

Rates of allergic sensitization and irritation to oxybenzone-containing sunscreen products: a quantitative meta-analysis of 64 exaggerated use studies

Patricia P. Agin, Karen Ruble, Steven J. Hermansky & Timothy J. McCarthy

Schering-Plough HealthCare Products Inc., Memphis, TN, USA

Summary

Key words:

human repeat insult patch test (HRIPT); oxybenzone; photoallergy; sunscreen; ultraviolet (UV)

Correspondence:

Patricia Agin, PhD, Schering-Plough HealthCare Products Inc., 3030 Jackson Avenue, Memphis, TN 38151, USA.

e-mail: patty.agin@spcorp.com

Accepted for publication:

5 March 2008

Conflicts of interest:

Patricia Agin and Karen Ruble are employees of Schering-Plough HealthCare Products Inc. Steve Hermansky and Timothy McCarthy are former employees of Schering-Plough HealthCare Products Inc.

Background/purpose: Oxybenzone is an active ingredient found in sunscreen products that absorbs a broad spectrum of ultraviolet (UV) light, with absorbance peaking in the UVB region and extending into the UVA region. Although the overall incidence of sensitization and irritation associated with oxybenzone in the general population remains unclear, a few studies have reported on the incidence in specific circumstances. However, the relevance of these studies to the general population is limited, because the sample populations reported in these papers generally have consisted of individuals who sought medical attention for pre-existing skin conditions. Therefore, the reported incidence of allergic reactions to oxybenzone in these studies may be overestimated as related to the general population. The objective of this meta-analysis was to determine the safety of oxybenzone in participants recruited from the general population.

Methods: The data from 64 unpublished exaggerated use human repeat insult patch tests (HRIPT) and photoallergy (PA) studies sponsored by Schering-Plough HealthCare Products Inc. between 1992 and 2006 were aggregated and analyzed to evaluate the irritancy and sensitization potential of sunscreen products containing oxybenzone at concentrations between 1% and 6%.

Results: Forty-eight of 19 570 possible dermal responses were considered to be suggestive of irritation or sensitization; the mean rate of responses across all formulations was 0.26%. Sensitization rates did not correlate significantly with oxybenzone concentration. The available re-challenge data indicated that only eight of these responses were contact allergies from oxybenzone, and the mean rate of contact allergy to oxybenzone was 0.07%. The source of the skin responses was not confirmed for 15 subjects who were lost to follow-up. However, all subjects were given the opportunity to participate in follow-up testing.

Conclusion: Our data indicate that sunscreen products formulated with 1–6% oxybenzone do not possess a significant sensitization or irritation potential for the general public. Furthermore, these data suggest that the incidence rate implied in the published literature overestimates the actual incidence of sensitization/irritation due to oxybenzone-containing sunscreen products in the general population.

Sunscreen products are recommended by medical professionals and health authorities as part of an overall sun safety program for children and adults (1–5). Sunscreen product use has increased over the last decade due to heightened awareness of skin cancer and photoaging risk factors (2, 6). Because of this heightened awareness and consumer demand, sunscreens ingredients are also commonly incorporated into facial and daily-use cosmetics to protect against sunburn, skin cancer, and photoaging and to preserve the cosmetic ingredients from photodegradation (2, 7). Although some people use sunscreens on a regular basis because of conditions that induce

atypical responses to sunlight or as daily defense against intermittent ultraviolet (UV) exposure, others use sunscreen products primarily to prevent sunburn when they are exposed to sunlight for longer periods of time (1, 4).

All sunscreens are chemical agents. Sunscreens can be classified in simple terms as either organic or physical agents. Physical sunscreens ingredients, such as titanium dioxide, produce a barrier that absorbs, scatters, and reflects UV light, thereby preventing radiation from reaching the skin (1, 8). In contrast, organic sunscreens such as benzophenones and cinnamates absorb certain wavelengths of light before they enter

the viable layers of the skin (1). Due to esthetic acceptability, organic agents are more commonly used than physical agents in over-the-counter sunscreens and cosmetic products (1, 7). Sunscreen products are often formulated with more than one active ingredient to provide balanced protection across the UV spectrum and to help achieve the desired sun protection factor (SPF) (1, 9).

