Safety of retinyl palmitate in sunscreens: A critical analysis

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In its annual sunscreen report, the Environmental Working Group[1] claimed that 41% of the sunscreens on the market contain retinyl palmitate (RP), an ester form of vitamin A. Based on its internal analysis of the data from the National Toxicology Program (NTP), the Environmental Working Group issued a health warning regarding the photocarcinogenic potential of sunscreens containing RP. This claim has received significant media coverage with many news organizations running stories such as "your sunscreen may give you cancer." In fact, the media frenzy has prompted the senior Senator from New York, Chuck Schumer, to urge the Food and Drug Administration (FDA) to address this issue. This has resulted in many individuals questioning the overall safety of sunscreens, and with some expressing strong reluctance to use sunscreens for photoprotection. In this short communication, we will provide a brief overview of the role of RP in skin physiology, critically analyze the currently available data, and conclude that there is no evidence that the inclusion of RP in sunscreens is photocarcinogenic in human beings.

RP is the storage form of retinol (vitamin A), an essential and endogenous nutrient for human beings. Retinol in human skin is converted and stored as RP. Upon physiologic demands, retinol and RP are converted to the active retinoic acids, which play important roles in many biologic functions. The interchangeable relationships among RP, retinol (vitamin A), and other retinoids are shown in Fig 1. In terms of pharmacologic or toxicologic profiles, there are no qualitative differences between RP and other retinoids.[2-4] Lastly, RP in sunscreens has the same pharmacologic, biological, and toxicologic profiles as endogenous RP in human skin.

Abbreviations used:

FDA: Food and Drug Administration
NTP: National Toxicology Program
RP: retinyl palmitate
UV: ultraviolet

In 2000, RP was selected for phototoxicity and photocarcinogenicity testing by the NTP, a Federal program designed to test the safety of compounds. It should be emphasized that mere selection for testing does not mean the chosen compounds are dangerous or unsafe. In fact, common ingredients, such as alpha- and beta-hydroxy acids, aloe vera, nanoscale TiO_2 and ZnO, are currently under review. RP was selected because of its widespread use in cosmetics and sunscreen products. According to the FDA's Voluntary Cosmetics Registration Program, the number of formulations containing RP increased from 355 in 1992 to 667 in 2000. It is worthy to note that RP has also been used as a food additive and approved for use in over-the-counter and prescription drugs by the FDA. Another reason for testing was RP exhibited many of the similar biologic and histologic effects on skin as seen with retinoic acid. Some of these effects include epidermal hyperplasia, fibroblast growth, and collagen synthesis, pharmacologic effects known to be desirable for reversing photoaging.

From 2002 to 2009, the FDA published 8 in vitro and 3 mice studies regarding RP. Four in vitro studies[5-8] showed the combination of RP and ultraviolet (UV) A induced reactive oxygen species. Three in vitro studies using mouse lymphoma cell culture[9-11] and one in vitro study with human skin Jurkat T cells[12] showed the combination of RP and UVA radiation can be photomutagenic. Three studies[13-15] with SKH-1 mice showed topically applied RP

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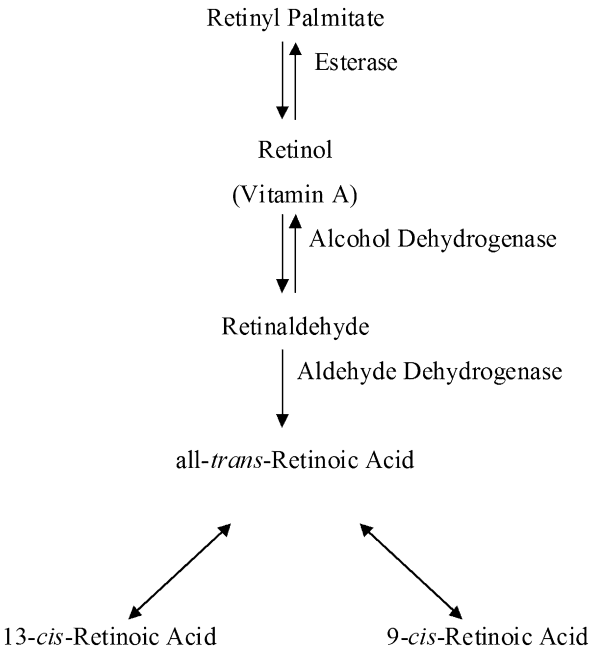

Fig 1. Interchangeable relationships among retinyl palmitate, retinol (vitamin A), and other retinoids.

expectedly altered the physiologic level of retinol in the skin of these animals. Although in one of the 3 studies the mice were exposed to radiation from a simulated solar light source, development of skin cancers was not reported in any of these studies.

On a casual glance, the generation of oxygen radicals and their potential for photomutagenicity may be a concern. However, the biological relevance of these findings in human beings is unclear. RP, vitamin A, and retinoic acid are lipid soluble antioxidants commonly located in the epidermis of human skin. Working in concert with other non-enzymatic antioxidants (eg, vitamins C and E) and enzymatic antioxidants (eg, superoxide dismutase, catalase, and glutathione reductase), vitamin A can neutralize free radicals. It is recognized that cooperation among the individual elements in the antioxidant system is required to attain the optimal protection. In isolation, nearly all non-enzymatic antioxidants are quickly depleted, and some can even become pro-oxidative (ie, produce radicals) when challenged with UV or other harmful stimuli. Therefore, when a sunscreen with RP is applied to human skin, a full profile of non-enzymatic and enzymatic antioxidants are available to mitigate the risk of the pro-oxidative state seen in these in vitro experiments, where RP is the only antioxidant present in the experimental system.

