0.3 MED SSL	Control Cream/ 0.6 MED SSL
Male			
Skin, Squamous Cell Papilloma			
Overall rate[a]	0/18 (0.0%)	3/18 (16.7%)	4/18 (22.2%)
Adjusted rate[b]	0/16.0 (0.0%)	3/15.6 (19.2%)	4/12.4 (32.1%)
Terminal rate[c]	0/16 (0.0%)	2/14 (14.3%)	0/0
Poly-3 test[d]	P=0.017	P=0.102	P=0.022
Skin, Carcinoma *in situ*			
Overall rate	0/18 (0.0%)	9/18 (50.0%)	13/18 (72.2%)
Adjusted rate	0/16.0 (0.0%)	9/15.6 (57.7%)	13/15.9 (82.0%)
Terminal rate	0/16 (0.0%)	8/14 (57.1%)	0/0
Poly-3 test	P=0.001	P=0.001	P=0.001
Skin, Squamous Cell Carcinoma			
Overall rate	0/18 (0.0%)	4/18 (22.2%)	17/18 (94.4%)
Adjusted rate	0/16.0 (0.0%)	4/15.6 (25.7%)	17/17.5 (97.1%)
Terminal rate	0/16 (0.0%)	3/14 (21.4%)	0/0
Poly-3 test	P=0.001	P=0.044	P=0.001
Skin, Carcinoma *in situ* or Squamous Cell Carcinoma			
Overall rate	0/18 (0.0%)	10/18 (55.6%)	18/18 (100.0%)
Adjusted rate	0/16.0 (0.0%)	10/15.6 (64.2%)	18/18.0 (100.0%)
Terminal rate	0/16 (0.0%)	9/14 (64.3%)	0/0
Poly-3 test	P=0.001	P=0.001	P=0.001
Female			
Skin, Squamous Cell Papilloma			
Overall rate	0/18 (0.0%)	2/18 (11.1%)	3/18 (16.7%)
Adjusted rate	0/15.5 (0.0%)	2/14.2 (14.1%)	3/12.1 (24.7%)
Terminal rate	0/15 (0.0%)	1/12 (8.3%)	0/1
Poly-3 test	P=0.045	P=0.212	P=0.067
Skin, Carcinoma *in situ*			
Overall rate	0/18 (0.0%)	8/18 (44.4%)	14/18 (77.8%)
Adjusted rate	0/15.5 (0.0%)	8/14.5 (55.2%)	14/16.4 (85.4%)
Terminal rate	0/15 (0.0%)	6/12 (50.0%)	1/1 (100.0%)
Poly-3 test	P=0.001	P=0.001	P=0.001

TABLE 16
Incidences of Skin Neoplasms in Mice Administered Control Cream and Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light

	Control Cream/ 0.0 MED SSL	Control Cream/ 0.3 MED SSL	Control Cream/ 0.6 MED SSL
Female (continued)			
Skin, Squamous Cell Carcinoma			
Overall rate	0/18 (0.0%)	4/18 (22.2%)	17/18 (94.4%)
Adjusted rate	0/15.5 (0.0%)	4/14.5 (27.6%)	17/17.5 (97.2%)
Terminal rate	0/15 (0.0%)	2/12 (16.7%)	1/1 (100.0%)
Poly-3 test	P=0.001	P=0.039	P=0.001
Skin, Carcinoma *in situ* or Squamous Cell Carcinoma			
Overall rate	0/18 (0.0%)	8/18 (44.4%)	17/18 (94.4%)
Adjusted rate	0/15.5 (0.0%)	8/14.5 (55.2%)	17/17.5 (97.2%)
Terminal rate	0/15 (0.0%)	6/12 (50.0%)	1/1 (100.0%)
Poly-3 test	P=0.001	P=0.001	P=0.001

[a] Number of neoplasm-bearing animals/number of animals with skin microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

carcinoma, and the combined incidence of carcinoma *in situ* or squamous cell carcinoma. The incidences of these lesions were significantly increased at each dose level of SSL, with the exception of squamous cell papilloma at 0.3 MED SSL.

In female mice treated with control cream, exposure to SSL resulted in positive trends in the incidences of squamous cell papilloma, carcinoma *in situ*, squamous cell carcinoma, and the combined incidence of carcinoma *in situ* or squamous cell carcinoma (Tables 16 and B2a,b,c,d). The incidences of these neoplasms were significantly increased at each dose level of SSL, with the exception of squamous cell papilloma at 0.3 and 0.6 MED SSL.

In male mice treated with control cream and exposed to 0.3 MED SSL, there was a significant induction of carcinoma *in situ*, squamous cell carcinoma, and the combined incidence of carcinoma *in situ* or squamous cell carcinoma compared to male mice receiving no cream and 0.3 MED SSL (Table 17). At 0.6 MED SSL, the male mice treated with control cream had increased incidences of squamous cell papilloma and carcinoma *in situ*.

In female mice treated with control cream and exposed to 0.3 MED SSL, there was a significant induction of carcinoma *in situ* and the combined incidence of carcinoma *in situ* or squamous cell carcinoma compared to female mice receiving no cream and 0.3 MED SSL (Table 17).

TABLE 17
Comparison of Skin Neoplasm Incidences in Male and Female Mice in the 1-Year Simulated Solar Light Study[a]

	Male (P value)	Female (P value)
Squamous Cell Papilloma		
No Cream vs. Control Cream		
0.0 MED SSL	—	0.663N
0.3 MED SSL	0.303	0.077
0.6 MED SSL	0.004	0.541
Carcinoma *in situ*		
No Cream vs. Control Cream		
0.0 MED SSL	—	—
0.3 MED SSL	0.001	0.001
0.6 MED SSL	0.010	0.239
Squamous Cell Carcinoma		
No Cream vs. Control Cream		
0.0 MED SSL	—	—
0.3 MED SSL	0.025	0.112
0.6 MED SSL	0.124	0.326
Carcinoma *in situ* or Squamous Cell Carcinoma		
No Cream vs. Control Cream		
0.0 MED SSL	—	—
0.3 MED SSL	0.001	0.010
0.6 MED SSL	0.131	0.838N

[a] Pairwise comparison of no cream and control cream groups at the same SSL exposure concentration. A lower incidence in the control cream group than in the corresponding no cream group is indicated by **N**.

Glycolic Acid

The incidences of skin neoplasms in male mice administered glycolic acid and exposed to SSL are summarized in Table 18. The induction of squamous cell papilloma in male mice showed SSL dose-related trends with control cream, 4%, and 10% glycolic acid. In comparison to the corresponding 0.0 MED SSL group, the incidences at 0.3 MED SSL were significantly increased in the presence of 4% glycolic acid and the incidences at 0.6 MED SSL were significantly increased in the presence of control cream and 10% glycolic acid. At a constant level of SSL (i.e., 0.0, 0.3, or 0.6 MED), treatment with glycolic acid did not change the incidences of squamous cell papilloma in male mice.

The induction of carcinoma *in situ* in male mice showed SSL dose-related positive trends with control cream, 4%, and 10% glycolic acid, with the incidences at 0.3 and 0.6 MED SSL being significantly increased compared to the corresponding 0.0 MED SSL group. At a constant level of SSL, treatment with glycolic acid did not change the incidence of carcinoma *in situ* in male mice.

The induction of squamous cell carcinoma in male mice showed SSL dose-related positive trends with control cream, 4%, and 10% glycolic acid, with the incidences at 0.3 and 0.6 MED SSL being significantly increased (with the exception of 4% glycolic acid at 0.3 MED SSL) compared to the corresponding 0.0 MED SSL group. At 0.3 MED SSL, there was a dose-related positive trend in the induction of squamous cell carcinoma in male mice with increasing glycolic acid concentration.

Basal cell carcinoma was induced only in mice that were treated with 10% glycolic acid and 0.3 MED SSL. However, this incidence was not statistically significant and was neither SSL nor glycolic acid dose-related.

TABLE 18
Incidences of Skin Neoplasms in Male Mice Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light and Administered Control Cream, 4%, or 10% Glycolic Acid

	Control Cream	4% Glycolic Acid Cream	10% Glycolic Acid Cream
Squamous Cell Papilloma			
0.0 MED SSL			
Overall rate[a]	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate[b]	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate[c]	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
Glycolic Acid Poly-3 test[d]	—[f]	—	—
SSL Poly-3 test[e]	P=0.017	P=0.017	P=0.026
0.3 MED SSL			
Overall rate	3/18 (16.7%)	7/18 (38.9%)	3/18 (16.7%)
Adjusted rate	3/15.6 (19.2%)	7/16.0 (43.7%)	3/15.6 (19.2%)
Terminal rate	2/14 (14.3%)	7/14 (50.0%)	2/11 (18.2%)
Glycolic Acid Poly-3 test	P=0.509	P=0.134	P=0.670
SSL Poly-3 test	P=0.102	P=0.002	P=0.093
0.6 MED SSL			
Overall rate	4/18 (22.2%)	2/18 (11.1%)	3/18 (16.7%)
Adjusted rate	4/12.4 (32.1%)	2/8.7 (23.1%)	3/9.7 (30.9%)
Terminal rate	0/0	0/0	0/0
Glycolic Acid Poly-3 test	P=0.577	P=0.514	P=0.659
SSL Poly-3 test	P=0.022	P=0.123	P=0.038
Carcinoma *in situ*			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
Glycolic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	9/18 (50.0%)	9/18 (50.0%)	10/18 (55.6%)
Adjusted rate	9/15.6 (57.7%)	9/16.7 (54.0%)	10/16.3 (61.2%)
Terminal rate	8/14 (57.1%)	7/14 (50.0%)	6/11 (54.5%)
Glycolic Acid Poly-3 test	P=0.487	P=0.555	P=0.564
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.6 MED SSL			
Overall rate	13/18 (72.2%)	11/18 (61.1%)	12/18 (66.7%)
Adjusted rate	13/15.9 (82.0%)	11/12.6 (87.3%)	12/13.9 (86.1%)
Terminal rate	0/0	0/0	0/0
Glycolic Acid Poly-3 test	P=0.495	P=0.568	P=0.596
SSL Poly-3 test	P=0.001	P=0.001	P=0.001

TABLE 18
Incidences of Skin Neoplasms in Male Mice Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light and Administered Control Cream, 4%, or 10% Glycolic Acid

	Control Cream	4% Glycolic Acid Cream	10% Glycolic Acid Cream
Squamous Cell Carcinoma			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
Glycolic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	4/18 (22.2%)	3/18 (16.7%)	9/18 (50.0%)
Adjusted rate	4/15.6 (25.7%)	3/16.6 (18.1%)	9/16.1 (55.8%)
Terminal rate	3/14 (21.4%)	1/14 (7.1%)	6/11 (54.5%)
Glycolic Acid Poly-3 test	P=0.033	P=0.464	P =0.080
SSL Poly-3 test	P=0.044	P=0.116	P=0.001
0.6 MED SSL			
Overall rate	17/18 (94.4%)	15/18 (83.3%)	15/18 (83.3%)
Adjusted rate	17/17.5 (97.1%)	15/15.2 (98.8%)	15/15.3 (98.2%)
Terminal rate	0/0	0/0	0/0
Glycolic Acid Poly-3 test	P=0.797	P=0.913	P=0.928
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
Basal Cell Carcinoma			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
Glycolic Acid Poly-3 test	—	—	—
SSL Poly-3 test	—	—	P=0.413
0.3 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	2/18 (11.1%)
Adjusted rate	0/15.4 (0.0%)	0/16.0 (0.0%)	2/15.2 (13.2%)
Terminal rate	0/14 (0.0%)	0/14 (0.0%)	2/11 (18.2%)
Glycolic Acid Poly-3 test	P=0.084	—	P=0.228
SSL Poly-3 test	—	—	P=0.207
0.6 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/10.6 (0.0%)	0/7.7 (0.0%)	0/8.5 (0.0%)
Terminal rate	0/0	0/0	0/0
Glycolic Acid Poly-3 test	—	—	—
SSL Poly-3 test	—	—	—

TABLE 18
Incidences of Skin Neoplasms in Male Mice Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light and Administered Control Cream, 4%, or 10% Glycolic Acid

	Control Cream	4% Glycolic Acid Cream	10% Glycolic Acid Cream
Carcinoma *in situ*, Squamous Cell Carcinoma, or Basal Cell Carcinoma			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
Glycolic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	10/18 (55.6%)	10/18 (55.6%)	12/18 (66.7%)
Adjusted rate	10/15.6 (64.2%)	10/17.0 (58.8%)	12/16.3 (73.5%)
Terminal rate	9/14 (64.3%)	7/14 (50.0%)	8/11 (72.7%)
Glycolic Acid Poly-3 test	P=0.337	P=0.519	P=0.426
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.6 MED SSL			
Overall rate	18/18 (100.0%)	15/18 (83.3%)	15/18 (83.3%)
Adjusted rate	18/18.0 (100.0%)	15/15.2 (98.8%)	15/15.3 (98.2%)
Terminal rate	0/0	0/0	0/0
Glycolic Acid Poly-3 test	P=0.919	P=1.000	P=1.00
SSL Poly-3 test	P=0.001	P=0.001	P=0.001

[a] Number of neoplasm-bearing animals/number of animals with skin microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test across the glycolic acid doses. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[e] In the 0.0 MED SSL block is the P value associated with the trend test across the SSL exposure levels. In the 0.3 and 0.6 MED SSL blocks are the P values corresponding to pairwise comparisons between the given SSL exposure levels and the 0.0 MED SSL group.
[f] Value of statistic cannot be computed.

The induction of carcinoma *in situ*, squamous cell carcinoma, or basal cell carcinoma (combined) in male mice showed SSL dose-related positive trends with control cream, 4%, and 10% glycolic acid, with the incidences at 0.3 and 0.6 MED SSL being significantly increased compared to the corresponding 0.0 MED SSL group. At a constant level of SSL, treatment with glycolic acid did not change the incidences of carcinoma *in situ*, squamous cell carcinoma, or basal cell carcinoma (combined) in male mice.

The incidences of skin neoplasms in female mice administered glycolic acid and exposed to SSL are summarized in Table 19. The induction of squamous cell papilloma in female mice showed SSL dose-related positive trends with control cream and 4% glycolic acid, with the incidence at 0.6 MED SSL being significantly increased in the presence of 4% glycolic acid compared to the corresponding 0.0 MED SSL group. At a constant level of SSL, treatment with glycolic acid did not change the incidences of squamous cell papilloma in female mice.

The induction of carcinoma *in situ* in female mice showed SSL dose-related positive trends with control cream, 4%, and 10% glycolic acid, with the incidences at 0.3 and 0.6 MED SSL being significantly increased compared to the corresponding 0.0 MED SSL group. At a constant level of SSL, treatment with glycolic acid did not change the incidences of carcinoma *in situ* in female mice.

The induction of squamous cell carcinoma in female mice showed SSL dose-related positive trends with control cream, 4%, and 10% glycolic acid, with the incidences at 0.3 and 0.6 MED SSL being significantly increased compared to the corresponding 0.0 MED SSL group. At a constant level of SSL, treatment with glycolic acid did not change the incidences of squamous cell carcinoma in female mice.

The combined incidences of carcinoma *in situ* or squamous cell carcinoma showed SSL dose-related positive trends with control cream, 4%, and 10% glycolic acid, with the incidences at 0.3 and 0.6 MED SSL being significantly increased when compared to the corresponding 0.0 MED SSL group. At a constant level of SSL, treatment with glycolic acid did not change the incidences of the combined tumors in female mice.

TABLE 19
Incidences of Skin Neoplasms in Female Mice Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light and Administered Control Cream, 4%, or 10% Glycolic Acid

	Control Cream	4% Glycolic Acid Cream	10% Glycolic Acid Cream
Squamous Cell Carcinoma			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
Glycolic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	4/18 (22.2%)	8/18 (44.4%)	6/18 (33.3%)
Adjusted rate	4/14.5 (27.6%)	8/17.1 (46.7%)	6/17.1 (35.1%)
Terminal rate	2/12 (16.7%)	3/12 (25.0%)	6/16 (37.5%)
Glycolic Acid Poly-3 test[d]	P=0.516	P=0.234	P=0.474
SSL Poly-3 test	P=0.039	P=0.001	P=0.007
0.6 MED SSL			
Overall rate	17/18 (94.4%)	16/18 (88.9%)	18/18 (100.0%)
Adjusted rate	17/17.5 (97.2%)	16/17.1 (93.3%)	18/18.0 (100.0%)
Terminal rate	1/1 (100.0%)	0/1 (0.0%)	1/1 (100.0%)
Glycolic Acid Poly-3 test	P=0.485	P=0.617	P=0.837
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
Carcinoma *in situ* or Squamous Cell Carcinoma			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
Glycolic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	8/18 (44.4%)	12/18 (66.7%)	8/18 (44.4%)
Adjusted rate	8/14.5 (55.2%)	12/17.1 (70.0%)	8/17.1 (46.8%)
Terminal rate	6/12 (50.0%)	7/12 (58.3%)	8/16 (50.0%)
Glycolic Acid Poly-3 test	P=0.300	P=0.313	P=0.456
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.6 MED SSL			
Overall rate	17/18 (94.4%)	17/18 (94.4%)	18/18 (100.0%)
Adjusted rate	17/17.5 (97.2%)	17/17.1 (99.2%)	18/18.0 (100.0%)
Terminal rate	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)
Glycolic Acid Poly-3 test	P=0.604	P=0.891	P=0.837
SSL Poly-3 test	P=0.001	P=0.001	P=0.001

[a] Number of neoplasm-bearing animals/number of animals with skin microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test across the glycolic acid doses. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[e] In the 0.0 MED SSL block is the P value associated with the trend test across the SSL exposure levels. In the 0.3 and 0.6 MED SSL blocks are the P values corresponding to pairwise comparisons between the given SSL exposure level and the 0.0 MED SSL group.
[f] Value of statistic cannot be computed.

Salicylic Acid

The incidences of skin neoplasms in male mice administered salicylic acid and exposed to SSL are summarized in Table 20. The induction of squamous cell papilloma in male mice showed SSL dose-related positive trends with control cream and 4% salicylic acid, with the incidences at 0.6 MED SSL being significantly increased in the presence of control cream and 4% salicylic acid. At a constant level of SSL (i.e., 0, 0.3, or 0.6 MED), treatment with salicylic acid did not change the incidences of squamous cell papilloma in male mice.

The induction of carcinoma *in situ* in male mice showed SSL dose-related positive trends with control cream, 2%, and 4% salicylic acid, with the incidences being significantly increased at 0.3 and 0.6 MED SSL, with the exception of 0.3 MED SSL in the presence of 4% salicylic acid. At 0.3 MED SSL, salicylic acid induced a dose-related negative trend in the incidences of carcinoma *in situ* in male mice, with the incidence being significantly decreased in the presence of 4% salicylic acid.

The induction of squamous cell carcinoma in male mice showed SSL dose-related positive trends with control cream, 2%, and 4% salicylic acid, with the incidence being significantly increased at 0.6 MED SSL and with control cream at 0.3 MED SSL compared to the corresponding 0.0 MED SSL group. At a constant level of SSL, treatment with salicylic acid did not change the incidences of squamous cell carcinoma in male mice.

The induction of carcinoma *in situ* or squamous cell carcinoma (combined) in male mice showed SSL dose-related positive trends with control cream, 2%, and 4% salicylic acid, with the incidences being significantly increased at 0.3 and 0.6 MED SSL, with the exception of 0.3 MED SSL in the presence of 4% salicylic acid. At 0.3 MED SSL, salicylic acid induced a dose-related negative trend in the incidences of these neoplasms in male mice, with the incidences being significantly decreased in the presence of 2% and 4% salicylic acid.

The incidences of skin neoplasms in female mice administered salicylic acid and exposed to SSL are summarized in Table 21. The induction of squamous cell papilloma in female mice showed SSL dose-related positive trends with control cream and 4% salicylic acid, with the incidence at 0.6 MED SSL being significantly increased in the presence of 4% salicylic acid. At a constant level of SSL, treatment with salicylic acid did not change the incidences of squamous cell papilloma in female mice.

The induction of carcinoma *in situ* in female mice showed SSL dose-related positive trends with control cream, 2%, and 4% salicylic acid, with the incidences being significantly increased at 0.3 and 0.6 MED SSL, with the exception of 0.3 MED SSL in the presence of 4% salicylic acid. At 0.3 MED SSL, salicylic acid induced a dose-related negative trend in the incidences of carcinoma *in situ* in female mice, with the incidence being significantly decreased in the presence of 4% salicylic acid.

The induction of squamous cell carcinoma in female mice showed SSL dose-related positive trends with control cream, 2%, and 4% salicylic acid, with the incidences being significantly increased at 0.3 MED SSL in the presence of control cream and 2% salicylic acid and at 0.6 MED SSL for all doses of salicylic acid. At a constant level of SSL, treatment with salicylic acid did not change the incidences of squamous cell carcinoma in female mice.

The induction of carcinoma *in situ* or squamous cell carcinoma (combined) in female mice showed SSL dose-related positive trends with control cream, 2%, and 4% salicylic acid, with the incidences being significantly increased at 0.3 and 0.6 MED SSL, with the exception of 0.3 MED SSL in the presence of 4% salicylic acid. At 0.3 MED SSL, salicylic acid induced a dose-related negative trend in the incidences of these neoplasms in female mice, with the incidence being significantly decreased in the presence of 4% salicylic acid.

TABLE 20
Incidences of Skin Neoplasms in Male Mice Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light and Administered Control Cream, 2%, or 4% Salicylic Acid

	Control Cream	2% Salicylic Acid Cream	4% Salicylic Acid Cream
Squamous Cell Papilloma			
0.0 MED SSL			
Overall rate[a]	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate[b]	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate[c]	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
Salicylic Acid Poly-3 test[d]	—[f]	—	—
SSL Poly-3 test[e]	P=0.017	P=0.107	P=0.008
0.3 MED SSL			
Overall rate	3/18 (16.7%)	3/18 (16.7%)	0/18 (0.0%)
Adjusted rate	3/15.6 (19.2%)	3/14.7 (20.5%)	0/17.3 (0.0%)
Terminal rate	2/14 (14.3%)	2/12 (16.7%)	0/15 (0.0%)
Salicylic Acid Poly-3 test	P=0.069	P=0.642	P=0.090
SSL Poly-3 test	P=0.102	P=0.080	—
0.6 MED SSL			
Overall rate	4/18 (22.2%)	2/18 (11.1%)	4/18 (22.2%)
Adjusted rate	4/12.4 (32.1%)	2/12.9 (15.5%)	4/13.7 (29.2%)
Terminal rate	0/0 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
Salicylic Acid Poly-3 test	P=0.548	P=0.299	P=0.605
SSL Poly-3 test	P=0.022	P=0.170	P=0.025
Carcinoma *in situ*			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
Salicylic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	9/18 (50.0%)	4/18 (22.2%)	1/18 (5.6%)
Adjusted rate	9/15.6 (57.7%)	4/14.7 (27.2%)	1/17.3 (5.8%)
Terminal rate	8/14 (57.1%)	2/12 (16.7%)	1/15 (6.7%)
Salicylic Acid Poly-3 test	P < 0.001N	P=0.087	P < 0.001N
SSL Poly-3 test	P=0.001	P=0.030	P=0.502
0.6 MED SSL			
Overall rate	13/18 (72.2%)	15/18 (83.3%)	13/18 (72.2%)
Adjusted rate	13/15.9 (82.0%)	15/16.4 (91.2%)	13/16.4 (79.4%)
Terminal rate	0/0 (0.0%)	2/2 (100.0%)	1/1 (100.0%)
Salicylic Acid Poly-3 test	P=0.509	P=0.380	P=0.614
SSL Poly-3 test	P=0.001	P=0.001	P=0.001

TABLE 20
Incidences of Skin Neoplasms in Male Mice Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light and Administered Control Cream, 2%, or 4% Salicylic Acid

	Control Cream	2% Salicylic Acid Cream	4% Salicylic Acid Cream
Squamous Cell Carcinoma			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
Salicylic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	4/18 (22.2%)	3/18 (16.7%)	1/18 (5.6%)
Adjusted rate	4/15.6 (25.7%)	3/14.7 (20.4%)	1/17.3 (5.8%)
Terminal rate	3/14 (21.4%)	1/12 (8.3%)	1/15 (6.7%)
Salicylic Acid Poly-3 test	P=0.093	P=0.534	P=0.134
SSL Poly-3 test	P=0.044	P=0.081	P=0.502
0.6 MED SSL			
Overall rate	17/18 (94.4%)	15/18 (83.3%)	14/18 (77.8%)
Adjusted rate	17/17.5 (97.1%)	15/16.8 (89.3%)	14/16.9 (83.0%)
Terminal rate	0/0	2/2 (100.0%)	1/1 (100.0%)
Salicylic Acid Poly-3 test	P=0.111	P=0.395	P=0.177
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
Carcinoma *in situ* or Squamous Cell Carcinoma			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
Salicylic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	10/18 (55.6%)	4/18 (22.2%)	2/18 (11.1%)
Adjusted rate	10/15.6 (64.2%)	4/14.7 (27.2%)	2/17.3 (11.6%)
Terminal rate	9/14 (64.3%)	2/12 (16.7%)	2/15 (13.3%)
Salicylic Acid Poly-3 test	P<0.001N	P=0.040N	P<0.001N
SSL Poly-3 test	P=0.001	P=0.030	P=0.235
0.6 MED SSL			
Overall rate	18/18 (100.0%)	17/18 (94.4%)	17/18 (94.4%)
Adjusted rate	18/18.0 (100.0%)	17/17.2 (99.1%)	17/17.8 (95.3%)
Terminal rate	0/0	2/2 (100.0%)	1/1 (100.0%)
Salicylic Acid Poly-3 test	P=0.317	P=1.000	P=0.579
SSL Poly-3 test	P=0.001	P=0.001	P=0.001

[a] Number of neoplasm-bearing animals/number of animals with skin microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test across the salicylic acid doses. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in the dosed group is indicated by **N**.
[e] In the 0.0 MED SSL block is the P value associated with the trend test across the SSL exposure levels. In the 0.3 and 0.6 MED SSL blocks are the P values corresponding to pairwise comparisons between the given SSL exposure level and the 0.0 MED SSL group.
[f] Value of statistic cannot be computed.

TABLE 21
Incidences of Skin Neoplasms in Female Mice Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light and Administered Control Cream, 2%, or 4% Salicylic Acid

	Control Cream	2% Salicylic Acid Cream	4% Salicylic Acid Cream
Squamous Cell Papilloma			
0.0 MED SSL			
Overall rate[a]	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate[b]	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate[c]	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
Salicylic Acid Poly-3 test[d]	—[f]	—	—
SSL Poly-3 test[e]	P=0.045	P=0.052	P=0.002
0.3 MED SSL			
Overall rate	2/18 (11.1%)	2/18 (11.1%)	0/17 (0.0%)
Adjusted rate	2/14.2 (14.1%)	2/15.1 (13.3%)	0/15.1 (0.0%)
Terminal rate	1/12 (8.3%)	2/14 (14.3%)	0/15 (0.0%)
Salicylic Acid Poly-3 test	P=0.154	P=0.677	P=0.218
SSL Poly-3 test	P=0.212	P=0.205	—
0.6 MED SSL			
Overall rate	3/18 (16.7%)	3/18 (16.7%)	5/18 (27.8%)
Adjusted rate	3/12.1 (24.7%)	3/14.3 (21.0%)	5/14.4 (34.6%)
Terminal rate	0/1 (0.0%)	1/6 (16.7%)	4/8 (50.0%)
Salicylic Acid Poly-3 test	P=0.346	P=0.595	P=0.448
SSL Poly-3 test	P=0.067	P=0.078	P=0.012
Carcinoma *in situ*			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
Salicylic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	8/18 (44.4%)	4/18 (22.2%)	0/17 (0.0%)
Adjusted rate	8/14.5 (55.2%)	4/15.1 (26.5%)	0/15.1 (0.0%)
Terminal rate	6/12 (50.0%)	4/14 (28.6%)	0/15 (0.0%)
Salicylic Acid Poly-3 test	P<0.001N	P=0.108	P<0.001N
SSL Poly-3 test	P=0.001	P=0.034	—
0.6 MED SSL			
Overall rate	14/18 (77.8%)	11/18 (61.1%)	11/18 (61.1%)
Adjusted rate	14/16.4 (85.4%)	11/16.5 (66.6%)	11/15.9 (69.2%)
Terminal rate	1/1 (100.0%)	3/6 (50.0%)	5/8 (62.5%)
Salicylic Acid Poly-3 test	P=0.179	P=0.173	P=0.228
SSL Poly-3 test	P=0.001	P=0.001	P=0.001

TABLE 21
Incidences of Skin Neoplasms in Female Mice Exposed to 0.0, 0.3, or 0.6 MED Simulated Solar Light and Administered Control Cream, 2%, or 4% Salicylic Acid

	Control Cream	2% Salicylic Acid Cream	4% Salicylic Acid Cream
Squamous Cell Carcinoma			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
Salicylic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	4/18 (22.2%)	5/18 (27.8%)	2/17 (11.8%)
Adjusted rate	4/14.5 (27.6%)	5/15.6 (32.1%)	2/15.1 (13.3%)
Terminal rate	2/12 (16.7%)	4/14 (28.6%)	2/15 (13.3%)
Salicylic Acid Poly-3 test	P=0.240	P=0.551	P=0.307
SSL Poly-3 test	P=0.039	P=0.014	P=0.219
0.6 MED SSL			
Overall rate	17/18 (94.4%)	15/18 (83.3%)	13/18 (72.2%)
Adjusted rate	17/17.5 (97.2%)	15/17.4 (86.2%)	13/16.6 (78.4%)
Terminal rate	1/1 (100.0%)	4/6 (66.7%)	5/8 (62.5%)
Salicylic Acid Poly-3 test	P=0.072	P=0.273	P=0.106
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
Carcinoma *in situ* or Squamous Cell Carcinoma			
0.0 MED SSL			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
Salicylic Acid Poly-3 test	—	—	—
SSL Poly-3 test	P=0.001	P=0.001	P=0.001
0.3 MED SSL			
Overall rate	8/18 (44.4%)	7/18 (38.9%)	2/17 (11.8%)
Adjusted rate	8/14.5 (55.2%)	7/15.6 (44.9%)	2/15.1 (13.3%)
Terminal rate	6/12 (50.0%)	6/14 (42.9%)	2/15 (13.3%)
Salicylic Acid Poly-3 test	P=0.012N	P=0.422	P=0.016N
SSL Poly-3 test	P=0.001	P=0.001	P=0.219
0.6 MED SSL			
Overall rate	17/18 (94.4%)	17/18 (94.4%)	14/18 (77.8%)
Adjusted rate	17/17.5 (97.2%)	17/18.0 (94.4%)	14/17.0 (82.3%)
Terminal rate	1/1 (100.0%)	5/6 (83.3%)	5/8 (62.5%)
Salicylic Acid Poly-3 test	P=0.104	P=0.677	P=0.182
SSL Poly-3 test	P=0.001	P=0.001	P=0.001

[a] Number of neoplasm-bearing animals/number of animals with skin microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test across the salicylic acid doses. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or lower incidence in a dosed group is indicated by **N**.
[e] In the 0.0 MED SSL block is the P value associated with the trend test across the SSL exposure levels. In the 0.3 and 0.6 MED SSL blocks are the P values corresponding to pairwise comparisons between the given SSL exposure level and the 0.0 MED SSL group.
[f] Value of statistic cannot be computed.

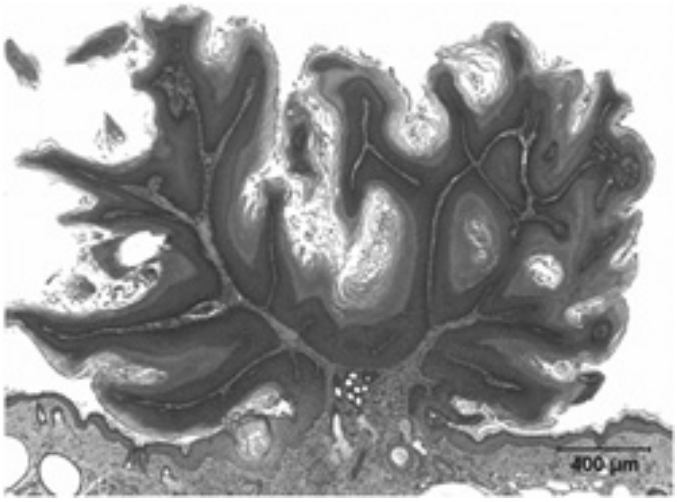


Plate 1
Photomicrograph of a squamous cell papilloma with branching pattern (animal CID 2760).

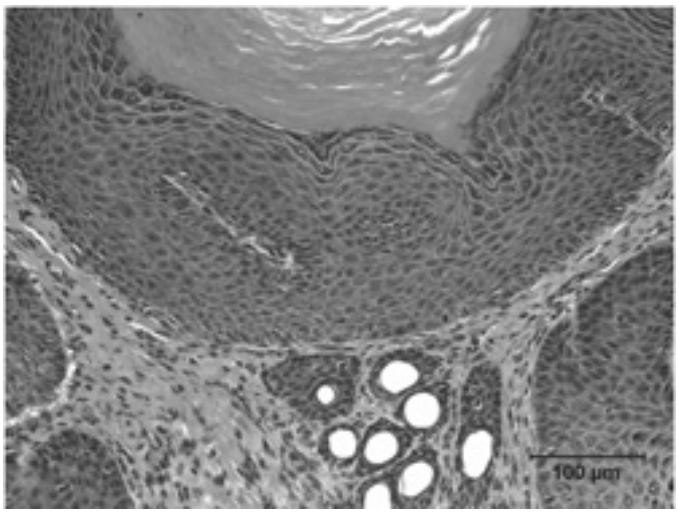


Plate 2
Photomicrograph of squamous cell papilloma showing the orderly arrangement of the well differentiated epithelium (animal CID 2760).

Plate 3
Photomicrograph of carcinoma *in situ* showing dispersion along the epidermis (animal CID 2839).

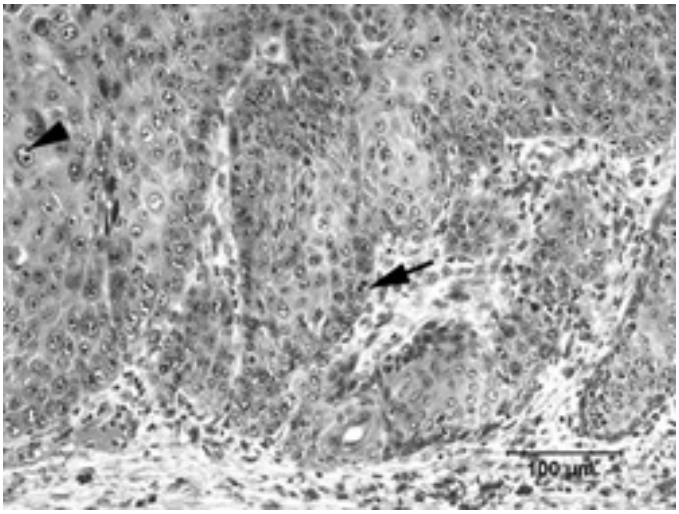


Plate 4
Photomicrograph of carcinoma *in situ* showing mitotic figures (arrow) and dysplastic cells (arrow head) (animal CID 2839).

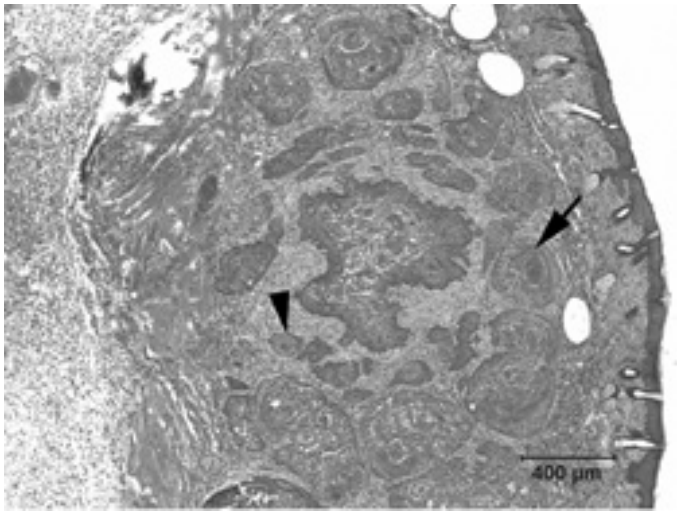


PLATE 5
Photomicrograph of representative squamous cell carcinoma showing invasion of the dermis and subcutis. This tumor also contains many pockets of hyperkeratin production (arrow) and keratin epithelial pearls (arrow head) (animal CID 2839).

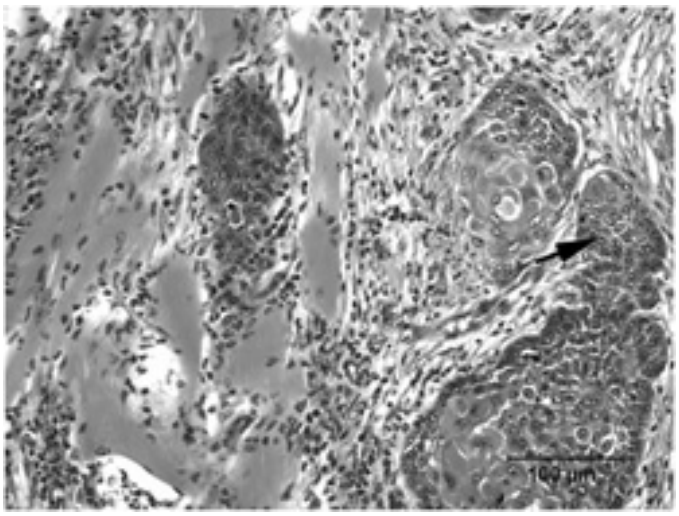


PLATE 6
Photomicrograph of squamous cell carcinoma with higher magnification showing atypical growth patterns and nuclei (arrow) (animal CID 2839).

DISCUSSION AND CONCLUSIONS

This study was designed to test the hypothesis that topical application of creams containing glycolic or salicylic acid to mice will enhance the rate of skin cancer induced by simulated solar light (SSL). In order to test this hypothesis, mice were treated 5 days per week in the mornings (0800 to 1100 hours) with cream and exposed to SSL in the afternoon (1200 to 1600 hours). This treatment continued for 40 weeks, followed by 12 weeks of no additional treatment prior to sacrifice.

Exposure to increasing doses of SSL resulted in a dose-dependent decrease in survival in male and female mice that were not treated with cream (Table 3 and Figure 1). Concomitant with a decrease in survival, there was a dose-dependent decrease in time to tumor, as reflected by both the mean and median time to tumor induction (Table 12 and Figure 13). Likewise, histopathologic examination of the skin neoplasms in mice not treated with cream demonstrated SSL dose-dependent trends in formation of carcinoma *in situ*, squamous cell carcinoma, and carcinoma *in situ* or squamous cell carcinoma (combined) in male mice and squamous cell papilloma, carcinoma *in situ*, squamous cell carcinoma, and carcinoma *in situ* or squamous cell carcinoma (combined) in female mice (Table 15). Since light sources that contain UVB are carcinogenic (IARC, 1992), these SSL dose-dependent trends were anticipated; nonetheless, it was necessary to establish a dose-trend with SSL because the study was designed to test the effects of topically applied creams containing glycolic acid and salicylic acid on the carcinogenesis of UVB-containing SSL.

The application of control cream did not appear to affect survival of male mice at any of the dose levels of SSL, although one statistical test (log-rank/Tarone's trend) did indicate a difference at 0.6 minimal erythema dose (MED) SSL (Table 4 and Figure 3). The application of control cream decreased survival in female mice at 0.3 and 0.6 MED SSL when compared to the respective no cream control group (Table 4 and Figure 4). In the absence of SSL, female mice treated with control cream also appeared to have decreased survival, although this did not reach statistical significance. The reason for these sex differences is not known. The application of control cream decreased the time to tumor for the onset of skin lesions in both male and female mice at 0.3 and 0.6 MED SSL (Table 12 and Figures 14 and 19). In male and female mice treated with control cream, there were also SSL dose-dependent trends in formation of squamous cell papilloma, carcinoma *in situ*, squamous cell carcinoma, and carcinoma *in situ* or squamous cell carcinoma (combined) (Table 16). At 0.3 MED SSL, the incidences of carcinoma *in situ* and carcinoma *in situ* or squamous cell carcinoma (combined) were increased in both male and female mice treated with control cream compared to mice not treated with control cream (Table 17). In male mice, the application of control cream also increased the incidences of squamous cell papilloma and carcinoma *in situ* at 0.6 MED SSL. These results indicate that the application of the control cream enhanced the photocarcinogenesis of SSL in the SKH-1 mice under these test conditions. They further indicate that the proper control groups for statistical comparison of the effects of glycolic acid or salicylic acid are mice that received the control cream, and not the mice untreated with cream.

The effect of the control cream has been noted in several other experiments. For instance, in a study with outbred hairless mice, the application of a peanut oil:isopropyl myristate (7:3) vehicle enhanced the photocarcinogenesis of a xenon arc light source (Gibbs *et al.*, 1985). In their highest light-dose group, the group median time to tumor occurred at approximately 29 weeks without application of topical agents, and decreased to 26 weeks in the group with topical application of vehicle. In the middle light-dose group, the effect of the vehicle was to decrease the median time to tumor from greater than 45 weeks to approximately 31 weeks. In the study of Bair *et al.* (2002), where the effect of topically applied sodium salicylate on the carcinogenesis of UVB light was examined in SKH-1 mice, the application of the control cream (Vanicream®) decreased the median time to tumor and increased the tumor multiplicity in the mice when compared to mice that only received UVB exposure.

The application of creams, emollients, oils, and other liquids or emulsions to the skin of test animals has had varying effects when compared to untreated test animals. These effects have included altered optical properties such as decreased light reflectance, increased light penetration, decreased or increased phototoxicity, altered photostability of the test compound, or altered test compound penetration into the skin. For this reason, the Center for Drug Evaluation and Research recommends that for drugs topically applied to the skin, the drug product (drug and vehicle) should be tested for adverse effects (FDA, 2000).

The inclusion of glycolic acid in the cream resulted in a dose-dependent increase in the survival of female mice that were exposed to 0.3 MED SSL (Table 5, glycolic acid trend test and Figure 8). This effect did not occur at 10% glycolic acid in female mice, nor did it occur in male mice at either dose level of glycolic acid (Table 5 and Figure 7). These results suggested that the inclusion of up to 10% glycolic acid was not deleterious to the mice with regard to survival. Analysis of the onset of skin tumors in the mice treated with glycolic acid-containing creams and SSL (Table 12) revealed no statistically significant glycolic acid dose effect on tumor incidence in either male or female mice, with the exception that a glycolic acid dose trend was detected at 0.3 MED SSL in male mice. In male mice, a glycolic acid dose-dependent increase in squamous cell carcinoma was detected at 0.3 MED SSL (Table 18). The inclusion of glycolic acid in the cream had no effect on the incidence of squamous cell papilloma, carcinoma *in situ*, or squamous cell carcinoma in female mice (Table 19). Therefore, it was concluded that the application of glycolic acid to male and female mice did not induce a consistent trend either in the onset of skin tumors or type of skin tumors induced by SSL in this study.

These results differ from those reported by Hong *et al.* (2001). In their study, SKH-1 mice were exposed 5 days/week to light emitted from a combination of UVB- and UVA-emitting fluorescent lamps and dosed twice each week with 8 mg glycolic acid/cm^2 in a polyethylene glycol vehicle at pH 3. The light alone induced tumors in mice starting at 9 weeks, increasing to 100% tumor incidence at 20 weeks. Application of glycolic acid delayed the onset of the first tumor to 12 weeks, and the incidence did not reach 100% of the treated mice by week 22. From these published data, the median time to tumor estimated for the light only group was approximately 9 weeks, while for the group receiving glycolic acid it was approximately 17 weeks. This increase in tumor latency was accompanied by a decrease in the number of tumors per mouse. Although the spectrum of the light and the frequency of application and dose of glycolic acid differed between the current study and that of Hong *et al.* (2001), the current results that glycolic acid did not affect SSL-induced tumor incidence and the results of Hong *et al.* (2001) indicating glycolic acid decreased or delayed tumor incidence support the conclusion that glycolic acid does not exacerbate the carcinogenesis of UVB-containing light.

Short-term studies with topical application of cream containing 4% or 10% glycolic acid to the skin of SKH-1 mice have demonstrated increased rates of cell proliferation 12 to 18 hours following a single administration (Sams *et al.*, 2001). Application of the cream for 3.5 weeks resulted in increased cell proliferation but did not induce epidermal thickening in these mice. The increased proliferation suggests that the pyrimidine dimer burden in the cells could lead to an increased level of mutations. This would be consistent with the studies by Kaidbey *et al.* (2003) where topical application of 10% glycolic acid in the same vehicle used in this study to the backs of Caucasian patients led to increased formation of apoptotic cells (i.e., sunburn cells) in response to UV radiation; however, although sunburn cells increased and the amount of light required to induce erythema decreased, the level of pyrimidine dimers in the skin of the exposed humans was not altered by the presence of 10% glycolic acid. This latter observation supports our results that suggest glycolic acid does not alter tumor incidence in SSL-exposed mice.

The inclusion of salicylic acid in the cream affected the survival of mice in the study. As shown in Table 6 and Figures 11 and 12, the inclusion of salicylic acid resulted in a dose-dependent increase in the survival of male and female mice receiving 0.6 MED SSL. The inclusion of salicylic acid in the creams also resulted in a dose-dependent increase in the time required to develop skin tumors in male mice at 0.3 and 0.6 MED SSL (Table 12 and Figure 17) and in female mice at 0.3 MED SSL (Table 12 and Figure 22). The application of salicylic acid in the cream resulted in dose-dependent decreased incidences of carcinoma *in situ* at 0.3 MED SSL in male and female mice (Tables 20 and 21), with the differences being significant at 4% salicylic acid. Although no significant differences were detected in the incidences of squamous cell carcinoma as a result of salicylic acid

treatment at 0.3 MED SSL, there were significant salicylic acid dose-dependent decreases in the incidences of combined skin cancers (carcinoma *in situ* or squamous cell carcinoma) in male and female mice at 0.3 MED SSL. The reason that salicylic acid did not have an effect at 0.6 MED SSL may be due to the high rate of induction of tumors in mice at this dose level of SSL. This leads to the conclusion that salicylic acid has a dose-dependent effect on the skin of SSL-exposed mice in which increased salicylic acid resulted in a decreased photocarcinogenic effect of SSL, and that under the test conditions of this study, salicylic acid was photoprotective.