Oxybenzone, which is also known as benzophenone-3 or 2-hydroxy-4-methoxybenzophenone, is the most frequently used benzophenone in sunscreen products (1, 10, 11). It has been estimated that oxybenzone can be found in 20–30% of all sunscreens, especially those with an SPF > 8 (6, 12). Oxybenzone was included in the FDA's original 1978 monograph proposing conditions for safety, efficacy, and labeling for sunscreen products and was determined by the FDA to be a safe and effective sunscreensing ingredient (1). It absorbs a broad spectrum of UV light, with absorption peaking in the UVB region (290–320 nm) and extending in the UVA region (320–400 nm) (1, 10, 13). This is especially important because UVB can cause both short-term (i.e., sunburn) and long-term (i.e., skin cancer, photoaging) damage, while UVA can contribute to photoaging by injuring the structural proteins located in the dermal layer of the skin (14, 15). While oxybenzone is nearly water insoluble, it is capable of being dissolved in ethyl alcohol, isopropyl alcohol, mineral oil, and linseed oil. Therefore, oxybenzone is often included in sun protection and cosmetic products containing other sunscreensing ingredients as well as oils and emulsifiers (1).

While sunscreensing ingredients such as oxybenzone protect the skin by absorbing radiation, consumers may develop sensitizations to them or to the inactive ingredients in sunscreens, such as emulsifiers, antioxidants, preservatives, or fragrances (7, 16–18). Fragrances are among the most common culprits causing photocontact or contact sensitization (7, 19). While risk factors associated with sunscreen allergy have not been formally established, it has been suggested that sensitization may be more common in women due to multiple product use and in people with pre-existing skin conditions, allergic hypersensitivities, and outdoor occupations (7, 18). The number of reported contact and photocontact sensitivities has grown over the past several years as the use of sunscreen and cosmetic products containing sun protection has increased (7).

Although the overall incidence of contact sensitization from oxybenzone remains uncertain, a few studies have reported on the incidence in specific circumstances (2, 7, 20–28). While numerous case studies of contact dermatitis and photocontact allergic dermatitis associated with oxybenzone have been reported (29–36), the utility of these studies in predicting the incidence of allergies in the general population is considered limited because the sample populations consisted of individuals who sought medical attention for pre-existing skin conditions. The results from such studies may overestimate the incidence of allergic reactions to oxybenzone because the sample population selected for each study does not represent the general population. Given the overall size of the population using sunscreen products each year, reports of sunscreen sensitizations and irritations are rare (2, 16, 17, 23, 28, 29, 36, 37).

We analyzed data from 64 unpublished human repeat insult patch tests (HRIPT) and photoallergy (PA) studies sponsored by Schering-Plough HealthCare Products Inc. between 1992 and 2006. These studies were designed to evaluate the safety of sunscreen products containing 1–6% oxybenzone before market release. The objective of this meta-analysis was to determine the rate of irritancy and sensitization potential of oxybenzone among participants recruited from the general population, rather than patients reporting skin conditions to physicians. The HRIPT and PA data sets were selected because both methods employ testing under occlusive, exaggerated conditions by repeated topical applications at the para-spinal region. These HRIPT and PA studies employed rigorous techniques that exaggerate the exposure conditions anticipated to be encountered under normal sunscreen use (38–40). Skin sensitization and irritation assessments are often complicated but can be simplified through the use of assessment tools such as HRIPT and PA tests (38).