A large animal study testing the photocarcinogenic potential of RP and UV radiation was completed by the NTP.[16] The findings have not been published in peer-reviewed literature, but the data are available online. In these experiments, 8 groups of SKH-1 hairless mice were exposed to varying concentrations of RP and doses of UV radiation, delivered via a solar simulator. Two concentrations of topical RP (0.1% and 0.5%) were used, while vehicle control was a pH 7 cream. Animals were irradiated with a solar simulator at doses of 6.75 and 13.7 mJ/cm^2. Although the methods are not described in detail in the NTP study, based on another photocarcinogenesis study performed by the same group, the protocol used was to expose mice to 0.3 minimal erythema dose (=6.75 mJ/cm^2) and 0.6 minimal erythema dose (=13.7 mJ/cm^2) of solar-simulated radiation 5 days per week for 40 weeks.[17] We have summarized the results in Table I, and performed comparisons between study groups using the 2-sample test for proportions. In the low-dose (6.75 mJ/cm^2) irradiated groups (Table I, groups 3 to 5), both 0.1% and 0.5% RP induced higher incidences of malignant lesions when compared with the vehicle control group, but only the 0.5% RP group showed a statistically significant difference. However, in the groups exposed to high-dose (13.5 mJ/cm^2) radiation (Table I, groups 6 to 8), no difference in the incidence of malignant neoplasms was observed between the vehicle control group and those animals exposed to either concentration of topical RP. Therefore, there is no conclusive evidence to indicate that the combination of RP and UV is photocarcinogenic. In fact, the results are similar to earlier studies[18-24] dating back to 1977, where researchers failed to conclusively find a photocarcinogenic effect associated with the combination of retinoic acid and UV exposure.

There are significant limitations in these unpublished NTP studies. It is important to mention that the mice in the above NTP study are highly susceptible to develop skin cancer after UV exposure. In fact, application of vehicle alone without RP, followed by low-dose or high-dose irradiation, resulted in 38% and 82% of mice, respectively, developing malignant skin lesions (Table I, groups 3 and 6). Vehicle cream alone, without UV exposure, induced benign neoplasms in 38% of the animals, and malignant neoplasms in 3% (Table I, group 2). Furthermore, mouse epidermis is significantly thinner than that of human beings, hence resulting in higher percutaneous absorption. Therefore, extreme caution is needed when extrapolating these animal study results to human beings.

Although there are no published human studies on the photocarcinogenic potential of topical RP or other retinoids, two observations from clinical medicine over the past 4 decades provide the strongest challenges to any notions that RP in sunscreens is photocarcinogenic. First, dermatologists routinely

Table I. Distribution of cutaneous neoplasms in mice by concentration of all-*trans*-retinyl palmitate and ultraviolet irradiance

Group	N	All-*trans*-retinyl palmitate concentration	Solar simulator, mJ/cm^2	Animals with benign neoplasms, %	*P* value*	Animals with malignant neoplasms, %	*P* value*
1	70	None	0	3	—	0	—
2	72	Vehicle pH 7	0	38	<.0001	3	.14
3	72	Vehicle pH 7	6.75	86	Referent	38	Referent
4	72	0.1%	6.75	88	.72	50	.28
5	71	0.5%	6.75	99	.0033	59	.003
6	72	Vehicle pH 7	13.7	83	Referent	82	Referent
7	72	0.1%	13.7	92	.103	85	.628
8	72	0.5%	13.7	86	.619	75	.307

Results abstracted from data of National Toxicology Program's TR-568 all-*trans*-retinyl palmitate study.[16]
**P* value based on 2-sample test for proportion. In all-*trans*-retinyl-palmitate groups (3-5 and 6-8), varying concentrations are compared with proportion observed for pH 7 vehicle.

prescribe various forms of topical retinoids to manage photoaging, acne, psoriasis, cutaneous T-cell lymphoma, and other skin conditions. In the more than 40 years that topical retinoids have been in use, millions of patients used them, and many of these patients are regularly followed up by dermatologists because of their underlying skin disease. There is no published evidence to suggest that topical retinoids increase the risk of photocarcinogenesis. Second, oral retinoids (ie, acitretin) are used for chemoprevention of skin cancers in individuals at high risk, such as transplant populations[25] and patients with xeroderma pigmentosum.[26]

In conclusion, based on currently available data from in vitro, animal, and human studies, there is no convincing evidence to support the notion that RP in sunscreens is photocarcinogenic. In fact, clinical observations spanning over decades suggest that retinoids are helpful in skin cancer chemoprevention. Correcting this false impression is an important and necessary step to ensure that the public continues to use sunscreen as a component of photoprotective strategy. More importantly, as dermatologists, we should take advantage of this opportunity and educate our patients about other photoprotection practices, such as avoiding excessive sun exposure, seeking shade, and wearing photoprotective clothing, hats, and sunglasses. These efforts should serve as the primary tactic to reduce skin cancers and minimize photoaging changes associated with UV exposure.

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