Bair *et al.* (2002) examined the effects of topical administration of sodium salicylate in SKH-1 mice exposed to light emitted from a UVB-fluorescent lamp. The mice were treated three times weekly with 10 or 40 µmole of salicylate one hour prior to irradiation. The time required to induce squamous cell carcinoma in 50% of the mice (median time to tumor) was approximately 17 weeks in mice receiving the control cream, and this increased to 20 and 21 weeks in the mice receiving topical treatment with 10 and 40 µmole of salicylate, respectively. The authors attributed the increased latency (reduction in tumor formation) to the UVB-absorbing properties of salicylate, as evidenced by decreased pyrimidine dimer formation estimated from immunohistochemical staining. While the dose of salicylate (mg/cm^2) used in this study was not stated, the results are consistent with the observations in the current study where topical application of salicylic acid increased the latency of tumor formation and reduced the extent of formation of skin tumors in response to SSL.

CONCLUSIONS

These experiments investigated the impact of topical application of a cosmetic formulation containing 4% or 10% glycolic acid (pH 3.5) or 2% or 4% salicylic acid (pH 4) on the photocarcinogenesis of filtered 6.5 kW xenon arc simulated solar light (SSL) in SKH-1 hairless mice. Taking into consideration the survival data, time to tumor data, and the pathology results, glycolic acid did not alter the photocarcinogenesis of SSL, and salicylic acid was photoprotective, reducing the carcinogenicity of 0.3 MED SSL.

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APPENDIX A
SUMMARY OF LESIONS IN MALE MICE IN THE 1-YEAR SIMULATED SOLAR LIGHT STUDY OF GLYCOLIC ACID AND SALICYLIC ACID

TABLE A1a
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund	3		2	1	1	
Natural deaths	2	2	1			1
Survivors						
Terminal sacrifice	31	16	15	17	17	17
Animals examined microscopically	36	18	18	18	18	18
Alimentary System						
Liver	(2)	(3)	(3)	(4)	(2)	
Hepatocellular adenoma	1 (50%)		1 (33%)	1 (25%)		
Hepatocellular adenoma, two	1 (50%)					
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
None						
Hematopoietic System						
Lymph node	(5)	(4)	(2)	(2)	(5)	(3)
Lymphoma malignant, lumbar					1 (20%)	
Spleen	(36)	(18)	(18)	(18)	(18)	(17)
Lymphoma malignant	1 (3%)				1 (6%)	
Thymus	(1)				(1)	
Lymphoma malignant	1 (100%)				1 (100%)	
Integumentary System						
None						
Musculoskeletal System						
None						
Nervous System						
None						

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

TABLE A1a
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Respiratory System						
Lung	(36)	(18)	(18)	(18)	(18)	(17)
Alveolar/bronchiolar adenoma	1 (3%)	1 (6%)	1 (6%)	1 (6%)		2 (12%)
Lymphoma malignant	1 (3%)				1 (6%)	
Special Senses System						
None						
Urinary System						
None						

TABLE A1b
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund	2	1	1	4	1	1
Natural deaths	2	3	1		3	2
Skin neoplasm greater than 10 mm			2	3	2	
Survivors						
Terminal sacrifice	32	14	14	11	12	15
Animals examined microscopically	36	18	18	18	18	18
Alimentary System						
Liver	(1)	(3)	(3)	(1)	(3)	
Hepatocellular adenoma		2 (67%)	1 (33%)		1 (33%)	
Lymphoma malignant					1 (33%)	
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
Preputial gland	(3)	(3)	(1)	(4)	(3)	(2)
Lymphoma malignant					1 (33%)	
Hematopoietic System						
Lymph node	(15)	(10)	(12)	(10)	(4)	(9)
Lymphoma malignant, axillary					1 (25%)	
Lymphoma malignant, inguinal					1 (25%)	
Lymphoma malignant, lumbar					1 (25%)	
Lymphoma malignant, mediastinal			1 (8%)			
Lymphoma malignant, pancreatic			1 (8%)			
Lymphoma malignant, renal			1 (8%)		1 (25%)	
Squamous cell carcinoma, metastatic, axillary, skin					1 (25%)	
Squamous cell carcinoma, metastatic, inguinal, skin						1 (11%)

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

TABLE A1b
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System (continued)						
Lymph node, mandibular	(8)	(3)	(6)	(5)	(5)	(3)
Lymphoma malignant					1 (20%)	
Lymph node, mesenteric	(4)	(2)		(3)	(1)	(3)
Lymphoma malignant					1 (100%)	
Spleen	(36)	(18)	(18)	(18)	(18)	(18)
Lymphoma malignant			1 (6%)		1 (6%)	
Thymus	(2)	(1)	(1)			
Lymphoma malignant			1 (100%)			
Integumentary System						
Skin, control	(36)	(18)	(18)	(18)	(18)	(18)
Carcinoma *in situ*		2 (11%)	1 (6%)			
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(18)
Basal cell carcinoma				2 (11%)		
Carcinoma *in situ*	2 (6%)	5 (28%)	2 (11%)	2 (11%)	3 (17%)	1 (6%)
Carcinoma *in situ*, five			1 (6%)	1 (6%)		
Carcinoma *in situ*, four	1 (3%)	2 (11%)	1 (6%)	2 (11%)		
Carcinoma *in situ*, greater than five		1 (6%)		2 (11%)		
Carcinoma *in situ*, three			3 (17%)			
Carcinoma *in situ*, two	1 (3%)	1 (6%)	2 (11%)	3 (17%)	1 (6%)	
Squamous cell carcinoma	1 (3%)	3 (17%)	1 (6%)	4 (22%)	2 (11%)	1 (6%)
Squamous cell carcinoma, five				1 (6%)		
Squamous cell carcinoma, three			1 (6%)	2 (11%)		
Squamous cell carcinoma, two		1 (6%)	1 (6%)	2 (11%)	1 (6%)	
Squamous cell papilloma	2 (6%)	2 (11%)	6 (33%)	2 (11%)	3 (17%)	
Squamous cell papilloma, five			1 (6%)			
Squamous cell papilloma, two	1 (3%)	1 (6%)		1 (6%)		
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
Lung	(36)	(18)	(18)	(18)	(18)	(18)
Alveolar/bronchiolar adenoma	3 (8%)	3 (17%)	2 (11%)	1 (6%)		1 (6%)
Lymphoma malignant			1 (6%)		1 (6%)	
Special Senses System						
None						
Urinary System						
None						

TABLE A1c
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund	3	3	3	6	6	5
Natural deaths	4		4	1		3
Skin neoplasm greater than 10 mm	26	15	11	11	10	9
Survivors						
Terminal sacrifice	3				2	1
Animals examined microscopically	36	18	18	18	18	18
Alimentary System						
Liver	(2)	(2)	(2)	(3)	(2)	(2)
Hepatocellular adenoma				1 (33%)		
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
None						
Hematopoietic System						
Lymph node	(28)	(18)	(13)	(13)	(15)	(13)
Lymphoma malignant, axillary			1 (8%)			
Lymphoma malignant, inguinal			1 (8%)			
Lymphoma malignant, lumbar			1 (8%)			
Lymphoma malignant, renal	1 (4%)					
Mast cell tumor NOS, lumbar					1 (7%)	
Mast cell tumor NOS, popliteal					1 (7%)	
Lymph node, mandibular	(11)	(7)	(8)	(6)	(9)	(7)
Lymphoma malignant			1 (13%)			
Spleen	(36)	(18)	(17)	(18)	(18)	(17)
Lymphoma malignant			1 (6%)			
Thymus	(1)					
Lymphoma malignant	1 (100%)					

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

TABLE A1c
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Integumentary System						
Skin, control	(36)	(18)	(18)	(18)	(18)	(18)
Carcinoma *in situ*		1 (6%)				1 (6%)
Squamous cell papilloma				1 (6%)		
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(18)
Carcinoma *in situ*	5 (14%)	4 (22%)	5 (28%)	7 (39%)	4 (22%)	1 (6%)
Carcinoma *in situ*, five		3 (17%)			1 (6%)	1 (6%)
Carcinoma *in situ*, four			1 (6%)	3 (17%)	1 (6%)	1 (6%)
Carcinoma *in situ*, greater than five		1 (6%)	1 (6%)		1 (6%)	
Carcinoma *in situ*, three	2 (6%)	3 (17%)	3 (17%)		4 (22%)	3 (17%)
Carcinoma *in situ*, two	6 (17%)	2 (11%)	1 (6%)	2 (11%)	4 (22%)	7 (39%)
Squamous cell carcinoma	20 (56%)	7 (39%)	6 (33%)	3 (17%)	7 (39%)	7 (39%)
Squamous cell carcinoma, four		1 (6%)	1 (6%)		2 (11%)	
Squamous cell carcinoma, greater than five			2 (11%)		1 (6%)	
Squamous cell carcinoma, three	1 (3%)	5 (28%)	4 (22%)	4 (22%)	2 (11%)	2 (11%)
Squamous cell carcinoma, two	7 (19%)	4 (22%)	2 (11%)	8 (44%)	3 (17%)	5 (28%)
Squamous cell papilloma		4 (22%)	2 (11%)	3 (17%)	2 (11%)	4 (22%)
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
Lung	(36)	(18)	(17)	(18)	(18)	(17)
Alveolar/bronchiolar adenoma	3 (8%)			2 (11%)	1 (6%)	1 (6%)
Alveolar/bronchiolar carcinoma						1 (6%)
Lymphoma malignant	1 (3%)					
Special Senses System						
None						
Urinary System						
Kidney	(1)	(1)	(1)	(2)	(1)	(3)
Lymphoma malignant			1 (100%)			

TABLE A1d
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.9 MED

	No Cream	
Disposition Summary		
Animals initially in study	36	
Early removal		
Moribund	18	
Natural deaths	6	
Skin neoplasm greater than 10 mm	12	
Survivors		
Terminal sacrifice		
Animals examined microscopically	35	
Alimentary System		
None		
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
None		
Hematopoietic System		
Lymph node	(20)	
Lymphoma malignant, renal	1	(5%)
Lymph node, mandibular	(8)	
Lymphoma malignant	1	(13%)
Lymph node, mesenteric	(2)	
Lymphoma malignant	1	(50%)
Spleen	(33)	
Lymphoma malignant	1	(3%)
Thymus	(1)	
Lymphoma malignant	1	(100%)

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

TABLE A1d
Summary of the Incidence of Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.9 MED

	No Cream
Integumentary System	
Skin, site of application	(35)
Carcinoma *in situ*	8 (23%)
Carcinoma *in situ*, five	2 (6%)
Carcinoma *in situ*, four	3 (9%)
Carcinoma *in situ*, greater than five	1 (3%)
Carcinoma *in situ*, three	1 (3%)
Carcinoma *in situ*, two	4 (11%)
Sarcoma	1 (3%)
Squamous cell carcinoma	8 (23%)
Squamous cell carcinoma, five	1 (3%)
Squamous cell carcinoma, four	3 (9%)
Squamous cell carcinoma, three	4 (11%)
Squamous cell carcinoma, two	17 (49%)
Squamous cell papilloma	2 (6%)
Musculoskeletal System	
None	
Nervous System	
None	
Respiratory System	
None	
Special Senses System	
None	
Urinary System	
None	

TABLE A2a
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Light Only

	0.0 MED	0.3 MED	0.6 MED	0.9 MED
Lung: Alveolar/bronchiolar Adenoma				
Overall rate[a]	1/36 (2.8%)	3/36 (8.3%)	3/36 (8.3%)	0/33 (0.0%)
Adjusted rate[b]	1/32.5 (3.1%)	3/32.7 (9.2%)	3/25.1 (11.9%)	0/11.4 (0.0%)
Terminal rate[c]	1/31 (3.2%)	3/32 (9.4%)	0/3 (0.0%)	0/0
First incidence (days)	365 (T)	365 (T)	298 (10 mm)[e]	—[f]
Poly-3 test[d]	P=0.273	P=0.306	P=0.217	P=0.671N
Skin (Site of Application): Squamous Cell Papilloma				
Overall rate	0/36 (0.0%)	3/36 (8.3%)	0/36 (0.0%)	2/35 (5.7%)
Adjusted rate	0/32.5 (0.0%)	3/32.7 (9.2%)	0/24.0 (0.0%)	2/13.4 (14.9%)
Terminal rate	0/31 (0.0%)	3/32 (9.4%)	0/3 (0.0%)	0/0
First incidence (days)	—	365 (T)	—	230
Poly-3 test	P=0.203	P=0.117	—[g]	P=0.105
Skin (Site of Application): Carcinoma *in situ*				
Overall rate	0/36 (0.0%)	4/36 (11.1%)	13/36 (36.1%)	19/35 (54.3%)
Adjusted rate	0/32.5 (0.0%)	4/32.7 (12.2%)	13/27.7 (46.9%)	19/24.9 (76.4%)
Terminal rate	0/31 (0.0%)	4/32 (12.5%)	2/3 (66.7%)	0/0
First incidence (days)	—	365 (T)	287	206
Poly-3 test	P=0.001	P=0.058	P=0.001	P=0.001
Skin (Site of Application): Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	1/36 (2.8%)	28/36 (77.8%)	33/35 (94.3%)
Adjusted rate	0/32.5 (0.0%)	1/32.7 (3.1%)	28/33.7 (83.1%)	33/33.2 (99.4%)
Terminal rate	0/31 (0.0%)	1/32 (3.1%)	1/3 (33.3%)	0/0
First incidence (days)	—	367 (T)	287	206
Poly-3 test	P=0.001	P=0.501	P=0.001	P=0.001
Skin (Site of Application): Carcinoma *in situ* or Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	5/36 (13.9%)	30/36 (83.3%)	33/35 (94.3%)
Adjusted rate	0/32.5 (0.0%)	5/32.7 (15.3%)	30/33.9 (88.5%)	33/33.2 (99.4%)
Terminal rate	0/31 (0.0%)	5/32 (15.6%)	2/3 (66.7%)	0/0
First incidence (days)	—	365 (T)	287	206
Poly-3 test	P=0.001	P=0.028	P=0.001	P=0.001
Skin (Site of Application): Squamous Cell Papilloma, Carcinoma *in situ*, or Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	6/36 (16.7%)	30/36 (83.3%)	33/35 (94.3%)
Adjusted rate	0/32.5 (0.0%)	6/32.7 (18.3%)	30/33.9 (88.5%)	33/33.2 (99.4%)
Terminal rate	0/31 (0.0%)	6/32 (18.8%)	2/3 (66.7%)	0/0
First incidence (days)	—	365 (T)	287	206
Poly-3 test	P=0.001	P=0.014	P=0.001	P=0.001
All Organs: Malignant Lymphoma				
Overall rate	1/36 (2.8%)	0/36 (0.0%)	1/36 (2.8%)	1/35 (2.9%)
Adjusted rate	1/33.4 (3.0%)	0/32.7 (0.0%)	1/24.2 (4.1%)	1/12.6 (7.9%)
Terminal rate	0/31 (0.0%)	0/32 (0.0%)	0/3 (0.0%)	0/0
First incidence (days)	171	—	342	276 (10 mm)
Poly-3 test	P=0.453	P=0.504N	P=0.684	P=0.525
All Organs: Benign Neoplasms				
Overall rate	3/36 (8.3%)	6/36 (16.7%)	3/36 (8.3%)	2/35 (5.7%)
Adjusted rate	3/32.5 (9.2%)	6/32.7 (18.3%)	3/25.1 (11.9%)	2/13.4 (14.9%)
Terminal rate	3/31 (9.7%)	6/32 (18.8%)	0/3 (0.0%)	0/0
First incidence (days)	365 (T)	365 (T)	298 (10 mm)	230
Poly-3 test	P=0.387	P=0.240	P=0.539	P=0.485

TABLE A2a
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Light Only

	0.0 MED	0.3 MED	0.6 MED	0.9 MED
All Organs: Malignant Neoplasms				
Overall rate	0/36 (0.0%)	5/36 (13.9%)	30/36 (83.3%)	33/35 (94.3%)
Adjusted rate	0/32.5 (0.0%)	5/32.7 (15.3%)	30/33.9 (88.5%)	33/33.2 (99.4%)
Terminal rate	0/31 (0.0%)	5/32 (15.6%)	2/3 (66.7%)	0/0
First incidence (days)	—	365 (T)	287	206
Poly-3 test	P=0.001	P=0.028	P=0.001	P=0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	3/36 (8.3%)	8/36 (22.2%)	30/36 (83.3%)	33/35 (94.3%)
Adjusted rate	3/32.5 (9.2%)	8/32.7 (24.5%)	30/33.9 (88.5%)	33/33.2 (99.4%)
Terminal rate	3/31 (9.7%)	8/32 (25.0%)	2/3 (66.7%)	0/0
First incidence (days)	365 (T)	365 (T)	287	206
Poly-3 test	P=0.001	P=0.093	P=0.001	P=0.001

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparison between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by **N**.
[e] First incidence occurred when an animal was removed from study due to a skin neoplasm 10 mm or greater.
[f] Not applicable; no neoplasms in animal group
[g] Value of statistic cannot be computed

TABLE A2b
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
Liver: Hepatocellular Adenoma		
0.0 MED		
Overall rate[a]	2/2 (100.0%)	0/3 (0.0%)
Adjusted rate[b]	2/2.0 (100.0%)	0/3.0 (0.0%)
Terminal rate[c]	2/2 (100.0%)	0/3 (0.0%)
First incidence (days)	365 (T)	—[e]
Poly-3 test[d]		—[f]
0.3 MED		
Overall rate	0/1 (0.0%)	2/3 (66.7%)
Adjusted rate	0/1.0 (0.0%)	2/2.3 (87.5%)
Terminal rate	0/1 (0.0%)	2/2 (100.0%)
First incidence (days)	—	365 (T)
Poly-3 test		P=0.351
0.6 MED		
Overall rate	0/2 (0.0%)	0/2 (0.0%)
Adjusted rate	0/1.3 (0.0%)	0/0.8 (0.0%)
Terminal rate	0/0	0/0
First incidence (days)	—	—
Poly-3 test		—
Skin (Control): Carcinoma *in situ*		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/32.5 (0.0%)	0/16.0 (0.0%)
Terminal rate	0/31 (0.0%)	0/16 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	0/36 (0.0%)	2/18 (11.1%)
Adjusted rate	0/32.7 (0.0%)	2/15.4 (13.0%)
Terminal rate	0/32 (0.0%)	2/14 (14.3%)
First incidence (days)	—	367 (T)
Poly-3 test		P=0.089
0.6 MED		
Overall rate	0/36 (0.0%)	1/18 (5.6%)
Adjusted rate	0/24.0 (0.0%)	1/10.9 (9.2%)
Terminal rate	0/3 (0.0%)	0/0
First incidence (days)	—	319 (10 mm)[g]
Poly-3 test		P=0.342

TABLE A2b
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
Skin (Site of Application): Squamous Cell Papilloma		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/32.5 (0.0%)	0/16.0 (0.0%)
Terminal rate	0/31 (0.0%)	0/16 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	3/36 (8.3%)	3/18 (16.7%)
Adjusted rate	3/32.7 (9.2%)	3/15.6 (19.2%)
Terminal rate	3/32 (9.4%)	2/14 (14.3%)
First incidence (days)	365 (T)	342
Poly-3 test		P=0.303
0.6 MED		
Overall rate	0/36 (0.0%)	4/18 (22.2%)
Adjusted rate	0/24.0 (0.0%)	4/12.4 (32.1%)
Terminal rate	0/3 (0.0%)	0/0
First incidence (days)	—	270 (10 mm)
Poly-3 test		P=0.004
Skin (Site of Application): Carcinoma *in situ*		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/32.5 (0.0%)	0/16.0 (0.0%)
Terminal rate	0/31 (0.0%)	0/16 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	4/36 (11.1%)	9/18 (50.0%)
Adjusted rate	4/32.7 (12.2%)	9/15.6 (57.7%)
Terminal rate	4/32 (12.5%)	8/14 (57.1%)
First incidence (days)	365 (T)	342
Poly-3 test		P=0.001
0.6 MED		
Overall rate	13/36 (36.1%)	13/18 (72.2%)
Adjusted rate	13/27.7 (46.9%)	13/15.9 (82.0%)
Terminal rate	2/3 (66.7%)	0/0
First incidence (days)	287	263 (10 mm)
Poly-3 test		P=0.010

TABLE A2b
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
Skin (Site of Application): Squamous Cell Carcinoma		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/32.5 (0.0%)	0/16.0 (0.0%)
Terminal rate	0/31 (0.0%)	0/16 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	1/36 (2.8%)	4/18 (22.2%)
Adjusted rate	1/32.7 (3.1%)	4/15.6 (25.7%)
Terminal rate	1/32 (3.1%)	3/14 (21.4%)
First incidence (days)	367 (T)	342
Poly-3 test		P=0.025
0.6 MED		
Overall rate	28/36 (77.8%)	17/18 (94.4%)
Adjusted rate	28/33.7 (83.1%)	17/17.5 (97.1%)
Terminal rate	1/3 (33.3%)	0/0
First incidence (days)	287	263 (10 mm)
Poly-3 test		P=0.124
Skin (Site of Application): Carcinoma *in situ* or Squamous Cell Carcinoma		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/32.5 (0.0%)	0/16.0 (0.0%)
Terminal rate	0/31 (0.0%)	0/16 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	5/36 (13.9%)	10/18 (55.6%)
Adjusted rate	5/32.7 (15.3%)	10/15.6 (64.2%)
Terminal rate	5/32 (15.6%)	9/14 (64.3%)
First incidence (days)	365 (T)	342
Poly-3 test		P=0.001
0.6 MED		
Overall rate	30/36 (83.3%)	18/18 (100.0%)
Adjusted rate	30/33.9 (88.5%)	18/18.0 (100.0%)
Terminal rate	2/3 (66.7%)	0/0
First incidence (days)	287	263 (10 mm)
Poly-3 test		P=0.131

TABLE A2b
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
Skin (Site of Application): Squamous Cell Papilloma, Carcinoma *in situ*, or Squamous Cell Carcinoma		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/32.5 (0.0%)	0/16.0 (0.0%)
Terminal rate	0/31 (0.0%)	0/16 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	6/36 (16.7%)	11/18 (61.1%)
Adjusted rate	6/32.7 (18.3%)	11/15.6 (70.6%)
Terminal rate	6/32 (18.8%)	10/14 (71.4%)
First incidence (days)	365 (T)	342
Poly-3 test		P=0.001
0.6 MED		
Overall rate	30/36 (83.3%)	18/18 (100.0%)
Adjusted rate	30/33.9 (88.5%)	18/18.0 (100.0%)
Terminal rate	2/3 (66.7%)	0/0
First incidence (days)	287	263 (10 mm)
Poly-3 test		P=0.131
All Organs: Benign Neoplasms		
0.0 MED		
Overall rate	3/36 (8.3%)	1/18 (5.6%)
Adjusted rate	3/32.5 (9.2%)	1/16.0 (6.2%)
Terminal rate	3/31 (9.7%)	1/16 (6.3%)
First incidence (days)	365 (T)	367 (T)
Poly-3 test		P=0.577N
0.3 MED		
Overall rate	6/36 (16.7%)	7/18 (38.9%)
Adjusted rate	6/32.7 (18.3%)	7/15.6 (44.9%)
Terminal rate	6/32 (18.8%)	6/14 (42.9%)
First incidence (days)	365 (T)	342
Poly-3 test		P=0.053
0.6 MED		
Overall rate	3/36 (8.3%)	4/18 (22.2%)
Adjusted rate	3/25.1 (11.9%)	4/12.4 (32.1%)
Terminal rate	0/3 (0.0%)	0/0
First incidence (days)	298 (10 mm)	270 (10 mm)
Poly-3 test		P=0.139

TABLE A2b
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
All Organs: Malignant Neoplasms		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/32.5 (0.0%)	0/16.0 (0.0%)
Terminal rate	0/31 (0.0%)	0/16 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	5/36 (13.9%)	11/18 (61.1%)
Adjusted rate	5/32.7 (15.3%)	11/15.6 (70.6%)
Terminal rate	5/32 (15.6%)	10/14 (71.4%)
First incidence (days)	365 (T)	342
Poly-3 test		P=0.001
0.6 MED		
Overall rate	30/36 (83.3%)	18/18 (100.0%)
Adjusted rate	30/33.9 (88.5%)	18/18.0 (100.0%)
Terminal rate	2/3 (66.7%)	0/0
First incidence (days)	287	263 (10 mm)
Poly-3 test		P=0.131
All Organs: Benign or Malignant Neoplasms		
0.0 MED		
Overall rate	3/36 (8.3%)	1/18 (5.6%)
Adjusted rate	3/32.5 (9.2%)	1/16.0 (6.2%)
Terminal rate	3/31 (9.7%)	1/16 (6.3%)
First incidence (days)	365 (T)	367 (T)
Poly-3 test		P=0.577N
0.3 MED		
Overall rate	8/36 (22.2%)	14/18 (77.8%)
Adjusted rate	8/32.7 (24.5%)	14/15.6 (89.8%)
Terminal rate	8/32 (25.0%)	13/14 (92.9%)
First incidence (days)	365 (T)	342
Poly-3 test		P=0.001
0.6 MED		
Overall rate	30/36 (83.3%)	18/18 (100.0%)
Adjusted rate	30/33.9 (88.5%)	18/18.0 (100.0%)
Terminal rate	2/3 (66.7%)	0/0
First incidence (days)	287	263 (10 mm)
Poly-3 test		P=0.131

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control cream group incidence are the P values corresponding to pairwise comparisons between the no cream and the control cream group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in the control cream group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed
[g] First incidence occurred when an animal was removed from study due to a skin neoplasm 10 mm or greater.

TABLE A2c
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Liver: Hepatocellular Adenoma			
0.0 MED			
Overall rate[a]	0/3 (0.0%)	1/3 (33.3%)	1/4 (25.0%)
Adjusted rate[b]	0/3.0 (0.0%)	1/3.0 (33.3%)	1/3.0 (33.3%)
Terminal rate[c]	0/3 (0.0%)	1/3 (33.3%)	1/3 (33.3%)
First incidence (days)	—[e]	384 (T)	366 (T)
Poly-3 test[d]	P=0.350	P=0.500	P=0.500
0.3 MED			
Overall rate	2/3 (66.7%)	1/3 (33.3%)	0/1 (0.0%)
Adjusted rate	2/2.3 (87.5%)	1/3.0 (33.3%)	0/0.7 (0.0%)
Terminal rate	2/2 (100.0%)	1/3 (33.3%)	0/0
First incidence (days)	365 (T)	367 (T)	—
Poly-3 test	P=0.243N	P=0.365N	P=0.573N
0.6 MED			
Overall rate	0/2 (0.0%)	0/2 (0.0%)	1/3 (33.3%)
Adjusted rate	0/0.8 (0.0%)	0/1.1 (0.0%)	1/1.9 (53.5%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	—[f]	327 (10 mm)[g]
Poly-3 test	P=0.436	—	P=0.676
Lung: Alveolar/bronchiolar Adenoma			
0.0 MED			
Overall rate	1/18 (5.6%)	1/18 (5.6%)	1/18 (5.6%)
Adjusted rate	1/16.0 (6.2%)	1/15.9 (6.3%)	1/17.0 (5.9%)
Terminal rate	1/16 (6.3%)	1/15 (6.7%)	1/17 (5.9%)
First incidence (days)	367 (T)	367 (T)	367 (T)
Poly-3 test	P=0.650N	P=0.759	P=0.748N
0.3 MED			
Overall rate	3/18 (16.7%)	2/18 (11.1%)	1/18 (5.6%)
Adjusted rate	3/15.4 (19.5%)	2/16.0 (12.5%)	1/15.3 (6.5%)
Terminal rate	3/14 (21.4%)	2/14 (14.3%)	0/11 (0.0%)
First incidence (days)	365 (T)	365 (T)	348 (10 mm)
Poly-3 test	P=0.235N	P=0.482N	P=0.299N
0.6 MED			
Overall rate	0/18 (0.0%)	0/17 (0.0%)	2/18 (11.1%)
Adjusted rate	0/10.6 (0.0%)	0/7.1 (0.0%)	2/9.6 (20.9%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	—	284 (10 mm)
Poly-3 test	P=0.075	—	P=0.200

TABLE A2c
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Lymph Node (Mandibular): Malignant Lymphoma			
0.0 MED			
Overall rate	0/3 (0.0%)	0/4 (0.0%)	0/4 (0.0%)
Adjusted rate	0/3.0 (0.0%)	0/3.8 (0.0%)	0/4.0 (0.0%)
Terminal rate	0/3 (0.0%)	0/3 (0.0%)	0/4 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/3 (0.0%)	0/6 (0.0%)	0/5 (0.0%)
Adjusted rate	0/3.0 (0.0%)	0/5.8 (0.0%)	0/4.2 (0.0%)
Terminal rate	0/3 (0.0%)	0/5 (0.0%)	0/3 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.6 MED			
Overall rate	0/7 (0.0%)	1/8 (12.5%)	0/6 (0.0%)
Adjusted rate	0/3.9 (0.0%)	1/4.1 (24.3%)	0/3.2 (0.0%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	334 (10 mm)	—
Poly-3 test	P=0.762N	P=0.512	—
Skin (Control): Squamous Cell Papilloma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.4 (0.0%)	0/16.0 (0.0%)	0/15.2 (0.0%)
Terminal rate	0/14 (0.0%)	0/14 (0.0%)	0/11 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.6 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	1/18 (5.6%)
Adjusted rate	0/10.6 (0.0%)	0/7.7 (0.0%)	1/9.1 (11.0%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	—	284 (10 mm)
Poly-3 test	P=0.256	—	P=0.469

TABLE A2c
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Skin (Control): Carcinoma *in situ*			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	2/18 (11.1%)	1/18 (5.6%)	0/18 (0.0%)
Adjusted rate	2/15.4 (13.0%)	1/16.0 (6.2%)	0/15.2 (0.0%)
Terminal rate	2/14 (14.3%)	1/14 (7.1%)	0/11 (0.0%)
First incidence (days)	367 (T)	366 (T)	—
Poly-3 test	P=0.160N	P=0.486N	P=0.234N
0.6 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	1/10.9 (9.2%)	0/7.7 (0.0%)	0/8.5 (0.0%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	319 (10 mm)	—	—
Poly-3 test	P=0.335N	P=0.569N	P=0.549N
Skin (Control): Squamous Cell Papilloma or Carcinoma *in situ*			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	2/18 (11.1%)	1/18 (5.6%)	0/18 (0.0%)
Adjusted rate	2/15.4 (13.0%)	1/16.0 (6.2%)	0/15.2 (0.0%)
Terminal rate	2/14 (14.3%)	1/14 (7.1%)	0/11 (0.0%)
First incidence (days)	367 (T)	366 (T)	—
Poly-3 test	P=0.160N	P=0.486N	P=0.234N
0.6 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	1/18 (5.6%)
Adjusted rate	1/10.9 (9.2%)	0/7.7 (0.0%)	1/9.1 (11.0%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	319 (10 mm)	—	284 (10 mm)
Poly-3 test	P=0.626	P=0.569N	P=0.726

TABLE A2c
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Skin (Site of Application): Squamous Cell Papilloma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	3/18 (16.7%)	7/18 (38.9%)	3/18 (16.7%)
Adjusted rate	3/15.6 (19.2%)	7/16.0 (43.7%)	3/15.6 (19.2%)
Terminal rate	2/14 (14.3%)	7/14 (50.0%)	2/11 (18.2%)
First incidence (days)	342	365 (T)	299 (10 mm)
Poly-3 test	P=0.509N	P=0.134	P=0.670N
0.6 MED			
Overall rate	4/18 (22.2%)	2/18 (11.1%)	3/18 (16.7%)
Adjusted rate	4/12.4 (32.1%)	2/8.7 (23.1%)	3/9.7 (30.9%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	270 (10 mm)	270	270
Poly-3 test	P=0.577N	P=0.514N	P=0.659N
Skin (Site of Application): Carcinoma *in situ*			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	9/18 (50.0%)	9/18 (50.0%)	10/18 (55.6%)
Adjusted rate	9/15.6 (57.7%)	9/16.7 (54.0%)	10/16.3 (61.2%)
Terminal rate	8/14 (57.1%)	7/14 (50.0%)	6/11 (54.5%)
First incidence (days)	342	304	299 (10 mm)
Poly-3 test	P=0.487	P=0.555N	P=0.564
0.6 MED			
Overall rate	13/18 (72.2%)	11/18 (61.1%)	12/18 (66.7%)
Adjusted rate	13/15.9 (82.0%)	11/12.6 (87.3%)	12/13.9 (86.1%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	263 (10 mm)	229	263
Poly-3 test	P=0.495	P=0.568	P=0.596

TABLE A2c
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Skin (Site of Application): Squamous Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	4/18 (22.2%)	3/18 (16.7%)	9/18 (50.0%)
Adjusted rate	4/15.6 (25.7%)	3/16.6 (18.1%)	9/16.1 (55.8%)
Terminal rate	3/14 (21.4%)	1/14 (7.1%)	6/11 (54.5%)
First incidence (days)	342	320 (10 mm)	299 (10 mm)
Poly-3 test	P=0.033	P=0.464N	P=0.080
0.6 MED			
Overall rate	17/18 (94.4%)	15/18 (83.3%)	15/18 (83.3%)
Adjusted rate	17/17.5 (97.1%)	15/15.2 (98.8%)	15/15.3 (98.2%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	263 (10 mm)	213	263
Poly-3 test	P=0.797	P=0.913	P=0.928
Skin (Site of Application): Basal Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	2/18 (11.1%)
Adjusted rate	0/15.4 (0.0%)	0/16.0 (0.0%)	2/15.2 (13.2%)
Terminal rate	0/14 (0.0%)	0/14 (0.0%)	2/11 (18.2%)
First incidence (days)	—	—	365 (T)
Poly-3 test	P=0.084	—	P=0.228
0.6 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/10.6 (0.0%)	0/7.7 (0.0%)	0/8.5 (0.0%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	—	—
Poly-3 test	—	—	—

TABLE A2c
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Skin (Site of Application): Carcinoma *in situ*, Squamous Cell Carcinoma, or Basal Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	10/18 (55.6%)	10/18 (55.6%)	12/18 (66.7%)
Adjusted rate	10/15.6 (64.2%)	10/17.0 (58.8%)	12/16.3 (73.5%)
Terminal rate	9/14 (64.3%)	7/14 (50.0%)	8/11 (72.7%)
First incidence (days)	342	304	299 (10 mm)
Poly-3 test	P=0.337	P=0.519N	P=0.426
0.6 MED			
Overall rate	18/18 (100.0%)	15/18 (83.3%)	15/18 (83.3%)
Adjusted rate	18/18.0 (100.0%)	15/15.2 (98.8%)	15/15.3 (98.2%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	263 (10 mm)	213	263
Poly-3 test	P=0.919N	P=1.000N	P=1.000N
Skin (Site of Application): Squamous Cell Papilloma, Carcinoma *in situ*, Squamous Cell Carcinoma, or Basal Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	11/18 (61.1%)	12/18 (66.7%)	12/18 (66.7%)
Adjusted rate	11/15.6 (70.6%)	12/17.0 (70.6%)	12/16.3 (73.5%)
Terminal rate	10/14 (71.4%)	9/14 (64.3%)	8/11 (72.7%)
First incidence (days)	342	304	299 (10 mm)
Poly-3 test	P=0.518	P=0.648	P=0.586
0.6 MED			
Overall rate	18/18 (100.0%)	15/18 (83.3%)	15/18 (83.3%)
Adjusted rate	18/18.0 (100.0%)	15/15.2 (98.8%)	15/15.3 (98.2%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	263 (10 mm)	213	263
Poly-3 test	P=0.919N	P=1.000N	P=1.000N

TABLE A2c
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
All Organs: Malignant Lymphoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	0/18 (0.0%)
Adjusted rate	0/15.4 (0.0%)	1/16.0 (6.2%)	0/15.2 (0.0%)
Terminal rate	0/14 (0.0%)	1/14 (7.1%)	0/11 (0.0%)
First incidence (days)	—	367 (T)	—
Poly-3 test	P=0.718N	P=0.508	—
0.6 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	0/18 (0.0%)
Adjusted rate	0/10.6 (0.0%)	1/7.9 (12.6%)	0/8.5 (0.0%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	334 (10 mm)	—
Poly-3 test	P=0.750	P=0.442	—
All Organs: Benign Neoplasms			
0.0 MED			
Overall rate	1/18 (5.6%)	2/18 (11.1%)	2/18 (11.1%)
Adjusted rate	1/16.0 (6.2%)	2/15.9 (12.6%)	2/17.0 (11.8%)
Terminal rate	1/16 (6.3%)	2/15 (13.3%)	2/17 (11.8%)
First incidence (days)	367 (T)	367 (T)	366 (T)
Poly-3 test	P=0.454	P=0.496	P=0.520
0.3 MED			
Overall rate	7/18 (38.9%)	8/18 (44.4%)	4/18 (22.2%)
Adjusted rate	7/15.6 (44.9%)	8/16.0 (50.0%)	4/15.8 (25.3%)
Terminal rate	6/14 (42.9%)	8/14 (57.1%)	2/11 (18.2%)
First incidence (days)	342	365 (T)	299 (10 mm)
Poly-3 test	P=0.154N	P=0.528	P=0.219N
0.6 MED			
Overall rate	4/18 (22.2%)	2/18 (11.1%)	6/18 (33.3%)
Adjusted rate	4/12.4 (32.1%)	2/8.7 (23.1%)	6/11.1 (54.3%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	270 (10 mm)	270	270
Poly-3 test	P=0.155	P=0.514N	P=0.236

TABLE A2c
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
All Organs: Malignant Neoplasms			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/15.9 (0.0%)	0/17.0 (0.0%)
Terminal rate	0/16 (0.0%)	0/15 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	11/18 (61.1%)	10/18 (55.6%)	12/18 (66.7%)
Adjusted rate	11/15.6 (70.6%)	10/17.0 (58.8%)	12/16.3 (73.5%)
Terminal rate	10/14 (71.4%)	7/14 (50.0%)	8/11 (72.7%)
First incidence (days)	342	304	299 (10 mm)
Poly-3 test	P=0.467	P=0.370N	P=0.586
0.6 MED			
Overall rate	18/18 (100.0%)	15/18 (83.3%)	15/18 (83.3%)
Adjusted rate	18/18.0 (100.0%)	15/15.2 (98.8%)	15/15.3 (98.2%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	263 (10 mm)	213	263
Poly-3 test	P=0.919N	P=1.000N	P=1.000N
All Organs: Benign or Malignant Neoplasms			
0.0 MED			
Overall rate	1/18 (5.6%)	2/18 (11.1%)	2/18 (11.1%)
Adjusted rate	1/16.0 (6.2%)	2/15.9 (12.6%)	2/17.0 (11.8%)
Terminal rate	1/16 (6.3%)	2/15 (13.3%)	2/17 (11.8%)
First incidence (days)	367 (T)	367 (T)	366 (T)
Poly-3 test	P=0.454	P=0.496	P=0.520
0.3 MED			
Overall rate	14/18 (77.8%)	13/18 (72.2%)	12/18 (66.7%)
Adjusted rate	14/15.6 (89.8%)	13/17.0 (76.5%)	12/16.3 (73.5%)
Terminal rate	13/14 (92.9%)	10/14 (71.4%)	8/11 (72.7%)
First incidence (days)	342	304	299 (10 mm)
Poly-3 test	P=0.205N	P=0.289N	P=0.215N
0.6 MED			
Overall rate	18/18 (100.0%)	15/18 (83.3%)	15/18 (83.3%)
Adjusted rate	18/18.0 (100.0%)	15/15.2 (98.8%)	15/15.3 (98.2%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	263 (10 mm)	213	263
Poly-3 test	P=0.919N	P=1.000N	P=1.000N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparison between the controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed
[g] First incidence occurred when an animal was removed from study due to a skin neoplasm 10 mm or greater.