Materials and methods

Study design

This meta-analysis included data from 64 unpublished studies that evaluated the safety of oxybenzone containing sunscreen formulas in participants recruited from the general population. All studies were sponsored by Schering-Plough HealthCare Products Inc. and were conducted at 10 independent clinical laboratories between 1992 and 2006 (Table 2). The studies were conducted in 143 test groups (79 HRIPT groups and 64 PA groups) consisting of 19 570 participants who were tested with 89 unique sunscreen formulas containing oxybenzone (Table 1). The participants of these studies were healthy males and females who were 18 years of age or older; all participants were willing to comply with study procedures and read and signed a written informed consent form. Participants did not have a history of photosensitivity and did not have known skin conditions or allergies that could have interfered with the proper conduct of the study. Use of systemic or topical corticosteroid, anti-inflammatory, antihistamine, or immunosuppressive medication was prohibited during the study.

The primary endpoint of this meta-analysis was the percentage of participants with possible irritation or sensitization, determined through clinical judgment, for any given oxybenzone-containing sunscreen product. In order to justify this level of analysis, it was necessary to examine potential confounding variables within the data sets, such as laboratory ($n = 10$), study ($n = 64$), unique formula ($n = 89$), and method of evaluation (PA vs. HRIPT); these variables are depicted in Fig. 1.

All outcomes from HRIPT and PA tests that investigators classified as indicative of irritation or sensitization were aggregated and analyzed to determine the percentage of possible dermal sensitization/irritation reactions. All participants who presented with dermal responses indicative of sensitization/irritation were provided with an opportunity to participate in follow-up testing to determine the source of sensitization/

Table 1. Characteristics of data summarized from 64 studies of oxybenzone-containing sunscreen products

	No.	Mode	Mean (SD)
Total number of test method groups	143		
Groups using PA methods	64 (45%)		
Groups using HRIPT methods	79 (55%)		
Total number of participants	19 570		
Number of participants per group	(range: 24–223)	200	136.85 (71.49)
Total number of unique formulas	89		
Number of unique formulas per study	(range: 1–5)	2	2.23 (1.05)
Total number of laboratories	10		
Number of studies per laboratory	(range: 1–13)	2	6.40 (4.27)
Percentage of oxybenzone in tested products	(range: 1–6%)	6%	4.32% (1.48)

PA, photoallergy; HRIPT, human repeat insult patch tests; SD, standard deviation

Table 2. Average percentage of oxybenzone concentration in formulas tested by laboratory

Laboratory	No. of formulas	Mean percentage of oxybenzone	95% CI
Laboratory 1 (HRIPT)	28	3.88	3.32–4.44
Laboratory 2 (PA)	22	4.41	3.78–5.04
Laboratory 3 (HRIPT)	25	4.41	3.81–5.00
Laboratory 4 (PA = 2, HRIPT = 4)	6	4.00	2.79–5.21
Laboratory 5 (HRIPT)	2	3.75	1.65–5.85
Laboratory 6 (HRIPT)	7	4.57	3.45–5.69
Laboratory 7 (PA)	18	4.47	3.77–5.17
Laboratory 8 (PA)	18	4.31	3.61–5.01
Laboratory 9 (PA)	2	4.35	2.25–6.45
Laboratory 10 (HRIPT)	11	4.96	4.06–5.85

Note. Oxybenzone concentration was missing for four formulas. ANOVA; $F(9,129) = 0.61$, $P > 0.79$.
CI, confidence interval; PA, photoallergy; HRIPT, human repeat insult patch tests.

irritation. This follow-up consisted of a re-challenge with either the sunscreen formula or the individual ingredients within the formula. In a conservative approach, all dermal responses representing allergy or indicating a need for follow-up testing were included in the analysis without consideration of re-challenge results. The rationale for this conservative approach was based on the inconsistent follow-up testing methodology and rate of follow-up noted across studies. Many participants declined further study participation or were lost to follow-up; therefore, the cause of the initial challenge response was inconclusive for these participants.