TABLE A2d
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salicylic Acid
Liver: Hepatocellular Adenoma			
0.0 MED			
Overall rate[a]	0/3 (0.0%)	0/2 (0.0%)	0/0
Adjusted rate[b]	0/3.0 (0.0%)	0/2.0 (0.0%)	0/0.0
Terminal rate[c]	0/3 (0.0%)	0/2 (0.0%)	0/0
First incidence (days)	—[e]	—	—
Poly-3 test[d]	—[f]	—	—
0.3 MED			
Overall rate	2/3 (66.7%)	1/3 (33.3%)	0/0
Adjusted rate	2/2.3 (87.5%)	1/2.4 (41.0%)	0/0.0
Terminal rate	2/2 (100.0%)	1/2 (50.0%)	0/0
First incidence (days)	365 (T)	366 (T)	—
Poly-3 test	P=0.463N	—	P=0.463N
0.6 MED			
Overall rate	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)
Adjusted rate	0/0.8 (0.0%)	0/0.8 (0.0%)	0/1.7 (0.0%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	—	—
Poly-3 test	—	—	—
Lung: Alveolar/bronchiolar Adenoma			
0.0 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	2/17 (11.8%)
Adjusted rate	1/16.0 (6.2%)	0/17.4 (0.0%)	2/17.0 (11.8%)
Terminal rate	1/16 (6.3%)	0/17 (0.0%)	2/17 (11.8%)
First incidence (days)	367 (T)	—	365 (T)
Poly-3 test	P=0.365	P=0.484N	P=0.520
0.3 MED			
Overall rate	3/18 (16.7%)	0/18 (0.0%)	1/18 (5.6%)
Adjusted rate	3/15.4 (19.5%)	0/14.3 (0.0%)	1/17.3 (5.8%)
Terminal rate	3/14 (21.4%)	0/12 (0.0%)	1/15 (6.7%)
First incidence (days)	365 (T)	—	367 (T)
Poly-3 test	P=0.154N	P=0.120N	P=0.257N
0.6 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	1/17 (5.9%)
Adjusted rate	0/10.6 (0.0%)	1/12.2 (8.2%)	1/12.8 (7.8%)
Terminal rate	0/0	0/2 (0.0%)	0/1 (0.0%)
First incidence (days)	—	341 (10 mm)[g]	306 (10 mm)
Poly-3 test	P=0.405	P=0.530	P=0.538

TABLE A2d
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salicylic Acid
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
0.0 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	2/17 (11.8%)
Adjusted rate	1/16.0 (6.2%)	0/17.4 (0.0%)	2/17.0 (11.8%)
Terminal rate	1/16 (6.3%)	0/17 (0.0%)	2/17 (11.8%)
First incidence (days)	367 (T)	—	365 (T)
Poly-3 test	P=0.365	P=0.484N	P=0.520
0.3 MED			
Overall rate	3/18 (16.7%)	0/18 (0.0%)	1/18 (5.6%)
Adjusted rate	3/15.4 (19.5%)	0/14.3 (0.0%)	1/17.3 (5.8%)
Terminal rate	3/14 (21.4%)	0/12 (0.0%)	1/15 (6.7%)
First incidence (days)	365 (T)	—	367 (T)
Poly-3 test	P=0.154N	P=0.120N	P=0.257N
0.6 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	2/17 (11.8%)
Adjusted rate	0/10.6 (0.0%)	1/12.2 (8.2%)	2/12.9 (15.5%)
Terminal rate	0/0	0/2 (0.0%)	0/1 (0.0%)
First incidence (days)	—	341 (10 mm)	306 (10 mm)
Poly-3 test	P=0.181	P=0.530	P=0.278
Lymph Node (Mandibular): Malignant Lymphoma			
0.0 MED			
Overall rate	0/3 (0.0%)	0/4 (0.0%)	0/3 (0.0%)
Adjusted rate	0/3.0 (0.0%)	0/4.0 (0.0%)	0/3.0 (0.0%)
Terminal rate	0/3 (0.0%)	0/4 (0.0%)	0/3 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/3 (0.0%)	1/5 (20.0%)	0/3 (0.0%)
Adjusted rate	0/3.0 (0.0%)	1/4.6 (21.6%)	0/3.0 (0.0%)
Terminal rate	0/3 (0.0%)	0/2 (0.0%)	0/3 (0.0%)
First incidence (days)	—	278	—
Poly-3 test	P=0.742	P=0.586	—
0.6 MED			
Overall rate	0/7 (0.0%)	0/9 (0.0%)	0/7 (0.0%)
Adjusted rate	0/3.9 (0.0%)	0/5.9 (0.0%)	0/4.7 (0.0%)
Terminal rate	0/0	0/1 (0.0%)	0/0
First incidence (days)	—	—	—
Poly-3 test	—	—	—

TABLE A2d
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salicylic Acid
Lymph Node (Mesenteric): Malignant Lymphoma			
0.0 MED			
Overall rate	0/3 (0.0%)	0/1 (0.0%)	0/4 (0.0%)
Adjusted rate	0/3.0 (0.0%)	0/1.0 (0.0%)	0/4.0 (0.0%)
Terminal rate	0/3 (0.0%)	0/1 (0.0%)	0/4 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/2 (0.0%)	1/1 (100.0%)	0/3 (0.0%)
Adjusted rate	0/2.0 (0.0%)	1/1.0 (100.0%)	0/3.0 (0.0%)
Terminal rate	0/2 (0.0%)	0/0	0/3 (0.0%)
First incidence (days)	—	278	—
Poly-3 test	—	—	—
0.6 MED			
Overall rate	0/0	0/0	0/1 (0.0%)
Adjusted rate	0/0.0	0/0.0	0/0.5 (0.0%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	—	—
Poly-3 test	—	—	—
Skin (Control): Carcinoma *in situ*			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	2/18 (11.1%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	2/15.4 (13.0%)	0/14.3 (0.0%)	0/17.3 (0.0%)
Terminal rate	2/14 (14.3%)	0/12 (0.0%)	0/15 (0.0%)
First incidence (days)	367 (T)	—	—
Poly-3 test	P=0.086N	P=0.248N	P=0.207N
0.6 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	1/18 (5.6%)
Adjusted rate	1/10.9 (9.2%)	0/12.0 (0.0%)	1/14.0 (7.1%)
Terminal rate	0/0	0/2 (0.0%)	0/1 (0.0%)
First incidence (days)	319 (10 mm)	—	235
Poly-3 test	P=0.660N	P=0.480N	P=0.705N

TABLE A2d
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salicylic Acid
Skin (Site of Application): Squamous Cell Papilloma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	3/18 (16.7%)	3/18 (16.7%)	0/18 (0.0%)
Adjusted rate	3/15.6 (19.2%)	3/14.7 (20.5%)	0/17.3 (0.0%)
Terminal rate	2/14 (14.3%)	2/12 (16.7%)	0/15 (0.0%)
First incidence (days)	342	320 (10 mm)	—
Poly-3 test	P=0.069N	P=0.642	P=0.090N
0.6 MED			
Overall rate	4/18 (22.2%)	2/18 (11.1%)	4/18 (22.2%)
Adjusted rate	4/12.4 (32.1%)	2/12.9 (15.5%)	4/13.7 (29.2%)
Terminal rate	0/0	0/2 (0.0%)	0/1 (0.0%)
First incidence (days)	270 (10 mm)	298 (10 mm)	327 (10 mm)
Poly-3 test	P=0.548N	P=0.299N	P=0.605N
Skin (Site of Application): Carcinoma *in situ*			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	9/18 (50.0%)	4/18 (22.2%)	1/18 (5.6%)
Adjusted rate	9/15.6 (57.7%)	4/14.7 (27.2%)	1/17.3 (5.8%)
Terminal rate	8/14 (57.1%)	2/12 (16.7%)	1/15 (6.7%)
First incidence (days)	342	320 (10 mm)	367 (T)
Poly-3 test	P<0.001N	P=0.087N	P<0.001N
0.6 MED			
Overall rate	13/18 (72.2%)	15/18 (83.3%)	13/18 (72.2%)
Adjusted rate	13/15.9 (82.0%)	15/16.4 (91.2%)	13/16.4 (79.4%)
Terminal rate	0/0	2/2 (100.0%)	1/1 (100.0%)
First incidence (days)	263 (10 mm)	235	235
Poly-3 test	P=0.509N	P=0.380	P=0.614N

TABLE A2d
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salicylic Acid
Skin (Site of Application): Squamous Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	4/18 (22.2%)	3/18 (16.7%)	1/18 (5.6%)
Adjusted rate	4/15.6 (25.7%)	3/14.7 (20.4%)	1/17.3 (5.8%)
Terminal rate	3/14 (21.4%)	1/12 (8.3%)	1/15 (6.7%)
First incidence (days)	342	320 (10 mm)	367 (T)
Poly-3 test	P=0.093N	P=0.534N	P=0.134N
0.6 MED			
Overall rate	17/18 (94.4%)	15/18 (83.3%)	14/18 (77.8%)
Adjusted rate	17/17.5 (97.1%)	15/16.8 (89.3%)	14/16.9 (83.0%)
Terminal rate	0/0	2/2 (100.0%)	1/1 (100.0%)
First incidence (days)	263 (10 mm)	235	270
Poly-3 test	P=0.111N	P=0.395N	P=0.177N
Skin (Site of Application): Carcinoma *in situ* or Squamous Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	10/18 (55.6%)	4/18 (22.2%)	2/18 (11.1%)
Adjusted rate	10/15.6 (64.2%)	4/14.7 (27.2%)	2/17.3 (11.6%)
Terminal rate	9/14 (64.3%)	2/12 (16.7%)	2/15 (13.3%)
First incidence (days)	342	320 (10 mm)	367 (T)
Poly-3 test	P<0.001N	P=0.040N	P<0.001N
0.6 MED			
Overall rate	18/18 (100.0%)	17/18 (94.4%)	17/18 (94.4%)
Adjusted rate	18/18.0 (100.0%)	17/17.2 (99.1%)	17/17.8 (95.3%)
Terminal rate	0/0	2/2 (100.0%)	1/1 (100.0%)
First incidence (days)	263 (10 mm)	235	235
Poly-3 test	P=0.317N	P=1.000N	P=0.579N

TABLE A2d
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salicylic Acid
Skin (Site of Application): Squamous Cell Papilloma, Carcinoma *in situ*, or Squamous Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	11/18 (61.1%)	5/18 (27.8%)	2/18 (11.1%)
Adjusted rate	11/15.6 (70.6%)	5/14.7 (34.0%)	2/17.3 (11.6%)
Terminal rate	10/14 (71.4%)	3/12 (25.0%)	2/15 (13.3%)
First incidence (days)	342	320 (10 mm)	367 (T)
Poly-3 test	P<0.001N	P=0.041N	P<0.001N
0.6 MED			
Overall rate	18/18 (100.0%)	17/18 (94.4%)	17/18 (94.4%)
Adjusted rate	18/18.0 (100.0%)	17/17.2 (99.1%)	17/17.8 (95.3%)
Terminal rate	0/0	2/2 (100.0%)	1/1 (100.0%)
First incidence (days)	263 (10 mm)	235	235
Poly-3 test	P=0.317N	P=1.000N	P=0.579N
All Organs: Malignant Lymphoma			
0.0 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	1/18.0 (5.6%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	266	—
Poly-3 test	P=0.719N	P=0.523	—
0.3 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	0/18 (0.0%)
Adjusted rate	0/15.4 (0.0%)	1/14.9 (6.7%)	0/17.3 (0.0%)
Terminal rate	0/14 (0.0%)	0/12 (0.0%)	0/15 (0.0%)
First incidence (days)	—	278	—
Poly-3 test	P=0.710N	P=0.493	—
0.6 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/10.6 (0.0%)	0/12.0 (0.0%)	0/13.3 (0.0%)
Terminal rate	0/0	0/2 (0.0%)	0/1 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—

TABLE A2d
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salicylic Acid
All Organs: Benign Neoplasms			
0.0 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	2/18 (11.1%)
Adjusted rate	1/16.0 (6.2%)	0/17.4 (0.0%)	2/17.1 (11.7%)
Terminal rate	1/16 (6.3%)	0/17 (0.0%)	2/17 (11.8%)
First incidence (days)	367 (T)	—	365 (T)
Poly-3 test	P=0.371	P=0.484N	P=0.522
0.3 MED			
Overall rate	7/18 (38.9%)	3/18 (16.7%)	1/18 (5.6%)
Adjusted rate	7/15.6 (44.9%)	3/14.7 (20.5%)	1/17.3 (5.8%)
Terminal rate	6/14 (42.9%)	2/12 (16.7%)	1/15 (6.7%)
First incidence (days)	342	320 (10 mm)	367 (T)
Poly-3 test	P=0.005N	P=0.147N	P=0.009N
0.6 MED			
Overall rate	4/18 (22.2%)	4/18 (22.2%)	5/18 (27.8%)
Adjusted rate	4/12.4 (32.1%)	4/13.1 (30.6%)	5/14.1 (35.4%)
Terminal rate	0/0	1/2 (50.0%)	0/1 (0.0%)
First incidence (days)	270 (10 mm)	298 (10 mm)	306 (10 mm)
Poly-3 test	P=0.510	P=0.638N	P=0.594
All Organs: Malignant Neoplasms			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/16.0 (0.0%)	0/17.4 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/16 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	11/18 (61.1%)	4/18 (22.2%)	2/18 (11.1%)
Adjusted rate	11/15.6 (70.6%)	4/14.7 (27.2%)	2/17.3 (11.6%)
Terminal rate	10/14 (71.4%)	2/12 (16.7%)	2/15 (13.3%)
First incidence (days)	342	320 (10 mm)	367 (T)
Poly-3 test	P<0.001N	P=0.015N	P<0.001N
0.6 MED			
Overall rate	18/18 (100.0%)	17/18 (94.4%)	17/18 (94.4%)
Adjusted rate	18/18.0 (100.0%)	17/17.2 (99.1%)	17/17.8 (95.3%)
Terminal rate	0/0	2/2 (100.0%)	1/1 (100.0%)
First incidence (days)	263 (10 mm)	235	235
Poly-3 test	P=0.317N	P=1.000N	P=0.579N

TABLE A2d
Statistical Analysis of Primary Neoplasms in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salicylic Acid
All Organs: Benign or Malignant Neoplasms			
0.0 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	2/18 (11.1%)
Adjusted rate	1/16.0 (6.2%)	0/17.4 (0.0%)	2/17.1 (11.7%)
Terminal rate	1/16 (6.3%)	0/17 (0.0%)	2/17 (11.8%)
First incidence (days)	367 (T)	—	365 (T)
Poly-3 test	P=0.371	P=0.484N	P=0.522
0.3 MED			
Overall rate	14/18 (77.8%)	5/18 (27.8%)	3/18 (16.7%)
Adjusted rate	14/15.6 (89.8%)	5/14.7 (34.0%)	3/17.3 (17.4%)
Terminal rate	13/14 (92.9%)	3/12 (25.0%)	3/15 (20.0%)
First incidence (days)	342	320 (10 mm)	367 (T)
Poly-3 test	P<0.001N	P<0.001N	P<0.001N
0.6 MED			
Overall rate	18/18 (100.0%)	17/18 (94.4%)	17/18 (94.4%)
Adjusted rate	18/18.0 (100.0%)	17/17.2 (99.1%)	17/17.8 (95.3%)
Terminal rate	0/0	2/2 (100.0%)	1/1 (100.0%)
First incidence (days)	263 (10 mm)	235	235
Poly-3 test	P=0.317N	P=1.000N	P=0.579N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparison between the controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed
[g] First incidence occurred when an animal was removed from study due to a skin neoplasm 10 mm or greater.

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund	3		2	1	1	
Natural deaths	2	2	1			1
Survivors						
Terminal sacrifice	31	16	15	17	17	17
Animals examined microscopically	36	18	18	18	18	18
Alimentary System						
Liver	(2)	(3)	(3)	(4)	(2)	
Eosinophilic focus			1 (33%)		1 (50%)	
Fatty change, mild			1 (33%)			
Inflammation, chronic, minimal				1 (25%)		
Necrosis, focal, mild		1 (33%)				
Necrosis, focal, moderate		2 (67%)		1 (25%)		
Tension lipidosis, mild					1 (50%)	
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
Preputial gland	(6)	(4)	(2)	(1)	(2)	(2)
Dilatation, duct	5 (83%)	4 (100%)	2 (100%)	1 (100%)	2 (100%)	2 (100%)
Inflammation, marked	1 (17%)					
Inflammation, suppurative, minimal	1 (17%)					

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

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System						
Bone marrow	(36)	(18)	(18)	(18)	(18)	(17)
Hyperplasia, mild, myeloid cell		1 (6%)	2 (11%)			
Hyperplasia, moderate, myeloid cell	1 (3%)		1 (6%)			
Lymph node	(5)	(4)	(2)	(2)	(5)	(3)
Foreign body, mild, lumbar		1 (25%)				
Hyperplasia, lymphoid, mild, axillary	2 (40%)	3 (75%)	1 (50%)	1 (50%)	3 (60%)	2 (67%)
Hyperplasia, lymphoid, mild, inguinal	2 (40%)	1 (25%)				2 (67%)
Hyperplasia, lymphoid, mild, lumbar	1 (20%)	1 (25%)			1 (20%)	1 (33%)
Hyperplasia, lymphoid, mild, renal				1 (50%)		
Hyperplasia, lymphoid, minimal, axillary		1 (25%)			1 (20%)	
Hyperplasia, lymphoid, minimal, inguinal					1 (20%)	
Hyperplasia, lymphoid, moderate, lumbar	1 (20%)					
Infiltration cellular, plasma cell, moderate, inguinal	1 (20%)					
Infiltration cellular, plasma cell, moderate, lumbar	2 (40%)					
Infiltration cellular, plasma cell, moderate, renal	1 (20%)					
Infiltration cellular, polymorphonuclear, moderate, inguinal			1 (50%)			
Infiltration cellular, polymorphonuclear, moderate, lumbar	1 (20%)		1 (50%)			
Infiltration cellular, polymorphonuclear, moderate, mediastinal			1 (50%)			
Infiltration cellular, polymorphonuclear, moderate, renal	1 (20%)					
Lymph node, mandibular	(5)	(3)	(4)	(4)	(4)	(3)
Dilatation, mild, sinus			1 (25%)			
Hemorrhage, mild		1 (33%)				
Hyperplasia, lymphoid, mild	3 (60%)	1 (33%)	1 (25%)	4 (100%)	2 (50%)	2 (67%)
Infiltration cellular, plasma cell, mild	2 (40%)	1 (33%)			2 (50%)	
Infiltration cellular, plasma cell, minimal	1 (20%)					
Infiltration cellular, polymorphonuclear, marked			1 (25%)			
Infiltration cellular, polymorphonuclear, moderate			1 (25%)			1 (33%)
Lymph node, mesenteric		(3)	(1)	(1)	(1)	(4)
Hyperplasia, lymphoid, mild		1 (33%)		1 (100%)		4 (100%)
Hyperplasia, lymphoid, minimal		2 (67%)			1 (100%)	
Infiltration cellular, polymorphonuclear, moderate			1 (100%)			
Spleen	(36)	(18)	(18)	(18)	(18)	(17)
Hematopoietic cell proliferation, mild	4 (11%)	4 (22%)	4 (22%)	2 (11%)	1 (6%)	1 (6%)
Hematopoietic cell proliferation, minimal	10 (28%)	6 (33%)	6 (33%)	5 (28%)	5 (28%)	4 (24%)
Hematopoietic cell proliferation, moderate	4 (11%)		3 (17%)	1 (6%)		1 (6%)
Hyperplasia, lymphoid, mild				1 (6%)		

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Integumentary System						
Skin, control	(36)	(18)	(18)	(18)	(18)	(18)
Acanthosis, mild	1 (3%)					
Cyst epithelial inclusion						1 (6%)
Cyst epithelial inclusion, tail	5 (14%)	2 (11%)	5 (28%)	5 (28%)	5 (28%)	5 (28%)
Inflammation, chronic active, marked, epidermis	1 (3%)					
Inflammation, chronic active, moderate, epidermis	1 (3%)				1 (6%)	
Inflammation, granulomatous, mild, dermis	6 (17%)	1 (6%)			2 (11%)	2 (11%)
Inflammation, granulomatous, mild, tail, dermis					1 (6%)	
Inflammation, granulomatous, minimal, dermis	26 (72%)	15 (83%)	15 (83%)	16 (89%)	14 (78%)	14 (78%)
Inflammation, pyogranulomatous, marked, dermis	1 (3%)					
Inflammation, pyogranulomatous, moderate, dermis					1 (6%)	
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(18)
Abscess			1 (6%)			
Acanthosis, mild					1 (6%)	
Acanthosis, minimal		2 (11%)	2 (11%)	1 (6%)		1 (6%)
Cyst epithelial inclusion			1 (6%)	2 (11%)		2 (11%)
Fibrosis, mild, dermis	1 (3%)					
Hyperplasia, mild, sebaceous gland					1 (6%)	
Hyperplasia, squamous, mild						1 (6%)
Inflammation, granulomatous, mild, dermis	13 (36%)	8 (44%)	4 (22%)	2 (11%)	8 (44%)	8 (44%)
Inflammation, granulomatous, minimal, dermis	21 (58%)	9 (50%)	12 (67%)	15 (83%)	8 (44%)	8 (44%)
Inflammation, pyogranulomatous, mild, dermis			1 (6%)			
Inflammation, pyogranulomatous, moderate, dermis				1 (6%)		
Necrosis, epidermis			1 (6%)			
Musculoskeletal System						
None						
Nervous System						
None						

TABLE A3a
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Respiratory System						
Lung	(36)	(18)	(18)	(18)	(18)	(17)
Hemorrhage, mild		1 (6%)				
Hyperplasia, minimal, alveolar epithelium				1 (6%)	1 (6%)	1 (6%)
Infiltration cellular, lymphocyte, minimal	1 (3%)				2 (11%)	
Inflammation, minimal, alveolus	3 (8%)		1 (6%)			1 (6%)
Special Senses System						
Eye	(1)		(1)	(1)	(2)	
Cataract				1 (100%)		
Inflammation, mild, cornea					1 (50%)	
Lacrimal gland	(1)	(1)				
Infiltration cellular, lymphocyte, mild		1 (100%)				
Infiltration cellular, lymphocyte, moderate	1 (100%)					
Urinary System						
None						

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund	2	1	1	4	1	1
Natural deaths	2	3	1		3	2
Skin neoplasm greater than 10 mm			2	3	2	
Survivors						
Terminal sacrifice	32	14	14	11	12	15
Animals examined microscopically	36	18	18	18	18	18
Alimentary System						
Esophagus				(1)		
Dilatation				1 (100%)		
Liver	(1)	(3)	(3)	(1)	(3)	
Angiectasis, moderate		1 (33%)				
Hematopoietic cell proliferation, marked				1 (100%)		
Infarct			1 (33%)			
Inflammation, diffuse, moderate			1 (33%)			
Metaplasia, osseous				1 (33%)		
Mesentery						(1)
Necrosis, fat						1 (100%)
Cardiovascular System						
Heart		(1)				
Infarct, moderate		1 (100%)				
Endocrine System						
None						
General Body System						
None						
Genital System						
Preputial gland	(3)	(3)	(1)	(4)	(3)	(2)
Atrophy, mild, parenchymal cell					1 (33%)	
Dilatation, duct	2 (67%)	3 (100%)		4 (100%)	3 (100%)	1 (50%)
Inflammation, marked	1 (33%)					
Inflammation, mild				1 (25%)		
Inflammation, moderate						1 (50%)
Inflammation, suppurative, moderate			1 (100%)			
Seminal vesicle	(1)	(1)	(1)			
Autolysis, marked		1 (100%)				
Decreased secretory fluid, mild			1 (100%)			
Distended	1 (100%)					

[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 Glycolic Acid and Salicylic Acid: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System						
Bone marrow	(36)	(18)	(18)	(18)	(18)	(18)
Hyperplasia, marked, myeloid cell				1 (6%)		
Hyperplasia, mild, myeloid cell	3 (8%)	2 (11%)	1 (6%)	5 (28%)	2 (11%)	2 (11%)
Hyperplasia, moderate, myeloid cell	2 (6%)		1 (6%)	2 (11%)		
Lymph node	(15)	(10)	(12)	(10)	(4)	(9)
Abscess, lumbar				1 (10%)		
Abscess, thoracic				1 (10%)		
Hematopoietic cell proliferation, marked, lumbar				1 (10%)		
Hematopoietic cell proliferation, marked, mediastinal				1 (10%)		
Hematopoietic cell proliferation, moderate, axillary				1 (10%)		
Hyperplasia, lymphoid, marked, axillary				1 (10%)		
Hyperplasia, lymphoid, mild, axillary	8 (53%)	4 (40%)	8 (67%)	5 (50%)	2 (50%)	8 (89%)
Hyperplasia, lymphoid, mild, inguinal	4 (27%)	2 (20%)	3 (25%)	6 (60%)	1 (25%)	2 (22%)
Hyperplasia, lymphoid, mild, lumbar	4 (27%)	2 (20%)	1 (8%)	2 (20%)		1 (11%)
Hyperplasia, lymphoid, mild, mediastinal		1 (10%)				
Hyperplasia, lymphoid, mild, pancreatic			1 (8%)	1 (10%)		
Hyperplasia, lymphoid, mild, popliteal		1 (10%)	1 (8%)			
Hyperplasia, lymphoid, mild, renal	1 (7%)	1 (10%)	1 (8%)			1 (11%)
Hyperplasia, lymphoid, mild, thoracic	1 (7%)		1 (8%)			
Hyperplasia, lymphoid, minimal, axillary	1 (7%)					
Hyperplasia, lymphoid, minimal, lumbar	1 (7%)					
Hyperplasia, lymphoid, minimal, popliteal	1 (7%)					
Hyperplasia, lymphoid, minimal, renal	1 (7%)					
Hyperplasia, lymphoid, moderate, axillary		1 (10%)		2 (20%)		
Hyperplasia, lymphoid, moderate, inguinal				2 (20%)		
Hyperplasia, lymphoid, moderate, lumbar		1 (10%)		1 (10%)		
Hyperplasia, lymphoid, moderate, mediastinal				2 (20%)		
Infiltration cellular, plasma cell, marked, mediastinal			1 (8%)			
Infiltration cellular, plasma cell, mild, axillary		1 (10%)	1 (8%)			
Infiltration cellular, plasma cell, mild, inguinal		1 (10%)				
Infiltration cellular, plasma cell, moderate, inguinal			1 (8%)			
Infiltration cellular, plasma cell, moderate, lumbar			1 (8%)			
Infiltration cellular, plasma cell, moderate, popliteal		1 (10%)				
Infiltration cellular, plasma cell, moderate, renal	1 (7%)					
Inflammation, moderate, lumbar		1 (10%)				
Lymph node, mandibular	(8)	(3)	(6)	(5)	(5)	(3)
Hyperplasia, lymphoid, mild	5 (63%)	2 (67%)	6 (100%)	4 (80%)	2 (40%)	3 (100%)
Infiltration cellular, plasma cell, mild	2 (25%)		1 (17%)			
Infiltration cellular, plasma cell, moderate	1 (13%)	1 (33%)	1 (17%)	1 (20%)	2 (40%)	
Lymph node, mesenteric	(4)	(2)		(3)	(1)	(3)
Hematopoietic cell proliferation, mild				1 (33%)		
Hematopoietic cell proliferation, moderate				1 (33%)		
Hyperplasia, lymphoid, mild	2 (50%)	2 (100%)		2 (67%)		2 (67%)
Hyperplasia, lymphoid, minimal	1 (25%)					

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System (continued)						
Spleen	(36)	(18)	(18)	(18)	(18)	(18)
Hematopoietic cell proliferation, marked		1 (6%)				
Hematopoietic cell proliferation, mild	12 (33%)	4 (22%)	8 (44%)	7 (39%)	5 (28%)	9 (50%)
Hematopoietic cell proliferation, minimal	14 (39%)	6 (33%)	4 (22%)	1 (6%)	8 (44%)	4 (22%)
Hematopoietic cell proliferation, moderate	1 (3%)	2 (11%)	2 (11%)	5 (28%)	2 (11%)	1 (6%)
Integumentary System						
Skin, control	(36)	(18)	(18)	(18)	(18)	(18)
Abscess, tail	1 (3%)	1 (6%)				
Cyst epithelial inclusion	2 (6%)	1 (6%)			1 (6%)	2 (11%)
Cyst epithelial inclusion, tail	5 (14%)	1 (6%)	3 (17%)	1 (6%)	3 (17%)	5 (28%)
Edema, mild		1 (6%)				
Hyperplasia, squamous, mild						1 (6%)
Hyperplasia, squamous, minimal					1 (6%)	
Inflammation, granulomatous, mild, dermis	3 (8%)	1 (6%)	2 (11%)	2 (11%)	5 (28%)	2 (11%)
Inflammation, granulomatous, minimal, dermis	32 (89%)	13 (72%)	15 (83%)	14 (78%)	11 (61%)	15 (83%)
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(18)
Abscess	1 (3%)	1 (6%)				
Acanthosis, mild	1 (3%)	1 (6%)	1 (6%)	2 (11%)		
Acanthosis, minimal	26 (72%)	12 (67%)	14 (78%)	10 (56%)	12 (67%)	3 (17%)
Cyst epithelial inclusion	2 (6%)	2 (11%)	3 (17%)	1 (6%)	2 (11%)	
Edema, moderate		1 (6%)				
Hyperplasia, squamous, marked	3 (8%)	3 (17%)	2 (11%)	2 (11%)	1 (6%)	1 (6%)
Hyperplasia, squamous, mild	2 (6%)	2 (11%)	7 (39%)	4 (22%)	3 (17%)	2 (11%)
Hyperplasia, squamous, minimal	4 (11%)			1 (6%)	1 (6%)	
Hyperplasia, squamous, moderate	2 (6%)	5 (28%)	5 (28%)	5 (28%)	1 (6%)	4 (22%)
Inflammation, chronic active, mild, epidermis			1 (6%)			
Inflammation, chronic active, moderate, epidermis				1 (6%)		
Inflammation, granulomatous, mild, dermis	18 (50%)	8 (44%)	9 (50%)	10 (56%)	10 (56%)	10 (56%)
Inflammation, granulomatous, minimal, dermis	18 (50%)	9 (50%)	8 (44%)	7 (39%)	6 (33%)	8 (44%)
Inflammation, pyogranulomatous, mild, dermis					1 (6%)	
Inflammation, pyogranulomatous, moderate, subcutaneous tissue		1 (6%)				
Musculoskeletal System						
None						
Nervous System						
None						

TABLE A3b
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Respiratory System						
Lung	(36)	(18)	(18)	(18)	(18)	(18)
Hemorrhage, mild		1 (6%)			1 (6%)	
Hyperplasia, mild, alveolar epithelium	1 (3%)		1 (6%)			
Hyperplasia, minimal, alveolar epithelium		1 (6%)	1 (6%)			
Infiltration cellular, lymphocyte, minimal	2 (6%)	2 (11%)				
Inflammation, marked, alveolus				1 (6%)		
Inflammation, marked, bronchiole						1 (6%)
Inflammation, mild, alveolus			1 (6%)	2 (11%)		
Inflammation, mild, bronchiole				1 (6%)		
Inflammation, minimal, alveolus		1 (6%)		2 (11%)		1 (6%)
Inflammation, moderate, alveolus						1 (6%)
Special Senses System						
Ear				(1)		
Hyperplasia, squamous, mild, pinna				1 (100%)		
Eye	(2)	(1)	(1)			
Inflammation, mild, cornea	1 (50%)					
Urinary System						
Kidney			(1)	(4)		(1)
Abscess				2 (50%)		
Cyst						1 (100%)
Infiltration cellular, lymphocyte, mild				2 (50%)		
Inflammation, suppurative, marked			1 (100%)			
Urethra	(4)	(2)	(1)	(2)	(2)	(4)
Hemorrhage, moderate, bulbourethral gland						1 (25%)
Urinary bladder		(1)	(1)			
Autolysis		1 (100%)				
Inflammation, mild			1 (100%)			

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early deaths						
Moribund	3	3	3	6	6	5
Natural deaths	4		4	1		3
Skin neoplasm greater than 10 mm	26	15	11	11	10	9
Survivors						
Terminal sacrifice	3				2	1
Animals examined microscopically	36	18	18	18	18	18
Alimentary System						
Liver	(2)	(2)	(2)	(3)	(2)	(2)
Abscess			1 (50%)			
Basophilic focus	1 (50%)					
Hematopoietic cell proliferation, mild		2 (100%)		1 (33%)	1 (50%)	
Infarct	1 (50%)		1 (50%)		1 (50%)	1 (50%)
Inflammation, diffuse, marked						2 (100%)
Necrosis, focal, marked						1 (50%)
Pancreas			(1)		(1)	(1)
Accessory spleen			1 (100%)			
Inflammation, chronic, moderate						1 (100%)
Cardiovascular System						
Heart	(1)					
Abscess, ventricle right, septum interventricular	1 (100%)					
Endocrine System						
None						
General Body System						
None						
Genital System						
Preputial gland	(3)		(2)		(2)	(2)
Atrophy, moderate, parenchymal cell			1 (50%)			
Dilatation, duct	3 (100%)		1 (50%)		1 (50%)	2 (100%)
Inflammation, marked			1 (50%)			
Inflammation, mild	1 (33%)				1 (50%)	
Seminal vesicle	(5)					
Decreased secretory fluid, moderate	1 (20%)					
Distended	2 (40%)					

[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 Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System						
Bone marrow	(36)	(18)	(17)	(18)	(18)	(17)
Hyperplasia, marked, myeloid cell				1 (6%)	1 (6%)	
Hyperplasia, mild, myeloid cell	17 (47%)	6 (33%)	7 (41%)	7 (39%)	9 (50%)	7 (41%)
Hyperplasia, moderate, myeloid cell	5 (14%)	3 (17%)	4 (24%)	3 (17%)	2 (11%)	1 (6%)
Lymph node	(28)	(18)	(13)	(13)	(15)	(13)
Hematopoietic cell proliferation, moderate, lumbar						1 (8%)
Hyperplasia, lymphoid, marked, mediastinal					1 (7%)	
Hyperplasia, lymphoid, mild	1 (4%)			1 (8%)		
Hyperplasia, lymphoid, mild, axillary	15 (54%)	10 (56%)	8 (62%)	6 (46%)	9 (60%)	11 (85%)
Hyperplasia, lymphoid, mild, inguinal	7 (25%)	10 (56%)	8 (62%)	4 (31%)	7 (47%)	9 (69%)
Hyperplasia, lymphoid, mild, lumbar	7 (25%)	3 (17%)		2 (15%)		4 (31%)
Hyperplasia, lymphoid, mild, renal	4 (14%)	1 (6%)	1 (8%)	2 (15%)		1 (8%)
Hyperplasia, lymphoid, mild, thoracic	2 (7%)			1 (8%)		
Hyperplasia, lymphoid, moderate, axillary	6 (21%)	5 (28%)	2 (15%)	6 (46%)	5 (33%)	1 (8%)
Hyperplasia, lymphoid, moderate, bronchial	1 (4%)	1 (6%)				
Hyperplasia, lymphoid, moderate, deep cervical						1 (8%)
Hyperplasia, lymphoid, moderate, inguinal	8 (29%)	1 (6%)		5 (38%)	1 (7%)	
Hyperplasia, lymphoid, moderate, lumbar		2 (11%)		1 (8%)		
Hyperplasia, lymphoid, moderate, mediastinal					1 (7%)	
Infiltration cellular, plasma cell, mild, axillary	3 (11%)	1 (6%)	3 (23%)	2 (15%)	2 (13%)	1 (8%)
Infiltration cellular, plasma cell, mild, inguinal	2 (7%)		2 (15%)	2 (15%)	1 (7%)	
Infiltration cellular, plasma cell, mild, lumbar				1 (8%)		1 (8%)
Infiltration cellular, plasma cell, mild, renal				1 (8%)		
Infiltration cellular, plasma cell, mild, thoracic				1 (8%)		
Infiltration cellular, plasma cell, moderate, axillary	4 (14%)	1 (6%)	3 (23%)	3 (23%)	1 (7%)	
Infiltration cellular, plasma cell, moderate, inguinal	5 (18%)		2 (15%)		3 (20%)	
Infiltration cellular, plasma cell, moderate, lumbar	3 (11%)	1 (6%)				
Lymph node, mandibular	(11)	(7)	(8)	(6)	(9)	(7)
Hyperplasia, lymphoid, mild	11 (100%)	6 (86%)	5 (63%)	5 (83%)	3 (33%)	4 (57%)
Hyperplasia, lymphoid, moderate			1 (13%)	1 (17%)	2 (22%)	
Infiltration cellular, plasma cell, mild	3 (27%)	1 (14%)	2 (25%)	4 (67%)	5 (56%)	2 (29%)
Infiltration cellular, plasma cell, moderate	3 (27%)	1 (14%)	2 (25%)	1 (17%)	2 (22%)	3 (43%)
Infiltration cellular, polymorphonuclear, moderate				1 (17%)		

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System (continued)						
Lymph node, mesenteric	(1)		(1)			(1)
Hyperplasia, lymphoid, mild	1 (100%)		1 (100%)			1 (100%)
Spleen	(36)	(18)	(17)	(18)	(18)	(17)
Hematopoietic cell proliferation, marked		1 (6%)				2 (12%)
Hematopoietic cell proliferation, mild	13 (36%)	6 (33%)	6 (35%)	6 (33%)	2 (11%)	3 (18%)
Hematopoietic cell proliferation, minimal					2 (11%)	1 (6%)
Hematopoietic cell proliferation, moderate	23 (64%)	11 (61%)	10 (59%)	12 (67%)	14 (78%)	10 (59%)
Hyperplasia, lymphoid, moderate						1 (6%)
Integumentary System						
Skin, control	(36)	(18)	(18)	(18)	(18)	(18)
Abscess						1 (6%)
Acanthosis, minimal	1 (3%)					1 (6%)
Cyst epithelial inclusion			1 (6%)			1 (6%)
Cyst epithelial inclusion, tail		1 (6%)				
Fibrosis, moderate, dermis					1 (6%)	
Hemorrhage, moderate	1 (3%)					
Hyperplasia, squamous, marked			1 (6%)			
Hyperplasia, squamous, mild						1 (6%)
Hyperplasia, squamous, minimal					1 (6%)	
Hyperplasia, squamous, moderate	1 (3%)				1 (6%)	
Inflammation, chronic active, marked, epidermis				1 (6%)		1 (6%)
Inflammation, chronic active, marked, tail, epidermis	2 (6%)			1 (6%)		
Inflammation, chronic active, mild, epidermis					1 (6%)	
Inflammation, chronic active, mild, tail, epidermis				1 (6%)		
Inflammation, chronic active, moderate, epidermis	1 (3%)					1 (6%)
Inflammation, chronic active, moderate, tail, epidermis			1 (6%)			2 (11%)
Inflammation, granulomatous, mild, dermis	6 (17%)	1 (6%)		1 (6%)	6 (33%)	1 (6%)
Inflammation, granulomatous, minimal, dermis	27 (75%)	17 (94%)	14 (78%)	15 (83%)	10 (56%)	16 (89%)
Inflammation, pyogranulomatous, marked, dermis				1 (6%)		2 (11%)
Inflammation, pyogranulomatous, marked, tail, dermis	2 (6%)					
Inflammation, pyogranulomatous, moderate, dermis					1 (6%)	1 (6%)
Necrosis, marked, epidermis			1 (6%)			
Necrosis, moderate, tail, epidermis		1 (6%)				

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Integumentary System (continued)						
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(18)
Abscess	2 (6%)			2 (11%)	1 (6%)	
Acanthosis, mild	7 (19%)	3 (17%)	4 (22%)	6 (33%)	5 (28%)	1 (6%)
Acanthosis, minimal	23 (64%)	12 (67%)	12 (67%)	10 (56%)	9 (50%)	13 (72%)
Acanthosis, moderate			1 (6%)			
Cyst epithelial inclusion						1 (6%)
Fibrosis, moderate, dermis	1 (3%)					
Hyperplasia, squamous, marked	7 (19%)	8 (44%)	7 (39%)	10 (56%)	10 (56%)	10 (56%)
Hyperplasia, squamous, mild	4 (11%)	3 (17%)	1 (6%)	1 (6%)	2 (11%)	2 (11%)
Hyperplasia, squamous, minimal		1 (6%)			1 (6%)	1 (6%)
Hyperplasia, squamous, moderate	6 (17%)	2 (11%)	3 (17%)	4 (22%)	1 (6%)	3 (17%)
Inflammation, chronic active, marked, epidermis	1 (3%)			1 (6%)	1 (6%)	1 (6%)
Inflammation, chronic active, mild, epidermis		1 (6%)			1 (6%)	1 (6%)
Inflammation, chronic active, moderate, epidermis	2 (6%)					
Inflammation, granulomatous, mild, dermis	22 (61%)	11 (61%)	12 (67%)	8 (44%)	10 (56%)	12 (67%)
Inflammation, granulomatous, minimal, dermis	12 (33%)	7 (39%)	3 (17%)	7 (39%)	6 (33%)	5 (28%)
Inflammation, pyogranulomatous, marked, dermis	1 (3%)		1 (6%)			
Inflammation, pyogranulomatous, mild, dermis					2 (11%)	
Musculoskeletal System						
Skeletal muscle	(1)				(1)	
Inflammation, pyogranulomatous, marked					1 (100%)	
Thrombosis, marked	1 (100%)					
Nervous System						
None						
Respiratory System						
Lung	(36)	(18)	(17)	(18)	(18)	(17)
Hemorrhage, mild		1 (6%)	1 (6%)	1 (6%)		
Hemorrhage, minimal			1 (6%)			
Hyperplasia, mild, alveolar epithelium			1 (6%)			
Hyperplasia, minimal, alveolar epithelium						1 (6%)
Infiltration cellular, lymphocyte, mild		4 (22%)		1 (6%)		
Infiltration cellular, lymphocyte, minimal	1 (3%)	2 (11%)			1 (6%)	
Inflammation, mild, alveolus	2 (6%)	1 (6%)		1 (6%)		1 (6%)
Inflammation, minimal, alveolus	6 (17%)	2 (11%)	4 (24%)	1 (6%)	1 (6%)	2 (12%)
Inflammation, moderate, alveolus	1 (3%)					
Inflammation, moderate, bronchiole	1 (3%)					
Leukocytosis, moderate			1 (6%)			

TABLE A3c
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Special Senses System						
Ear				(1)		
Inflammation, suppurative, marked				1 (100%)		
Eye	(2)		(1)	(1)	(1)	
Cataract	1 (50%)					
Inflammation, marked, cornea				1 (100%)		
Inflammation, mild, cornea					1 (100%)	
Inflammation, moderate, anterior chamber				1 (100%)		
Urinary System						
Kidney	(1)	(1)	(1)	(2)	(1)	(3)
Cyst			1 (100%)			
Embolus bacterial, marked						1 (33%)
Infarct					1 (100%)	
Infiltration cellular, lymphocyte, marked						1 (33%)
Infiltration cellular, lymphocyte, mild		1 (100%)		1 (50%)		
Infiltration cellular, lymphocyte, minimal	1 (100%)			1 (50%)		
Inflammation, suppurative, mild						1 (33%)
Inflammation, suppurative, minimal						1 (33%)
Inflammation, suppurative, moderate						1 (33%)

TABLE A3d
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.9 MED

	No Cream
Disposition Summary	
Animals initially in study	36
Early removal	
Moribund	18
Natural deaths	6
Skin neoplasm greater than 10 mm	12
Survivors	
Terminal sacrifice	
Animals examined microscopically	35
Alimentary System	
Liver	(3)
Infarct	1 (33%)
Inflammation, chronic, minimal	1 (33%)
Cardiovascular System	
None	
Endocrine System	
None	
General Body System	
None	
Genital System	
Preputial gland	(3)
Dilatation, duct	2 (67%)
Inflammation, marked	1 (33%)
Inflammation, minimal	1 (33%)

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

TABLE A3d
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.9 MED

	No Cream	
Hematopoietic System		
Bone marrow	(33)	
Hyperplasia, mild, myeloid cell	17	(52%)
Hyperplasia, moderate, myeloid cell	9	(27%)
Lymph node	(20)	
Hyperplasia, lymphoid, mild	1	(5%)
Hyperplasia, lymphoid, mild, axillary	12	(60%)
Hyperplasia, lymphoid, mild, deep cervical	2	(10%)
Hyperplasia, lymphoid, mild, inguinal	11	(55%)
Hyperplasia, lymphoid, mild, lumbar	6	(30%)
Hyperplasia, lymphoid, mild, mediastinal	2	(10%)
Hyperplasia, lymphoid, mild, pancreatic	1	(5%)
Hyperplasia, lymphoid, mild, renal	4	(20%)
Hyperplasia, lymphoid, moderate, axillary	1	(5%)
Hyperplasia, lymphoid, moderate, inguinal	4	(20%)
Hyperplasia, lymphoid, moderate, lumbar	2	(10%)
Hyperplasia, lymphoid, moderate, pancreatic	2	(10%)
Hyperplasia, lymphoid, moderate, renal	1	(5%)
Infiltration cellular, plasma cell, marked, renal	1	(5%)
Infiltration cellular, plasma cell, mild, axillary	1	(5%)
Infiltration cellular, plasma cell, mild, inguinal	2	(10%)
Infiltration cellular, plasma cell, mild, lumbar	1	(5%)
Infiltration cellular, plasma cell, mild, mediastinal	1	(5%)
Infiltration cellular, plasma cell, moderate, axillary	2	(10%)
Infiltration cellular, plasma cell, moderate, deep cervical	1	(5%)
Infiltration cellular, plasma cell, moderate, inguinal	2	(10%)
Infiltration cellular, plasma cell, moderate, lumbar	2	(10%)
Lymph node, mandibular	(8)	
Hyperplasia, lymphoid, mild	5	(63%)
Infiltration cellular, plasma cell, mild	1	(13%)
Infiltration cellular, plasma cell, moderate	5	(63%)
Lymph node, mesenteric	(2)	
Hyperplasia, lymphoid, mild	1	(50%)
Spleen	(33)	
Hematopoietic cell proliferation, marked	1	(3%)
Hematopoietic cell proliferation, mild	10	(30%)
Hematopoietic cell proliferation, moderate	21	(64%)

TABLE A3d
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.9 MED

	No Cream	
Integumentary System		
Skin, control	(35)	
Acanthosis, minimal	1	(3%)
Hyperplasia, squamous, moderate	1	(3%)
Inflammation, chronic active, marked, epidermis	1	(3%)
Inflammation, granulomatous, minimal, dermis	26	(74%)
Inflammation, pyogranulomatous, mild, dermis	1	(3%)
Skin, site of application	(35)	
Abscess	2	(6%)
Acanthosis, mild	7	(20%)
Acanthosis, minimal	21	(60%)
Hyperplasia, squamous, marked	12	(34%)
Hyperplasia, squamous, moderate	7	(20%)
Inflammation, chronic active, marked, epidermis	3	(9%)
Inflammation, chronic active, moderate, epidermis	1	(3%)
Inflammation, granulomatous, mild, dermis	18	(51%)
Inflammation, granulomatous, minimal, dermis	11	(31%)
Musculoskeletal System		
Bone	(1)	
Hyperostosis	1	(100%)
Nervous System		
None		
Respiratory System		
Lung	(33)	
Hemorrhage, mild	1	(3%)
Infiltration cellular, lymphocyte, minimal	1	(3%)
Inflammation, mild, alveolus	1	(3%)
Inflammation, minimal, alveolus	5	(15%)
Leukocytosis, mild	1	(3%)
Special Senses System		
Eye	(3)	
Cataract	1	(33%)
Inflammation, mild, cornea	1	(33%)
Lacrimal gland	(3)	
Infiltration cellular, lymphocyte, moderate	3	(100%)
Urinary System		
Kidney	(2)	
Infiltration cellular, lymphocyte, minimal	2	(100%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE MICE IN THE 1-YEAR SIMULATED SOLAR LIGHT STUDY OF GLYCOLIC ACID AND SALICYLIC ACID

TABLE B1a
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund						2
Natural deaths	2	3	1	1	1	2
Survivors						
Terminal sacrifice	34	15	17	17	17	14
Animals examined microscopically	36	18	18	18	18	18
Alimentary System						
Liver	(1)	(1)		(1)	(2)	(2)
Hepatocellular adenoma	1 (100%)				1 (50%)	1 (50%)
Lymphoma malignant						1 (50%)
Stomach, forestomach			(1)			
Squamous cell papilloma			1 (100%)			
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
Ovary	(20)	(8)	(13)	(12)	(10)	(12)
Cystadenoma	1 (5%)	1 (13%)				
Uterus	(20)	(4)	(5)	(5)	(5)	(5)
Polyp stromal	3 (15%)					
Hematopoietic System						
Lymph node	(10)	(6)	(7)	(1)	(4)	(5)
Lymphoma malignant, axillary	2 (20%)		1 (14%)			1 (20%)
Lymphoma malignant, inguinal	1 (10%)					
Lymphoma malignant, lumbar	1 (10%)					1 (20%)
Lymphoma malignant, mediastinal	1 (10%)					1 (20%)
Lymphoma malignant, renal	2 (20%)					1 (20%)
Lymphoma malignant, thoracic	1 (10%)					
Lymph node, mandibular	(4)	(8)	(5)	(4)	(5)	(3)
Lymphoma malignant	1 (25%)					
Lymph node, mesenteric	(8)	(2)	(3)	(1)	(4)	(2)
Lymphoma malignant	1 (13%)		1 (33%)			1 (50%)
Spleen	(36)	(18)	(18)	(18)	(18)	(18)
Lymphoma malignant	2 (6%)					
Thymus	(1)		(2)		(1)	(1)
Lymphoma malignant	1 (100%)		2 (100%)			1 (100%)

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

TABLE B1a
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Integumentary System						
Skin, control	(36)	(18)	(18)	(18)	(18)	(18)
Squamous cell papilloma					1 (6%)	
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(18)
Squamous cell papilloma	1 (3%)					
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
Lung	(36)	(18)	(18)	(18)	(18)	(18)
Alveolar/bronchiolar adenoma				1 (6%)	1 (6%)	1 (6%)
Lymphoma malignant						1 (6%)
Special Senses System						
None						
Urinary System						
Kidney			(2)			(1)
Lymphoma malignant						1 (100%)

TABLE B1b
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund	1	2			2	1
Natural deaths	2	2	1	2	1	2
Skin neoplasm greater than 10 mm	1	2	5		1	
Survivors						
Terminal sacrifice	32	12	12	16	14	15
Animals examined microscopically	36	18	18	18	18	17
Alimentary System						
Liver	(1)	(4)	(2)	(2)		(1)
Hepatocellular adenoma	1 (100%)			1 (50%)		
Hepatocellular carcinoma				1 (50%)		
Lymphoma malignant			1 (50%)	1 (50%)		1 (100%)
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
Ovary	(19)	(9)	(12)	(9)	(8)	(9)
Cystadenoma	1 (5%)			1 (11%)		
Lymphoma malignant				1 (11%)		
Tubulostromal adenoma	1 (5%)					
Uterus	(17)	(7)	(3)	(8)	(12)	(5)
Polyp stromal	1 (6%)				1 (8%)	

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

TABLE B1b
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System						
Bone marrow	(35)	(18)	(18)	(17)	(18)	(17)
Lymphoma malignant						1 (6%)
Lymph node	(17)	(10)	(9)	(11)	(9)	(6)
Lymphoma malignant, axillary			2 (22%)	2 (18%)		
Lymphoma malignant, inguinal			1 (11%)			1 (17%)
Lymphoma malignant, lumbar			2 (22%)			1 (17%)
Lymphoma malignant, mediastinal			2 (22%)			
Lymphoma malignant, pancreatic			1 (11%)			
Lymphoma malignant, renal			2 (22%)			2 (33%)
Squamous cell carcinoma, metastatic, axillary, skin		1 (10%)				
Squamous cell carcinoma, metastatic, inguinal, skin				1 (9%)		
Lymph node, mandibular	(8)	(5)	(3)	(5)	(5)	(7)
Lymphoma malignant			2 (67%)	1 (20%)		2 (29%)
Lymph node, mesenteric	(6)	(2)	(2)	(4)	(1)	(2)
Lymphoma malignant			2 (100%)	2 (50%)		2 (100%)
Spleen	(35)	(18)	(18)	(17)	(18)	(17)
Lymphoma malignant			2 (11%)	2 (12%)		2 (12%)
Thymus						(1)
Lymphoma malignant						1 (100%)
Integumentary System						
Mammary gland	(1)					
Carcinoma	1 (100%)					
Skin, control	(36)	(18)	(18)	(18)	(18)	(17)
Carcinoma *in situ*	1 (3%)				1 (6%)	1 (6%)
Fibrous histiocytoma, tail	1 (3%)					
Squamous cell papilloma		1 (6%)				
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(17)
Carcinoma *in situ*	2 (6%)	5 (28%)	6 (33%)	3 (17%)	2 (11%)	
Carcinoma *in situ*, five				1 (6%)		
Carcinoma *in situ*, four		1 (6%)	1 (6%)			
Carcinoma *in situ*, greater than five		1 (6%)	1 (6%)			
Carcinoma *in situ*, three		1 (6%)		1 (6%)	1 (6%)	
Carcinoma *in situ*, two	2 (6%)		1 (6%)	2 (11%)	1 (6%)	
Lymphoma malignant						1 (6%)
Squamous cell carcinoma	3 (8%)	2 (11%)	6 (33%)	5 (28%)	4 (22%)	2 (12%)
Squamous cell carcinoma, three		1 (6%)	1 (6%)			
Squamous cell carcinoma, two		1 (6%)	1 (6%)	1 (6%)	1 (6%)	
Squamous cell papilloma		1 (6%)	1 (6%)	3 (17%)	2 (11%)	
Squamous cell papilloma, two		1 (6%)	1 (6%)			
Musculoskeletal System						
None						
Nervous System						
None						

TABLE B1b
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Respiratory System						
Lung	(35)	(18)	(18)	(17)	(18)	(17)
Alveolar/bronchiolar adenoma	1 (3%)	1 (6%)	1 (6%)	1 (6%)		1 (6%)
Alveolar/bronchiolar adenoma, two	1 (3%)					
Alveolar/bronchiolar carcinoma		1 (6%)				
Carcinoma, metastatic, mammary gland	1 (3%)					
Lymphoma malignant			1 (6%)	1 (6%)		1 (6%)
Special Senses System						
Eye	(3)	(1)		(2)	(1)	(4)
Adenoma, lids	1 (33%)					
Lymphoma malignant						1 (25%)
Urinary System						
Kidney	(1)				(1)	
Lymphoma malignant	1 (100%)					

TABLE B1c
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund	2	3	1	2	1	1
Natural deaths	2	1	1			1
Skin neoplasm greater than 10 mm	23	13	15	15	11	8
Survivors						
Terminal sacrifice	9	1	1	1	6	8
Animals examined microscopically	36	18	18	18	18	18
Alimentary System						
Liver	(5)	(2)	(2)		(4)	(3)
Hepatocellular adenoma	1 (20%)		1 (50%)			
Lymphoma malignant	2 (40%)	1 (50%)				
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
Ovary	(22)	(8)	(8)	(8)	(11)	(11)
Granulosa cell tumor malignant					1 (9%)	
Uterus	(12)	(2)	(1)	(3)	(11)	(6)
Polyp stromal					2 (18%)	1 (17%)

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

TABLE B1c
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System						
Lymph node	(30)	(16)	(15)	(17)	(16)	(15)
Granulosa cell tumor malignant, metastatic, lumbar, ovary					1 (6%)	
Lymphoma malignant, axillary		1 (6%)				
Lymphoma malignant, lumbar	1 (3%)					
Lymphoma malignant, mediastinal		1 (6%)				
Squamous cell carcinoma, metastatic, axillary, skin	1 (3%)	1 (6%)	3 (20%)	1 (6%)		
Squamous cell carcinoma, metastatic, inguinal, skin			1 (7%)			
Squamous cell carcinoma, metastatic, skin						1 (7%)
Lymph node, mandibular	(15)	(6)	(8)	(7)	(6)	(7)
Lymphoma malignant		1 (17%)				
Squamous cell carcinoma, metastatic, skin		1 (17%)				
Lymph node, mesenteric	(2)	(2)		(3)	(2)	(2)
Lymphoma malignant	1 (50%)					
Spleen	(36)	(18)	(17)	(18)	(18)	(18)
Lymphoma malignant	1 (6%)					
Integumentary System						
Skin, control	(36)	(18)	(18)	(18)	(18)	(18)
Lymphoma malignant		1 (6%)				
Squamous cell papilloma	1 (3%)			1 (6%)		
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(18)
Carcinoma *in situ*	9 (25%)	5 (28%)	4 (22%)	6 (33%)	2 (11%)	5 (28%)
Carcinoma *in situ*, five		2 (11%)	2 (11%)		1 (6%)	1 (6%)
Carcinoma *in situ*, four	3 (8%)	1 (6%)	2 (11%)	1 (6%)		1 (6%)
Carcinoma *in situ*, greater than five	2 (6%)	1 (6%)	2 (11%)	1 (6%)		
Carcinoma *in situ*, three	2 (6%)	3 (17%)	2 (11%)		4 (22%)	1 (6%)
Carcinoma *in situ*, two	7 (19%)	2 (11%)	2 (11%)	4 (22%)	4 (22%)	3 (17%)
Lymphoma malignant	1 (3%)	1 (6%)				
Squamous cell carcinoma	18 (50%)	9 (50%)	5 (28%)	9 (50%)	9 (50%)	7 (39%)
Squamous cell carcinoma, five	1 (3%)			1 (6%)		
Squamous cell carcinoma, four	1 (3%)		1 (6%)	1 (6%)	1 (6%)	
Squamous cell carcinoma, greater than five				1 (6%)		
Squamous cell carcinoma, three	4 (11%)	3 (17%)	4 (22%)	3 (17%)		1 (6%)
Squamous cell carcinoma, two	7 (19%)	5 (28%)	6 (33%)	3 (17%)	5 (28%)	5 (28%)
Squamous cell papilloma	6 (17%)	2 (11%)	3 (17%)	1 (6%)	2 (11%)	5 (28%)
Squamous cell papilloma, four			1 (6%)			
Squamous cell papilloma, three					1 (6%)	
Squamous cell papilloma, two		1 (6%)		1 (6%)		
Musculoskeletal System						
None						
Nervous System						
None						

TABLE B1c
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Respiratory System						
Lung	(36)	(18)	(17)	(18)	(18)	(18)
Alveolar/bronchiolar adenoma	3 (8%)	1 (6%)			1 (6%)	
Lymphoma malignant		1 (6%)				
Squamous cell carcinoma, metastatic, skin			1 (6%)			
Special Senses System						
None						
Urinary System						
None						

TABLE B1d
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.9 MED

	No Cream
Disposition Summary	
Animals initially in study	36
Early removal	
Moribund	16
Natural deaths	1
Skin neoplasm greater than 10 mm	19
Survivors	
Terminal sacrifice	
Animals examined microscopically	36
Alimentary System	
None	
Cardiovascular System	
None	
Endocrine System	
Pituitary gland	(1)
Adenoma, pars intermedia	1 (100%)
General Body System	
None	
Genital System	
Ovary	(12)
Cystadenoma	1 (8%)
Uterus	(3)
Polyp adenomatous	1 (33%)
Hematopoietic System	
Lymph node	(29)
Squamous cell carcinoma, metastatic, axillary, skin	1 (3%)
Squamous cell carcinoma, metastatic, inguinal, skin	2 (7%)
Squamous cell carcinoma, metastatic, lumbar, skin	1 (3%)

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

TABLE B1d
Summary of the Incidence of Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.9 MED

	No Cream
Integumentary System	
Skin, site of application	(36)
Carcinoma *in situ*	11 (31%)
Carcinoma *in situ*, three	1 (3%)
Carcinoma *in situ*, two	6 (17%)
Squamous cell carcinoma	14 (39%)
Squamous cell carcinoma, five	2 (6%)
Squamous cell carcinoma, four	4 (11%)
Squamous cell carcinoma, greater than five	1 (3%)
Squamous cell carcinoma, three	3 (8%)
Squamous cell carcinoma, two	11 (31%)
Squamous cell papilloma	3 (8%)
Musculoskeletal System	
None	
Nervous System	
None	
Respiratory System	
None	
Special Senses System	
None	
Urinary System	
None	

TABLE B2a
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Light Only

	0.0 MED	0.3 MED	0.6 MED	0.9 MED
Liver: Hepatocellular Adenoma				
Overall rate[a]	1/1 (100.0%)	1/1 (100.0%)	1/5 (20.0%)	0/4 (0.0%)
Adjusted rate[b]	1/1.0 (100.0%)	1/1.0 (100.0%)	1/4.7 (21.1%)	0/2.1 (0.0%)
Terminal rate[c]	1/1 (100.0%)	1/1 (100.0%)	0/1 (0.0%)	0/0
First incidence (days)	366 (T)	366 (T)	360 (10 mm)[f]	—[g]
Poly-3 test[d]	P=0.012N	—[e]	P=0.352N	P=0.001N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/36 (0.0%)	2/35 (5.7%)	3/36 (8.3%)	0/35 (0.0%)
Adjusted rate	0/36.0 (0.0%)	2/33.3 (6.0%)	3/29.0 (10.4%)	0/15.6 (0.0%)
Terminal rate	0/34 (0.0%)	2/32 (6.3%)	0/9 (0.0%)	0/0
First incidence (days)	—	366 (T)	277 (10 mm)	—
Poly-3 test	P=0.137	P=0.220	P=0.083	—
Ovary: Cystadenoma				
Overall rate	1/20 (5.0%)	1/19 (5.3%)	0/22 (0.0%)	1/12 (8.3%)
Adjusted rate	1/20.0 (5.0%)	1/19.0 (5.3%)	0/17.5 (0.0%)	1/5.9 (17.0%)
Terminal rate	1/20 (5.0%)	1/19 (5.3%)	0/6 (0.0%)	0/0
First incidence (days)	365 (T)	366 (T)	—	271 (10 mm)
Poly-3 test	P=0.642N	P=0.749	P=0.526N	P=0.474
Ovary: Cystadenoma or Tubulostromal Adenoma				
Overall rate	1/20 (5.0%)	2/19 (10.5%)	0/22 (0.0%)	1/12 (8.3%)
Adjusted rate	1/20.0 (5.0%)	2/19.0 (10.5%)	0/17.5 (0.0%)	1/5.9 (17.0%)
Terminal rate	1/20 (5.0%)	2/19 (10.5%)	0/6 (0.0%)	0/0
First incidence (days)	365 (T)	366 (T)	—	271 (10 mm)
Poly-3 test	P=0.627N	P=0.482	P=0.526N	P=0.474
Skin (Control): Squamous Cell Papilloma				
Overall rate	0/36 (0.0%)	0/36 (0.0%)	1/36 (2.8%)	0/36 (0.0%)
Adjusted rate	0/36.0 (0.0%)	0/33.7 (0.0%)	1/28.2 (3.5%)	0/15.8 (0.0%)
Terminal rate	0/34 (0.0%)	0/32 (0.0%)	1/9 (11.1%)	0/0
First incidence (days)	—	—	367 (T)	—
Poly-3 test	P=0.356	—	P=0.452	—
Skin (Control): Carcinoma *in situ*				
Overall rate	0/36 (0.0%)	1/36 (2.8%)	0/36 (0.0%)	0/36 (0.0%)
Adjusted rate	0/36.0 (0.0%)	1/33.7 (3.0%)	0/28.2 (0.0%)	0/15.8 (0.0%)
Terminal rate	0/34 (0.0%)	1/32 (3.1%)	0/9 (0.0%)	0/0
First incidence (days)	—	367 (T)	—	—
Poly-3 test	P=0.741N	P=0.487	—	—
Skin (Control): Squamous Cell Papilloma or Carcinoma *in situ*				
Overall rate	0/36 (0.0%)	1/36 (2.8%)	1/36 (2.8%)	0/36 (0.0%)
Adjusted rate	0/36.0 (0.0%)	1/33.7 (3.0%)	1/28.2 (3.5%)	0/15.8 (0.0%)
Terminal rate	0/34 (0.0%)	1/32 (3.1%)	1/9 (11.1%)	0/0
First incidence (days)	—	367 (T)	367 (T)	—
Poly-3 test	P=0.397	P=0.487	P=0.452	—
Skin (Site of Application): Squamous Cell Papilloma				
Overall rate	1/36 (2.8%)	0/36 (0.0%)	6/36 (16.7%)	3/36 (8.3%)
Adjusted rate	1/36.0 (2.8%)	0/33.7 (0.0%)	6/29.4 (20.4%)	3/17.5 (17.1%)
Terminal rate	1/34 (2.9%)	0/32 (0.0%)	2/9 (22.2%)	0/0
First incidence (days)	366 (T)	—	311 (10 mm)	227
Poly-3 test	P=0.006	P=0.513N	P=0.027	P=0.118

TABLE B2a
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Light Only

	0.0 MED	0.3 MED	0.6 MED	0.9 MED
Skin (Site of Application): Carcinoma *in situ*				
Overall rate	0/36 (0.0%)	4/36 (11.1%)	23/36 (63.9%)	18/36 (50.0%)
Adjusted rate	0/36.0 (0.0%)	4/33.7 (11.9%)	23/31.6 (72.7%)	18/25.9 (69.4%)
Terminal rate	0/34 (0.0%)	4/32 (12.5%)	6/9 (66.7%)	0/0
First incidence (days)	—	365 (T)	270	227
Poly-3 test	P=0.001	P=0.050	P=0.001	P=0.001
Skin (Site of Application): Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	3/36 (8.3%)	31/36 (86.1%)	35/36 (97.2%)
Adjusted rate	0/36.0 (0.0%)	3/33.7 (8.9%)	31/34.7 (89.5%)	35/35.1 (99.6%)
Terminal rate	0/34 (0.0%)	3/32 (9.4%)	7/9 (77.8%)	0/0
First incidence (days)	—	365 (T)	270	223
Poly-3 test	P=0.001	P=0.105	P=0.001	P=0.001
Skin (Site of Application): Carcinoma *in situ* or Squamous Cell Carcinoma				
Overall rate	0/36 (0.0%)	6/36 (16.7%)	34/36 (94.4%)	35/36 (97.2%)
Adjusted rate	0/36.0 (0.0%)	6/33.7 (17.8%)	34/34.7 (98.0%)	35/35.1 (99.6%)
Terminal rate	0/34 (0.0%)	6/32 (18.8%)	9/9 (100.0%)	0/0
First incidence (days)	—	365 (T)	270	223
Poly-3 test	P=0.001	P=0.011	P=0.001	P=0.001
Skin (Site of Application): Squamous Cell Papilloma, Carcinoma *in situ*, or Squamous Cell Carcinoma				
Overall rate	1/36 (2.8%)	6/36 (16.7%)	34/36 (94.4%)	35/36 (97.2%)
Adjusted rate	1/36.0 (2.8%)	6/33.7 (17.8%)	34/34.7 (98.0%)	35/35.1 (99.6%)
Terminal rate	1/34 (2.9%)	6/32 (18.8%)	9/9 (100.0%)	0/0
First incidence (days)	366 (T)	365 (T)	270	223
Poly-3 test	P=0.001	P=0.043	P=0.001	P=0.001
Uterus: Stromal Polyp				
Overall rate	3/20 (15.0%)	1/17 (5.9%)	0/12 (0.0%)	0/3 (0.0%)
Adjusted rate	3/20.0 (15.0%)	1/16.8 (6.0%)	0/9.5 (0.0%)	0/1.1 (0.0%)
Terminal rate	3/20 (15.0%)	1/16 (6.3%)	0/3 (0.0%)	0/0
First incidence (days)	365 (T)	365 (T)	—	—
Poly-3 test	P=0.145N	P=0.367N	P=0.281N	P=0.723N
Uterus: Stromal Polyp or Adenomatous Polyp				
Overall rate	3/20 (15.0%)	1/17 (5.9%)	0/12 (0.0%)	1/3 (33.3%)
Adjusted rate	3/20.0 (15.0%)	1/16.8 (6.0%)	0/9.5 (0.0%)	1/1.5 (66.7%)
Terminal rate	3/20 (15.0%)	1/16 (6.3%)	0/3 (0.0%)	0/0
First incidence (days)	365 (T)	365 (T)	—	311 (10 mm)
Poly-3 test	P=0.396N	P=0.367N	P=0.281N	P=0.362
All Organs: Malignant Lymphoma				
Overall rate	2/36 (5.6%)	1/36 (2.8%)	2/36 (5.6%)	0/36 (0.0%)
Adjusted rate	2/36.0 (5.6%)	1/33.7 (3.0%)	2/28.3 (7.1%)	0/15.8 (0.0%)
Terminal rate	1/34 (2.9%)	1/32 (3.1%)	1/9 (11.1%)	0/0
First incidence (days)	364	365 (T)	360 (10 mm)	—
Poly-3 test	P=0.516N	P=0.523N	P=0.604	P=0.442N
All Organs: Benign Neoplasms				
Overall rate	6/36 (16.7%)	6/36 (16.7%)	11/36 (30.6%)	5/36 (13.9%)
Adjusted rate	6/36.0 (16.7%)	6/33.7 (17.8%)	11/30.2 (36.4%)	5/18.5 (27.0%)
Terminal rate	6/34 (17.6%)	6/32 (18.8%)	3/9 (33.3%)	0/0
First incidence (days)	365 (T)	365 (T)	277 (10 mm)	227
Poly-3 test	P=0.057	P=0.574	P=0.059	P=0.311

TABLE B2a
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Light Only

	0.0 MED	0.3 MED	0.6 MED	0.9 MED
All Organs: Malignant Neoplasms				
Overall rate	0/36 (0.0%)	8/36 (22.2%)	34/36 (94.4%)	35/36 (97.2%)
Adjusted rate	0/36.0 (0.0%)	8/33.9 (23.6%)	34/34.7 (98.0%)	35/35.1 (99.6%)
Terminal rate	0/34 (0.0%)	7/32 (21.9%)	9/9 (100.0%)	0/0
First incidence (days)	—	339 (10 mm)	270	223
Poly-3 test	P=0.001	P=0.002	P=0.001	P=0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	6/36 (16.7%)	13/36 (36.1%)	34/36 (94.4%)	35/36 (97.2%)
Adjusted rate	6/36.0 (16.7%)	13/33.9 (38.4%)	34/34.7 (98.0%)	35/35.1 (99.6%)
Terminal rate	6/34 (17.6%)	12/32 (37.5%)	9/9 (100.0%)	0/0
First incidence (days)	365 (T)	339 (10 mm)	270	223
Poly-3 test	P=0.001	P=0.036	P=0.001	P=0.001

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparison between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Value of statistic cannot be computed
[f] First incidence occurred when an animal was removed from study due to a skin neoplasm 10 mm or greater.
[g] Not applicable; no neoplasms in animal group

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
Ovary: Cystadenoma or Tubulostromal Adenoma		
0.0 MED		
Overall rate[a]	1/20 (5.0%)	1/8 (12.5%)
Adjusted rate[b]	1/20.0 (5.0%)	1/8.0 (12.5%)
Terminal rate[c]	1/20 (5.0%)	1/8 (12.5%)
First incidence (days)	365 (T)	366 (T)
Poly-3 test[d]		P=0.545
0.3 MED		
Overall rate	2/19 (10.5%)	0/9 (0.0%)
Adjusted rate	2/19.0 (10.5%)	0/8.5 (0.0%)
Terminal rate	2/19 (10.5%)	0/7 (0.0%)
First incidence (days)	366 (T)	—[e]
Poly-3 test		P=0.428N
0.6 MED		
Overall rate	0/22 (0.0%)	0/8 (0.0%)
Adjusted rate	0/17.5 (0.0%)	0/5.5 (0.0%)
Terminal rate	0/6 (0.0%)	0/1 (0.0%)
First incidence (days)	—	—
Poly-3 test		—[f]
Skin (Control): Squamous Cell Papilloma		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/36.0 (0.0%)	0/15.5 (0.0%)
Terminal rate	0/34 (0.0%)	0/15 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	0/36 (0.0%)	1/18 (5.6%)
Adjusted rate	0/33.7 (0.0%)	1/14.0 (7.1%)
Terminal rate	0/32 (0.0%)	1/12 (8.3%)
First incidence (days)	—	367 (T)
Poly-3 test		P=0.329
0.6 MED		
Overall rate	1/36 (2.8%)	0/18 (0.0%)
Adjusted rate	1/28.2 (3.5%)	0/11.0 (0.0%)
Terminal rate	1/9 (11.1%)	0/1 (0.0%)
First incidence (days)	367 (T)	—
Poly-3 test		P=0.678N

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
Skin (Control): Carcinoma *in situ*		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/36.0 (0.0%)	0/15.5 (0.0%)
Terminal rate	0/34 (0.0%)	0/15 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	1/36 (2.8%)	0/18 (0.0%)
Adjusted rate	1/33.7 (3.0%)	0/14.0 (0.0%)
Terminal rate	1/32 (3.1%)	0/12 (0.0%)
First incidence (days)	367 (T)	—
Poly-3 test		P=0.668N
0.6 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/28.2 (0.0%)	0/11.0 (0.0%)
Terminal rate	0/9 (0.0%)	0/1 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
Skin (Control): Squamous Cell Papilloma or Carcinoma *in situ*		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/36.0 (0.0%)	0/15.5 (0.0%)
Terminal rate	0/34 (0.0%)	0/15 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	1/36 (2.8%)	1/18 (5.6%)
Adjusted rate	1/33.7 (3.0%)	1/14.0 (7.1%)
Terminal rate	1/32 (3.1%)	1/12 (8.3%)
First incidence (days)	367 (T)	367 (T)
Poly-3 test		P=0.552
0.6 MED		
Overall rate	1/36 (2.8%)	0/18 (0.0%)
Adjusted rate	1/28.2 (3.5%)	0/11.0 (0.0%)
Terminal rate	1/9 (11.1%)	0/1 (0.0%)
First incidence (days)	367 (T)	—
Poly-3 test		P=0.678N

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
Skin (Site of Application): Squamous Cell Papilloma		
0.0 MED		
Overall rate	1/36 (2.8%)	0/18 (0.0%)
Adjusted rate	1/36.0 (2.8%)	0/15.5 (0.0%)
Terminal rate	1/34 (2.9%)	0/15 (0.0%)
First incidence (days)	366 (T)	—
Poly-3 test		P=0.663N
0.3 MED		
Overall rate	0/36 (0.0%)	2/18 (11.1%)
Adjusted rate	0/33.7 (0.0%)	2/14.2 (14.1%)
Terminal rate	0/32 (0.0%)	1/12 (8.3%)
First incidence (days)	—	339 (10 mm)[g]
Poly-3 test		P=0.077
0.6 MED		
Overall rate	6/36 (16.7%)	3/18 (16.7%)
Adjusted rate	6/29.4 (20.4%)	3/12.1 (24.7%)
Terminal rate	2/9 (22.2%)	0/1 (0.0%)
First incidence (days)	311 (10 mm)	304 (10 mm)
Poly-3 test		P=0.541
Skin (Site of Application): Carcinoma *in situ*		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/36.0 (0.0%)	0/15.5 (0.0%)
Terminal rate	0/34 (0.0%)	0/15 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	4/36 (11.1%)	8/18 (44.4%)
Adjusted rate	4/33.7 (11.9%)	8/14.5 (55.2%)
Terminal rate	4/32 (12.5%)	6/12 (50.0%)
First incidence (days)	365 (T)	325 (10 mm)
Poly-3 test		P=0.001
0.6 MED		
Overall rate	23/36 (63.9%)	14/18 (77.8%)
Adjusted rate	23/31.6 (72.7%)	14/16.4 (85.4%)
Terminal rate	6/9 (66.7%)	1/1 (100.0%)
First incidence (days)	270	269 (10 mm)
Poly-3 test		P=0.239

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
Skin (Site of Application): Squamous Cell Carcinoma		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/36.0 (0.0%)	0/15.5 (0.0%)
Terminal rate	0/34 (0.0%)	0/15 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	3/36 (8.3%)	4/18 (22.2%)
Adjusted rate	3/33.7 (8.9%)	4/14.5 (27.6%)
Terminal rate	3/32 (9.4%)	2/12 (16.7%)
First incidence (days)	365 (T)	325 (10 mm)
Poly-3 test		P=0.112
0.6 MED		
Overall rate	31/36 (86.1%)	17/18 (94.4%)
Adjusted rate	31/34.7 (89.5%)	17/17.5 (97.2%)
Terminal rate	7/9 (77.8%)	1/1 (100.0%)
First incidence (days)	270	269 (10 mm)
Poly-3 test		P=0.326
Skin (Site of Application): Carcinoma *in situ* or Squamous Cell Carcinoma		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/36.0 (0.0%)	0/15.5 (0.0%)
Terminal rate	0/34 (0.0%)	0/15 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	6/36 (16.7%)	8/18 (44.4%)
Adjusted rate	6/33.7 (17.8%)	8/14.5 (55.2%)
Terminal rate	6/32 (18.8%)	6/12 (50.0%)
First incidence (days)	365 (T)	325 (10 mm)
Poly-3 test		P=0.010
0.6 MED		
Overall rate	34/36 (94.4%)	17/18 (94.4%)
Adjusted rate	34/34.7 (98.0%)	17/17.5 (97.2%)
Terminal rate	9/9 (100.0%)	1/1 (100.0%)
First incidence (days)	270	269 (10 mm)
Poly-3 test		P=0.838N

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
Skin (Site of Application): Squamous Cell Papilloma, Carcinoma *in situ*, or Squamous Cell Carcinoma		
0.0 MED		
Overall rate	1/36 (2.8%)	0/18 (0.0%)
Adjusted rate	1/36.0 (2.8%)	0/15.5 (0.0%)
Terminal rate	1/34 (2.9%)	0/15 (0.0%)
First incidence (days)	366 (T)	—
Poly-3 test		P=0.663N
0.3 MED		
Overall rate	6/36 (16.7%)	9/18 (50.0%)
Adjusted rate	6/33.7 (17.8%)	9/14.5 (62.1%)
Terminal rate	6/32 (18.8%)	7/12 (58.3%)
First incidence (days)	365 (T)	325 (10 mm)
Poly-3 test		P=0.002
0.6 MED		
Overall rate	34/36 (94.4%)	17/18 (94.4%)
Adjusted rate	34/34.7 (98.0%)	17/17.5 (97.2%)
Terminal rate	9/9 (100.0%)	1/1 (100.0%)
First incidence (days)	270	269 (10 mm)
Poly-3 test		P=0.838N
Uterus: Stromal Polyp		
0.0 MED		
Overall rate	3/20 (15.0%)	0/4 (0.0%)
Adjusted rate	3/20.0 (15.0%)	0/4.0 (0.0%)
Terminal rate	3/20 (15.0%)	0/4 (0.0%)
First incidence (days)	365 (T)	—
Poly-3 test		P=0.500N
0.3 MED		
Overall rate	1/17 (5.9%)	0/7 (0.0%)
Adjusted rate	1/16.8 (6.0%)	0/7.0 (0.0%)
Terminal rate	1/16 (6.3%)	0/7 (0.0%)
First incidence (days)	365 (T)	—
Poly-3 test		P=0.673N
0.6 MED		
Overall rate	0/12 (0.0%)	0/2 (0.0%)
Adjusted rate	0/9.5 (0.0%)	0/2.0 (0.0%)
Terminal rate	0/3 (0.0%)	0/2 (0.0%)
First incidence (days)	—	—
Poly-3 test		—

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
All Organs: Malignant Lymphoma		
0.0 MED		
Overall rate	2/36 (5.6%)	0/18 (0.0%)
Adjusted rate	2/36.0 (5.6%)	0/15.5 (0.0%)
Terminal rate	1/34 (2.9%)	0/15 (0.0%)
First incidence (days)	364	—
Poly-3 test		P=0.439N
0.3 MED		
Overall rate	1/36 (2.8%)	0/18 (0.0%)
Adjusted rate	1/33.7 (3.0%)	0/14.0 (0.0%)
Terminal rate	1/32 (3.1%)	0/12 (0.0%)
First incidence (days)	365 (T)	—
Poly-3 test		P=0.668N
0.6 MED		
Overall rate	2/36 (5.6%)	1/18 (5.6%)
Adjusted rate	2/28.3 (7.1%)	1/11.5 (8.7%)
Terminal rate	1/9 (11.1%)	0/1 (0.0%)
First incidence (days)	360 (10 mm)	290
Poly-3 test		P=0.679
All Organs: Benign Neoplasms		
0.0 MED		
Overall rate	6/36 (16.7%)	1/18 (5.6%)
Adjusted rate	6/36.0 (16.7%)	1/15.5 (6.5%)
Terminal rate	6/34 (17.6%)	1/15 (6.7%)
First incidence (days)	365 (T)	366 (T)
Poly-3 test		P=0.303N
0.3 MED		
Overall rate	6/36 (16.7%)	4/18 (22.2%)
Adjusted rate	6/33.7 (17.8%)	4/14.2 (28.2%)
Terminal rate	6/32 (18.8%)	3/12 (25.0%)
First incidence (days)	365 (T)	339 (10 mm)
Poly-3 test		P=0.346
0.6 MED		
Overall rate	11/36 (30.6%)	4/18 (22.2%)
Adjusted rate	11/30.2 (36.4%)	4/12.5 (32.0%)
Terminal rate	3/9 (33.3%)	0/1 (0.0%)
First incidence (days)	277 (10 mm)	304 (10 mm)
Poly-3 test		P=0.531N

TABLE B2b
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: No Cream versus Control Cream

	No Cream	Control Cream
All Organs: Malignant Neoplasms		
0.0 MED		
Overall rate	0/36 (0.0%)	0/18 (0.0%)
Adjusted rate	0/36.0 (0.0%)	0/15.5 (0.0%)
Terminal rate	0/34 (0.0%)	0/15 (0.0%)
First incidence (days)	—	—
Poly-3 test		—
0.3 MED		
Overall rate	8/36 (22.2%)	8/18 (44.4%)
Adjusted rate	8/33.9 (23.6%)	8/14.5 (55.2%)
Terminal rate	7/32 (21.9%)	6/12 (50.0%)
First incidence (days)	339 (10 mm)	325 (10 mm)
Poly-3 test		P=0.036
0.6 MED		
Overall rate	34/36 (94.4%)	17/18 (94.4%)
Adjusted rate	34/34.7 (98.0%)	17/17.5 (97.2%)
Terminal rate	9/9 (100.0%)	1/1 (100.0%)
First incidence (days)	270	269 (10 mm)
Poly-3 test		P=0.838N
All Organs: Benign or Malignant Neoplasms		
0.0 MED		
Overall rate	6/36 (16.7%)	1/18 (5.6%)
Adjusted rate	6/36.0 (16.7%)	1/15.5 (6.5%)
Terminal rate	6/34 (17.6%)	1/15 (6.7%)
First incidence (days)	365 (T)	366 (T)
Poly-3 test		P=0.303N
0.3 MED		
Overall rate	13/36 (36.1%)	9/18 (50.0%)
Adjusted rate	13/33.9 (38.4%)	9/14.5 (62.1%)
Terminal rate	12/32 (37.5%)	7/12 (58.3%)
First incidence (days)	339 (10 mm)	325 (10 mm)
Poly-3 test		P=0.120
0.6 MED		
Overall rate	34/36 (94.4%)	17/18 (94.4%)
Adjusted rate	34/34.7 (98.0%)	17/17.5 (97.2%)
Terminal rate	9/9 (100.0%)	1/1 (100.0%)
First incidence (days)	270	269 (10 mm)
Poly-3 test		P=0.838N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control cream group incidence are the P values corresponding to pairwise comparisons between the no cream and the control cream group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in the control cream group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed
[g] First incidence occurred when an animal was removed from study due to a skin neoplasm 10 mm or greater.

TABLE B2c
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Liver: Hepatocellular Adenoma			
0.0 MED			
Overall rate[a]	0/1 (0.0%)	0/0	0/1 (0.0%)
Adjusted rate[b]	0/1.0 (0.0%)	0/0	0/1.0 (0.0%)
Terminal rate[c]	0/1 (0.0%)	0/0	0/1 (0.0%)
First incidence (days)	—[e]	—	—
Poly-3 test[d]	—[f]	—	—
0.3 MED			
Overall rate	0/4 (0.0%)	0/2 (0.0%)	1/2 (50.0%)
Adjusted rate	0/3.2 (0.0%)	0/2.0 (0.0%)	1/1.8 (56.6%)
Terminal rate	0/3 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
First incidence (days)	—	—	367 (T)
Poly-3 test	P=0.180	—	P=0.358
0.6 MED			
Overall rate	0/2 (0.0%)	1/2 (50.0%)	0/0
Adjusted rate	0/0.9 (0.0%)	1/1.5 (68.4%)	0/0
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	318 (10 mm)[g]	—
Poly-3 test	P=0.619	—	P=0.619
Liver: Hepatocellular Adenoma or Carcinoma			
0.0 MED			
Overall rate	0/1 (0.0%)	0/0	0/1 (0.0%)
Adjusted rate	0/1.0 (0.0%)	0/0	0/1.0 (0.0%)
Terminal rate	0/1 (0.0%)	0/0	0/1 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/4 (0.0%)	0/2 (0.0%)	1/2 (50.0%)
Adjusted rate	0/3.2 (0.0%)	0/2.0 (0.0%)	1/1.8 (56.6%)
Terminal rate	0/3 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
First incidence (days)	—	—	367 (T)
Poly-3 test	P=0.180	—	P=0.358
0.6 MED			
Overall rate	0/2 (0.0%)	1/2 (50.0%)	0/0
Adjusted rate	0/0.9 (0.0%)	1/1.5 (68.4%)	0/0
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	318 (10 mm)	—
Poly-3 test	P=0.619	—	P=0.619

TABLE B2c
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Lung: Alveolar/bronchiolar Adenoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	1/18 (5.6%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	1/17.1 (5.8%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	1/17 (5.9%)
First incidence (days)	—	—	366 (T)
Poly-3 test	P=0.303	—	P=0.520
0.3 MED			
Overall rate	1/18 (5.6%)	1/18 (5.6%)	1/17 (5.9%)
Adjusted rate	1/14.0 (7.1%)	1/16.0 (6.2%)	1/16.8 (6.0%)
Terminal rate	1/12 (8.3%)	1/12 (8.3%)	1/16 (6.3%)
First incidence (days)	365 (T)	367 (T)	366 (T)
Poly-3 test	P=0.635N	P=0.731N	P=0.719N
0.6 MED			
Overall rate	1/18 (5.6%)	0/17 (0.0%)	0/18 (0.0%)
Adjusted rate	1/11.4 (8.8%)	0/11.5 (0.0%)	0/10.5 (0.0%)
Terminal rate	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
First incidence (days)	318 (10 mm)	—	—
Poly-3 test	P=0.343N	P=0.499N	P=0.516N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	1/18 (5.6%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	1/17.1 (5.8%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	1/17 (5.9%)
First incidence (days)	—	—	366 (T)
Poly-3 test	P=0.303	—	P=0.520
0.3 MED			
Overall rate	2/18 (11.1%)	1/18 (5.6%)	1/17 (5.9%)
Adjusted rate	2/14.2 (14.1%)	1/16.0 (6.2%)	1/16.8 (6.0%)
Terminal rate	1/12 (8.3%)	1/12 (8.3%)	1/16 (6.3%)
First incidence (days)	339 (10 mm)	367 (T)	366 (T)
Poly-3 test	P=0.391N	P=0.457N	P=0.441N
0.6 MED			
Overall rate	1/18 (5.6%)	0/17 (0.0%)	0/18 (0.0%)
Adjusted rate	1/11.4 (8.8%)	0/11.5 (0.0%)	0/10.5 (0.0%)
Terminal rate	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
First incidence (days)	318 (10 mm)	—	—
Poly-3 test	P=0.343N	P=0.499N	P=0.516N

TABLE B2c
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Lymph Node (Mandibular): Malignant Lymphoma			
0.0 MED			
Overall rate	0/8 (0.0%)	0/5 (0.0%)	0/4 (0.0%)
Adjusted rate	0/7.1 (0.0%)	0/5.0 (0.0%)	0/4.0 (0.0%)
Terminal rate	0/7 (0.0%)	0/5 (0.0%)	0/4 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/5 (0.0%)	2/3 (66.7%)	1/5 (20.0%)
Adjusted rate	0/3.9 (0.0%)	2/3.0 (66.7%)	1/5.0 (20.0%)
Terminal rate	0/3 (0.0%)	1/2 (50.0%)	1/5 (20.0%)
First incidence (days)	—	366 (T)	365 (T)
Poly-3 test	P=0.631	P=0.091	P=0.548
0.6 MED			
Overall rate	1/6 (16.7%)	0/8 (0.0%)	0/7 (0.0%)
Adjusted rate	1/3.7 (27.3%)	0/5.5 (0.0%)	0/4.0 (0.0%)
Terminal rate	0/0	0/1 (0.0%)	0/0
First incidence (days)	290	—	—
Poly-3 test	P=0.319N	P=0.415N	P=0.482N
Lymph Node (Mesenteric): Malignant Lymphoma			
0.0 MED			
Overall rate	0/2 (0.0%)	1/3 (33.3%)	0/1 (0.0%)
Adjusted rate	0/1.4 (0.0%)	1/3.0 (33.3%)	0/1.0 (0.0%)
Terminal rate	0/1 (0.0%)	1/3 (33.3%)	0/1 (0.0%)
First incidence (days)	—	365 (T)	—
Poly-3 test	P=0.777N	P=0.637	—
0.3 MED			
Overall rate	0/2 (0.0%)	2/2 (100.0%)	2/4 (50.0%)
Adjusted rate	0/1.2 (0.0%)	2/2.0 (100.0%)	2/4.0 (50.0%)
Terminal rate	0/1 (0.0%)	1/1 (100.0%)	1/3 (33.3%)
First incidence (days)	—	366 (T)	335
Poly-3 test	P=0.710N	P=0.162	P=0.524
0.6 MED			
Overall rate	0/2 (0.0%)	0/0	0/3 (0.0%)
Adjusted rate	0/1.2 (0.0%)	0/0	0/1.4 (0.0%)
Terminal rate	0/0	0/0	0/0
First incidence (days)	—	—	—
Poly-3 test	—	—	—

TABLE B2c
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Skin (Control): Squamous Cell Papilloma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	1/14.0 (7.1%)	0/16.0 (0.0%)	0/17.1 (0.0%)
Terminal rate	1/12 (8.3%)	0/12 (0.0%)	0/16 (0.0%)
First incidence (days)	367 (T)	—	—
Poly-3 test	P=0.356N	P=0.473N	P=0.460N
0.6 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	1/18 (5.6%)
Adjusted rate	0/11.0 (0.0%)	0/11.6 (0.0%)	1/11.2 (9.0%)
Terminal rate	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
First incidence (days)	—	—	256 (10 mm)
Poly-3 test	P=0.284	—	P=0.502
Skin (Site of Application): Squamous Cell Papilloma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	2/18 (11.1%)	2/18 (11.1%)	3/18 (16.7%)
Adjusted rate	2/14.2 (14.1%)	2/16.0 (12.5%)	3/17.1 (17.6%)
Terminal rate	1/12 (8.3%)	2/12 (16.7%)	3/16 (18.8%)
First incidence (days)	339 (10 mm)	365 (T)	365 (T)
Poly-3 test	P=0.494	P=0.654N	P=0.587
0.6 MED			
Overall rate	3/18 (16.7%)	4/18 (22.2%)	2/18 (11.1%)
Adjusted rate	3/12.1 (24.7%)	4/12.5 (32.1%)	2/11.5 (17.5%)
Terminal rate	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)
First incidence (days)	304 (10 mm)	298 (10 mm)	256 (10 mm)
Poly-3 test	P=0.425N	P=0.516	P=0.530N

TABLE B2c
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Skin (Site of Application): Carcinoma *in situ*			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	8/18 (44.4%)	9/18 (50.0%)	7/18 (38.9%)
Adjusted rate	8/14.5 (55.2%)	9/16.3 (55.4%)	7/17.1 (41.0%)
Terminal rate	6/12 (50.0%)	6/12 (50.0%)	7/16 (43.8%)
First incidence (days)	325 (10 mm)	339 (10 mm)	365 (T)
Poly-3 test	P=0.255N	P=0.636	P=0.332N
0.6 MED			
Overall rate	14/18 (77.8%)	14/18 (77.8%)	12/18 (66.7%)
Adjusted rate	14/16.4 (85.4%)	14/16.2 (86.3%)	12/15.9 (75.4%)
Terminal rate	1/1 (100.0%)	1/1 (100.0%)	0/1 (0.0%)
First incidence (days)	269 (10 mm)	283 (10 mm)	235
Poly-3 test	P=0.276N	P=0.693	P=0.378N
Skin (Site of Application): Squamous Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	4/18 (22.2%)	8/18 (44.4%)	6/18 (33.3%)
Adjusted rate	4/14.5 (27.6%)	8/17.1 (46.7%)	6/17.1 (35.1%)
Terminal rate	2/12 (16.7%)	3/12 (25.0%)	6/16 (37.5%)
First incidence (days)	325 (10 mm)	250 (10 mm)	365 (T)
Poly-3 test	P=0.516	P=0.234	P=0.474
0.6 MED			
Overall rate	17/18 (94.4%)	16/18 (88.9%)	18/18 (100.0%)
Adjusted rate	17/17.5 (97.2%)	16/17.1 (93.3%)	18/18.0 (100.0%)
Terminal rate	1/1 (100.0%)	0/1 (0.0%)	1/1 (100.0%)
First incidence (days)	269 (10 mm)	283 (10 mm)	201
Poly-3 test	P=0.485	P=0.617N	P=0.837

TABLE B2c
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
Skin (Site of Application): Carcinoma *in situ* or Squamous Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	8/18 (44.4%)	12/18 (66.7%)	8/18 (44.4%)
Adjusted rate	8/14.5 (55.2%)	12/17.1 (70.0%)	8/17.1 (46.8%)
Terminal rate	6/12 (50.0%)	7/12 (58.3%)	8/16 (50.0%)
First incidence (days)	325 (10 mm)	250 (10 mm)	365 (T)
Poly-3 test	P=0.300N	P=0.313	P=0.456N
0.6 MED			
Overall rate	17/18 (94.4%)	17/18 (94.4%)	18/18 (100.0%)
Adjusted rate	17/17.5 (97.2%)	17/17.1 (99.2%)	18/18.0 (100.0%)
Terminal rate	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)
First incidence (days)	269 (10 mm)	283 (10 mm)	201
Poly-3 test	P=0.604	P=0.891	P=0.837
Skin (Site of Application): Squamous Cell Papilloma, Carcinoma *in situ*, or Squamous Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	9/18 (50.0%)	12/18 (66.7%)	9/18 (50.0%)
Adjusted rate	9/14.5 (62.1%)	12/17.1 (70.0%)	9/17.1 (52.7%)
Terminal rate	7/12 (58.3%)	7/12 (58.3%)	9/16 (56.3%)
First incidence (days)	325 (10 mm)	250 (10 mm)	365 (T)
Poly-3 test	P=0.312N	P=0.464	P=0.432N
0.6 MED			
Overall rate	17/18 (94.4%)	17/18 (94.4%)	18/18 (100.0%)
Adjusted rate	17/17.5 (97.2%)	17/17.1 (99.2%)	18/18.0 (100.0%)
Terminal rate	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)
First incidence (days)	269 (10 mm)	283 (10 mm)	201
Poly-3 test	P=0.604	P=0.891	P=0.837

TABLE B2c
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
All Organs: Malignant Lymphoma			
0.0 MED			
Overall rate	0/18 (0.0%)	2/18 (11.1%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	2/18.0 (11.1%)	0/17.1 (0.0%)
Terminal rate	0/15 (0.0%)	1/17 (5.9%)	0/17 (0.0%)
First incidence (days)	—	101	—
Poly-3 test	P=0.577N	P=0.269	—
0.3 MED			
Overall rate	0/18 (0.0%)	2/18 (11.1%)	2/18 (11.1%)
Adjusted rate	0/14.0 (0.0%)	2/16.0 (12.5%)	2/17.3 (11.5%)
Terminal rate	0/12 (0.0%)	1/12 (8.3%)	1/16 (6.3%)
First incidence (days)	—	366 (T)	335
Poly-3 test	P=0.297	P=0.264	P=0.284
0.6 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	1/11.5 (8.7%)	0/11.6 (0.0%)	0/10.5 (0.0%)
Terminal rate	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)
First incidence (days)	290	—	—
Poly-3 test	P=0.339N	P=0.499N	P=0.519N
All Organs: Benign Neoplasms			
0.0 MED			
Overall rate	1/18 (5.6%)	1/18 (5.6%)	1/18 (5.6%)
Adjusted rate	1/15.5 (6.5%)	1/17.0 (5.9%)	1/17.1 (5.8%)
Terminal rate	1/15 (6.7%)	1/17 (5.9%)	1/17 (5.9%)
First incidence (days)	366 (T)	365 (T)	366 (T)
Poly-3 test	P=0.647N	P=0.739N	P=0.738N
0.3 MED			
Overall rate	4/18 (22.2%)	3/18 (16.7%)	6/18 (33.3%)
Adjusted rate	4/14.2 (28.2%)	3/16.0 (18.7%)	6/17.1 (35.1%)
Terminal rate	3/12 (25.0%)	3/12 (25.0%)	6/16 (37.5%)
First incidence (days)	339 (10 mm)	365 (T)	365 (T)
Poly-3 test	P=0.353	P=0.429N	P=0.489
0.6 MED			
Overall rate	4/18 (22.2%)	5/18 (27.8%)	2/18 (11.1%)
Adjusted rate	4/12.5 (32.0%)	5/12.8 (39.1%)	2/11.5 (17.5%)
Terminal rate	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)
First incidence (days)	304 (10 mm)	298 (10 mm)	256 (10 mm)
Poly-3 test	P=0.276N	P=0.519	P=0.360N

TABLE B2c
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Glycolic Acid

	Control Cream	4% Glycolic Acid	10% Glycolic Acid
All Organs: Malignant Neoplasms			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.0 (0.0%)	0/17.1 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/17 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	8/18 (44.4%)	12/18 (66.7%)	9/18 (50.0%)
Adjusted rate	8/14.5 (55.2%)	12/17.1 (70.0%)	9/17.1 (52.7%)
Terminal rate	6/12 (50.0%)	7/12 (58.3%)	9/16 (56.3%)
First incidence (days)	325 (10 mm)	250 (10 mm)	365 (T)
Poly-3 test	P=0.439N	P=0.313	P=0.584N
0.6 MED			
Overall rate	17/18 (94.4%)	17/18 (94.4%)	18/18 (100.0%)
Adjusted rate	17/17.5 (97.2%)	17/17.1 (99.2%)	18/18.0 (100.0%)
Terminal rate	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)
First incidence (days)	269 (10 mm)	283 (10 mm)	201
Poly-3 test	P=0.604	P=0.891	P=0.837
All Organs: Benign or Malignant Neoplasms			
0.0 MED			
Overall rate	1/18 (5.6%)	1/18 (5.6%)	1/18 (5.6%)
Adjusted rate	1/15.5 (6.5%)	1/17.0 (5.9%)	1/17.1 (5.8%)
Terminal rate	1/15 (6.7%)	1/17 (5.9%)	1/17 (5.9%)
First incidence (days)	366 (T)	365 (T)	366 (T)
Poly-3 test	P=0.647N	P=0.739N	P=0.738N
0.3 MED			
Overall rate	9/18 (50.0%)	12/18 (66.7%)	11/18 (61.1%)
Adjusted rate	9/14.5 (62.1%)	12/17.1 (70.0%)	11/17.1 (64.4%)
Terminal rate	7/12 (58.3%)	7/12 (58.3%)	11/16 (68.8%)
First incidence (days)	325 (10 mm)	250 (10 mm)	365 (T)
Poly-3 test	P=0.583	P=0.464	P=0.593
0.6 MED			
Overall rate	17/18 (94.4%)	17/18 (94.4%)	18/18 (100.0%)
Adjusted rate	17/17.5 (97.2%)	17/17.1 (99.2%)	18/18.0 (100.0%)
Terminal rate	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)
First incidence (days)	269 (10 mm)	283 (10 mm)	201
Poly-3 test	P=0.604	P=0.891	P=0.837

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparison between the controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed
[g] First incidence occurred when an animal was removed from study due to a skin neoplasm 10 mm or greater.