HRIPT

Sunscreen formulation test articles containing combinations of sunscreen active ingredients were evaluated over 6 weeks using a three-phase procedure: (1) induction, (2) rest, and (3) challenge. The induction phase included nine consecutive occlusive applications of the test article and subsequent evaluations of the patch sites at 48-h intervals. Following the ninth evaluation, the

participants underwent a 10- to 14-day rest phase. During the challenge phase, participants had a test article patch applied to the original patch site used during the induction phase. The challenge patch (P1) was removed 48 h after application, and the skin was observed for any reactions. After the evaluation, another challenge patch containing the same test article was applied to a naïve location on the back adjacent to the original site. This second challenge patch (P2) was removed 48 h after application and evaluated. At the same time, the original patch test site was also observed for any delayed reaction (96-h evaluation). This methodology is sensitive and reliable because of the presentation of challenge at two patch sites, the use of an extended scoring timeline, and the use of a re-challenge procedure (38–40).

Human PA

Sunscreen formulation test articles were evaluated over 6 weeks using an occlusive patch procedure involving three phases: (1) induction, (2) rest, and (3) challenge. During the induction phase, $20 \mu\text{L}/\text{cm}^2$ of the test material was applied to a separate patch. The patch was then applied directly to a specific skin site. Patches consisting of non-woven cotton cloth were attached to the skin with occlusive tape. Twenty-four hours later, the occlusive tape was removed, the site was wiped, and $2 \mu\text{L}/\text{cm}^2$ of the test article was reapplied to the skin. After 5–15 min, the test site was irradiated with two times a participant's minimum effective dose (MED) of UVA/UVB. This induction procedure was repeated twice weekly for three consecutive weeks and was followed by a 9–16-day untreated rest period. During the challenge phase, two 24-h occlusive patches ($5 \mu\text{L}/\text{cm}^2$ of the formula/patch) were applied on naïve sites, followed by application of $2 \mu\text{L}/\text{cm}^2$ of the test article to the sites, with irradiation 15 min later on one site with $10 \text{ J}/\text{cm}^2$ UVA+0.5 MED UVA/UVB. An additional patch site without product was also irradiated. The challenge sites evaluated included the following: test article/irradiated, test article/non-irradiated, and sham/irradiated. Each challenge site was then evaluated at 24, 48, and 72 h following irradiation.

Statistical analysis

Statistical analyses were performed using one-way analysis of variance (ANOVA) followed by Tukey's Honestly Significant