TABLE B2d
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salycylic Acid
Liver: Hepatocellular Adenoma			
0.0 MED			
Overall rate[a]	0/1 (0.0%)	1/2 (50.0%)	1/2 (50.0%)
Adjusted rate[b]	0/1.0 (0.0%)	1/2.0 (50.0%)	1/2.0 (50.0%)
Terminal rate[c]	0/1 (0.0%)	1/2 (50.0%)	0/1 (0.0%)
First incidence (days)	—[e]	366 (T)	342
Poly-3 test[d]	P=0.466	P=0.614	P=0.614
0.3 MED			
Overall rate	0/4 (0.0%)	0/0	0/1 (0.0%)
Adjusted rate	0/3.2 (0.0%)	0/0.0	0/0.1 (0.0%)
Terminal rate	0/3 (0.0%)	0/0	0/0
First incidence (days)	—	—	—
Poly-3 test	—[f]	—	—
0.6 MED			
Overall rate	0/2 (0.0%)	0/4 (0.0%)	0/3 (0.0%)
Adjusted rate	0/0.9 (0.0%)	0/2.0 (0.0%)	0/1.5 (0.0%)
Terminal rate	0/0	0/0	0/1 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
Lung: Alveolar/bronchiolar Adenoma			
0.0 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	1/18 (5.6%)
Adjusted rate	0/15.5 (0.0%)	1/17.1 (5.9%)	1/15.9 (6.3%)
Terminal rate	0/15 (0.0%)	1/17 (5.9%)	1/14 (7.1%)
First incidence (days)	—	365 (T)	367 (T)
Poly-3 test	P=0.342	P=0.519	P=0.506
0.3 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	1/17 (5.9%)
Adjusted rate	1/14.0 (7.1%)	0/15.1 (0.0%)	1/15.1 (6.6%)
Terminal rate	1/12 (8.3%)	0/14 (0.0%)	1/15 (6.7%)
First incidence (days)	365 (T)	—	367 (T)
Poly-3 test	P=0.678N	P=0.485N	P=0.745N
0.6 MED			
Overall rate	1/18 (5.6%)	1/18 (5.6%)	0/18 (0.0%)
Adjusted rate	1/11.4 (8.8%)	1/13.8 (7.3%)	0/14.3 (0.0%)
Terminal rate	0/1 (0.0%)	1/6 (16.7%)	0/8 (0.0%)
First incidence (days)	318 (10 mm)[g]	367 (T)	—
Poly-3 test	P=0.293N	P=0.721N	P=0.454N

TABLE B2d
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salycylic Acid
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	1/18 (5.6%)
Adjusted rate	0/15.5 (0.0%)	1/17.1 (5.9%)	1/15.9 (6.3%)
Terminal rate	0/15 (0.0%)	1/17 (5.9%)	1/14 (7.1%)
First incidence (days)	—	365 (T)	367 (T)
Poly-3 test	P=0.342	P=0.519	P=0.506
0.3 MED			
Overall rate	2/18 (11.1%)	0/18 (0.0%)	1/17 (5.9%)
Adjusted rate	2/14.2 (14.1%)	0/15.1 (0.0%)	1/15.1 (6.6%)
Terminal rate	1/12 (8.3%)	0/14 (0.0%)	1/15 (6.7%)
First incidence (days)	339 (10 mm)	—	367 (T)
Poly-3 test	P=0.366N	P=0.217N	P=0.479N
0.6 MED			
Overall rate	1/18 (5.6%)	1/18 (5.6%)	0/18 (0.0%)
Adjusted rate	1/11.4 (8.8%)	1/13.8 (7.3%)	0/14.3 (0.0%)
Terminal rate	0/1 (0.0%)	1/6 (16.7%)	0/8 (0.0%)
First incidence (days)	318 (10 mm)	367 (T)	—
Poly-3 test	P=0.293N	P=0.721N	P=0.454N
Lymph Node (Mandibular): Malignant Lymphoma			
0.0 MED			
Overall rate	0/8 (0.0%)	0/5 (0.0%)	0/3 (0.0%)
Adjusted rate	0/7.1 (0.0%)	0/5.0 (0.0%)	0/3.0 (0.0%)
Terminal rate	0/7 (0.0%)	0/5 (0.0%)	0/3 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/5 (0.0%)	0/5 (0.0%)	2/7 (28.6%)
Adjusted rate	0/3.9 (0.0%)	0/5.0 (0.0%)	2/7.0 (28.6%)
Terminal rate	0/3 (0.0%)	0/5 (0.0%)	1/6 (16.7%)
First incidence (days)	—	—	151
Poly-3 test	P=0.155	—	P=0.370
0.6 MED			
Overall rate	1/6 (16.7%)	0/6 (0.0%)	0/7 (0.0%)
Adjusted rate	1/3.7 (27.3%)	0/4.4 (0.0%)	0/5.2 (0.0%)
Terminal rate	0/0	0/2 (0.0%)	0/3 (0.0%)
First incidence (days)	290	—	—
Poly-3 test	P=0.258N	P=0.460N	P=0.429N

TABLE B2d
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salycylic Acid
Lymph Node (Mesenteric): Malignant Lymphoma			
0.0 MED			
Overall rate	0/2 (0.0%)	0/4 (0.0%)	1/2 (50.0%)
Adjusted rate	0/1.4 (0.0%)	0/4.0 (0.0%)	1/2.0 (50.0%)
Terminal rate	0/1 (0.0%)	0/4 (0.0%)	1/2 (50.0%)
First incidence (days)	—	—	366 (T)
Poly-3 test	P=0.255	—	P=0.570
0.3 MED			
Overall rate	0/2 (0.0%)	0/1 (0.0%)	2/2 (100.0%)
Adjusted rate	0/1.2 (0.0%)	0/1.0 (0.0%)	2/2.0 (100.0%)
Terminal rate	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)
First incidence (days)	—	—	151
Poly-3 test	P=0.002	—	P=0.162
0.6 MED			
Overall rate	0/2 (0.0%)	0/2 (0.0%)	0/2 (0.0%)
Adjusted rate	0/1.2 (0.0%)	0/1.5 (0.0%)	0/1.5 (0.0%)
Terminal rate	0/0	0/1 (0.0%)	0/1 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
Skin (Control): Squamous Cell Papilloma			
0.0 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	1/17.1 (5.9%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	1/17 (5.9%)	0/14 (0.0%)
First incidence (days)	—	366 (T)	—
Poly-3 test	P=0.725N	P=0.519	—
0.3 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	0/17 (0.0%)
Adjusted rate	1/14.0 (7.1%)	0/15.1 (0.0%)	0/15.1 (0.0%)
Terminal rate	1/12 (8.3%)	0/14 (0.0%)	0/15 (0.0%)
First incidence (days)	367 (T)	—	—
Poly-3 test	P=0.282N	P=0.485N	P=0.485N
0.6 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/11.0 (0.0%)	0/13.8 (0.0%)	0/14.3 (0.0%)
Terminal rate	0/1 (0.0%)	0/6 (0.0%)	0/8 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—

TABLE B2d
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salycylic Acid
Skin (Control): Carcinoma *in situ*			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	1/17 (5.9%)
Adjusted rate	0/14.0 (0.0%)	1/15.1 (6.6%)	1/15.1 (6.6%)
Terminal rate	0/12 (0.0%)	1/14 (7.1%)	1/15 (6.7%)
First incidence (days)	—	366 (T)	365 (T)
Poly-3 test	P=0.365	P=0.515	P=0.515
0.6 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/11.0 (0.0%)	0/13.8 (0.0%)	0/14.3 (0.0%)
Terminal rate	0/1 (0.0%)	0/6 (0.0%)	0/8 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
Skin (Control): Squamous Cell Papilloma or Carcinoma *in situ*			
0.0 MED			
Overall rate	0/18 (0.0%)	1/18 (5.6%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	1/17.1 (5.9%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	1/17 (5.9%)	0/14 (0.0%)
First incidence (days)	—	366 (T)	—
Poly-3 test	P=0.725N	P=0.519	—
0.3 MED			
Overall rate	1/18 (5.6%)	1/18 (5.6%)	1/17 (5.9%)
Adjusted rate	1/14.0 (7.1%)	1/15.1 (6.6%)	1/15.1 (6.6%)
Terminal rate	1/12 (8.3%)	1/14 (7.1%)	1/15 (6.7%)
First incidence (days)	367 (T)	366 (T)	365 (T)
Poly-3 test	P=0.629N	P=0.745N	P=0.745N
0.6 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/11.0 (0.0%)	0/13.8 (0.0%)	0/14.3 (0.0%)
Terminal rate	0/1 (0.0%)	0/6 (0.0%)	0/8 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—

TABLE B2d
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salycylic Acid
Skin (Site of Application): Squamous Cell Papilloma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	2/18 (11.1%)	2/18 (11.1%)	0/17 (0.0%)
Adjusted rate	2/14.2 (14.1%)	2/15.1 (13.3%)	0/15.1 (0.0%)
Terminal rate	1/12 (8.3%)	2/14 (14.3%)	0/15 (0.0%)
First incidence (days)	339 (10 mm)	365 (T)	—
Poly-3 test	P=0.154N	P=0.677N	P=0.218N
0.6 MED			
Overall rate	3/18 (16.7%)	3/18 (16.7%)	5/18 (27.8%)
Adjusted rate	3/12.1 (24.7%)	3/14.3 (21.0%)	5/14.4 (34.6%)
Terminal rate	0/1 (0.0%)	1/6 (16.7%)	4/8 (50.0%)
First incidence (days)	304 (10 mm)	318 (10 mm)	353 (10 mm)
Poly-3 test	P=0.346	P=0.595N	P=0.448
Skin (Site of Application): Carcinoma *in situ*			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	8/18 (44.4%)	4/18 (22.2%)	0/17 (0.0%)
Adjusted rate	8/14.5 (55.2%)	4/15.1 (26.5%)	0/15.1 (0.0%)
Terminal rate	6/12 (50.0%)	4/14 (28.6%)	0/15 (0.0%)
First incidence (days)	325 (10 mm)	365 (T)	—
Poly-3 test	P<0.001N	P=0.108N	P<0.001N
0.6 MED			
Overall rate	14/18 (77.8%)	11/18 (61.1%)	11/18 (61.1%)
Adjusted rate	14/16.4 (85.4%)	11/16.5 (66.6%)	11/15.9 (69.2%)
Terminal rate	1/1 (100.0%)	3/6 (50.0%)	5/8 (62.5%)
First incidence (days)	269 (10 mm)	269	283 (10 mm)
Poly-3 test	P=0.179N	P=0.173N	P=0.228N

TABLE B2d
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salycylic Acid
Skin (Site of Application): Squamous Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	4/18 (22.2%)	5/18 (27.8%)	2/17 (11.8%)
Adjusted rate	4/14.5 (27.6%)	5/15.6 (32.1%)	2/15.1 (13.3%)
Terminal rate	2/12 (16.7%)	4/14 (28.6%)	2/15 (13.3%)
First incidence (days)	325 (10 mm)	290 (10 mm)	366 (T)
Poly-3 test	P=0.240N	P=0.551	P=0.307N
0.6 MED			
Overall rate	17/18 (94.4%)	15/18 (83.3%)	13/18 (72.2%)
Adjusted rate	17/17.5 (97.2%)	15/17.4 (86.2%)	13/16.6 (78.4%)
Terminal rate	1/1 (100.0%)	4/6 (66.7%)	5/8 (62.5%)
First incidence (days)	269 (10 mm)	283 (10 mm)	283 (10 mm)
Poly-3 test	P=0.072N	P=0.273N	P=0.106N
Skin (Site of Application): Carcinoma *in situ* or Squamous Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	8/18 (44.4%)	7/18 (38.9%)	2/17 (11.8%)
Adjusted rate	8/14.5 (55.2%)	7/15.6 (44.9%)	2/15.1 (13.3%)
Terminal rate	6/12 (50.0%)	6/14 (42.9%)	2/15 (13.3%)
First incidence (days)	325 (10 mm)	290 (10 mm)	366 (T)
Poly-3 test	P=0.012N	P=0.422N	P=0.016N
0.6 MED			
Overall rate	17/18 (94.4%)	17/18 (94.4%)	14/18 (77.8%)
Adjusted rate	17/17.5 (97.2%)	17/18.0 (94.4%)	14/17.0 (82.3%)
Terminal rate	1/1 (100.0%)	5/6 (83.3%)	5/8 (62.5%)
First incidence (days)	269 (10 mm)	269	283 (10 mm)
Poly-3 test	P=0.104N	P=0.677N	P=0.182N

TABLE B2d
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salycylic Acid
Skin (Site of Application): Squamous Cell Papilloma, Carcinoma *in situ*, or Squamous Cell Carcinoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	9/18 (50.0%)	9/18 (50.0%)	2/17 (11.8%)
Adjusted rate	9/14.5 (62.1%)	9/15.6 (57.7%)	2/15.1 (13.3%)
Terminal rate	7/12 (58.3%)	8/14 (57.1%)	2/15 (13.3%)
First incidence (days)	325 (10 mm)	290 (10 mm)	366 (T)
Poly-3 test	P=0.003N	P=0.551N	P=0.005N
0.6 MED			
Overall rate	17/18 (94.4%)	17/18 (94.4%)	14/18 (77.8%)
Adjusted rate	17/17.5 (97.2%)	17/18.0 (94.4%)	14/17.0 (82.3%)
Terminal rate	1/1 (100.0%)	5/6 (83.3%)	5/8 (62.5%)
First incidence (days)	269 (10 mm)	269	283 (10 mm)
Poly-3 test	P=0.104N	P=0.677N	P=0.182N
Uterus: Stromal Polyp			
0.0 MED			
Overall rate	0/4 (0.0%)	0/5 (0.0%)	0/5 (0.0%)
Adjusted rate	0/4.0 (0.0%)	0/5.0 (0.0%)	0/4.9 (0.0%)
Terminal rate	0/4 (0.0%)	0/5 (0.0%)	0/4 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	0/7 (0.0%)	1/12 (8.3%)	0/5 (0.0%)
Adjusted rate	0/7.0 (0.0%)	1/12.0 (8.3%)	0/5.0 (0.0%)
Terminal rate	0/7 (0.0%)	1/12 (8.3%)	0/5 (0.0%)
First incidence (days)	—	367 (T)	—
Poly-3 test	P=0.719	P=0.606	—
0.6 MED			
Overall rate	0/2 (0.0%)	2/11 (18.2%)	1/6 (16.7%)
Adjusted rate	0/1.4 (0.0%)	2/9.2 (21.8%)	1/5.6 (17.8%)
Terminal rate	0/0	1/4 (25.0%)	1/5 (20.0%)
First incidence (days)	—	332 (10 mm)	366 (T)
Poly-3 test	P=0.655	P=0.691	P=0.749

TABLE B2d
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salycylic Acid
All Organs: Malignant Lymphoma			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	2/18 (11.1%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	2/16.8 (11.9%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	1/14 (7.1%)
First incidence (days)	—	—	183
Poly-3 test	P=0.097	—	P=0.252
0.3 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	2/17 (11.8%)
Adjusted rate	0/14.0 (0.0%)	0/15.1 (0.0%)	2/16.0 (12.5%)
Terminal rate	0/12 (0.0%)	0/14 (0.0%)	1/15 (6.7%)
First incidence (days)	—	—	151
Poly-3 test	P=0.100	—	P=0.264
0.6 MED			
Overall rate	1/18 (5.6%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	1/11.5 (8.7%)	0/13.8 (0.0%)	0/14.3 (0.0%)
Terminal rate	0/1 (0.0%)	0/6 (0.0%)	0/8 (0.0%)
First incidence (days)	290	—	—
Poly-3 test	P=0.282N	P=0.465N	P=0.457N
All Organs: Benign Neoplasms			
0.0 MED			
Overall rate	1/18 (5.6%)	3/18 (16.7%)	2/18 (11.1%)
Adjusted rate	1/15.5 (6.5%)	3/17.1 (17.6%)	2/16.1 (12.4%)
Terminal rate	1/15 (6.7%)	3/17 (17.6%)	1/14 (7.1%)
First incidence (days)	366 (T)	365 (T)	342
Poly-3 test	P=0.419	P=0.336	P=0.514
0.3 MED			
Overall rate	4/18 (22.2%)	3/18 (16.7%)	1/17 (5.9%)
Adjusted rate	4/14.2 (28.2%)	3/15.1 (19.9%)	1/15.1 (6.6%)
Terminal rate	3/12 (25.0%)	3/14 (21.4%)	1/15 (6.7%)
First incidence (days)	339 (10 mm)	365 (T)	367 (T)
Poly-3 test	P=0.103N	P=0.464N	P=0.144N
0.6 MED			
Overall rate	4/18 (22.2%)	5/18 (27.8%)	6/18 (33.3%)
Adjusted rate	4/12.5 (32.0%)	5/14.5 (34.4%)	6/14.4 (41.5%)
Terminal rate	0/1 (0.0%)	2/6 (33.3%)	5/8 (62.5%)
First incidence (days)	304 (10 mm)	318 (10 mm)	353 (10 mm)
Poly-3 test	P=0.378	P=0.611	P=0.456

TABLE B2d
Statistical Analysis of Primary Neoplasms in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: Salicylic Acid

	Control Cream	2% Salicylic Acid	4% Salycylic Acid
All Organs: Malignant Neoplasms			
0.0 MED			
Overall rate	0/18 (0.0%)	0/18 (0.0%)	0/18 (0.0%)
Adjusted rate	0/15.5 (0.0%)	0/17.1 (0.0%)	0/15.9 (0.0%)
Terminal rate	0/15 (0.0%)	0/17 (0.0%)	0/14 (0.0%)
First incidence (days)	—	—	—
Poly-3 test	—	—	—
0.3 MED			
Overall rate	8/18 (44.4%)	8/18 (44.4%)	3/17 (17.6%)
Adjusted rate	8/14.5 (55.2%)	8/15.6 (51.3%)	3/15.1 (19.9%)
Terminal rate	6/12 (50.0%)	7/14 (50.0%)	3/15 (20.0%)
First incidence (days)	325 (10 mm)	290 (10 mm)	365 (T)
Poly-3 test	P=0.034N	P=0.560N	P=0.048N
0.6 MED			
Overall rate	17/18 (94.4%)	17/18 (94.4%)	14/18 (77.8%)
Adjusted rate	17/17.5 (97.2%)	17/18.0 (94.4%)	14/17.0 (82.3%)
Terminal rate	1/1 (100.0%)	5/6 (83.3%)	5/8 (62.5%)
First incidence (days)	269 (10 mm)	269	283 (10 mm)
Poly-3 test	P=0.104N	P=0.677N	P=0.182N
All Organs: Benign or Malignant Neoplasms			
0.0 MED			
Overall rate	1/18 (5.6%)	3/18 (16.7%)	2/18 (11.1%)
Adjusted rate	1/15.5 (6.5%)	3/17.1 (17.6%)	2/16.1 (12.4%)
Terminal rate	1/15 (6.7%)	3/17 (17.6%)	1/14 (7.1%)
First incidence (days)	366 (T)	365 (T)	342
Poly-3 test	P=0.419	P=0.336	P=0.514
0.3 MED			
Overall rate	9/18 (50.0%)	10/18 (55.6%)	3/17 (17.6%)
Adjusted rate	9/14.5 (62.1%)	10/15.6 (64.2%)	3/15.1 (19.9%)
Terminal rate	7/12 (58.3%)	9/14 (64.3%)	3/15 (20.0%)
First incidence (days)	325 (10 mm)	290 (10 mm)	365 (T)
Poly-3 test	P=0.011N	P=0.602	P=0.019N
0.6 MED			
Overall rate	17/18 (94.4%)	17/18 (94.4%)	15/18 (83.3%)
Adjusted rate	17/17.5 (97.2%)	17/18.0 (94.4%)	15/17.0 (88.2%)
Terminal rate	1/1 (100.0%)	5/6 (83.3%)	6/8 (75.0%)
First incidence (days)	269 (10 mm)	269	283 (10 mm)
Poly-3 test	P=0.240N	P=0.677N	P=0.357N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals with tissue microscopically examined
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparison between the controls and that dosed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed
[g] First incidence occurred when an animal was removed from study due to a skin neoplasm 10 mm or greater.

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund						2
Natural deaths	2	3	1	1	1	2
Survivors						
Terminal sacrifice	34	15	17	17	17	14
Animals examined microscopically	36	18	18	18	18	18
Alimentary System						
Intestine large, colon		(1)				
Necrosis, marked		1 (100%)				
Intestine small		(1)				
Dilatation		1 (100%)				
Liver	(1)	(1)		(1)	(2)	(2)
Eosinophilic focus				1 (100%)		
Hematopoietic cell proliferation, mild					1 (50%)	
Tension lipidosis, mild					1 (50%)	
Stomach, glandular	(1)					
Cyst	1 (100%)					
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
Clitoral gland	(2)					
Abscess	1 (50%)					
Ectasia, moderate, duct	1 (50%)					
Ovary	(20)	(8)	(13)	(12)	(10)	(12)
Amyloid deposition, moderate				1 (8%)		
Cyst	18 (90%)	8 (100%)	13 (100%)	11 (92%)	9 (90%)	12 (100%)
Uterus	(20)	(4)	(5)	(5)	(5)	(5)
Dilatation	1 (5%)					1 (20%)
Hyperplasia, cystic, mild, endometrium	17 (85%)	2 (50%)	3 (60%)	4 (80%)	4 (80%)	4 (80%)
Hyperplasia, cystic, minimal, endometrium	1 (5%)			1 (20%)	1 (20%)	
Hyperplasia, cystic, moderate, endometrium	1 (5%)	1 (25%)	2 (40%)			
Vagina	(1)					
Dilatation	1 (100%)					

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

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System						
Bone marrow	(36)	(18)	(18)	(18)	(18)	(18)
Hyperplasia, mild, myeloid cell	2 (6%)	3 (17%)		1 (6%)		
Hyperplasia, minimal, myeloid cell			1 (6%)	1 (6%)		
Hyperplasia, moderate, myeloid cell			1 (6%)			
Lymph node	(10)	(6)	(7)	(1)	(4)	(5)
Hematopoietic cell proliferation, mild, inguinal					1 (25%)	
Hematopoietic cell proliferation, mild, renal					1 (25%)	
Hematopoietic cell proliferation, moderate, axillary					1 (25%)	
Hyperplasia, lymphoid, marked, renal			1 (14%)			
Hyperplasia, lymphoid, mild, axillary	2 (20%)	3 (50%)	3 (43%)	1 (100%)	2 (50%)	2 (40%)
Hyperplasia, lymphoid, mild, inguinal		1 (17%)				
Hyperplasia, lymphoid, mild, lumbar	1 (10%)	2 (33%)	1 (14%)			1 (20%)
Hyperplasia, lymphoid, mild, pancreatic			1 (14%)			1 (20%)
Hyperplasia, lymphoid, mild, renal	3 (30%)	1 (17%)	1 (14%)			1 (20%)
Hyperplasia, lymphoid, mild, thoracic	1 (10%)					
Hyperplasia, lymphoid, minimal,renal	1 (10%)					
Hyperplasia, lymphoid, moderate, inguinal			2 (29%)			
Hyperplasia, lymphoid, moderate, lumbar		1 (17%)				
Infiltration cellular, histiocyte, mild, lumbar						1 (20%)
Infiltration cellular, histiocyte, mild, thoracic						1 (20%)
Inflammation, mild, axillary			1 (14%)			
Inflammation, mild, inguinal			1 (14%)			
Lymph node, mandibular	(4)	(8)	(5)	(4)	(5)	(3)
Hematopoietic cell proliferation, moderate					1 (20%)	
Hyperplasia, lymphoid, marked			1 (20%)			
Hyperplasia, lymphoid, mild	1 (25%)	5 (63%)	3 (60%)	3 (75%)	3 (60%)	2 (67%)
Hyperplasia, lymphoid, minimal		1 (13%)			1 (20%)	
Infiltration cellular, histiocyte, mild		1 (13%)				
Infiltration cellular, plasma cell, mild	1 (25%)	2 (25%)		1 (25%)		
Infiltration cellular, plasma cell, moderate	1 (25%)					1 (33%)
Infiltration cellular, polymorphonuclear, mild	1 (25%)					
Inflammation, mild			1 (20%)			
Pigmentation, moderate					1 (20%)	
Lymph node, mesenteric	(8)	(2)	(3)	(1)	(4)	(2)
Hematopoietic cell proliferation, mild					1 (25%)	
Hyperplasia, lymphoid, marked		1 (50%)				
Hyperplasia, lymphoid, mild	6 (75%)		2 (67%)	1 (100%)	4 (100%)	1 (50%)
Hyperplasia, lymphoid, minimal	1 (13%)					
Hyperplasia, lymphoid, moderate		1 (50%)				
Spleen	(36)	(18)	(18)	(18)	(18)	(18)
Hematopoietic cell proliferation, mild	4 (11%)	2 (11%)	5 (28%)	4 (22%)	9 (50%)	3 (17%)
Hematopoietic cell proliferation, minimal	3 (8%)			2 (11%)		2 (11%)
Hyperplasia, lymphoid, marked	1 (3%)					
Hyperplasia, lymphoid, mild			1 (6%)		1 (6%)	2 (11%)
Hyperplasia, lymphoid, moderate	1 (3%)	1 (6%)				
Pigmentation, moderate	1 (3%)					
Thymus	(1)		(2)		(1)	(1)
Hyperplasia, lymphoid, mild					1 (100%)	

TABLE B3a
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.0 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Integumentary System						
Skin, control	(36)	(18)	(18)	(18)	(18)	(18)
Cyst epithelial inclusion	1 (3%)				2 (11%)	
Cyst epithelial inclusion, tail	9 (25%)	5 (28%)	3 (17%)	12 (67%)	5 (28%)	3 (17%)
Inflammation, granulomatous, mild, dermis	7 (19%)	1 (6%)	2 (11%)	3 (17%)	2 (11%)	
Inflammation, granulomatous, mild, tail, dermis	1 (3%)					
Inflammation, granulomatous, minimal, dermis	25 (69%)	13 (72%)	13 (72%)	14 (78%)	14 (78%)	16 (89%)
Inflammation, granulomatous, moderate, dermis	2 (6%)					
Inflammation, pyogranulomatous, moderate, subcutaneous tissue	1 (3%)					
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(18)
Acanthosis, mild			1 (6%)		1 (6%)	1 (6%)
Acanthosis, minimal		3 (17%)	4 (22%)	2 (11%)	5 (28%)	6 (33%)
Cyst epithelial inclusion		1 (6%)			1 (6%)	1 (6%)
Hyperplasia, squamous, minimal		1 (6%)				
Infiltration cellular, mast cell, mild				1 (6%)		
Infiltration cellular, mast cell, moderate			2 (11%)			
Inflammation, granulomatous, mild, dermis	19 (53%)	4 (22%)	3 (17%)	7 (39%)	7 (39%)	5 (28%)
Inflammation, granulomatous, minimal, dermis	15 (42%)	12 (67%)	11 (61%)	10 (56%)	9 (50%)	11 (61%)
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
Lung	(36)	(18)	(18)	(18)	(18)	(18)
Hyperplasia, minimal, alveolar epithelium	2 (6%)			1 (6%)		2 (11%)
Infiltration cellular, histiocyte, minimal					1 (6%)	
Infiltration cellular, lymphocyte, mild	2 (6%)	2 (11%)		1 (6%)	3 (17%)	
Infiltration cellular, lymphocyte, minimal	2 (6%)		2 (11%)	1 (6%)	3 (17%)	2 (11%)
Inflammation, minimal, alveolus			3 (17%)		1 (6%)	
Special Senses System						
Eye	(3)	(1)	(1)	(1)	(2)	
Cataract	1 (33%)	1 (100%)		1 (100%)	1 (50%)	
Inflammation, mild, cornea			1 (100%)		1 (50%)	
Inflammation, minimal, cornea	1 (33%)					
Urinary System						
Kidney			(2)			(1)
Infiltration cellular, lymphocyte, mild			1 (50%)			
Inflammation, chronic, moderate			1 (50%)			

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund	1	2			2	1
Natural deaths	2	2	1	2	1	2
Skin neoplasm greater than 10 mm	1	2	5		1	
Survivors						
Terminal sacrifice	32	12	12	16	14	15
Animals examined microscopically	36	18	18	18	18	17
Alimentary System						
Intestine large, colon			(1)			
Hyperplasia, lymphoid, mild			1 (100%)			
Liver	(1)	(4)	(2)	(2)		(1)
Hemorrhage, minimal			1 (50%)			
Inflammation, chronic, minimal		1 (25%)				
Inflammation, diffuse, moderate		1 (25%)				
Mesentery	(1)	(1)	(1)	(1)		
Abscess	1 (100%)	1 (100%)				
Inflammation, marked			1 (100%)			
Necrosis, fat				1 (100%)		
Pancreas				(1)		(1)
Accessory spleen						1 (100%)
Inflammation, chronic, mild				1 (100%)		
Cardiovascular System						
Heart		(1)				
Thrombosis, marked, atrium		1 (100%)				
Endocrine System						
None						
General Body System						
None						

[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 Glycolic Acid and Salicylic Acid: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Genital System						
Clitoral gland	(4)				(2)	(1)
Ectasia, mild, duct	1 (25%)				2 (100%)	1 (100%)
Ectasia, moderate, duct	2 (50%)					
Inflammation, marked	1 (25%)					
Ovary	(19)	(9)	(12)	(9)	(8)	(9)
Abscess						1 (11%)
Angiectasis, minimal		1 (11%)				
Cyst	17 (89%)	8 (89%)	12 (100%)	8 (89%)	8 (100%)	9 (100%)
Uterus	(17)	(7)	(3)	(8)	(12)	(5)
Dilatation				1 (13%)	1 (8%)	
Hyperplasia, cystic, marked, endometrium						1 (20%)
Hyperplasia, cystic, mild, endometrium	14 (82%)	7 (100%)	3 (100%)	7 (88%)	11 (92%)	4 (80%)
Hyperplasia, cystic, minimal, endometrium	1 (6%)					
Hyperplasia, cystic, moderate, endometrium	2 (12%)					
Vagina				(1)		
Dilatation				1 (100%)		
Hematopoietic System						
Bone marrow	(35)	(18)	(18)	(17)	(18)	(17)
Hyperplasia, mild, myeloid cell	3 (9%)	4 (22%)	2 (11%)	2 (12%)	2 (11%)	1 (6%)
Hyperplasia, moderate, myeloid cell		1 (6%)	1 (6%)	1 (6%)		
Lymph node	(17)	(10)	(9)	(11)	(9)	(6)
Hemorrhage, moderate, mediastinal		1 (10%)				
Hyperplasia, lymphoid, mild, axillary	13 (76%)	6 (60%)	6 (67%)	8 (73%)	8 (89%)	3 (50%)
Hyperplasia, lymphoid, mild, inguinal	4 (24%)	1 (10%)	3 (33%)			2 (33%)
Hyperplasia, lymphoid, mild, lumbar	3 (18%)					1 (17%)
Hyperplasia, lymphoid, mild, pancreatic	1 (6%)					
Hyperplasia, lymphoid, mild, popliteal						1 (17%)
Hyperplasia, lymphoid, mild, renal	1 (6%)	1 (10%)		1 (9%)	2 (22%)	
Hyperplasia, lymphoid, mild, thoracic	1 (6%)					
Hyperplasia, lymphoid, moderate, axillary		1 (10%)				
Hyperplasia, lymphoid, moderate, inguinal		1 (10%)				
Hyperplasia, lymphoid, moderate, lumbar						1 (17%)
Hyperplasia, lymphoid, moderate, mediastinal		1 (10%)				
Hyperplasia, lymphoid, moderate, renal	1 (6%)					
Infiltration cellular, plasma cell, moderate, inguinal			1 (11%)			
Infiltration cellular, plasma cell, moderate, lumbar						1 (17%)
Lymph node, mandibular	(8)	(5)	(3)	(5)	(5)	(7)
Hyperplasia, lymphoid, mild	8 (100%)	3 (60%)	1 (33%)	3 (60%)	4 (80%)	5 (71%)
Hyperplasia, lymphoid, moderate		1 (20%)			1 (20%)	
Infiltration cellular, plasma cell, mild	1 (13%)	1 (20%)				
Infiltration cellular, plasma cell, moderate		1 (20%)		1 (20%)		
Lymph node, mesenteric	(6)	(2)	(2)	(4)	(1)	(2)
Hyperplasia, lymphoid, mild	6 (100%)	2 (100%)		2 (50%)	1 (100%)	
Spleen	(35)	(18)	(18)	(17)	(18)	(17)
Hematopoietic cell proliferation, mild	19 (54%)	11 (61%)	9 (50%)	8 (47%)	10 (56%)	10 (59%)
Hematopoietic cell proliferation, minimal	9 (26%)	1 (6%)	1 (6%)	2 (12%)	5 (28%)	
Hematopoietic cell proliferation, moderate	3 (9%)	4 (22%)	6 (33%)	4 (24%)	3 (17%)	4 (24%)
Hyperplasia, lymphoid, mild				1 (6%)		1 (6%)

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Integumentary System						
Skin, control	(36)	(18)	(18)	(18)	(18)	(17)
Acanthosis, minimal	1 (3%)			1 (6%)		
Cyst epithelial inclusion	3 (8%)	1 (6%)			2 (11%)	
Cyst epithelial inclusion, tail	7 (19%)	1 (6%)	4 (22%)	6 (33%)	3 (17%)	3 (18%)
Hemorrhage, mild, tail		1 (6%)				
Hyperplasia, squamous, mild						1 (6%)
Hyperplasia, squamous, moderate		1 (6%)			1 (6%)	
Infiltration cellular, mast cell, moderate		1 (6%)				
Inflammation, chronic active, mild, tail, epidermis	1 (3%)					
Inflammation, granulomatous, mild, dermis	2 (6%)	3 (17%)	3 (17%)			
Inflammation, granulomatous, minimal, dermis	26 (72%)	10 (56%)	11 (61%)	14 (78%)	16 (89%)	14 (82%)
Inflammation, granulomatous, moderate, dermis				1 (6%)		
Inflammation, pyogranulomatous, mild, dermis						1 (6%)
Inflammation, pyogranulomatous, mild, tail, dermis				1 (6%)		
Inflammation, pyogranulomatous, moderate, dermis						1 (6%)
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(17)
Acanthosis, mild	4 (11%)	3 (17%)	3 (17%)	5 (28%)	2 (11%)	2 (12%)
Acanthosis, minimal	24 (67%)	12 (67%)	12 (67%)	11 (61%)	12 (67%)	12 (71%)
Acanthosis, moderate			1 (6%)			
Cyst epithelial inclusion		2 (11%)			1 (6%)	
Hyperplasia, squamous, marked	3 (8%)	5 (28%)	3 (17%)	4 (22%)	4 (22%)	3 (18%)
Hyperplasia, squamous, mild	7 (19%)	4 (22%)	4 (22%)	3 (17%)		2 (12%)
Hyperplasia, squamous, minimal	3 (8%)		1 (6%)			
Hyperplasia, squamous, moderate	3 (8%)	3 (17%)	4 (22%)	6 (33%)	1 (6%)	1 (6%)
Inflammation, granulomatous, mild, dermis	21 (58%)	7 (39%)	8 (44%)	8 (44%)	4 (22%)	7 (41%)
Inflammation, granulomatous, minimal, dermis	13 (36%)	6 (33%)	8 (44%)	8 (44%)	13 (72%)	9 (53%)
Inflammation, granulomatous, moderate, dermis			1 (6%)			
Inflammation, pyogranulomatous, marked, dermis		1 (6%)				
Musculoskeletal System						
None						
Nervous System						
None						

TABLE B3b
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.3 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Respiratory System						
Lung	(35)	(18)	(18)	(17)	(18)	(17)
Hemorrhage, mild			1 (6%)			
Hyperplasia, mild, alveolar epithelium					1 (6%)	
Hyperplasia, minimal, alveolar epithelium	2 (6%)	2 (11%)		1 (6%)		1 (6%)
Infiltration cellular, lymphocyte, mild	2 (6%)	1 (6%)	2 (11%)	1 (6%)	1 (6%)	
Infiltration cellular, lymphocyte, minimal	2 (6%)	1 (6%)	1 (6%)	1 (6%)	4 (22%)	1 (6%)
Inflammation, mild, alveolus					1 (6%)	
Inflammation, minimal, alveolus	1 (3%)	1 (6%)	2 (11%)	2 (12%)		1 (6%)
Inflammation, moderate, alveolus					1 (6%)	
Inflammation, moderate, artery		1 (6%)				
Inflammation, moderate, bronchiole					1 (6%)	
Inflammation, moderate, peribronchial		1 (6%)				
Special Senses System						
Eye	(3)	(1)		(2)	(1)	(4)
Cataract		1 (100%)				2 (50%)
Inflammation, minimal, cornea		1 (100%)				1 (25%)
Inflammation, moderate, conjunctiva	1 (33%)					
Inflammation, moderate, cornea						1 (25%)
Urinary System						
Kidney	(1)				(1)	
Abscess					1 (100%)	

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Disposition Summary						
Animals initially in study	36	18	18	18	18	18
Early removal						
Moribund	2	3	1	2	1	1
Natural deaths	2	1	1			1
Skin neoplasm greater than 10 mm	23	13	15	15	11	8
Survivors						
Terminal sacrifice	9	1	1	1	6	8
Animals examined microscopically	36	18	18	18	18	18
Alimentary System						
Liver	(5)	(2)	(2)		(4)	(3)
Abscess						1 (33%)
Cyst					1 (25%)	
Fatty change, moderate					1 (25%)	
Hematopoietic cell proliferation, mild	1 (20%)	1 (50%)				1 (33%)
Hematopoietic cell proliferation, moderate			1 (50%)			
Infiltration cellular, lymphocyte, mild			1 (50%)			
Infiltration cellular, lymphocyte, minimal					1 (25%)	
Inflammation, chronic, mild		1 (50%)				
Inflammation, chronic, moderate					1 (25%)	
Inflammation, diffuse, moderate						1 (33%)
Pancreas				(1)		
Accessory spleen				1 (100%)		
Cardiovascular System						
None						
Endocrine System						
None						
General Body System						
None						
Genital System						
Clitoral gland	(3)		(1)		(1)	(1)
Abscess	1 (33%)					
Ectasia, mild, duct	1 (33%)				1 (100%)	
Ectasia, moderate, duct	1 (33%)					1 (100%)
Inflammation, moderate			1 (100%)			
Ovary	(22)	(8)	(8)	(8)	(11)	(11)
Cyst	22 (100%)	8 (100%)	8 (100%)	8 (100%)	10 (91%)	11 (100%)
Uterus	(12)	(2)	(1)	(3)	(11)	(6)
Hyperplasia, cystic, marked, endometrium	1 (17%)					
Hyperplasia, cystic, mild, endometrium	11 (92%)	2 (100%)	2 (67%)	11 (100%)	4 (67%)	
Hyperplasia, cystic, minimal, endometrium	1 (100%)					
Hyperplasia, cystic, moderate, endometrium	1 (8%)	1 (33%)	1 (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 Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System						
Bone marrow	(36)	(18)	(17)	(18)	(18)	(18)
Hyperplasia, marked, myeloid cell			1 (6%)	1 (6%)		
Hyperplasia, mild, myeloid cell	19 (53%)	6 (33%)	8 (47%)	6 (33%)	4 (22%)	10 (56%)
Hyperplasia, moderate, myeloid cell		2 (11%)		6 (33%)	1 (6%)	1 (6%)
Lymph node	(30)	(16)	(15)	(17)	(16)	(15)
Hyperplasia, lymphoid, marked, axillary		1 (6%)				
Hyperplasia, lymphoid, marked, inguinal		1 (6%)				
Hyperplasia, lymphoid, mild		2 (13%)				
Hyperplasia, lymphoid, mild, axillary	20 (67%)	3 (19%)	6 (40%)	7 (41%)	9 (56%)	6 (40%)
Hyperplasia, lymphoid, mild, deep cervical					1 (6%)	
Hyperplasia, lymphoid, mild, iliac			1 (7%)			
Hyperplasia, lymphoid, mild, inguinal	20 (67%)	3 (19%)	6 (40%)	9 (53%)	11 (69%)	5 (33%)
Hyperplasia, lymphoid, mild, lumbar	6 (20%)	3 (19%)	2 (13%)	1 (6%)	1 (6%)	1 (7%)
Hyperplasia, lymphoid, mild, mediastinal	1 (3%)					
Hyperplasia, lymphoid, mild, pancreatic				1 (6%)		
Hyperplasia, lymphoid, mild, popliteal	1 (3%)	1 (6%)				
Hyperplasia, lymphoid, mild, prefemoral		1 (6%)				
Hyperplasia, lymphoid, mild, renal	1 (3%)			3 (18%)	1 (6%)	1 (7%)
Hyperplasia, lymphoid, mild, thoracic	1 (3%)			1 (6%)	2 (13%)	
Hyperplasia, lymphoid, moderate		1 (6%)				
Hyperplasia, lymphoid, moderate, axillary	4 (13%)	6 (38%)	5 (33%)	6 (35%)	1 (6%)	3 (20%)
Hyperplasia, lymphoid, moderate, inguinal	1 (3%)	2 (13%)	3 (20%)	4 (24%)	1 (6%)	1 (7%)
Hyperplasia, lymphoid, moderate, lumbar	1 (3%)	1 (6%)		1 (6%)		
Hyperplasia, lymphoid, moderate, mediastinal						1 (7%)
Hyperplasia, lymphoid, moderate, renal				1 (6%)		
Hyperplasia, lymphoid, moderate, thoracic	1 (3%)					
Infiltration cellular, plasma cell, marked, axillary						1 (7%)
Infiltration cellular, plasma cell, marked, mediastinal						2 (13%)
Infiltration cellular, plasma cell, marked, renal						1 (7%)
Infiltration cellular, plasma cell, mild, axillary				1 (6%)	1 (6%)	1 (7%)
Infiltration cellular, plasma cell, mild, inguinal				1 (6%)		
Infiltration cellular, plasma cell, mild, lumbar				1 (6%)		
Infiltration cellular, plasma cell, mild, renal				1 (6%)		
Infiltration cellular, plasma cell, moderate				1 (6%)		
Infiltration cellular, plasma cell, moderate, axillary	1 (3%)	3 (19%)	3 (20%)	3 (18%)	1 (6%)	
Infiltration cellular, plasma cell, moderate, inguinal	2 (7%)		2 (13%)	2 (12%)		
Infiltration cellular, plasma cell, moderate, lumbar			2 (13%)	1 (6%)		
Infiltration cellular, plasma cell, moderate, renal				2 (12%)		
Infiltration cellular, polymorphonuclear, moderate, axillary				1 (6%)		

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Hematopoietic System (continued)						
Lymph node (continued)	(30)	(16)	(15)	(17)	(16)	(15)
Infiltration cellular, polymorphonuclear, moderate, pancreatic				1 (6%)		
Infiltration cellular, polymorphonuclear, moderate, renal				1 (6%)		
Lymph node, mandibular	(15)	(6)	(8)	(7)	(6)	(7)
Abscess		1 (17%)				
Hyperplasia, lymphoid, mild	13 (87%)	3 (50%)	4 (50%)	5 (71%)	4 (67%)	2 (29%)
Hyperplasia, lymphoid, moderate		1 (17%)	3 (38%)	1 (14%)	1 (17%)	1 (14%)
Infiltration cellular, plasma cell, marked						1 (14%)
Infiltration cellular, plasma cell, mild	2 (13%)		1 (13%)			2 (29%)
Infiltration cellular, plasma cell, moderate	2 (13%)		4 (50%)	6 (86%)	1 (17%)	1 (14%)
Infiltration cellular, polymorphonuclear, moderate				1 (14%)		
Lymph node, mesenteric	(2)	(2)		(3)	(2)	(2)
Abscess						1 (50%)
Hyperplasia, lymphoid, mild	1 (50%)	2 (100%)		2 (67%)	2 (100%)	
Hyperplasia, lymphoid, moderate				1 (33%)		
Infiltration cellular, polymorphonuclear, moderate				1 (33%)		1 (50%)
Spleen	(36)	(18)	(17)	(18)	(18)	(18)
Hematopoietic cell proliferation, marked				1 (6%)		
Hematopoietic cell proliferation, mild	18 (50%)	10 (56%)	8 (47%)	7 (39%)	11 (61%)	11 (61%)
Hematopoietic cell proliferation, minimal	1 (3%)		1 (6%)			3 (17%)
Hematopoietic cell proliferation, moderate	17 (47%)	7 (39%)	8 (47%)	10 (56%)	6 (33%)	4 (22%)
Hyperplasia, lymphoid, mild	1 (3%)					
Integumentary System						
Skin, control	(36)	(18)	(18)	(18)	(18)	(18)
Abscess						1 (6%)
Acanthosis, mild				1 (6%)		
Cyst epithelial inclusion	2 (6%)	1 (6%)			2 (11%)	
Cyst epithelial inclusion, tail	3 (8%)	1 (6%)		2 (11%)	2 (11%)	5 (28%)
Hyperplasia, squamous, marked		1 (6%)				
Hyperplasia, squamous, mild	1 (3%)					
Inflammation, chronic active, marked, epidermis		1 (6%)				
Inflammation, granulomatous, mild, dermis	3 (8%)	1 (6%)	1 (6%)	2 (11%)		2 (11%)
Inflammation, granulomatous, minimal, dermis	26 (72%)	12 (67%)	15 (83%)	15 (83%)	15 (83%)	14 (78%)
Inflammation, pyogranulomatous, marked, dermis						1 (6%)
Inflammation, pyogranulomatous, moderate, dermis		1 (6%)				
Inflammation, pyogranulomatous, moderate, subcutaneous tissue	1 (3%)		1 (6%)			
Necrosis, marked, epidermis						1 (6%)