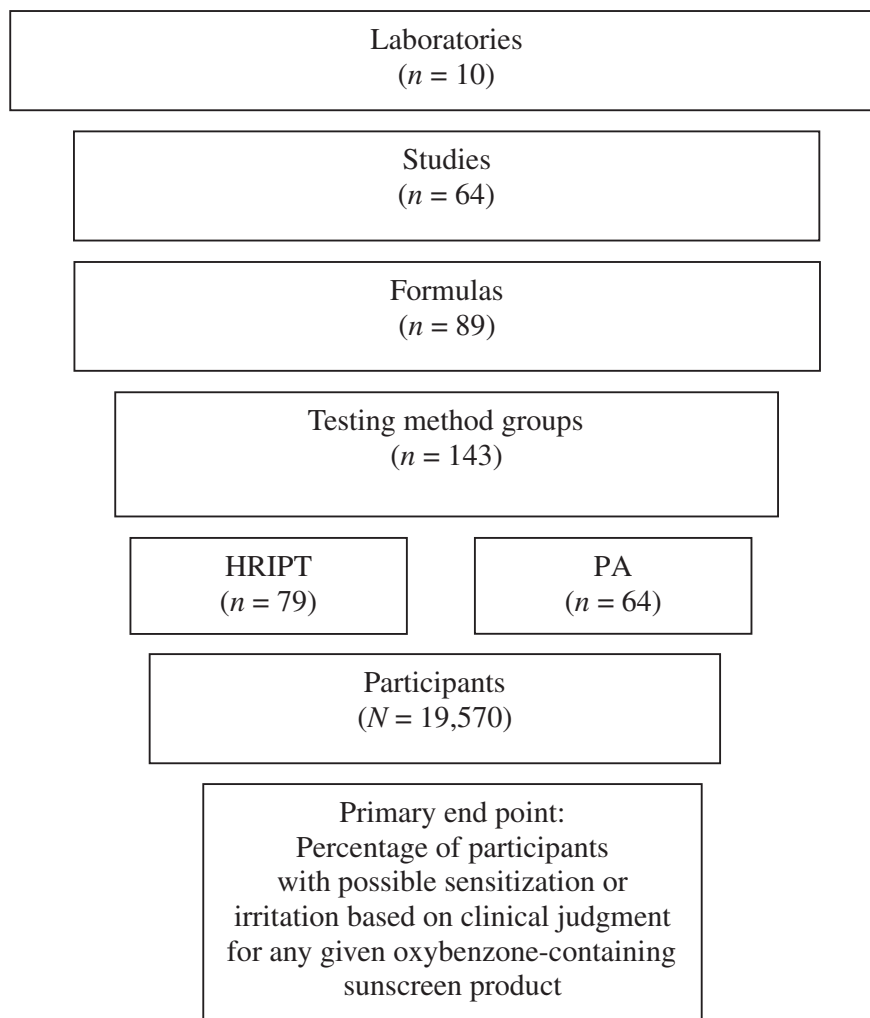


Fig. 1. Potential confounding variables within the data.

Difference (HSD) analysis. Significance for all tests was set at $P < 0.05$. The data were also analyzed with Pearson's correlation coefficient. JMP software version 7 (SAS Institute, Cary, NC, USA) was used for the data analysis.

Results

Characteristics of the data analyzed from the 64 studies of oxybenzone-containing sunscreen products are presented in Table 1. The average ($\pm$ SD) number of participants per testing method group was 136.85 ± 71.49 (range: 24–223), and the mean number of unique oxybenzone-containing formulas evaluated in each study was 2.23 ± 1.05 (range: 1–5). Most laboratories conducted on average two studies (range: 1–13). Oxybenzone concentrations per formula ranged from 1% to 6%, with the majority of formulas containing 6% oxybenzone. The average percentage of oxybenzone concentration in the formulas tested was not significantly different among the laboratories [Table 2; $F(9, 129) = 0.61$; $P > 0.79$]. As the data in Table 3 demonstrate, there were no significant differences in mean

percent sensitization by testing method [$F(1, 141) = 0.009$; $P > 0.92$].

With the conservative approach used in this analysis, 48 of 19 570 participants exhibited possible dermal responses that were classified as suggestive of irritation or sensitization, regardless of causality. As Table 4 demonstrates, the mean rate of responses across all formulations was 0.26. Sensitization rates were not significantly related to oxybenzone concentration [Pearson's $r(139) = -0.04$, $P > 0.68$]. Re-challenge data were available for 35 of the 48 potential sensitization responses. The re-challenge data indicated that eight of these responses resulted from oxybenzone. Available challenge data and investigator notes indicated that the remaining 27 responses were related to other factors, such as the formula, inactive ingredients, or pre-existing allergies. With incorporation of the re-challenge data into analyses, the mean rate of contact allergy of subjects to oxybenzone was found to be 0.07%. The source of the skin responses was not confirmed for 15 subjects who were lost to follow-up. However, all subjects were given the opportunity to participate in follow-up testing.

Table 3. Sensitization rates by method of testing

	No. of formulas	Mean percent sensitization	95% CI
Test Method ^a			
PA	64	0.27	0.03–0.51
HRIPT	79	0.26	0.16–0.38

^aOne-way ANOVA; $F(1,141) = 0.009$; $P > 0.92$.
CI, confidence interval; PA, photoallergy test; HRIPT, human repeat insult patch tests.