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Integumentary System (continued)						
Skin, site of application	(36)	(18)	(18)	(18)	(18)	(18)
Abscess				2 (11%)		1 (6%)
Acanthosis, mild	9 (25%)	7 (39%)		2 (11%)	3 (17%)	6 (33%)
Acanthosis, minimal	24 (67%)	8 (44%)	15 (83%)	13 (72%)	12 (67%)	11 (61%)
Acanthosis, moderate		2 (11%)	1 (6%)	2 (11%)		
Cyst epithelial inclusion	1 (3%)	1 (6%)		1 (6%)	2 (11%)	1 (6%)
Hyperplasia, squamous, marked	10 (28%)	10 (56%)	4 (22%)	9 (50%)	8 (44%)	2 (11%)
Hyperplasia, squamous, mild	4 (11%)	2 (11%)	1 (6%)	4 (22%)	2 (11%)	5 (28%)
Hyperplasia, squamous, moderate	6 (17%)	6 (33%)	5 (28%)	1 (6%)	5 (28%)	4 (22%)
Inflammation, chronic active, marked, dermis	1 (3%)					
Inflammation, chronic active, marked, epidermis	1 (3%)	1 (6%)				1 (6%)
Inflammation, chronic active, mild, epidermis		1 (6%)				
Inflammation, chronic active, moderate, epidermis		2 (11%)			3 (17%)	
Inflammation, granulomatous, mild, dermis	25 (69%)	10 (56%)	10 (56%)	15 (83%)	11 (61%)	12 (67%)
Inflammation, granulomatous, minimal, dermis	5 (14%)	6 (33%)	4 (22%)	2 (11%)	4 (22%)	4 (22%)
Inflammation, granulomatous, moderate, dermis	1 (3%)					
Inflammation, pyogranulomatous, marked, dermis		1 (6%)		1 (6%)		
Inflammation, pyogranulomatous, moderate, dermis				1 (6%)	1 (6%)	
Musculoskeletal System						
None						
Nervous System						
None						
Respiratory System						
Lung	(36)	(18)	(17)	(18)	(18)	(18)
Hemorrhage, minimal			1 (6%)	1 (6%)		
Hyperplasia, mild, alveolar epithelium					1 (6%)	
Hyperplasia, minimal, alveolar epithelium	2 (6%)			1 (6%)	1 (6%)	
Infiltration cellular, lymphocyte, mild	2 (6%)			1 (6%)	1 (6%)	
Infiltration cellular, lymphocyte, minimal				2 (11%)		2 (11%)
Inflammation, mild, alveolus	2 (6%)		2 (12%)		3 (17%)	
Inflammation, mild, peribronchial						1 (6%)
Inflammation, minimal, alveolus	9 (25%)	6 (33%)	4 (24%)	5 (28%)	3 (17%)	2 (11%)
Inflammation, moderate, peribronchial				1 (6%)		

TABLE B3c
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.6 MED

	No Cream	Control Cream	4% Glycolic Acid	10% Glycolic Acid	2% Salicylic Acid	4% Salicylic Acid
Special Senses System						
Eye		(1)		(1)	(1)	(1)
Cataract				1 (100%)		1 (100%)
Hyperplasia, squamous, minimal, lids		1 (100%)				
Urinary System						
Kidney				(1)	(1)	
Inflammation, suppurative, marked				1 (100%)		

TABLE B3d
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]: 0.9 MED

	No Cream
Disposition Summary	
Animals initially in study	36
Early removal	
Moribund	16
Natural deaths	1
Skin neoplasm greater than 10 mm	19
Survivors	
Terminal sacrifice	
Animals examined microscopically	36
Alimentary System	
Liver	(4)
Abscess	1 (25%)
Hematopoietic cell proliferation, mild	2 (50%)
Infiltration cellular, lymphocyte, minimal	1 (25%)
Mesentery	(1)
Necrosis, fat	1 (100%)
Pancreas	(1)
Accessory spleen	1 (100%)
Cardiovascular System	
None	
Endocrine System	
None	
General Body System	
None	
Genital System	
Clitoral gland	(4)
Dilatation, duct	2 (50%)
Ectasia, moderate, duct	2 (50%)
Inflammation, mild	1 (25%)
Ovary	(12)
Cyst	11 (92%)
Uterus	(3)
Dilatation	2 (67%)

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

TABLE B3d
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.9 MED

	No Cream	
Hematopoietic System		
Bone marrow	(35)	
Hyperplasia, mild, myeloid cell	19	(54%)
Hyperplasia, moderate, myeloid cell	8	(23%)
Lymph node	(29)	
Hyperplasia, lymphoid, mild, axillary	14	(48%)
Hyperplasia, lymphoid, mild, deep cervical	2	(7%)
Hyperplasia, lymphoid, mild, inguinal	13	(45%)
Hyperplasia, lymphoid, mild, lumbar	7	(24%)
Hyperplasia, lymphoid, mild, renal	4	(14%)
Hyperplasia, lymphoid, mild, thoracic	2	(7%)
Hyperplasia, lymphoid, moderate, axillary	5	(17%)
Hyperplasia, lymphoid, moderate, inguinal	5	(17%)
Hyperplasia, lymphoid, moderate, lumbar	3	(10%)
Hyperplasia, lymphoid, moderate, mediastinal	1	(3%)
Hyperplasia, lymphoid, moderate, renal	2	(7%)
Infiltration cellular, plasma cell, marked, axillary	1	(3%)
Infiltration cellular, plasma cell, mild, axillary	2	(7%)
Infiltration cellular, plasma cell, mild, inguinal	2	(7%)
Infiltration cellular, plasma cell, moderate, axillary	2	(7%)
Infiltration cellular, plasma cell, moderate, inguinal	4	(14%)
Infiltration cellular, plasma cell, moderate, lumbar	1	(3%)
Infiltration cellular, plasma cell, moderate, renal	1	(3%)
Infiltration cellular, plasma cell, moderate, thoracic	1	(3%)
Lymph node, mandibular	(14)	
Hyperplasia, lymphoid, mild	6	(43%)
Hyperplasia, lymphoid, moderate	3	(21%)
Infiltration cellular, plasma cell, mild	1	(7%)
Infiltration cellular, plasma cell, moderate	6	(43%)
Lymph node, mesenteric	(1)	
Hyperplasia, lymphoid, moderate	1	(100%)
Spleen	(35)	
Hematopoietic cell proliferation, marked	6	(17%)
Hematopoietic cell proliferation, mild	5	(14%)
Hematopoietic cell proliferation, moderate	24	(69%)

TABLE B3d
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.9 MED

	No Cream
Integumentary System	
Skin, control	(36)
Cyst epithelial inclusion	2 (6%)
Cyst epithelial inclusion, tail	1 (3%)
Hyperplasia, squamous, moderate	1 (3%)
Inflammation, granulomatous, mild, dermis	3 (8%)
Inflammation, granulomatous, minimal, dermis	27 (75%)
Inflammation, pyogranulomatous, moderate, subcutaneous tissue	1 (3%)
Skin, site of application	(36)
Abscess	2 (6%)
Acanthosis, mild	10 (28%)
Acanthosis, minimal	23 (64%)
Acanthosis, moderate	1 (3%)
Cyst epithelial inclusion	2 (6%)
Hyperplasia, squamous, marked	8 (22%)
Hyperplasia, squamous, mild	2 (6%)
Hyperplasia, squamous, moderate	2 (6%)
Inflammation, chronic active, moderate, epidermis	1 (3%)
Inflammation, granulomatous, mild, dermis	29 (81%)
Inflammation, granulomatous, minimal, dermis	7 (19%)
Inflammation, pyogranulomatous, mild, subcutaneous tissue	2 (6%)
Musculoskeletal System	
Bone	(2)
Fracture	1 (50%)
Skeletal muscle	(1)
Cyst	1 (100%)
Nervous System	
None	
Respiratory System	
Lung	(35)
Hemorrhage, minimal	1 (3%)
Infiltration cellular, lymphocyte, minimal	1 (3%)
Inflammation, mild, alveolus	2 (6%)
Inflammation, minimal, alveolus	12 (34%)
Inflammation, moderate, peribronchial	1 (3%)

TABLE B3d
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid: 0.9 MED

	No Cream
Special Senses System	
Eye	(3)
Cataract	2 (67%)
Inflammation, mild, cornea	1 (33%)
Urinary System	
None	

APPENDIX C
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Glycolic Acid and Salicylic Acid Creams

Glycolic and salicylic acid creams were obtained from Cosmetech Laboratories, Inc. (Fairfield, NJ); glycolic acid creams 4% (by weight) in lot CLI 10220/5 and 10% (by weight) in lot CLI 10220/9 and salicylic acid creams 2% (by weight) in lot CLI 10220/16 and 4% (by weight) in lot CLI 10220/10 were used in the 1-year dermal study. Determination of the glycolic acid (lots CLI 10220/5 and CLI 10220/9) and salicylic acid (lots CLI 10220/16 and CLI 10220/10) concentrations and pH of the creams was performed by the study laboratory at the National Center for Toxicological Research (Jefferson, AR). Reports on analyses performed in support of the study on the effect of glycolic acid and salicylic acid on the photocarcinogenicity of simulated solar light are on file at the National Center for Toxicological Research.

The concentrations of glycolic and salicylic acid creams were determined using high performance liquid chromatography (HPLC) with a Varian (Palo Alto, CA) system, a Phenomenex Prodigy ODS-3 column [4.6 × 250 mm, 5 µm pore size (Phenomenex, Torrance, CA)], using mobile phase A for glycolic acid or mobile phase B for salicylic acid, with ultraviolet detection at 210 nm for glycolic acid or 298 nm for salicylic acid. The pH of each cream was determined using a Sentron 1001 pH meter (Gig Harbor, WA).

A: Mobile phase: A) 0.05 M monobasic ammonium phosphate, pH 3.0 and B) acetonitrile; 100% A with linear change from 0.3 mL/minute to 0.5 mL/minute in 15 minutes, then linear change at 1.0 mL/minute to 50% A:50% B in 3 minutes, hold for 12 minutes, then linear change to 100% A in 5 minutes, followed by a linear reduction in flow rate to 0.5 mL/minute in 1 minute and a 9 minute hold.

B: Mobile phase (1.0 mL/minute flow rate throughout): A) 0.05 M monobasic ammonium phosphate, pH 3.0 and B) acetonitrile; 65% A:35% B for 10 minutes, then linear change to 100% B in 5 minutes, hold for 5 minutes, then linear change to 65% A:35% B in 5 minutes and a 10 minute hold.

Initial analyses on the glycolic acid creams indicated a mean of 3.90% and 10.04% glycolic acid in the 4% and 10% glycolic acid stock creams, respectively, and a mean pH of 3.5 (Tables C1 and C2); initial analyses of the salicylic acid creams indicated a mean of 2.20% and 4.65% salicylic acid in the 2% and 4% salicylic acid stock creams, respectively, and a mean pH of 3.9 (Tables C3 and C4).

To ensure stability, the bulk cream containers were capped, sealed with Parafilm® and tape, and stored protected from light at room temperature.

Control Cream

Control cream was obtained from Cosmetech Laboratories, Inc., in one lot (CLI 10220/4), which was used in the 1-year dermal studies. The absence of glycolic acid and salicylic acid in the control cream was confirmed using HPLC as described above, and the pH of the control cream was determined as described above. The composition of the control cream as reported on the manufacturer's batch sheet was (percent by weight): deionized water (70.02%), 96% glycerin (3.25%), 2% Keltrol T solution (8.00%), Veegum ultra (1.20%), cetearyl alcohol (2.50%), Eutanol G (4.00%), dimethicone DC 200-100 (0.80%), Lipomulse 165 (2.40%), Brij 721 (Steareth-21) (2.40%), Lipowax D (4.00%), Germaben II (1.00%), and a 10% solution of 85% phosphoric acid (0.43%, q.s. pH to 3.5). Upon receipt, the mean pH was determined to be 3.61 by the study laboratory. The pH of the bulk cream was monitored once during the 1-year study by the study laboratory using pH determination as described above. No change in pH was detected.

Dispensation and Analysis of Dose Formulations

Dose formulations were dispensed approximately once a month. Stock creams were either mixed with a metal spatula or shaken vigorously, then aliquots of approximately 100 g were weighed into 8 ounce plastic straight sided jars, capped, sealed with tape, and stored at room temperature (Table C5).

Periodic analyses of the bulk formulations were conducted by the study laboratory using HPLC by the system previously described and using pH determination as previously described. Formulations were analyzed approximately once a month. Of the glycolic acid samples analyzed, all 12 of the 4% creams and all 12 of the 10% creams were within 10% of target concentrations (Table C1); 24 of 27 pH determinations were within 10% of target (Table C2). Of the salicylic acid samples analyzed, all 12 of the 2% creams and 9 of 12 of the 4% creams were within 10% of target concentrations (Table C3); 21 of 26 pH determinations were within 10% of target concentrations (Table C4).

TABLE C1
Results of Analyses of Glycolic Acid Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]

Date Extracted	Date Analyzed	Target Concentration (%)	Determined Concentration[b] (%)	Difference from Target (%)
Initial analyses				
June 14, 2000	June 15, 2000	4.00	3.82[c]	–5
		4.00	4.00[c]	0
		10.00	9.74[c]	–3
		10.00	10.59[c]	+6
	June 26, 2000	4.00	4.01 ± 0.12	0
		4.00	3.77 ± 0.26	–6
		10.00	9.61 ± 0.26	–4
		10.00	10.40 ± 0.17	+4
Periodic analyses				
July 10, 2000	July 10, 2000	4.00	4.00 ± 0.18	0
		4.00	4.14 ± 0.14	+4
		10.00	9.70 ± 0.17	–3
		10.00	10.10 ± 0.16	+1
August 14, 2000	August 14, 2000	4.00	3.82 ± 0.22	–5
		10.00	9.63 ± 0.22	–4
September 18, 2000	September 18, 2000	4.00	4.13 ± 0.22	+3
		10.00	10.15 ± 0.49	+2
October 10, 2000	October 10, 2000	4.00	3.89 ± 0.06	–3
		10.00	9.68 ± 0.40	–3
November 14, 2000	November 14, 2000	4.00	3.82 ± 0.05	–5
		10.00	9.82 ± 0.20	–2
December 11, 2000	December 11, 2000	4.00	3.96 ± 0.12	–1
		4.00	3.95 ± 0.04[d]	–1
		10.00	9.92 ± 0.11	–1
		10.00	9.98 ± 0.14	0
January 16, 2001	January 16, 2001	4.00	3.89 ± 0.34	–3
		10.00	10.00 ± 0.12	0
February 12, 2001	February 12, 2001	4.00	3.98 ± 0.12	–1
		10.00	9.75 ± 0.45	–3
March 12, 2000	March 12, 2001	4.00	4.15 ± 0.05	+4
		10.00	9.63 ± 0.26	–4
April 18, 2000	April 18, 2001	4.00	3.90 ± 0.20	–3
		10.00	9.60 ± 0.36	–4

[a] Formulations were prepared by Cosmetech Laboratories, Inc.; 4% prepared June 5, 2000; 10% prepared May 26, 2000.
[b] Results of triplicate analyses mean ± standard deviation
[c] n=1
[d] n=2

TABLE C2
Results of pH Determinations of Glycolic Acid Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]

Date Analyzed	Glycolic Acid %	Target pH	Determined pH	Difference from Target (%)
Initial analyses				
June 15, 2000	0	3.5	3.64	+4
	0	3.5	3.58	+2
	4	3.5	3.46	–1
	4	3.5	3.46	–1
	10	3.5	3.38	–3
	10	3.5	3.37	–4
Periodic analyses				
July 11, 2000	4	3.5	3.54	+1
	4	3.5	3.51	0
	10	3.5	3.43	–2
	10	3.5	3.44	–2
August 17, 2000	4	3.5	3.48	–1
	10	3.5	3.42	–2
September 19, 2000	4	3.5	3.67	+5
	10	3.5	3.57	+2
October 10, 2000	0	3.5	3.69	+5
	4	3.5	3.60	+3
	10	3.5	3.54	+1
November 16, 2000	4	3.5	3.51	0
	10	3.5	3.42	–2
December 15, 2000	4	3.5	3.51	0
	4	3.5	3.49	0
	10	3.5	3.42	–2
	10	3.5	3.44	–2
January 18, 2001	4	3.5	3.51	0
	10	3.5	3.44	–2
February 20, 2001	4	3.5	3.17	–9
	10	3.5	3.13	–11
March 14, 2001	4	3.5	3.48	–1
	10	3.5	3.39	–3
April 19, 2001	4	3.5	3.99	+14
	10	3.5	4.00	+14
May 14, 2001	4	3.5	3.58	+2
	10	3.5	3.59	+3

[a] Formulations were prepared by Cosmetech Laboratories, Inc.; 4% prepared June 5, 2000; 10% prepared May 26, 2000.

TABLE C3
Results of Analyses of Salicylic Acid Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]

Date Extracted	Date Analyzed	Target Concentration (%)	Determined Concentration[b] (%)	Difference from Target (%)
Initial analyses				
June 14, 2000	June 14, 2000[c]	2.00	2.30	+15
		2.00	2.16	+8
		4.00	4.89	+22
		4.00	4.87	+22
	June 28, 2000	2.00	2.17 ± 0.04	+9
		2.00	2.21 ± 0.04	+11
		4.00	4.55 ± 0.10	+14
		4.00	4.60 ± 0.04	+15
Periodic analyses				
July 12, 2000	July 12, 2000	2.00	2.14 ± 0.04	+7
		2.00	2.14 ± 0.05	+7
		4.00	4.38 ± 0.07	+10
		4.00	4.37 ± 0.18	+9
August 15, 2000	August 15, 2000	2.00	1.90 ± 0.10	–5
		4.00	3.89 ± 0.09	–3
August 23, 2000	August 23, 2000[d]	2.00	1.95 ± 0.17	–3
		2.00	1.74 ± 0.05[e]	–13
		4.00	4.05 ± 0.20	+1
		4.00	4.17 ± 0.04[e]	+4
August 28, 2000	August 28, 2000[d]	2.00	1.77 ± 0.06[e,f]	–12
August 28, 2000	August 29, 2000[d]	2.00	2.11 ± 0.06[e,f]	+6
		4.00	4.09 ± 0.08[e,g]	+2
September 18, 2000	September 19, 2000	2.00	1.97 ± 0.05	–2
		4.00	4.08 ± 0.12	+2
October 11, 2000	October 12, 2000	2.00	2.07 ± 0.02	+4
		4.00	4.22 ± 0.11	+6
November 15, 2000	November 15, 2000	2.00	1.89 ± 0.03	–6
		4.00	3.98 ± 0.14	–1
December 15, 2000	December 15, 2000	2.00	2.18 ± 0.03	+9
		2.00	2.11 ± 0.06	+6
		4.00	4.60 ± 0.09	+15
		4.00	4.33 ± 0.21	+8
January 17, 2001	January 18, 2001	2.00	2.07 ± 0.06	+4
		4.00	4.52 ± 0.04	+13
February 13, 2001	February 13, 2001	2.00	2.10 ± 0.06	+5
		4.00	4.40 ± 0.04	+10
March 13, 2001	March 13, 2001	2.00	1.95 ± 0.02	–3
		4.00	3.80 ±0.05	–5

TABLE C3
Results of Analyses of Salicylic Acid Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]

Date Extracted	Date Analyzed	Target Concentration (%)	Determined Concentration[b] (%)	Difference from Target (%)
Periodic analyses (continued)				
April 19, 2001	April 19, 2001[h]	2.00	2.37 ± 0.06	+19
		4.00	4.87 ± 0.15	+22
	April 23, 2001[i]	2.00	2.10 ± 0.06	+5
		4.00	4.50 ± 0.15	+13

[a] Formulations were prepared by Cosmetech Laboratories, Inc.; 2% prepared May 17, 2000; 4% prepared June 2, 2000.
[b] Results of triplicate analyses mean ± standard deviation
[c] n=1
[d] Results of reanalysis for out of trend investigation; results not included in calculations
[e] n=2
[f] n=12
[g] n=9
[h] Reanalyzed; results not included in calculations
[i] Results of reanalysis

TABLE C4
Results of pH Determinations of Salicylic Acid Dose Formulations Administered Dermally to SKH-1 Mice in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]

Date Analyzed	Salicylic Acid %	Target pH	Determined pH	Difference from Target (%)
Initial analyses				
June 15, 2000	2	4.0	3.94	–2
	2	4.0	3.95	–1
	4	4.0	3.95	–1
	4	4.0	3.89	–3
Periodic analyses				
July 11, 2000	2	4.0	3.95	–1
	2	4.0	3.96	–1
	4	4.0	3.97	–1
	4	4.0	3.91	–2
August 17, 2000	2	4.0	3.83	–4
	4	4.0	3.83	–4
September 19, 2000	2	4.0	3.75	–6
	4	4.0	3.95	–1
October 10, 2000	2	4.0	3.96	–1
	4	4.0	3.85	–4
November 16, 2000	2	4.0	3.47	–13
	4	4.0	3.87	–3
December 15, 2000	2	4.0	3.85	–4
	2	4.0	3.87	–3
	4	4.0	3.87	–3
	4	4.0	3.89	–3
January 18, 2001	2	4.0	3.46	–14
	4	4.0	3.68	–8
February 20, 2001	2	4.0	3.63	–9
	4	4.0	3.56	–11
March 14, 2001	2	4.0	3.82	–5
	4	4.0	3.86	–4
April 19, 2001	2	4.0	4.77	+19
	4	4.0	4.50	+13
May 14, 2001	2	4.0	3.89	–3
	4	4.0	3.85	–4

[a] Formulations were prepared by Cosmetech Laboratories, Inc.; 2% prepared May 17, 2000; 4% prepared June 2, 2000.

TABLE C5
Dispensation and Storage of Dose Formulations in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid

	Glycolic Acid	Salicylic Acid
Dispensation	Dose formulations were dispensed approximately once a month. Stock creams were either mixed with a metal spatula (which had been rinsed with water, ethanol, and dried) or shaken vigorously. Aliquots of approximately 100 g were weighed into 8 ounce plastic straight sided jars and capped.	Same as glycolic acid
Chemical Lot Numbers		
4%	CLI 10220/5	2% CLI 10220/16
10%	CLI 10220/9	4% CLI 102201/10
Control cream	CLI 10220/4	Control cream CLI 10220/4
Maximum Storage Time	Stock formulations were stored for the duration of the study. Dispensed formulations were stored for approximately 1 month.	Same as glycolic acid
Storage Conditions	Stock bottles were sealed with Parafilm® and tape, protected from light, and stored at room temperature.	Same as glycolic acid.
	Dispensed cream jars for dosing were capped, sealed with tape, protected from light, and stored at room temperature.	Same as glycolic acid
Study Laboratory	National Center for Toxicological Research Jefferson, AR	National Center for Toxicological Research Jefferson, AR

APPENDIX D
SPECTRAL IRRADIANCE OF THE SIMULATED SOLAR LIGHT

SPECTRAL IRRADIANCE OF THE SIMULATED SOLAR LIGHT

METHODS

Simulated solar light (SSL) was created by filtering the output from a 6.5 kWatt (kW) long-arc xenon arc lamp (Atlas Electric Devices Co., Chicago, IL) through a Schott WG-320 glass filter (Schott Glass Technologies, Southbridge, MA). At weekly intervals during the 1-year study, irradiance of the filtered light was measured 2 meters from the light source using an Optronics OL-754 spectroradiometer (Optronic Laboratories, Inc., Orlando, FL). Excel® was used to calculate the mean and standard deviation of the 45 weekly measurements of the irradiance at each wavelength from 250 to 450 nm. The relative standard deviation for each wavelength was determined by dividing each standard deviation by the corresponding mean and multiplying by 100.

The average weighted irradiance at each wavelength ($W \bullet CIE/cm^2$ per nm) was determined by multiplying the average irradiance (W/cm^2 per nm) 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, 1987, 1998). 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 values for the SSL output of the filtered 6.5 kW xenon arc lamp were very consistent over the course of the study and are listed in Table D1 and plotted on linear and semilogarithmic scales in Figure D1. The Schott WG-320 glass filter decreased the spectral emissions by over three orders of magnitude between 320 and 290 nm (Figure D1 - Panel B). The relative standard deviation of the spectrum was highest (10.6%) at 250 nm, and decreased to a minimum (2.7%) at 441 nm (Table D1 and Figure D2). The average irradiance was lowest and the relative standard deviation was highest (ranging from 10.6% to 8.3%) for the portion of the spectrum between 250 and 290 nm; throughout the remainder of the measured spectrum, irradiance and relative standard deviation were generally inversely related (Table D1 and Figures D1 and D2). The overall mean relative standard deviation of the measured spectrum was 4.99% (Table D1).

Values for the average weighted irradiance at each wavelength in the SSL spectrum are listed in Table D1 and plotted on linear and semilogarithmic scales in Figure D3. During the study, the average weighted spectral output of the light source was very consistent. The largest contribution to the weighted irradiance of the xenon arc lamp was from light emitted between 295 and 320 nm (Figure D3 - Panel A). The overall sum of the average weighted irradiance values measured 2 meters from the 6.5 kW xenon arc lamp was 2.81×10^{-6} $W \bullet CIE/cm^2$ over the spectral range from 250 to 450 nm (Table D1).

TABLE D1
Irradiance and Weighted Irradiance in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]

Wavelength	S_{er}	Irradiance ($W/cm^2/nm$)	Weighted Irradiance ($W•CIE/cm^2/nm$)	Relative Standard Deviation (%)
250	1	4.48E-09 ± 4.76E-10	4.48E-09 ± 4.76E-10	1.063E+01
251	1	4.74E-09 ± 4.92E-10	4.74E-09 ± 4.92E-10	1.038E+01
252	1	5.06E-09 ± 5.26E-10	5.06E-09 ± 5.26E-10	1.039E+01
253	1	5.32E-09 ± 5.51E-10	5.32E-09 ± 5.51E-10	1.036E+01
254	1	5.62E-09 ± 5.83E-10	5.62E-09 ± 5.83E-10	1.037E+01
255	1	5.90E-09 ± 5.76E-10	5.90E-09 ± 5.76E-10	9.766E+00
256	1	6.12E-09 ± 6.06E-10	6.12E-09 ± 6.06E-10	9.890E+00
257	1	6.42E-09 ± 6.51E-10	6.42E-09 ± 6.51E-10	1.014E+00
258	1	6.64E-09 ± 6.18E-10	6.64E-09 ± 6.18E-10	9.311E+00
259	1	6.90E-09 ± 6.73E-10	6.90E-09 ± 6.73E-10	9.751E+00
260	1	7.19E-09 ± 7.07E-10	7.19E-09 ± 7.07E-10	9.826E+00
261	1	7.47E-09 ± 7.02E-10	7.47E-09 ± 7.02E-10	9.390E+00
262	1	7.70E-09 ± 7.30E-10	7.70E-09 ± 7.30E-10	9.481E+00
263	1	7.92E-09 ± 7.52E-10	7.92E-09 ± 7.52E-10	9.489E+00
264	1	8.15E-09 ± 7.44E-10	8.15E-09 ± 7.44E-10	9.121E+00
265	1	8.41E-09 ± 7.17E-10	8.41E-09 ± 7.17E-10	8.532E+00
266	1	8.68E-09 ± 8.03E-10	8.68E-09 ± 8.03E-10	9.254E+00
267	1	8.88E-09 ± 7.78E-10	8.88E-09 ± 7.78E-10	8.762E+00
268	1	9.08E-09 ± 8.11E-10	9.08E-09 ± 8.11E-10	8.931E+00
269	1	9.38E-09 ± 8.21E-10	9.38E-09 ± 8.21E-10	8.757E+00
270	1	9.66E-09 ± 8.38E-10	9.66E-09 ± 8.38E-10	8.672E+00
271	1	9.99E-09 ± 8.93E-10	9.99E-09 ± 8.93E-10	8.938E+00
272	1	1.02E-08 ± 8.88E-10	1.02E-08 ± 8.88E-10	8.699E+00
273	1	1.04E-08 ± 8.92E-10	1.04E-08 ± 8.92E-10	8.589E+00
274	1	1.07E-08 ± 9.29E-10	1.07E-08 ± 9.29E-10	8.688E+00
275	1	1.09E-08 ± 9.40E-10	1.09E-08 ± 9.40E-10	8.598E+00
276	1	1.12E-08 ± 9.82E-10	1.12E-08 ± 9.82E-10	8.794E+00
277	1	1.15E-08 ± 9.90E-10	1.15E-08 ± 9.90E-10	8.646E+00
278	1	1.18E-08 ± 1.02E-09	1.18E-08 ± 1.02E-09	8.686E+00
279	1	1.21E-08 ± 1.05E-09	1.21E-08 ± 1.05E-09	8.703E+00
280	1	1.24E-08 ± 1.09E-09	1.24E-08 ± 1.09E-09	8.729E+00
281	1	1.27E-08 ± 1.10E-09	1.27E-08 ± 1.10E-09	8.679E+00
282	1	1.29E-08 ± 1.10E-09	1.29E-08 ± 1.10E-09	8.525E+00
283	1	1.33E-08 ± 1.14E-09	1.33E-08 ± 1.14E-09	8.589E+00
284	1	1.36E-08 ± 1.16E-09	1.36E-08 ± 1.16E-09	8.485E+00
285	1	1.39E-08 ± 1.22E-09	1.39E-08 ± 1.22E-09	8.770E+00
286	1	1.43E-08 ± 1.22E-09	1.43E-08 ± 1.22E-09	8.517E+00
287	1	1.47E-08 ± 1.23E-09	1.47E-08 ± 1.23E-09	8.349E+00
288	1	1.50E-08 ± 1.29E-09	1.50E-08 ± 1.29E-09	8.603E+00
289	1	1.53E-08 ± 1.30E-09	1.53E-08 ± 1.30E-09	8.471E+00
290	1	1.74E-08 ± 1.54E-09	1.74E-08 ± 1.54E-09	8.878E+00
291	1	1.84E-08 ± 1.48E-09	1.84E-08 ± 1.48E-09	8.052E+00
292	1	1.95E-08 ± 1.48E-09	1.95E-08 ± 1.48E-09	7.566E+00
293	1	2.21E-08 ± 1.62E-09	2.21E-08 ± 1.62E-09	7.312E+00
294	1	2.70E-08 ± 1.79E-09	2.70E-08 ± 1.79E-09	6.610E+00
295	1	3.57E-08 ± 2.39E-09	3.57E-08 ± 2.39E-09	6.687E+00
296	1	4.92E-08 ± 2.92E-09	4.92E-08 ± 2.92E-09	5.942E+00
297	1	6.96E-08 ± 3.78E-09	6.96E-08 ± 3.78E-09	5.428E+00
298	1	9.85E-08 ± 5.48E-09	9.85E-08 ± 5.48E-09	5.567E+00

TABLE D1
Irradiance and Weighted Irradiance in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid

Wavelength	S_{er}	Irradiance ($W/cm^2/nm$)	Weighted Irradiance ($W•CIE/cm^2/nm$)	Relative Standard Deviation (%)
299	0.805378	1.38E-07 ± 6.98E-09	1.11E-07 ± 5.62E-09	5.048E+00
300	0.648634	1.88E-07 ± 8.75E-09	1.22E-07 ± 5.68E-09	4.661E+00
301	0.522396	2.50E-07 ± 1.15E-08	1.31E-07 ± 6.01E-09	4.594E+00
302	0.420727	3.22E-07 ± 1.40E-08	1.36E-07 ± 5.91E-09	4.356E+00
303	0.338844	4.02E-07 ± 1.64E-08	1.36E-07 ± 5.55E-09	4.072E+00
304	0.272898	4.89E-07 ± 2.34E-08	1.34E-07 ± 6.39E-09	4.789E+00
305	0.219786	5.99E-07 ± 2.91E-08	1.32E-07 ± 6.40E-09	4.860E+00
306	0.177011	7.10E-07 ± 2.57E-08	1.26E-07 ± 4.54E-09	3.612E+00
307	0.142561	8.21E-07 ± 2.95E-08	1.17E-07 ± 4.21E-09	3.595E+00
308	0.114815	9.35E-07 ± 3.45E-08	1.07E-07 ± 3.96E-09	3.685E+00
309	0.092470	1.05E-06 ± 3.52E-08	9.71E-08 ± 3.26E-09	3.351E+00
310	0.074473	1.16E-06 ± 4.27E-08	8.67E-08 ± 3.18E-09	3.669E+00
311	0.059979	1.28E-06 ± 4.39E-08	7.69E-08 ± 2.63E-09	3.423E+00
312	0.048306	1.40E-06 ± 4.82E-08	6.78E-08 ± 2.33E-09	3.430E+00
313	0.038905	1.52E-06 ± 5.12E-08	5.90E-08 ± 1.99E-09	3.377E+00
314	0.031333	1.60E-06 ± 5.30E-08	5.01E-08 ± 1.66E-09	3.312E+00
315	0.025235	1.69E-06 ± 5.54E-08	4.26E-08 ± 1.40E-09	3.281E+00
316	0.020324	1.78E-06 ± 5.58E-08	3.61E-08 ± 1.13E-09	3.136E+00
317	0.016368	1.87E-06 ± 5.88E-08	3.05E-08 ± 9.62E-10	3.150E+00
318	0.013183	1.95E-06 ± 6.30E-08	2.57E-08 ± 8.31E-10	3.234E+00
319	0.010617	2.03E-06 ± 6.28E-08	2.15E-08 ± 6.67E-10	3.095E+00
320	0.008551	2.11E-06 ± 6.50E-08	1.81E-08 ± 5.55E-10	3.075E+00
321	0.006887	2.19E-06 ± 7.11E-08	1.51E-08 ± 4.89E-10	3.247E+00
322	0.005546	2.29E-06 ± 7.31E-08	1.27E-08 ± 4.05E-10	3.189E+00
323	0.004467	2.36E-06 ± 7.35E-08	1.06E-08 ± 3.28E-10	3.108E+00
324	0.003598	2.39E-06 ± 7.30E-08	8.59E-09 ± 2.62E-10	3.057E+00
325	0.002897	2.44E-06 ± 7.53E-08	7.06E-09 ± 2.18E-10	3.091E+00
326	0.002334	2.49E-06 ± 7.35E-08	5.81E-09 ± 1.72E-10	2.952E+00
327	0.001879	2.54E-06 ± 7.75E-08	4.78E-09 ± 1.46E-10	3.047E+00
328	0.001514	2.59E-06 ± 7.95E-08	3.93E-09 ± 1.20E-10	3.066E+00
329	0.001462	2.64E-06 ± 7.84E-08	3.87E-09 ± 1.15E-10	2.965E+00
330	0.001413	2.70E-06 ± 7.94E-08	3.81E-09 ± 1.12E-10	2.944E+00
331	0.001365	2.74E-06 ± 8.38E-08	3.74E-09 ± 1.14E-10	3.056E+00
332	0.001318	2.79E-06 ± 8.23E-08	3.68E-09 ± 1.09E-10	2.951E+00
333	0.001274	2.84E-06 ± 8.49E-08	3.61E-09 ± 1.08E-10	2.992E+00
334	0.001230	2.88E-06 ± 8.18E-08	3.55E-09 ± 1.01E-10	2.835E+00
335	0.001189	2.93E-06 ± 8.85E-08	3.48E-09 ± 1.05E-10	3.024E+00
336	0.001148	2.97E-06 ± 8.61E-08	3.41E-09 ± 9.88E-11	2.896E+00
337	0.001109	3.02E-06 ± 8.84E-08	3.35E-09 ± 9.80E-11	2.929E+00
338	0.001072	3.06E-06 ± 8.75E-08	3.28E-09 ± 9.37E-11	2.856E+00
339	0.001035	3.10E-06 ± 8.95E-08	3.21E-09 ± 9.26E-11	2.884E+00
340	0.001000	3.14E-06 ± 9.09E-08	3.14E-09 ± 9.09E-11	2.892E+00
341	0.000966	3.18E-06 ± 9.06E-08	3.07E-09 ± 8.76E-11	2.850E+00
342	0.000933	3.22E-06 ± 9.09E-08	3.00E-09 ± 8.48E-11	2.824E+00
343	0.000902	3.26E-06 ± 9.30E-08	2.94E-09 ± 8.39E-11	2.855E+00
344	0.000871	3.29E-06 ± 9.24E-08	2.87E-09 ± 8.05E-11	2.806E+00
345	0.000841	3.35E-06 ± 1.07E-07	2.81E-09 ± 9.01E-11	3.201E+00
346	0.000813	3.38E-06 ± 1.11E-07	2.75E-09 ± 8.99E-11	3.268E+00
347	0.000785	3.42E-06 ± 1.11E-07	2.68E-09 ± 8.75E-11	3.262E+00
348	0.000759	3.45E-06 ± 1.12E-07	2.62E-09 ± 8.53E-11	3.256E+00
349	0.000733	3.48E-06 ± 1.14E-07	2.55E-09 ± 8.37E-11	3.280E+00
350	0.000708	3.52E-06 ± 1.15E-07	2.49E-09 ± 8.16E-11	3.275E+00

TABLE D1
Irradiance and Weighted Irradiance in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid

Wavelength	S_{er}	Irradiance ($W/cm^2/nm$)	Weighted Irradiance ($W•CIE/cm^2/nm$)	Relative Standard Deviation (%)
351	0.000684	3.55E-06 ± 1.14E-07	2.43E-09 ± 7.79E-11	3.205E+00
352	0.000661	3.58E-06 ± 1.15E-07	2.37E-09 ± 7.61E-11	3.216E+00
353	0.000638	3.61E-06 ± 1.17E-07	2.31E-09 ± 7.48E-11	3.245E+00
354	0.000617	3.64E-06 ± 1.17E-07	2.25E-09 ± 7.24E-11	3.221E+00
355	0.000596	3.68E-06 ± 1.18E-07	2.19E-09 ± 7.04E-11	3.212E+00
356	0.000575	3.71E-06 ± 1.19E-07	2.13E-09 ± 6.83E-11	3.202E+00
357	0.000556	3.73E-06 ± 1.20E-07	2.07E-09 ± 6.66E-11	3.215E+00
358	0.000537	3.75E-06 ± 1.21E-07	2.02E-09 ± 6.52E-11	3.236E+00
359	0.000519	3.78E-06 ± 1.19E-07	1.96E-09 ± 6.19E-11	3.161E+00
360	0.000501	3.81E-06 ± 1.22E-07	1.91E-09 ± 6.11E-11	3.200E+00
361	0.000484	3.86E-06 ± 1.23E-07	1.87E-09 ± 5.96E-11	3.190E+00
362	0.000468	3.88E-06 ± 1.24E-07	1.82E-09 ± 5.79E-11	3.188E+00
363	0.000452	3.90E-06 ± 1.26E-07	1.76E-09 ± 5.71E-11	3.243E+00
364	0.000437	3.93E-06 ± 1.27E-07	1.72E-09 ± 5.54E-11	3.224E+00
365	0.000422	3.97E-06 ± 1.30E-07	1.68E-09 ± 5.47E-11	3.261E+00
366	0.000407	4.02E-06 ± 1.29E-07	1.64E-09 ± 5.24E-11	3.202E+00
367	0.000394	4.08E-06 ± 1.29E-07	1.60E-09 ± 5.06E-11	3.155E+00
368	0.000380	4.13E-06 ± 1.32E-07	1.57E-09 ± 5.01E-11	3.186E+00
369	0.000367	4.19E-06 ± 1.32E-07	1.54E-09 ± 4.85E-11	3.153E+00
370	0.000355	4.22E-06 ± 1.35E-07	1.50E-09 ± 4.80E-11	3.208E+00
371	0.000343	4.18E-06 ± 1.31E-07	1.43E-09 ± 4.50E-11	3.144E+00
372	0.000331	4.14E-06 ± 1.27E-07	1.37E-09 ± 4.20E-11	3.062E+00
373	0.000320	4.13E-06 ± 1.26E-07	1.32E-09 ± 4.02E-11	3.043E+00
374	0.000309	4.15E-06 ± 1.25E-07	1.28E-09 ± 3.87E-11	3.020E+00
375	0.000299	4.18E-06 ± 1.25E-07	1.25E-09 ± 3.72E-11	2.987E+00
376	0.000288	4.22E-06 ± 1.25E-07	1.22E-09 ± 3.61E-11	2.968E+00
377	0.000279	4.25E-06 ± 1.26E-07	1.18E-09 ± 3.50E-11	2.958E+00
378	0.000269	4.31E-06 ± 1.28E-07	1.16E-09 ± 3.44E-11	2.962E+00
379	0.000260	4.38E-06 ± 1.29E-07	1.14E-09 ± 3.34E-11	2.932E+00
380	0.000251	4.48E-06 ± 1.33E-07	1.13E-09 ± 3.34E-11	2.968E+00
381	0.000243	4.51E-06 ± 1.32E-07	1.09E-09 ± 3.19E-11	2.918E+00
382	0.000234	4.48E-06 ± 1.31E-07	1.05E-09 ± 3.07E-11	2.928E+00
383	0.000227	4.44E-06 ± 1.28E-07	1.01E-09 ± 2.91E-11	2.888E+00
384	0.000219	4.42E-06 ± 1.28E-07	9.68E-10 ± 2.80E-11	2.897E+00
385	0.000211	4.42E-06 ± 1.29E-07	9.33E-10 ± 2.74E-11	2.931E+00
386	0.000204	4.42E-06 ± 1.28E-07	9.03E-10 ± 2.62E-11	2.905E+00
387	0.000197	4.43E-06 ± 1.29E-07	8.74E-10 ± 2.55E-11	2.922E+00
388	0.000191	4.48E-06 ± 1.29E-07	8.54E-10 ± 2.45E-11	2.873E+00
389	0.000184	4.60E-06 ± 1.34E-07	8.47E-10 ± 2.47E-11	2.912E+00
390	0.000178	4.73E-06 ± 1.40E-07	8.40E-10 ± 2.49E-11	2.964E+00
391	0.000172	4.75E-06 ± 1.39E-07	8.16E-10 ± 2.38E-11	2.921E+00
392	0.000166	4.78E-06 ± 1.41E-07	7.94E-10 ± 2.34E-11	2.951E+00
393	0.000160	4.89E-06 ± 1.43E-07	7.84E-10 ± 2.29E-11	2.918E+00
394	0.000155	5.07E-06 ± 1.50E-07	7.85E-10 ± 2.33E-11	2.965E+00
395	0.000150	5.53E-06 ± 1.61E-07	8.27E-10 ± 2.40E-11	2.905E+00
396	0.000145	5.83E-06 ± 1.72E-07	8.42E-10 ± 2.49E-11	2.954E+00
397	0.000140	5.89E-06 ± 1.73E-07	8.22E-10 ± 2.42E-11	2.942E+00
398	0.000135	5.68E-06 ± 1.68E-07	7.67E-10 ± 2.27E-11	2.957E+00
399	0.000130	5.24E-06 ± 1.56E-07	6.82E-10 ± 2.03E-11	2.973E+00
400	0.000126	5.01E-06 ± 1.49E-07	6.31E-10 ± 1.87E-11	2.967E+00

TABLE D1
Irradiance and Weighted Irradiance in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid

Wavelength	S_{er}	Irradiance ($W/cm^2/nm$)	Weighted Irradiance ($W \bullet CIE/cm^2/nm$)	Relative Standard Deviation (%)
401	0	4.95E-06 ± 1.47E-07	—[b]	2.963E+00
402	0	4.95E-06 ± 1.44E-07	—	2.913E+00
403	0	4.97E-06 ± 1.44E-07	—	2.905E+00
404	0	5.00E-06 ± 1.44E-07	—	2.872E+00
405	0	5.07E-06 ± 1.48E-07	—	2.921E+00
406	0	5.10E-06 ± 1.48E-07	—	2.897E+00
407	0	5.18E-06 ± 1.50E-07	—	2.902E+00
408	0	5.46E-06 ± 1.56E-07	—	2.864E+00
409	0	5.43E-06 ± 1.61E-07	—	2.960E+00
410	0	5.31E-06 ± 1.54E-07	—	2.897E+00
411	0	5.46E-06 ± 1.59E-07	—	2.905E+00
412	0	5.70E-06 ± 1.63E-07	—	2.867E+00
413	0	5.49E-06 ± 1.59E-07	—	2.898E+00
414	0	5.32E-06 ± 1.54E-07	—	2.891E+00
415	0	5.28E-06 ± 1.54E-07	—	2.913E+00
416	0	5.28E-06 ± 1.51E-07	—	2.865E+00
417	0	5.30E-06 ± 1.55E-07	—	2.918E+00
418	0	5.37E-06 ± 1.56E-07	—	2.904E+00
419	0	5.80E-06 ± 1.65E-07	—	2.843E+00
420	0	5.99E-06 ± 1.80E-07	—	3.011E+00
421	0	5.58E-06 ± 1.64E-07	—	2.944E+00
422	0	5.44E-06 ± 1.58E-07	—	2.905E+00
423	0	5.44E-06 ± 1.58E-07	—	2.912E+00
424	0	5.48E-06 ± 1.59E-07	—	2.907E+00
425	0	5.49E-06 ± 1.60E-07	—	2.912E+00
426	0	5.47E-06 ± 1.61E-07	—	2.938E+00
427	0	5.47E-06 ± 1.61E-07	—	2.940E+00
428	0	5.47E-06 ± 1.61E-07	—	2.942E+00
429	0	5.47E-06 ± 1.59E-07	—	2.913E+00
430	0	5.47E-06 ± 1.63E-07	—	2.973E+00
431	0	5.48E-06 ± 1.63E-07	—	2.971E+00
432	0	5.51E-06 ± 1.63E-07	—	2.955E+00
433	0	5.53E-06 ± 1.63E-07	—	2.952E+00
434	0	5.56E-06 ± 1.61E-07	—	2.898E+00
435	0	5.60E-06 ± 1.63E-07	—	2.906E+00
436	0	5.69E-06 ± 1.60E-07	—	2.819E+00
437	0	5.88E-06 ± 1.66E-07	—	2.824E+00
438	0	6.16E-06 ± 1.70E-07	—	2.762E+00
439	0	6.19E-06 ± 1.81E-07	—	2.929E+00
440	0	5.78E-06 ± 1.64E-07	—	2.834E+00
441	0	5.85E-06 ± 1.60E-07	—	2.742E+00
442	0	5.95E-06 ± 1.66E-07	—	2.784E+00
443	0	5.83E-06 ± 1.65E-07	—	2.825E+00
444	0	5.79E-06 ± 1.62E-07	—	2.791E+00
445	0	5.81E-06 ± 1.60E-07	—	2.760E+00
446	0	5.77E-06 ± 1.64E-07	—	2.851E+00
447	0	5.75E-06 ± 1.62E-07	—	2.811E+00
448	0	5.80E-06 ± 1.65E-07	—	2.840E+00
449	0	6.16E-06 ± 1.75E-07	—	2.840E+00
450	0	8.85E-06 ± 2.44E-07	—	2.760E+00
			Overall Summary: 2.81E-06 ± 1.38E-07 ($W \bullet CIE/cm^2$)	**Overall Average:** 4.99E+00

[a] Irradiance values are presented as mean ± standard deviation for 45 measurements at each wavelength; S_{er} = CIE human erythema action spectrum weighting function (CIE, 1987, 1998); W=Watts; weighted irradiance = irradiance • S_{er}

[b] Not applicable; S_{er} = 0

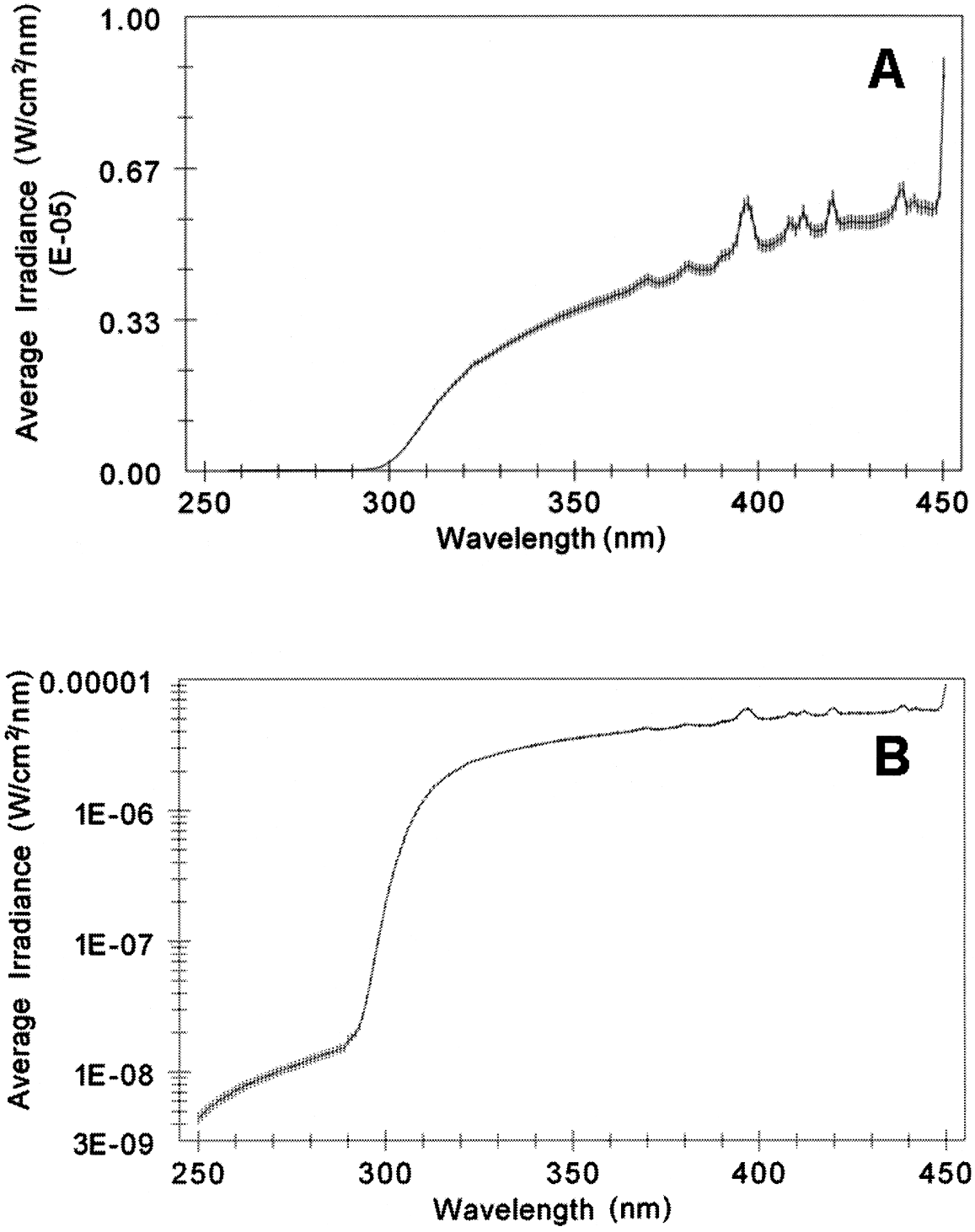

Figure D1
Average Irradiance in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid
Average ± standard deviation (n=45 at each wavelength) on a linear (A) or semilogarithmic (B) scale

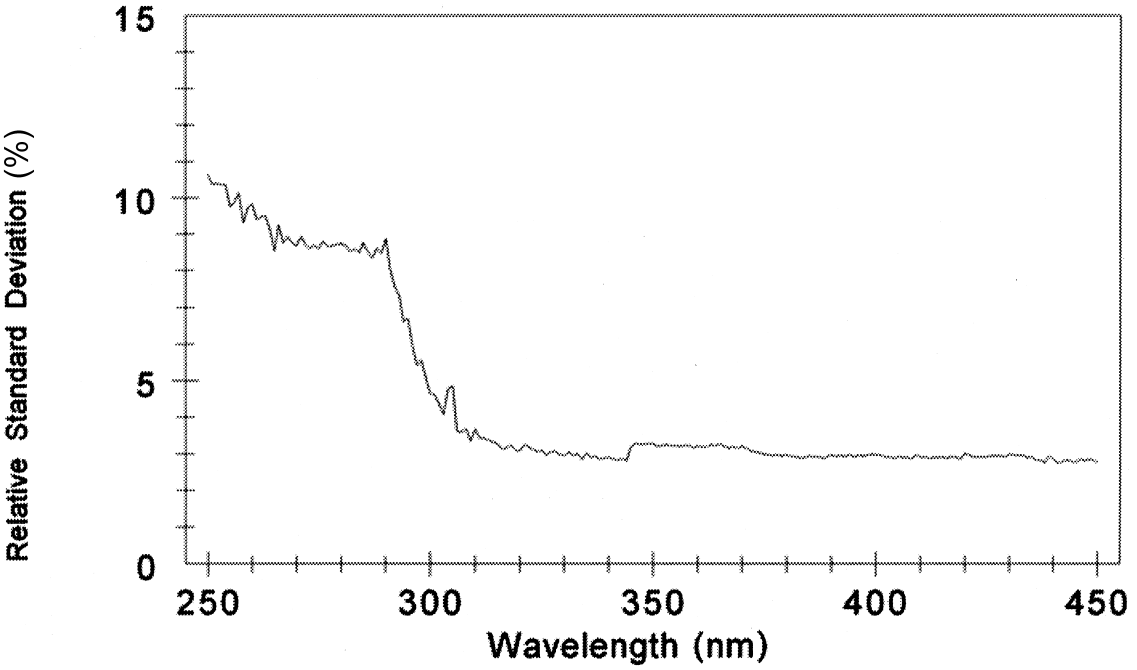

FIGURE D2
Relative Standard Deviation of the Average Irradiance in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid

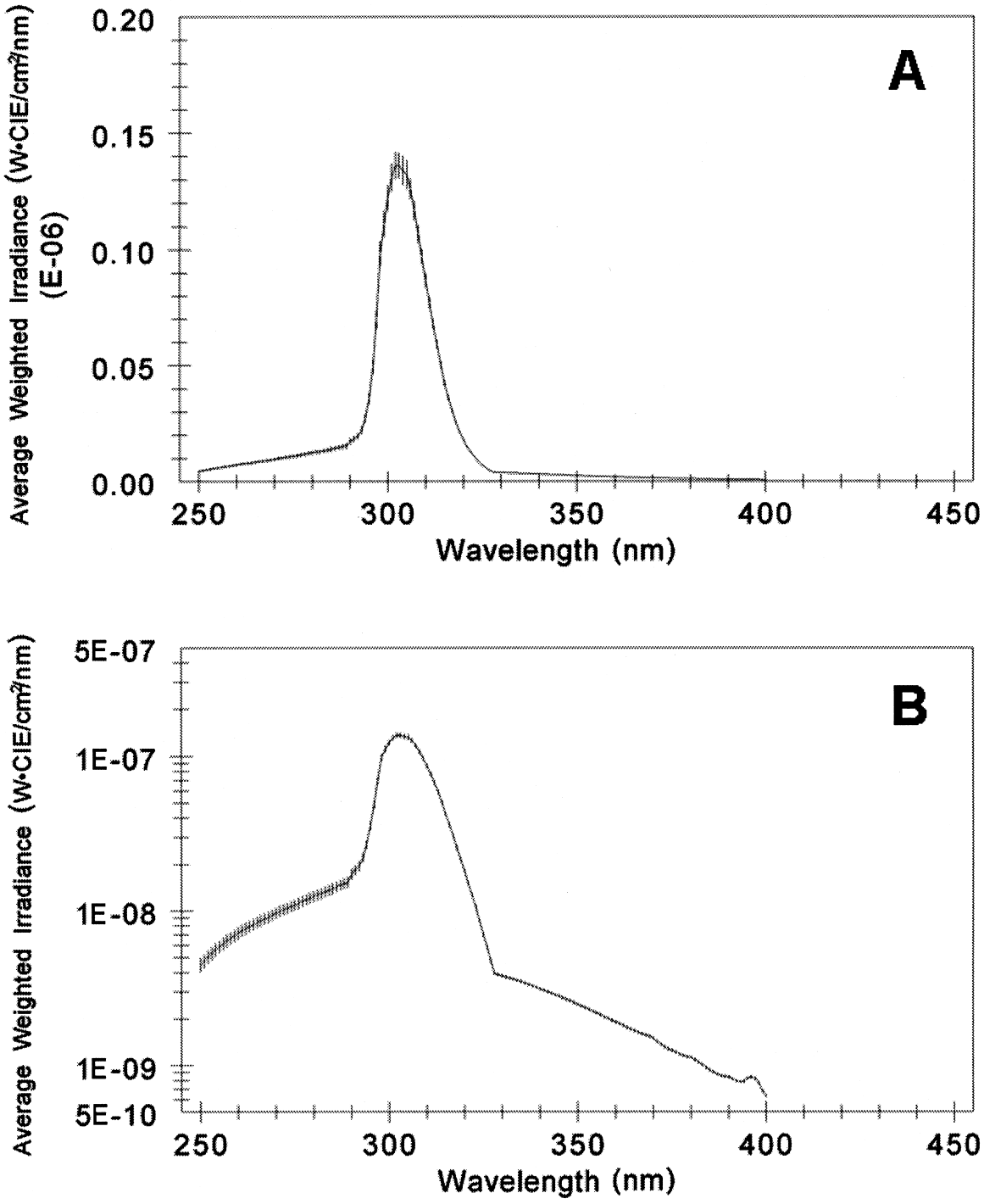

Figure D3
Average Weighted Irradiance in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid
Average ± standard deviation (n=45 at each wavelength) on a linear (A) or semilogarithmic (B) scale. Irradiance was weighted by application of the CIE human erythema action spectrum weighting function (CIE, 1987, 1998).

APPENDIX E
DOSIMETRY OF THE SIMULATED SOLAR LIGHT

DOSIMETRY OF THE SIMULATED SOLAR LIGHT

METHODS AND RESULTS

As described in Appendix D, the spectral irradiance of the simulated solar light (SSL) from a filtered 6.5 kWatt (kW) xenon arc light source was measured using a spectroradiometer and recorded in units of W/cm^2 per nm. Measured irradiance was multiplied by human erythemal action spectrum weighting factors defined by the Commission Internationale de l'Éclairage (CIE) to generate full-spectrum weighted irradiance values with units of $W•CIE/cm^2$ (Appendix D; CIE, 1998). Because 1 W/second equals 1 Joule (J), weighted irradiances can be converted to units of $mJ•CIE/cm^2$ per hour following timed exposures to SSL.

The current study was designed to report irradiation from the SSL source in units of erythemally effective radiation. By international convention, an erythemally effective ultraviolet radiant exposure of 100 J/m^2 (10 $mJ•CIE/cm^2$) is defined as one standard erythema dose (1 SED) with optical radiation in the 100 to 400 nm wavelength range; a related subjective measure of dose based on reddening of the skin has been defined as the minimal erythema dose (MED) (CIE, 1998). Using a Solar Light PMA2101 erythemally weighted dosimeter (Solar Light Co., Inc., Glenside, PA) in conjunction with the spectroradiometer, it was experimentally determined that for the SKH-1 mice used in this study, 22.830 $mJ•CIE/cm^2$ of radiant energy was equal to 1.0 MED. By design, 0.3, 0.6, and 0.9 MED SSL were selected as the erythemally effective daily doses for the current study, and by the relationship above, these doses were equivalent to 6.85, 13.70, and 20.55 $mJ•CIE/cm^2$ per day.

Using the spectroradiometer, dosimetry was monitored daily and maintained within a 2% tolerance range for the cumulative weekly target doses. Accordingly, doses were adjusted each Friday to achieve the desired weekly target (± 2%) based on cumulative daily measurements of weighted irradiance exposures from the first 4 days of the week. During the studies, mice were exposed to 0, 0.3, 0.6, or 0.9 MED SSL for 40 weeks, but due to staggered loading and start dates to accommodate handling limitations, the racks were occupied for 45 weeks. The SSL dose was measured 5 days a week for 45 weeks for each rack where mice were housed; all animals on the same rack received the same SSL dose.

A summary of the dose of SSL delivered to each treatment group throughout the study is presented in Table E1. The results indicated that mice were exposed to 99.97% to 100.26% of the target doses, with a relative standard deviation less than 1% in all dose groups.

TABLE E1
Doses of Light in the 1-Year Simulated Solar Light Study of Glycolic Acid and Salicylic Acid[a]

Group	Animal Rack Number	Daily Light Dose[b]	Targeted Daily Weighted Irradiance ($mJ \cdot CIE/cm^2$)	Determined Daily Weighted Irradiance ($mJ \cdot CIE/cm^2$)[c]	Relative Standard Deviation (%)	Percent of Target
Male						
No cream	9 and 10	0.3 MED	6.85	6.8669 ± 0.0406	0.59	100.25
Control cream	9	0.3 MED	6.85	6.8680 ± 0.0376	0.55	100.26
Cream, 4% glycolic acid	9	0.3 MED	6.85	6.8680 ± 0.0376	0.55	100.26
Cream, 10% glycolic acid	9	0.3 MED	6.85	6.8680 ± 0.0376	0.55	100.26
Cream, 2% salicylic acid	10	0.3 MED	6.85	6.8659 ± 0.0438	0.64	100.23
Cream, 4% salicylic acid	10	0.3 MED	6.85	6.8659 ± 0.0438	0.64	100.23
No cream	11 and 12	0.6 MED	13.70	13.7140 ± 0.0558	0.41	100.10
Control cream	11	0.6 MED	13.70	13.7050 ± 0.0395	0.29	100.04
Cream, 4% glycolic acid	11	0.6 MED	13.70	13.7050 ± 0.0395	0.29	100.04
Cream, 10% glycolic acid	11	0.6 MED	13.70	13.7050 ± 0.0395	0.29	100.04
Cream, 2% salicylic acid	12	0.6 MED	13.70	13.7179 ± 0.0620	0.45	100.13
Cream, 4% salicylic acid	12	0.6 MED	13.70	13.7179 ± 0.0620	0.45	100.13
No cream	14	0.9 MED	20.55	20.5619 ± 0.0459	0.22	100.06
Female						
No cream	3 and 4	0.3 MED	6.85	6.8632 ± 0.0459	0.67	100.19
Control cream	3	0.3 MED	6.85	6.8602 ± 0.0430	0.63	100.15
Cream, 4% glycolic acid	3	0.3 MED	6.85	6.8602 ± 0.0430	0.63	100.15
Cream, 10% glycolic acid	3	0.3 MED	6.85	6.8602 ± 0.0430	0.63	100.15
Cream, 2% salicylic acid	4	0.3 MED	6.85	6.8662 ± 0.0489	0.71	100.24
Cream, 4% salicylic acid	4	0.3 MED	6.85	6.8662 ± 0.0489	0.71	100.24
No cream	5 and 6	0.6 MED	13.70	13.7020 ± 0.0506	0.37	100.01
Control cream	5	0.6 MED	13.70	13.7079 ± 0.0457	0.33	100.06
Cream, 4% glycolic acid	5	0.6 MED	13.70	13.7079 ± 0.0457	0.33	100.06
Cream, 10% glycolic acid	5	0.6 MED	13.70	13.7079 ± 0.0457	0.33	100.06
Cream, 2% salicylic acid	6	0.6 MED	13.70	13.6961 ± 0.0550	0.40	99.97
Cream, 4% salicylic acid	6	0.6 MED	13.70	13.6961 ± 0.0550	0.40	99.97
No cream	13	0.9 MED	20.55	20.5523 ± 0.0627	0.31	100.01

[a] Groups of male (racks 7 and 8) and female (racks 1 and 2) mice exposed to 0.0 MED of simulated solar light are not presented in this table.
[b] MED = minimal erythema dose
[c] Mean daily dose ± standard deviation (n=45)

APPENDIX F
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-31 RAT AND MOUSE RATION

TABLE F1
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%)	2.0
Dicalcium phosphate[b]	1.5
Soy oil	1.5
Brewer's dried yeast	1.0
Ground limestone[b]	0.5
Premixes	0.5
Salt	0.5

[a] Ingredients are ground to pass through a U.S. Standard Screen No. 16 before mixing.
[b] The specific ingredient requirement is for cadmium content not to exceed 1 mg/kg.

TABLE F2
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 IU	
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 F3
Nutrient Composition of NIH-31 Rat and Mouse Ration[a]

Nutrient	Mean ± SD	Minimum	Number of Samples
Crude protein (% by weight)	19.3 ± 0.5	18.0	6
Crude fat (% by weight)	5.18 ± 1.04	4.0	6
Volatiles (% by weight)	7.1 ± 2.6	11.8 (max)	6
Vitamins			
A (µg/g)	11.5 ± 2.1	10.3	6
E (µg/g)	56.9 ± 2.9	45	6
B_1 (mg/g)	0.099 ± 0.008	0.075	6
Minerals			
Selenium (µg/g)	0.42 ± 0.02	0.05 (0.65 max)	6

[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 F4
Contaminant Levels in NIH-31 Rat and Mouse Ration[a]

	Mean ± SD	Number of Lots (Number Positive)
Arsenic (µg/g)	0.17 ± 0.01	6 (3)
Cadmium (µg/g)	<0.20	6 (0)
Lead (µg/g)	0.64 ± 0.15	6 (6)
Aflatoxin B_1 (ppb)	<0.25	6 (0)
Aflatoxin B_2(ppb)	<0.25	6 (0)
Aflatoxin G_1 (ppb)	<0.25	6 (0)
Aflatoxin G_2 (ppb)	<0.10	6 (0)
Total Fumonisin (ppb)	93 ± 53	6 (6)
Pesticides (ppb)		
Heptachlor	<10.0	1 (0)
Total DDT	<5.0	3 (0)
Dieldrin	<5.0	3 (0)
PCB	<25	3 (0)
Malathion	243	3 (1)
Lindane	<1.0	3 (0)

[a] Analyses for nutrient and contaminant content of NIH-31 diet were performed by standard operating procedures developed and/or validated by the NCTR Division of Chemistry.

APPENDIX G
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 randomly selected mice 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 using a commercially prepared Murine Antibody Test Kit (PerImmune, Inc., Rockville, MD). The laboratory serology methods and viral 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 Analysis
MICE	
1-Year Study	
ELISA	
Ectromelia virus	13, 27, and 39 weeks
GDVII (mouse encephalomyelitis virus)	13, 27, and 39 weeks
LCM (lymphocytic choriomeningitis virus)	13, 27, and 39 weeks
MVM (minute virus of mice)	13, 27, and 39 weeks
MHV	13, 27, and 39 weeks
Mycoplasma pulmonis	13, 27, and 39 weeks
PVM (pneumonia virus of mice)	13, 27, and 39 weeks
Reovirus 3	13, 27, and 39 weeks
Sendai	13, 27, and 39 weeks

RESULTS

All test results were negative.

APPENDIX H
STATISTICAL ANALYSIS
OF SKIN TUMOR MULTIPLICITY

STATISTICAL ANALYSIS OF SKIN TUMOR MULTIPLICITY

BACKGROUND

Two workshops were held by the National Toxicology Program's Technical Reports Review Subcommittee to consider the proper statistical methods for analysis of skin tumor multiplicity in photocarcinogenicity studies. As a result of these workshops, multiplicity analysis based on the Andersen-Gill recurrent events model (Therneau and Grambsch, 2000) was requested. This appendix details the *ad hoc* analysis of skin tumor multiplicity that occurred in mice that received 0.3 or 0.6 minimal erythema dose (MED) of simulated solar light (SSL) per day and control cream or creams containing alpha (glycolic) or beta (salicylic) hydroxy acids.

During the course of executing the Andersen-Gill model (first model), examination of the literature revealed that several other statistical approaches had been used to test for significant differences in tumor multiplicity between test groups. A second model (DuBowski *et al.*, 1998) uses a Kruskal-Wallis analysis at selective time points in the bioassay to test for tumor multiplicity effects while using a Chi-square analysis to test for homogeneity of incidence (referred to as the Kruskal-Wallis method). An analysis described by Akritas and Arnold (1994) extends the Kruskal-Wallis method to allow trend testing and comparisons to controls in both the incidence and multiplicity tests (referred to as the Akritas-Arnold method). A third model (Wei-Lin-Weissfeld; Therneau and Grambsch, 2000) simplifies the usual Wei-Lin-Weissfeld recurrent events model by assuming the strata are equivalent and pooling them (this model might also be derived from the standard Cox model with correlated events within an animal). A fourth model (Kodell-Chen-Molefe; Molefe *et al.*, 2005) combines an initiation event (negative binomial) with a Weibull model for tumor development. Although this fourth model has been used in the past for data sets constructed similarly to the data set used in the 1-year study in the current Technical Report, it was not used in the analysis reported here.

METHODS

Each of the statistical modeling approaches mentioned above has inherent strengths; however, they agree for the most part in the significance of the differences between test groups. In an effort to summarize the analyses of the data, this appendix focuses on the analyses where time-point comparisons were made using the Kruskal-Wallis method and linear trend tests were analyzed using the Akritas-Arnold method.

The data set used in this Appendix is the clinical observation database for the 1-year study, which contains the number of skin tumors on each animal, with each tumor having a size descriptor (0 to 1 mm, 1 to 2 mm, etc.). This data set and extraction technique was also used for the statistical analyses of time to first tumor (≥1 mm in diameter) reported as part of the 1-year study.

The skin tumor burden in each of the groups was analyzed using a distribution-free Kruskal-Wallis one-way method. The number of tumors (≥1 mm in diameter) for each of the mice was carried forward in the group burden after removal (Last-Observation-Carried-Forward, LOCF). This corrects for a downward trend in the group tumor burden (i.e., censoring) after a tumor-bearing animal is removed for necropsy. The analysis method described by DuBowski *et al.* (1998) assumes that for groups with LOCF, clear asymptotes will occur in the tumor burden for each group. This did not always occur in each test in the data set; therefore, a consistent time point was chosen (50 weeks) as a point where an asymptote either did occur or should have occurred.

The incidences of tumors in the absence of light and in the presence of light only are not shown in this Appendix. The most relevant comparisons for tumor multiplicity at a given dose of light are the effects of creams containing glycolic acid or salicylic acid compared to the control cream.

RESULTS

Male Mice

0.3 MED/Day Simulated Solar Light

Figure H1 shows skin tumor burdens in males exposed to 0.3 MED SSL and treated with control cream or creams containing glycolic acid or salicylic acid. The upper panel shows group mean incidences of males with at least one skin tumor 1 mm or greater in diameter, and the lower panel shows group mean skin tumor multiplicity in the same groups. Statistical analysis of the incidences of skin tumors is reported in Table H1 as the probability of significant difference between the weekly (and overall) mean incidences in the hydroxy acid-dosed and control cream groups, along with the results of weekly and overall analyses for dose-related trends. Statistical analysis of skin tumor multiplicity is similarly tabulated in Table H2, and effects of the hydroxy acids on skin tumor multiplicity are shown graphically as relative treatment effects in Figure H2.

There were no treatment-related effects of glycolic acid on the incidences of skin tumors in males treated with 0.3 MED SSL (Figure H1 upper panel and Table H1). This result is not in agreement with the decreased time to tumor data reported for the 1-year study in Table 12 as a positive dose-related trend (P=0.034) for glycolic acid at 0.3 MED SSL.

The inclusion of 4% salicylic acid reduced tumor incidences (P≤0.05N) during weeks 43 to 53 (Table H1). When the analysis was conducted across all time points ("Max" in Table H1), there was a negative overall dose trend for salicylic acid and the overall mean incidence of skin tumors in the 4% salicylic acid group was decreased. The results with 4% salicylic acid agree with the time to tumor data reported for the 1-year study in Table 12, where a significant dose trend (P=0.008N) was detected for salicylic acid and the 4% salicylic acid group mean was significantly increased (P=0.003N) compared to that of the control cream group.

Treatment with 10% glycolic acid increased tumor multiplicity (P≤0.05) at several time points between weeks 32 and 44; however, this did not result in a significant overall dose trend for glycolic acid or a significant overall multiplicity effect for 10% glycolic acid (Figure H1 lower panel and Table H2). These data contradict the data in Table 12 as described earlier, where glycolic acid induced a dose-dependent decrease in the mean time to tumor (P=0.034). These results suggest that this glycolic acid effect is a marginal effect at the threshold of statistical sensitivity.

Tumor multiplicity was decreased (P≤0.05N) by the inclusion of both 2% and 4% salicylic acid, resulting in a negative overall dose trend for salicylic acid and decreased overall mean multiplicity for each dose of salicylic acid (Table H2).

The relative treatment effects of the hydroxy acids are clearly seen in Figure H2; 10% glycolic acid transiently increased tumor multiplicity, and both doses of salicylic acid decreased tumor multiplicity.

0.6 MED/Day Simulated Solar Light

Neither glycolic nor salicylic acid affected the incidences of skin tumors (Figure H3 upper panel and Table H3) or skin tumor multiplicity (Figure H3 lower panel and Table H4). Accordingly, no relative treatment effects were seen for either hydroxy acid (Figure H4).

Female Mice

0.3 MED/Day Simulated Solar Light

The inclusion of glycolic acid in the creams did not result in consistent differences in skin tumor incidences between treated groups of females and the control cream group; however, from weeks 30 to 35, application of cream containing 10% glycolic acid did result in decreased tumor incidences (P≤0.05N) (Figure H5 upper panel

and Table H5). This additionally resulted in negative dose-trend effects during weeks 30 to 35, but not a trend at the asymptote (50 weeks). This result is consistent with the time to tumor data reported for the 1-year study in Table 12.

The inclusion of 4% salicylic acid reduced tumor incidences ($P \leq 0.05N$) during weeks 30 to 53 (Table H5). When the analysis was conducted across all time points, there was a negative overall dose trend for salicylic acid and the overall mean incidence of skin tumors in the 4% salicylic acid group was decreased. This result agrees with the time to tumor results reported in Table 12, where a significant dose trend was detected for salicylic acid and the mean for the 4% salicylic acid group was greater than that for the control cream group.

Tumor multiplicity was decreased by 10% glycolic acid ($P \leq 0.05N$) during weeks 28 to 36; however, there was no overall dose trend effect for glycolic acid and no overall multiplicity effect for 10% glycolic acid (Figure H5 lower panel and Table H6).

Tumor multiplicity was decreased by 4% salicylic acid at week 24 and from week 28 onward. This resulted in a negative overall dose trend for salicylic acid and decreased overall mean multiplicity for the 4% salicylic acid group.

Figure H6 clearly shows the decreased tumor multiplicity in mice treated with 4% salicylic acid as a reduction in relative treatment effect.

0.6 MED/Day Simulated Solar Light

There were no consistent effects of glycolic or salicylic acid on the incidences of skin tumors (Figure H7 upper panel and Table H7). These results agree with the time to tumor data reported for the 1-year study in Table 12.

The glycolic acid tumor multiplicity data (Figure H7 lower panel and Table H8) agree with the time to tumor data for the 1-year study (Table 12) indicating no treatment effect. However, analysis of tumor multiplicity revealed a negative effect of 4% salicylic acid ($P \leq 0.05N$) between weeks 38 and 53. In addition, there was a negative overall dose trend for salicylic acid, and overall mean multiplicity was decreased in the 4% salicylic acid group. This is graphically illustrated in Figure H8, showing a decreased relative treatment effect for 4% salicylic acid starting at week 38. The tumor multiplicity data with salicylic acid indicates a protective effect at 0.6 MED SSL, an effect not seen with the tumor incidence data. This suggests that tumor multiplicity may be a more sensitive measure of the effects of topically applied chemicals than tumor incidence.

CONCLUSIONS

This analysis of skin tumor multiplicity in mice has extended the observations that were made for the time to tumor of mice with skin tumors. In general, the effects of glycolic and salicylic acids on tumor multiplicity were consistent with the effects on the tumor incidence, with the following exceptions: glycolic acid in male mice at 0.3 MED SSL was shown not to affect tumorigenesis in this analysis, and decreased tumor multiplicity in female mice treated with salicylic acid at 0.6 MED SSL was the only indication of a protective effect of the beta hydroxy acid in this group. The added value of tumor multiplicity analysis is the ability to generate weekly pairwise comparisons and test for an overall dose trend effect, which may explain the protective effect seen with salicylic acid at 0.6 MED SSL in female mice in this study.

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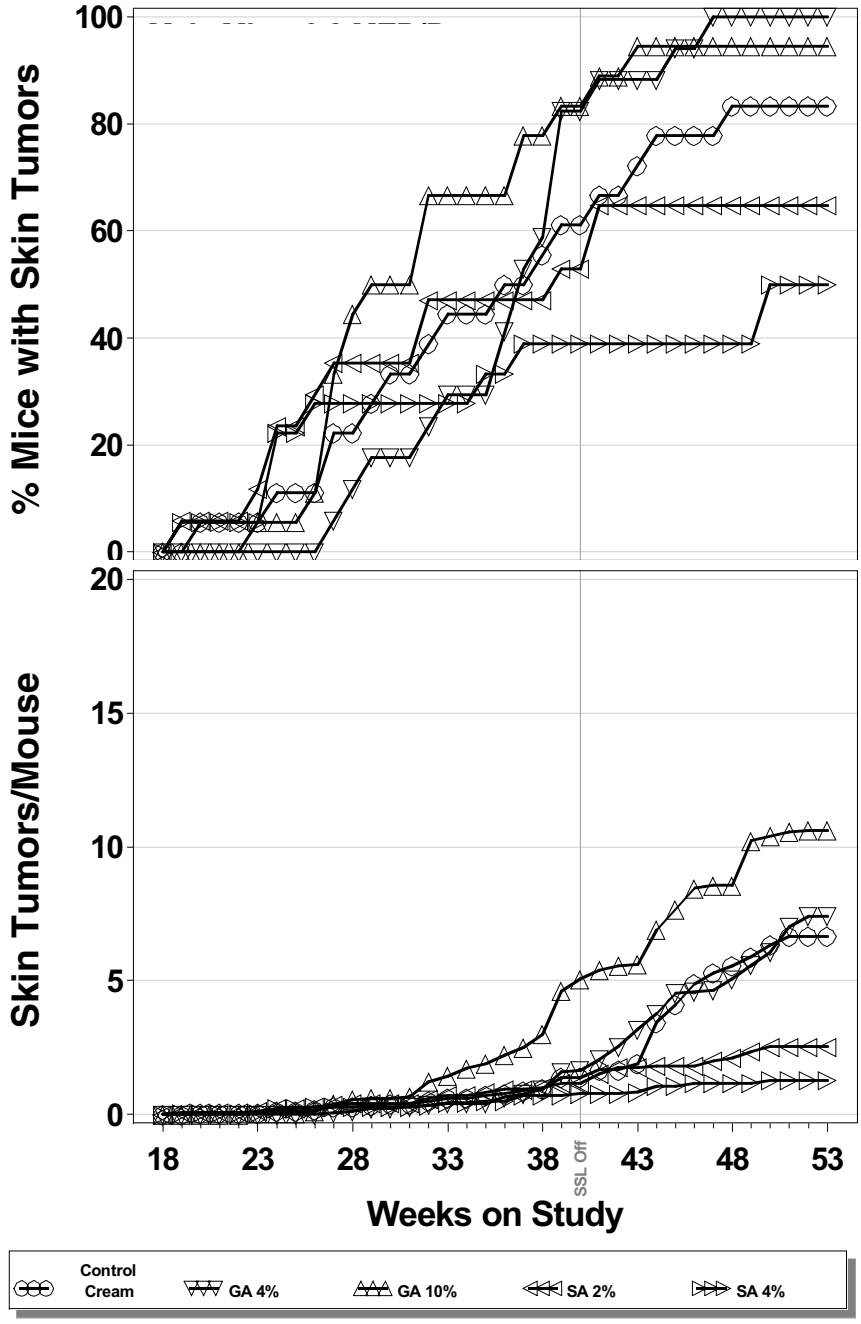

FIGURE H1
Skin Tumor Burden in Male Mice Treated with 0.3 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid
The upper panel shows the group mean percentage of mice with tumors (incidence), while the lower panel shows tumor multiplicity (average number of tumors/mouse) in each group with Last-Observation-Carried-Forward.
MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

TABLE H1
Skin Tumor Incidence Analysis for Male Mice Treated with 0.3 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid

		Males					
		GA			SA		
SSL	Week	Trend	4%–Control	10%–Control	Trend	2%–Control	4%–Control
0.3 MED/Day	Max[1]	0.200	0.301	0.301	**0.028 N ***	0.132 N	**0.038 N ***
	18	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]
	19	0.500 [4]	0.500 [3]	0.500 [3]	0.333	0.500	0.500
	20	0.333 N	0.500 N	0.500 N	0.500	0.500	0.500
	21	0.333 N	0.500 N	0.500 N	0.500	0.500	0.500
	22	0.333 N	0.500 N	0.500 N	0.500	0.500	0.500
	23	0.500	0.500 N	0.500	0.500	0.500	0.500
	24	0.366 N	0.243 N	0.500 N	0.263	0.329	0.329
	25	0.366 N	0.243 N	0.500 N	0.263	0.329	0.329
	26	0.500	0.243 N	0.500	0.161	0.201	0.201
	27	0.271	0.169 N	0.356	0.427	0.356	0.500
	28	0.093	0.329 N	0.144	0.427	0.356	0.500
	29	0.107	0.345 N	0.153	0.500	0.500	0.500
	30	0.191	0.222 N	0.250	0.430 N	0.500	0.500 N
	31	0.191	0.222 N	0.250	0.430 N	0.500	0.500 N
	32	0.066	0.235 N	0.091	0.304 N	0.500	0.362 N
	33	0.123	0.244 N	0.157	0.199 N	0.500 N	0.244 N
	34	0.123	0.244 N	0.157	0.199 N	0.500 N	0.244 N
	35	0.123	0.244 N	0.157	0.307 N	0.500 N	0.367 N
	36	0.205	0.369 N	0.250	0.202 N	0.500 N	0.250 N
	37	0.065	0.500	0.082	0.309 N	0.500 N	0.369 N
	38	0.116	0.500	0.144	0.204 N	0.370 N	0.253 N
	39	0.093	0.235	0.132	0.124 N	0.369 N	0.159 N
	40[2]	0.093	0.235	0.132	0.124 N	0.369 N	0.159 N
	41	0.075	0.222	0.114	0.067 N	0.500 N	0.091 N
	42	0.075	0.222	0.114	0.067 N	0.500 N	0.091 N
	43	0.060	0.345	0.089	**0.032 N ***	0.362 N	**0.046 N ***
	44	0.123	0.500	0.169	**0.014 N ***	0.235 N	**0.020 N ***
	45	0.110	0.329	0.169	**0.014 N ***	0.235 N	**0.020 N ***
	46	0.110	0.329	0.169	**0.014 N ***	0.235 N	**0.020 N ***
	47	0.095	0.169	0.169	**0.014 N ***	0.235 N	**0.020 N ***
	48	0.200	0.301	0.301	**0.005 N ***	0.132 N	**0.008 N ***
	49	0.200	0.301	0.301	**0.005 N ***	0.132 N	**0.008 N ***
	50	0.200	0.301	0.301	**0.028 N ***	0.132 N	**0.038 N ***
	51	0.200	0.301	0.301	**0.028 N ***	0.132 N	**0.038 N ***
	52	0.200	0.301	0.301	**0.028 N ***	0.132 N	**0.038 N ***
	53	0.200	0.301	0.301	**0.028 N ***	0.132 N	**0.038 N ***

* Effect is significant at 5%.
Tests are uncorrected exact one-sided Cochran-Armitage tests. N is appended if the test was negative (indicating left-tailed P values). All P values represent the result of using the Last-Observation-Carried-Forward convention. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

[1] Max represents the analysis of maximum tumor incidence over all times.

[2] SSL discontinued at this time point.

[3] Compared groups all had 0% incidence; P value is implicit.

TABLE H2
Skin Tumor Multiplicity Analysis for Male Mice Treated with 0.3 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid

		Males					
		GA			SA		
SSL	Week	Linear Trend[1,3]	4% – Control[2,3]	10% – Control[2,3]	Linear Trend[1,3]	2% – Control[2,3]	4% – Control[2,3]
0.3 MED/Day	Max[5]	0.141	0.055	0.091	**0.001 N ***	**0.040 N ***	**0.001 N ***
	18						
	19	1.000	1.000	1.000	0.392	0.304	0.392
	20	0.485 N	0.585 N	0.632 N	1.000	0.790	1.000
	21	0.508 N	0.537 N	0.635 N	1.000	0.787	1.000
	22	0.510 N	0.562 N	0.661 N	1.000	0.777	1.000
	23	0.882	0.569 N	1.000	1.000	0.357	1.000
	24	0.692 N	0.315 N	0.489 N	0.253	0.206	0.253
	25	0.726 N	0.334 N	0.514 N	0.273	0.219	0.273
	26	0.953	0.321 N	0.831 N	0.233	0.161	0.233
	27	0.360	0.228 N	0.458	0.760	0.437	0.760
	28	0.090	0.468 N	0.135	0.795	0.413	0.795
	29	0.095	0.578 N	0.130	0.904 N	0.639	0.904 N
	30	0.187	0.334 N	0.238	0.644 N	0.884	0.644 N
	31	0.160	0.377 N	0.219	0.655 N	0.894	0.655 N
	32	**0.020 ***	0.386 N	**0.035 ***	0.497 N	0.665	0.497 N
	33	**0.045 ***	0.387 N	0.070	0.430 N	0.824	0.430 N
	34	**0.031 ***	0.369 N	0.056	0.416 N	0.848	0.416 N
	35	**0.030 ***	0.306 N	**0.048 ***	0.472 N	0.842	0.472 N
	36	**0.032 ***	0.629 N	0.061	0.382 N	0.906	0.382 N
	37	**0.012 ***	0.928 N	**0.016 ***	0.647 N	0.920	0.647 N
	38	**0.008 ***	0.956	**0.013 ***	0.519 N	0.942 N	0.519 N
	39	**0.011 ***	0.540	**0.011 ***	0.220 N	0.761 N	0.220 N
	40[4]	**0.002 ***	0.426	**0.001 ***	0.300 N	0.784 N	0.300 N
	41	**0.003 ***	0.250	**0.003 ***	0.132 N	0.884	0.132 N
	42	**0.011 ***	0.055	**0.007 ***	0.169 N	0.643	0.169 N
	43	**0.005 ***	0.061	**0.005 ***	0.081 N	0.951	0.081 N
	44	**0.038 ***	0.376	**0.040 ***	**0.016 N ***	0.318 N	**0.016 N ***
	45	0.056	0.259	0.052	**0.002 N ***	0.182 N	**0.002 N ***
	46	0.087	0.431	0.090	**0.010 N ***	0.115 N	**0.010 N ***
	47	0.082	0.361	0.081	**0.003 N ***	0.109 N	**0.003 N ***
	48	0.099	0.274	0.095	**0.003 N ***	0.085 N	**0.003 N ***
	49	0.100	0.254	0.094	**0.003 N ***	0.111 N	**0.003 N ***
	50	0.106	0.114	0.084	**0.003 N ***	0.087 N	**0.003 N ***
	51	0.100	0.081	0.073	**<.001 N ***	**0.029 N ***	**<.001 N ***
	52	0.105	0.052	0.084	**<.001 N ***	**0.044 N ***	**<.001 N ***
	53	0.120	0.055	0.080	**0.003 N ***	**0.041 N ***	**0.003 N ***

* Effect is significant at 5%.
MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

[1] Trend test result is the Monte-Carlo exact two-sided P value for the null hypothesis of no hydroxy-acid effect against the alternative hypothesis of a linear dose trend in tumor multiplicity. The direction of the trend is positive unless N is appended to the value.

[2] P values represent the Monte-Carlo exact two-sided P values for the null hypothesis of no difference from control against the alternative hypothesis that there is a difference. The hydroxy-acid dose response is increased unless an N is appended to the value.

[3] All P values represent the result of using the Last-Observation-Carried-Forward convention.

[4] SSL discontinued at this time point.

[5] Max represents the analysis of the maximum tumor multiplicity over all times.

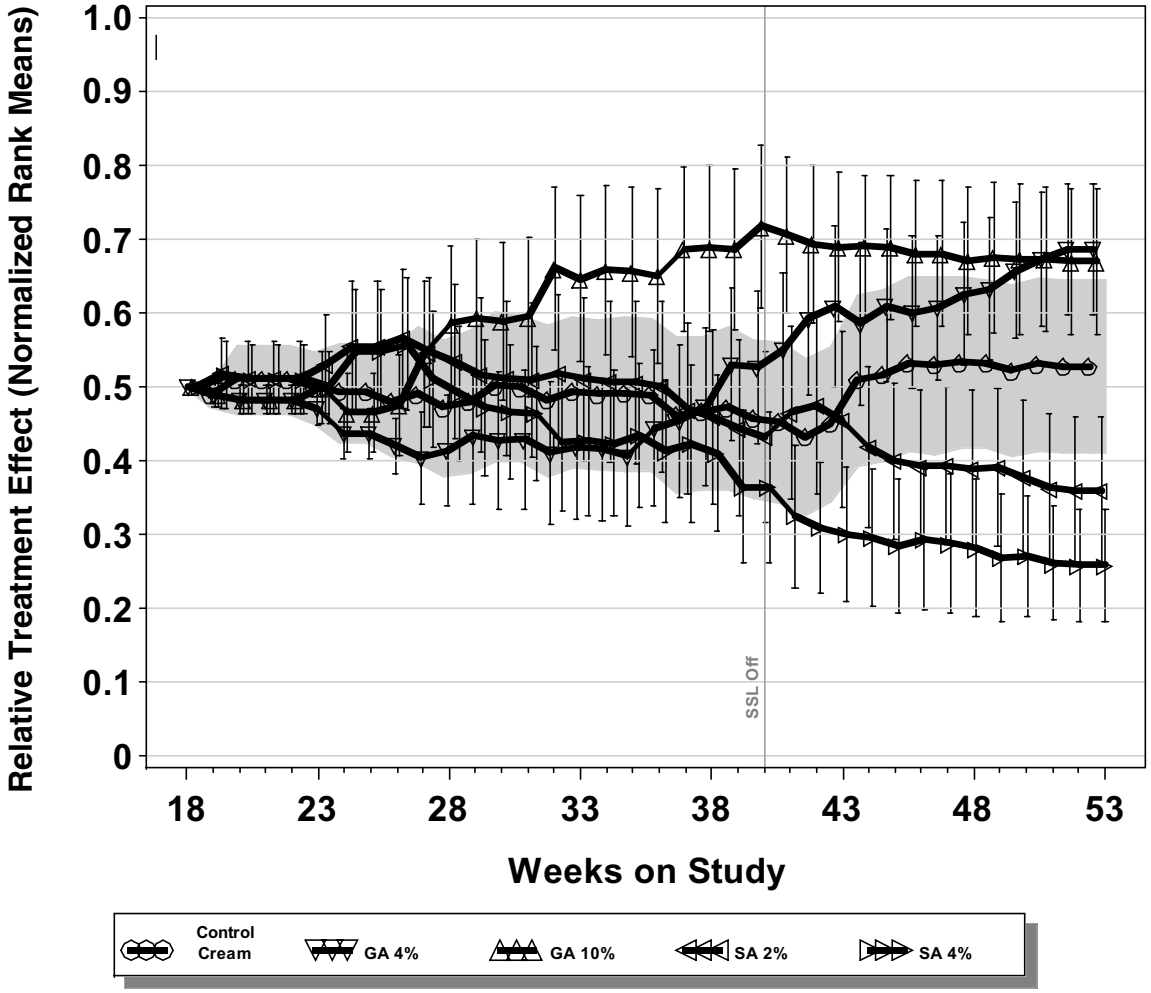

FIGURE H2
Relative Treatment Effect of Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid on the Photocarcinogenesis of 0.3 MED SSL in Male Mice
The graph shows the relative risk at each week, with the grey area showing the 95% confidence limits for the group receiving control cream. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

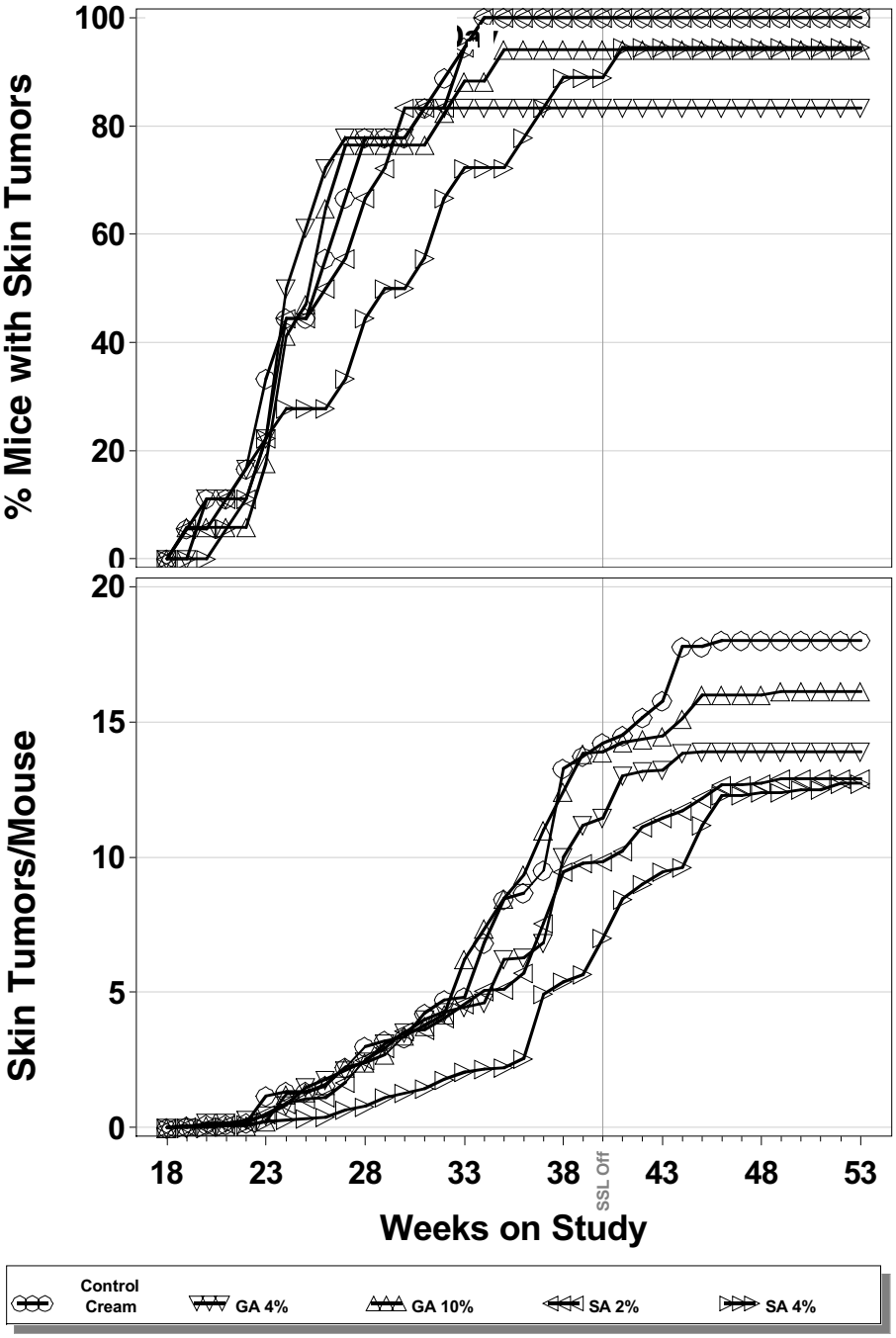

FIGURE H3
Skin Tumor Burden in Male Mice Treated with 0.6 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid
The upper panel shows the group mean percentage of mice with tumors (incidence), while the lower panel shows tumor multiplicity (average number of tumors/mouse) in each group with Last-Observation-Carried-Forward. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

TABLE H3
Skin Tumor Incidence Analysis for Male Mice Treated with 0.6 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid

		Males					
		GA			SA		
SSL	Week	Trend	4%–Control	10%–Control	Trend	2%–Control	4%–Control
0.6 MED/Day	Max[1]	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	18	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]
	19	0.500	0.500 N	0.500	0.333 N	0.500	0.500 N
	20	0.390 N	0.500	0.500 N	0.144 N	0.500 N	0.243 N
	21	0.390 N	0.500	0.500 N	0.390 N	0.500	0.500 N
	22	0.233 N	0.500 N	0.301 N	0.404 N	0.500 N	0.500 N
	23	0.168 N	0.356 N	0.222 N	0.287 N	0.356 N	0.356 N
	24	0.434 N	0.500	0.500 N	0.199 N	0.500 N	0.244 N
	25	0.500	0.253	0.500 N	0.199 N	0.500 N	0.244 N
	26	0.432	0.244	0.500	0.067 N	0.500 N	0.088 N
	27	0.427	0.356	0.500	**0.034 N** *	0.367 N	**0.047 N** *
	28	0.424 N	0.500	0.500 N	**0.029 N** *	0.356 N	**0.043 N** *
	29	0.424 N	0.500	0.500 N	0.057 N	0.500 N	0.082 N
	30	0.424 N	0.500	0.500 N	0.051 N	0.500	0.082 N
	31	0.271 N	0.500	0.345 N	**0.044 N** *	0.500	0.073 N
	32	0.255 N	0.500 N	0.329 N	0.075 N	0.500 N	0.114 N
	33	0.233 N	0.301 N	0.301 N	**0.041 N** *	0.500	0.089 N
	34	0.095 N	0.114 N	0.114 N	**0.003 N** *	0.500 [4]	**0.023 N** *
	35	0.200 N	0.114 N	0.243 N	**0.003 N** *	0.500 [4]	**0.023 N** *
	36	0.200 N	0.114 N	0.243 N	**0.010 N** *	0.500 [4]	0.052 N
	37	0.200 N	0.114 N	0.243 N	**0.033 N** *	0.500 [4]	0.114 N
	38	0.200 N	0.114 N	0.243 N	0.107 N	0.500 [4]	0.243 N
	39	0.200 N	0.114 N	0.243 N	0.107 N	0.500 [4]	0.243 N
	40[2]	0.200 N	0.114 N	0.243 N	0.107 N	0.500 [4]	0.243 N
	41	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	42	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	43	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	44	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	45	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	46	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	47	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	48	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	49	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	50	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	51	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	52	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N
	53	0.200 N	0.114 N	0.243 N	0.333 N	0.500 [4]	0.500 N

* Effect is significant at 5%.
Tests are uncorrected exact one-sided Cochran-Armitage tests. N is appended if the test was negative (indicating left-tailed P values). All P values represent the result of using the Last-Observation-Carried-Forward convention. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid;

[1] Max represents the analysis of maximum tumor incidence over all times.

[2] SSL discontinued at this time point.

[3] Compared groups all had 0% incidence; P value is implicit.

[4] Compared groups all had 100% incidence; P value is implicit.

TABLE H4
Skin Tumor Multiplicity Analysis for Male Mice Treated with 0.6 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid

		Males					
		GA			SA		
SSL	Week	Linear Trend[1,3]	4% – Control[2,3]	10% – Control[2,3]	Linear Trend[1,3]	2% – Control[2,3]	4% – Control[2,3]
0.6 MED/Day	Max[5]	0.860 N	0.254 N	0.770 N	0.155 N	0.179 N	0.155 N
	18						
	19	0.784	0.543 N	0.772	0.558 N	1.000	0.558 N
	20	0.571 N	0.770	0.698 N	0.285 N	0.629 N	0.285 N
	21	0.615 N	0.876	0.728 N	0.711 N	1.000	0.711 N
	22	0.364 N	0.837	0.435 N	0.672 N	0.766 N	0.672 N
	23	0.248 N	0.491 N	0.236 N	0.333 N	0.429 N	0.333 N
	24	0.967	0.783	0.949	0.185 N	0.946 N	0.185 N
	25	0.834	0.220	0.730	0.247 N	0.886	0.247 N
	26	0.498	0.173	0.414	0.093 N	0.886 N	0.093 N
	27	0.494	0.420	0.472	0.056 N	0.573 N	0.056 N
	28	0.900	0.705	0.857	**0.016 N** *	0.892 N	**0.016 N** *
	29	0.972 N	0.646	0.991	**0.043 N** *	0.884 N	**0.043 N** *
	30	0.626	0.441	0.581	**0.047 N** *	0.856	**0.047 N** *
	31	0.928	0.491	0.882	**0.036 N** *	0.735 N	**0.036 N** *
	32	0.676	0.495	0.623	0.053 N	0.703 N	0.053 N
	33	0.271	0.439	0.249	0.062 N	0.933	0.062 N
	34	0.474	0.681 N	0.542	**0.006 N** *	0.611 N	**0.006 N** *
	35	0.445	0.940 N	0.465	**0.001 N** *	0.151 N	**0.001 N** *
	36	0.312	0.832 N	0.346	**0.002 N** *	0.260 N	**0.002 N** *
	37	0.398	0.635 N	0.463	**0.041 N** *	0.742 N	**0.041 N** *
	38	0.681 N	0.205 N	0.599 N	**0.001 N** *	0.271 N	**0.001 N** *
	39	0.896	0.449 N	0.983	**<.001 N** *	0.250 N	**<.001 N** *
	40[4]	0.937 N	0.445 N	0.858 N	**0.003 N** *	0.165 N	**0.003 N** *
	41	0.986 N	0.746 N	0.948 N	**0.025 N** *	0.227 N	**0.025 N** *
	42	0.758 N	0.555 N	0.723 N	**0.026 N** *	0.285 N	**0.026 N** *
	43	0.645 N	0.432 N	0.595 N	**0.021 N** *	0.208 N	**0.021 N** *
	44	0.609 N	0.272 N	0.537 N	**0.009 N** *	0.151 N	**0.009 N** *
	45	0.884 N	0.237 N	0.780 N	**0.033 N** *	0.154 N	**0.033 N** *
	46	0.819 N	0.257 N	0.700 N	0.112 N	0.176 N	0.112 N
	47	0.830 N	0.236 N	0.722 N	0.116 N	0.154 N	0.116 N
	48	0.837 N	0.232 N	0.728 N	0.124 N	0.172 N	0.124 N
	49	0.849 N	0.233 N	0.747 N	0.139 N	0.188 N	0.139 N
	50	0.848 N	0.260 N	0.743 N	0.130 N	0.168 N	0.130 N
	51	0.854 N	0.253 N	0.730 N	0.133 N	0.187 N	0.133 N
	52	0.856 N	0.270 N	0.753 N	0.181 N	0.195 N	0.181 N
	53	0.865 N	0.263 N	0.752 N	0.165 N	0.201 N	0.165 N

* Effect is significant at 5%.
MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

[1] Trend test result is the Monte-Carlo exact two-sided P value for the null hypothesis of no hydroxy-acid effect against the alternative hypothesis of a linear dose trend in tumor multiplicity. The direction of the trend is positive unless N is appended to the value.

[2] P values represent the Monte-Carlo exact two-sided P values for the null hypothesis of no difference from control against the alternative hypothesis that there is a difference. The hydroxy-acid dose response is increased unless an N is appended to the value.

[3] All P values represent the result of using the Last-Observation-Carried-Forward convention.

[4] SSL discontinued at this time point.

[5] Max represents the analysis of maximum tumor multiplicity over all times.

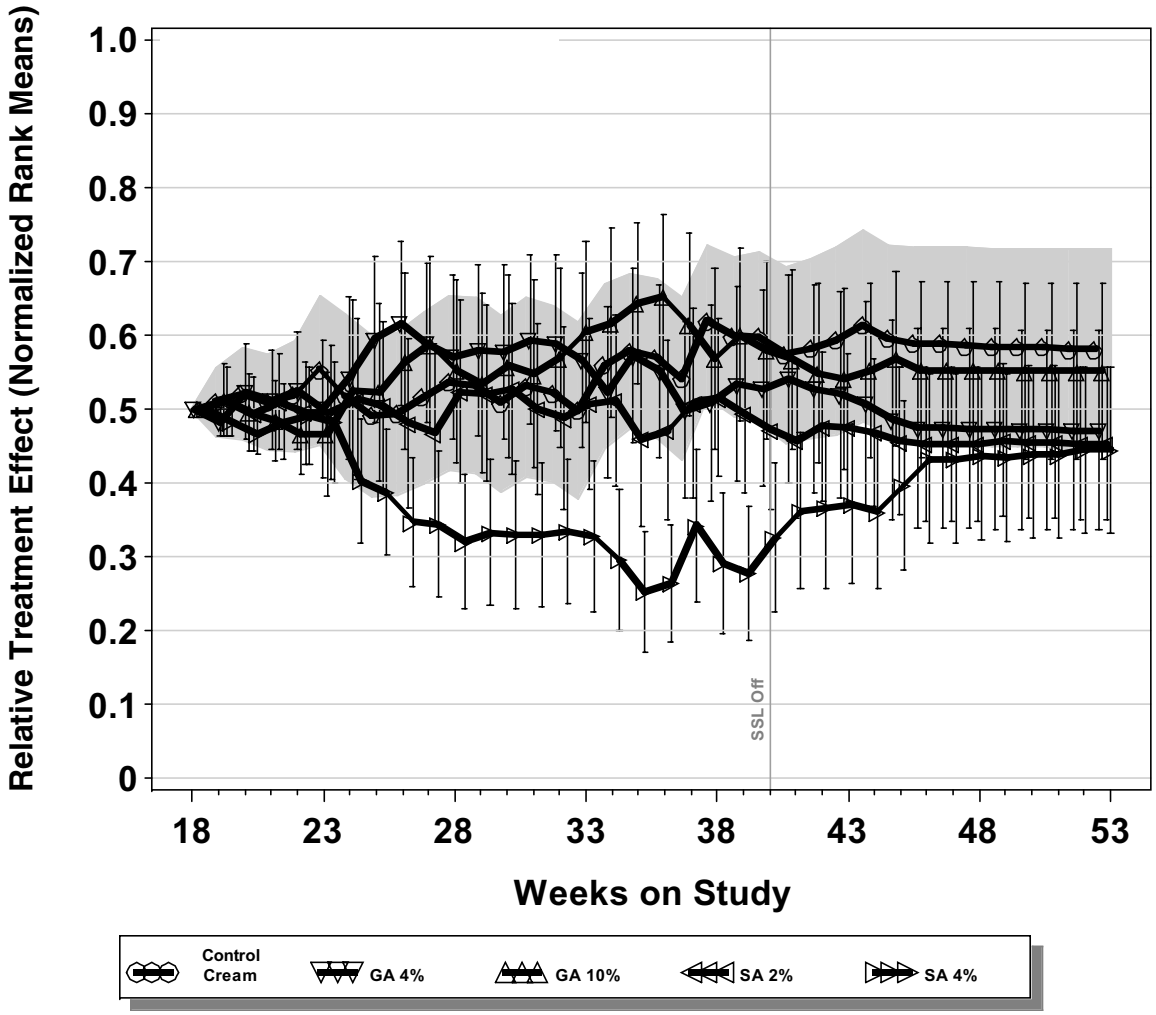

FIGURE H4
Relative Treatment Effect of Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid on the Photocarcinogenesis of 0.6 MED SSL in Male Mice
The graph shows the relative risk at each week, with the grey area showing the 95% confidence limits for the group receiving control cream. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

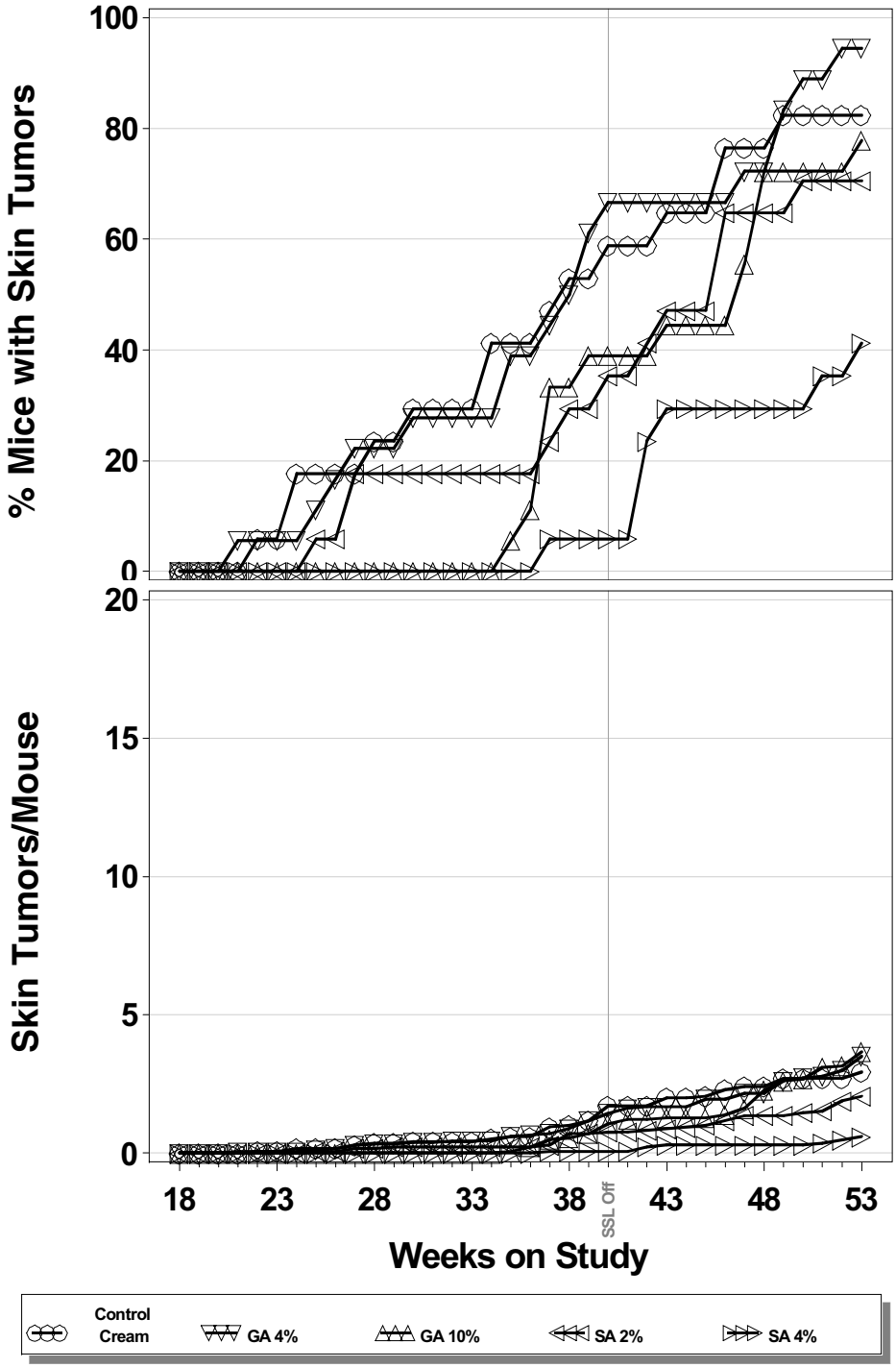

FIGURE H5

Skin Tumor Burden in Female Mice Treated with 0.3 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid

The upper panel shows the group mean percentage of mice with tumors (incidence), while the lower panel shows tumor multiplicity (average number of tumors/mouse) in each group with Last-Observation-Carried-Forward. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

TABLE H5
Skin Tumor Incidence Analysis for Female Mice Treated with 0.3 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid

		Females					
		GA			SA		
SSL	Week	Trend	4%–Control	10%–Control	Trend	2%–Control	4%–Control
0.3 MED/Day	Max[1]	0.500	0.169	0.500	**0.013 N ***	0.356 N	**0.020 N ***
	18	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]
	19	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]
	20	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]
	21	0.500	0.500	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]
	22	0.333 N	0.500	0.500 N	0.333 N	0.500 N	0.500 N
	23	0.333 N	0.500	0.500 N	0.333 N	0.500 N	0.500 N
	24	0.056 N	0.301 N	0.114 N	**0.033 N ***	0.114 N	0.114 N
	25	0.077 N	0.500 N	0.114 N	0.056 N	0.301 N	0.114 N
	26	0.095 N	0.500 N	0.114 N	0.056 N	0.301 N	0.114 N
	27	0.110 N	0.500	0.114 N	0.095 N	0.500 N	0.114 N
	28	0.051 N	0.500 N	0.052 N	**0.041 N ***	0.500 N	0.052 N
	29	0.051 N	0.500 N	0.052 N	**0.041 N ***	0.500 N	0.052 N
	30	**0.026 N ***	0.500	**0.023 N ***	**0.016 N ***	0.345 N	**0.023 N ***
	31	**0.026 N ***	0.500	**0.023 N ***	**0.016 N ***	0.345 N	**0.023 N ***
	32	**0.026 N ***	0.500	**0.023 N ***	**0.016 N ***	0.345 N	**0.023 N ***
	33	**0.026 N ***	0.500	**0.023 N ***	**0.016 N ***	0.345 N	**0.023 N ***
	34	**0.004 N ***	0.362 N	**0.004 N ***	**0.002 N ***	0.132 N	**0.004 N ***
	35	**0.020 N ***	0.500 N	**0.020 N ***	**0.002 N ***	0.132 N	**0.004 N ***
	36	0.051 N	0.500 N	0.061 N	**0.002 N ***	0.132 N	**0.004 N ***
	37	0.307 N	0.500 N	0.367 N	**0.005 N ***	0.144 N	**0.009 N ***
	38	0.203 N	0.500	0.250 N	**0.002 N ***	0.153 N	**0.004 N ***
	39	0.311 N	0.369	0.369 N	**0.002 N ***	0.153 N	**0.004 N ***
	40[2]	0.204 N	0.367	0.253 N	**<.001 N ***	0.157 N	**0.001 N ***
	41	0.204 N	0.367	0.253 N	**<.001 N ***	0.157 N	**0.001 N ***
	42	0.204 N	0.367	0.253 N	**0.030 N ***	0.253 N	**0.043 N ***
	43	0.202 N	0.500	0.253 N	**0.033 N ***	0.253 N	**0.046 N ***
	44	0.202 N	0.500	0.253 N	**0.033 N ***	0.253 N	**0.046 N ***
	45	0.202 N	0.500	0.253 N	**0.033 N ***	0.253 N	**0.046 N ***
	46	0.063 N	0.500 N	0.088 N	**0.006 N ***	0.362 N	**0.009 N ***
	47	0.191 N	0.500 N	0.244 N	**0.006 N ***	0.362 N	**0.009 N ***
	48	0.500	0.500 N	0.500 N	**0.006 N ***	0.362 N	**0.009 N ***
	49	0.422 N	0.500	0.500 N	**0.002 N ***	0.235 N	**0.003 N ***
	50	0.419 N	0.329	0.500 N	**0.002 N ***	0.356 N	**0.003 N ***
	51	0.419 N	0.329	0.500 N	**0.005 N ***	0.356 N	**0.009 N ***
	52	0.417 N	0.169	0.500 N	**0.005 N ***	0.356 N	**0.009 N ***
	53	0.500	0.169	0.500	**0.013 N ***	0.356 N	**0.020 N ***

* Effect is significant at 5%.
Tests are uncorrected exact one-sided Cochran-Armitage tests. N is appended if the test was negative (indicating left-tailed P values). All P values represent the result of using the Last-Observation-Carried-Forward convention. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

[1] Max represents the analysis of maximum tumor incidence over all times.

[2] SSL discontinued at this time point.

[3] Compared groups all had 0% incidence. P value is implicit.

TABLE H6
Skin Tumor Multiplicity Analysis for Female Mice Treated with 0.3 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid

		Females					
		GA			SA		
SSL	Week	Linear Trend[1,3]	4% – Control[2,3]	10% – Control[2,3]	Linear Trend[1,3]	2% – Control[2,3]	4% – Control[2,3]
0.3 MED/Day	Max[5]	0.639	0.135	0.535	**0.005 N ***	0.556 N	**0.005 N ***
	18						
	19						
	20						
	21	0.576 N	0.369	1.000	1.000	1.000	1.000
	22	0.151 N	0.647 N	0.302 N	0.548 N	0.558 N	0.548 N
	23	0.136 N	0.626 N	0.283 N	0.542 N	0.585 N	0.542 N
	24	**0.013 N ***	**0.045 N ***	**0.011 N ***	**0.027 N ***	**0.035 N ***	**0.027 N ***
	25	**0.020 N ***	0.319 N	**0.041 N ***	0.064 N	0.123 N	0.064 N
	26	**0.032 N ***	0.752 N	**0.042 N ***	0.053 N	0.146 N	0.053 N
	27	0.068 N	0.746	0.080 N	0.086 N	0.811 N	0.086 N
	28	**0.018 N ***	0.853 N	**0.028 N ***	**0.041 N ***	0.491 N	**0.041 N ***
	29	**0.031 N ***	0.892 N	**0.039 N ***	**0.037 N ***	0.606 N	**0.037 N ***
	30	**0.007 N ***	0.895 N	**0.012 N ***	**0.013 N ***	0.311 N	**0.013 N ***
	31	**0.010 N ***	0.897 N	**0.014 N ***	**0.018 N ***	0.315 N	**0.018 N ***
	32	**0.014 N ***	0.959 N	**0.022 N ***	**0.018 N ***	0.342 N	**0.018 N ***
	33	**0.012 N ***	0.950 N	**0.017 N ***	**0.023 N ***	0.327 N	**0.023 N ***
	34	**<.001 N ***	0.338 N	**<.001 N ***	**0.002 N ***	0.066 N	**0.002 N ***
	35	**0.005 N ***	0.920 N	**0.008 N ***	**<.001 N ***	0.065 N	**<.001 N ***
	36	**0.029 N ***	0.991 N	**0.037 N ***	**0.007 N ***	0.078 N	**0.007 N ***
	37	0.339 N	0.969 N	0.371 N	**0.009 N ***	0.137 N	**0.009 N ***
	38	0.252 N	0.934	0.283 N	**0.004 N ***	0.195 N	**0.004 N ***
	39	0.318 N	0.547	0.392 N	**0.003 N ***	0.145 N	**0.003 N ***
	40[4]	0.203 N	0.680	0.248 N	**0.002 N ***	0.111 N	**0.002 N ***
	41	0.252 N	0.622	0.314 N	**<.001 N ***	0.127 N	**<.001 N ***
	42	0.245 N	0.604	0.305 N	**0.015 N ***	0.208 N	**0.015 N ***
	43	0.262 N	0.776	0.319 N	**0.018 N ***	0.193 N	**0.018 N ***
	44	0.265 N	0.801	0.305 N	**0.008 N ***	0.215 N	**0.008 N ***
	45	0.284 N	0.727	0.330 N	**0.020 N ***	0.243 N	**0.020 N ***
	46	0.067 N	0.725 N	0.076 N	**<.001 N ***	0.214 N	**<.001 N ***
	47	0.252 N	0.874	0.295 N	**0.001 N ***	0.286 N	**0.001 N ***
	48	0.918 N	0.862	0.918 N	**<.001 N ***	0.294 N	**<.001 N ***
	49	0.654 N	0.599	0.707 N	**<.001 N ***	0.121 N	**<.001 N ***
	50	0.632 N	0.336	0.726 N	**<.001 N ***	0.198 N	**<.001 N ***
	51	0.944 N	0.290	0.942	**<.001 N ***	0.272 N	**<.001 N ***
	52	0.989	0.200	0.863	**0.003 N ***	0.414 N	**0.003 N ***
	53	0.693	0.162	0.563	**0.004 N ***	0.575 N	**0.004 N ***

* Effect is significant at 5%.

[1] Trend test result is the Monte-Carlo exact two-sided P value for the null hypothesis of no hydroxy-acid effect against the alternative hypothesis of a linear dose trend in tumor multiplicity. The direction of the trend is positive unless N is appended to the value.

[2] P values represent the Monte-Carlo exact two-sided P values for the null hypothesis of no difference from control against the alternative hypothesis that there is a difference. The hydroxy-acid dose response is increased unless an N is appended to the value.

[3] All P values represent the results of using the Last-Observation-Carried-Forward convention.

[4] SSL discontinued at this time point.

[5] Max represents the analysis of maximum tumor multiplicity over all times.

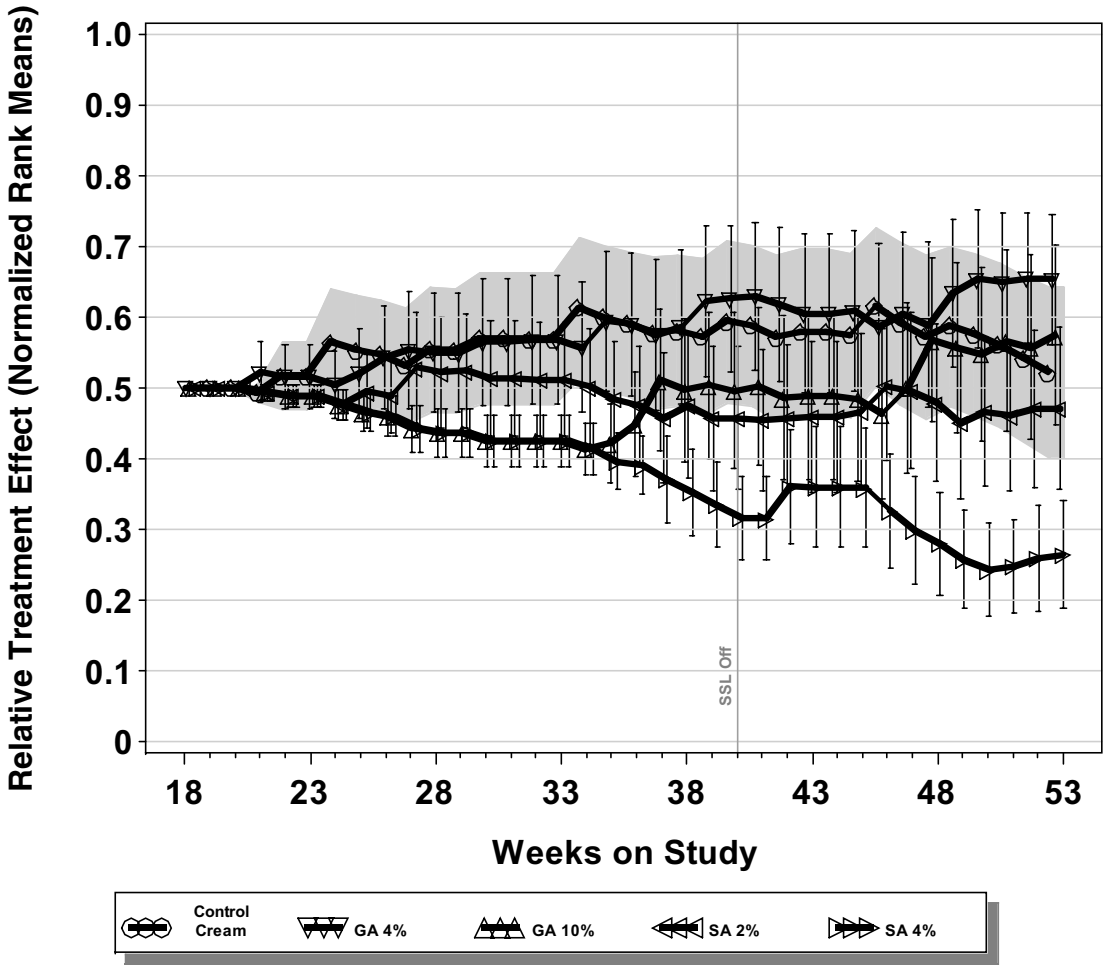

FIGURE H6
Relative Treatment Effect of Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid on the Photocarcinogenesis of 0.3 MED SSL in Female Mice
The graph shows the relative risk at each week, with the grey area showing the 95% confidence limits for the group receiving control cream. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

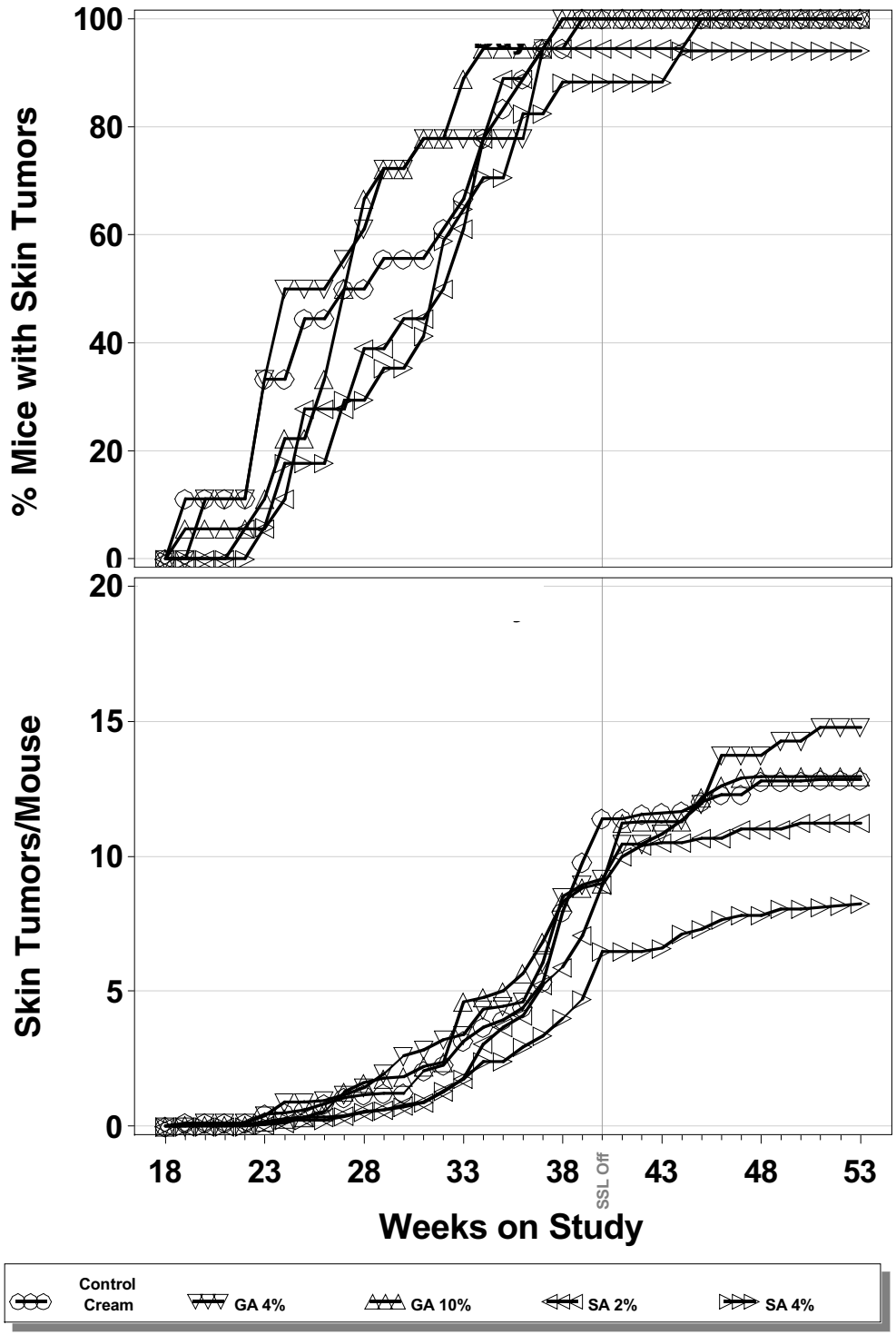

FIGURE H7

Skin Tumor Burden in Female Mice Treated with 0.6 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid

The upper panel shows the group mean percentage of mice with tumors (incidence), while the lower panel shows tumor multiplicity (average number of tumors/mouse) in each group with Last-Observation-Carried-Forward. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

TABLE H7
Skin Tumor Incidence Analysis for Female Mice Treated with 0.6 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid

		Females					
		GA			SA		
SSL	Week	Trend	4%–Control	10%–Control	Trend	2%–Control	4%–Control
0.6 MED/Day	Max[1]	0.500 [4]	0.500 [4]	0.500 [4]	0.107 N	0.500 [4]	0.243 N
	18	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]	0.500 [3]
	19	0.366 N	0.243 N	0.500 N	0.107 N	0.243 N	0.243 N
	20	0.390 N	0.500	0.500 N	0.107 N	0.243 N	0.243 N
	21	0.390 N	0.500	0.500 N	0.107 N	0.243 N	0.243 N
	22	0.390 N	0.500	0.500 N	0.144 N	0.500 N	0.243 N
	23	0.093 N	0.500	0.114 N	**0.016 N** *	**0.044 N** *	**0.044 N** *
	24	0.302 N	0.250	0.356 N	0.153 N	0.114 N	0.222 N
	25	0.118 N	0.500	0.144 N	0.051 N	0.244 N	0.073 N
	26	0.309 N	0.500	0.367 N	0.051 N	0.244 N	0.073 N
	27	0.500	0.500	0.500	0.113 N	0.153 N	0.153 N
	28	0.201	0.369	0.250	0.118 N	0.369 N	0.153 N
	29	0.191	0.244	0.244	0.121 N	0.253 N	0.157 N
	30	0.191	0.244	0.244	0.122 N	0.370 N	0.157 N
	31	0.103	0.144	0.144	0.204 N	0.370 N	0.253 N
	32	0.179	0.235	0.235	0.434 N	0.369 N	0.500 N
	33	0.082	0.356	0.114	0.432 N	0.500 N	0.500 N
	34	0.135	0.500	0.169	0.287 N	0.500	0.356 N
	35	0.245	0.500 N	0.301	0.153 N	0.500	0.222 N
	36	0.404	0.329 N	0.500	0.245 N	0.500	0.329 N
	37	0.500	0.500	0.500	0.095 N	0.500	0.169 N
	38	0.333	0.500	0.500	0.200 N	0.500	0.301 N
	39	0.500 [4]	0.500 [4]	0.500 [4]	0.056 N	0.500 N	0.114 N
	40[2]	0.500 [4]	0.500 [4]	0.500 [4]	0.056 N	0.500 N	0.114 N
	41	0.500 [4]	0.500 [4]	0.500 [4]	0.056 N	0.500 N	0.114 N
	42	0.500 [4]	0.500 [4]	0.500 [4]	0.056 N	0.500 N	0.114 N
	43	0.500 [4]	0.500 [4]	0.500 [4]	0.056 N	0.500 N	0.114 N
	44	0.500 [4]	0.500 [4]	0.500 [4]	0.144 N	0.500 N	0.243 N
	45	0.500 [4]	0.500 [4]	0.500 [4]	0.107 N	0.500 [4]	0.243 N
	46	0.500 [4]	0.500 [4]	0.500 [4]	0.107 N	0.500 [4]	0.243 N
	47	0.500 [4]	0.500 [4]	0.500 [4]	0.107 N	0.500 [4]	0.243 N
	48	0.500 [4]	0.500 [4]	0.500 [4]	0.107 N	0.500 [4]	0.243 N
	49	0.500 [4]	0.500 [4]	0.500 [4]	0.107 N	0.500 [4]	0.243 N
	50	0.500 [4]	0.500 [4]	0.500 [4]	0.107 N	0.500 [4]	0.243 N
	51	0.500 [4]	0.500 [4]	0.500 [4]	0.107 N	0.500 [4]	0.243 N
	52	0.500 [4]	0.500 [4]	0.500 [4]	0.107 N	0.500 [4]	0.243 N
	53	0.500 [4]	0.500 [4]	0.500 [4]	0.107 N	0.500 [4]	0.243 N

* Effect is significant at 5%.

Tests are uncorrected exact one-sided Cochran-Armitage tests. N is appended if the trend was negative (indicating left-tailed P values). All P values represent the results of using the Last-Observation-Carried-Forward convenvention. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid

[1] Max represents the analysis of maximum tumor incidence over all times.

[2] SSL discontinued at this time point.

[3] Compared groups all had 0% incidence. P value is implicit.

[4] Compared groups all had 100% incidence. P value is implicit.

TABLE H8
Skin Tumor Multiplicity Analysis for Female Mice Treated with 0.6 MED SSL and Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid

		Females					
		GA			SA		
SSL	Week	Linear Trend[1,3]	4% – Control[2,3]	10% – Control[2,3]	Linear Trend[1,3]	2% – Control[2,3]	4% – Control[2,3]
0.6 MED/Day	Max[5]	0.801 N	0.479	0.875 N	**0.025 N ***	0.365 N	**0.025 N ***
	18						
	19	0.647 N	0.150 N	0.352 N	0.142 N	0.155 N	0.142 N
	20	0.404 N	1.000	0.467 N	0.226 N	0.226 N	0.226 N
	21	0.433 N	1.000	0.495 N	0.236 N	0.250 N	0.236 N
	22	0.489 N	1.000	0.672 N	0.277 N	0.683 N	0.277 N
	23	0.056 N	0.934 N	0.083 N	**0.029 N ***	**0.020 N ***	**0.029 N ***
	24	0.315 N	0.260	0.399 N	0.318 N	0.129 N	0.318 N
	25	0.143 N	0.661	0.185 N	0.105 N	0.237 N	0.105 N
	26	0.302 N	0.784	0.355 N	0.098 N	0.198 N	0.098 N
	27	0.925	0.945	0.909	0.087 N	0.081 N	0.087 N
	28	0.481	0.727	0.487	0.116 N	0.197 N	0.116 N
	29	0.413	0.310	0.372	0.142 N	0.149 N	0.142 N
	30	0.412	0.158	0.348	0.203 N	0.302 N	0.203 N
	31	0.333	0.182	0.285	0.260 N	0.256 N	0.260 N
	32	0.487	0.142	0.391	0.530 N	0.417 N	0.530 N
	33	0.112	0.494	0.116	0.306 N	0.258 N	0.306 N
	34	0.347	0.467	0.330	0.259 N	0.790 N	0.259 N
	35	0.472	0.706	0.472	0.137 N	0.927 N	0.137 N
	36	0.487	0.973 N	0.517	0.164 N	0.876 N	0.164 N
	37	0.564	0.600	0.536	0.106 N	0.792 N	0.106 N
	38	0.958	0.904 N	0.981	**0.007 N ***	0.122 N	**0.007 N ***
	39	0.672 N	0.453 N	0.629 N	**0.005 N ***	0.124 N	**0.005 N ***
	40[4]	0.170 N	0.164 N	0.140 N	**0.006 N ***	0.138 N	**0.006 N ***
	41	0.762 N	0.284 N	0.696 N	**0.010 N ***	0.443 N	**0.010 N ***
	42	0.744 N	0.257 N	0.657 N	**0.007 N ***	0.528 N	**0.007 N ***
	43	0.702 N	0.346 N	0.632 N	**0.005 N ***	0.545 N	**0.005 N ***
	44	0.637 N	0.518 N	0.595 N	**0.015 N ***	0.535 N	**0.015 N ***
	45	0.907 N	0.622 N	0.884 N	**0.019 N ***	0.477 N	**0.019 N ***
	46	0.927 N	0.744	0.964 N	**0.025 N ***	0.452 N	**0.025 N ***
	47	0.958	0.731	0.909	**0.024 N ***	0.542 N	**0.024 N ***
	48	0.891 N	0.956	0.899 N	**0.009 N ***	0.342 N	**0.009 N ***
	49	0.874 N	0.630	0.923 N	**0.018 N ***	0.367 N	**0.018 N ***
	50	0.849 N	0.647	0.914 N	**0.017 N ***	0.409 N	**0.017 N ***
	51	0.813 N	0.494	0.887 N	**0.017 N ***	0.400 N	**0.017 N ***
	52	0.834 N	0.491	0.896 N	**0.021 N ***	0.377 N	**0.021 N ***
	53	0.779 N	0.458	0.874 N	**0.028 N ***	0.406 N	**0.028 N ***

* Effect is significant at 5%.
MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA= salicylic acid

[1] Trend test result is the Monte-Carlo exact two-sided P value for the null hypothesis of no hydroxy-acid effect against the alternative hypothesis of a linear dose trend in tumor multiplicity. The direction of the trend is positive unless N is appended to the value.

[2] P values represent the Monte-Carlo exact two-sided P values for the null hypothesis of no difference from control against the alternative hypothesis that there is a difference. The hydroxy-acid dose response is increased unless an N is appended to the value.

[3] All P values represent the result of using the Last-Observation-Carried-Forward convention.

[4] SSL discontinued at this time point.

[5] Max represents the analysis of maximum tumor multiplicity over all times.

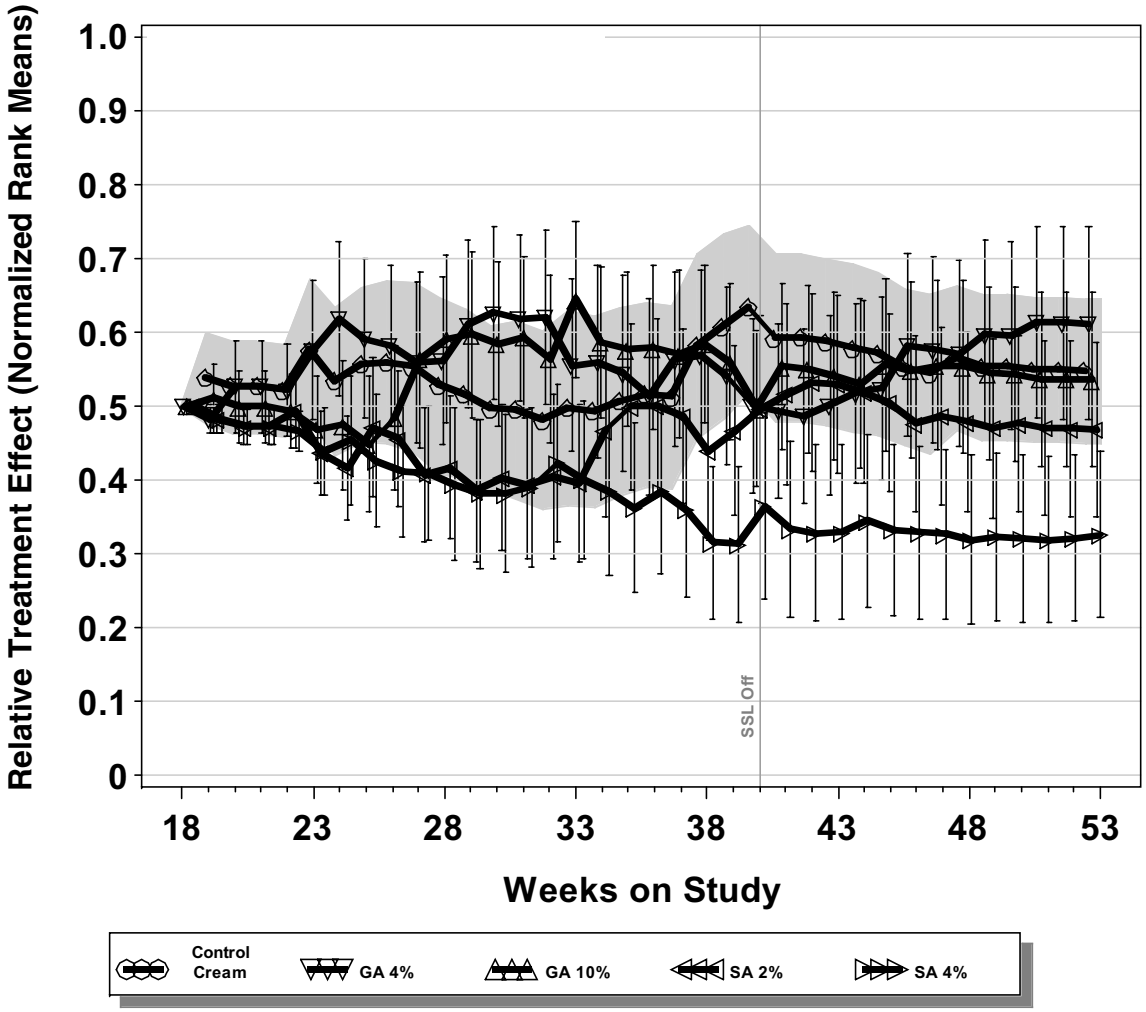

FIGURE H8
Relative Treatment Effect of Topically Applied Control Cream or Creams Containing Glycolic or Salicylic Acid on the Photocarcinogenesis of 0.6 MED SSL in Female Mice
The graph shows the relative risk at each week, with the grey area showing the 95% confidence limits for the group receiving control cream. MED=minimal erythema dose; SSL=simulated solar light; GA=glycolic acid; SA=salicylic acid