Table 4. Overall average proportion of responses observed across 19 570 participants for 89 formulas containing oxybenzone

	Mean percent sensitization	SD	95% CI
Rate of response observed	0.26	0.72	0.15–0.38
Rate of contact allergy to oxybenzone on re-challenge	0.07	0.46	– 1.74–0.15

Note. Response average is calculated from 64 studies with 89 unique formulas. Oxybenzone concentrations per formula ranged from 1% to 6%. Sensitization rates were not significantly related to oxybenzone concentration [Pearson's $r(139) = -0.04$, $P > 0.68$].
CI, confidence interval; SD, standard deviation.

Discussion

This meta-analysis evaluated unpublished data from 64 HRIPT and PA studies testing oxybenzone-containing sunscreen formulas that also included other sunscreen active ingredients. These studies were conducted at 10 independent laboratories. These studies, conducted between 1992 and 2006, included participants recruited from the general public. The results of this meta-analysis show an extremely low rate of irritation or sensitization reactions to oxybenzone among participants tested under exaggerated use conditions.

Few adverse events associated with oxybenzone have been reported in the general population despite the prevalence of sunscreen use (10, 17, 37, 41). Contrary to our findings, a few published studies suggest that sunscreen sensitizations, particularly photosensitivities to oxybenzone, are underreported (12). However, it is important to keep in mind that the rates of sunscreen sensitizations may be influenced by a number of factors, including sensitivities resulting from pre-existing skin conditions, excipients, fragrances, preservative systems, or the use of high concentrations of sunscreen product. Each of these factors is discussed in more detail below.

The majority of published studies documenting cases of sensitizations/irritations associated with oxybenzone were conducted in individuals who had sought medical attention for pre-existing skin conditions. These conditions include, but are not limited to, contact dermatitis (2, 23), psoriasis (29), photodermatitis (21, 27, 29), photosensitivity dermatitis/

actinic reticuloid syndrome (24), polymorphic light eruption (20, 24, 31, 42), persistent light reactivity (20), chronic actinic dermatitis (23), and severe acute dermatitis (30). While it is well known that patients with photodermatoses are more sensitive to light than people without skin conditions, several studies have recently shown that patients with photodermatoses may also have an increased risk of developing sensitization or irritation to the active ingredients found in sunscreen formulations, such as oxybenzone (7, 17, 18, 21, 24–26, 43).

Consumers can develop adverse reactions caused by the excipients found in sunscreen formulations, including emulsifiers, oils, alcohols, thickeners, preservatives, and fragrances (16, 17). A 7-month, randomized longitudinal study conducted by Foley *et al.* (44) showed that 114 of 603 participants complained of an adverse reaction occurring with the use of a frequently applied sunscreen product; of these, 90 participants were found to have clinical findings consistent with an inflammatory skin condition. The active ingredients in the sunscreen product did not cause an allergic reaction in any of the 49 patch or photopatch-tested participants; most irritations were caused by sunscreen excipients (44). Likewise, Nixon *et al.* (43) conducted a prospective study during which patch tests were conducted in 73 patients with a medical history of sunscreen reactions. They reported fewer positive patch test reactions to active sunscreen ingredients ($n = 11$) than to fragrances and preservatives ($n = 17$); only three of the positive patch test results were to benzophenones (43). DeLeo *et al.* (22) conducted a study to analyze the photopatch test results from the Columbia Presbyterian Medical Center Environmental Dermatology Unit from 1985 to 1990. They found that 63 positive contact and photocontact responses occurred in 37 of 187 patients with suspected photosensitivity. Positive responses were reported for active ingredients ($n = 25$), antibacterials ($n = 14$), fragrances ($n = 14$), and other ($n = 10$) (22). Schauder *et al.* (7) summarized their published and unpublished data from 1981 to 1996 on 402 patients with suspected photosensitivity. They reported 178 allergic and 14 photoallergic reactions to fragrance materials and 24 allergic and three photoallergic reactions to preservatives in the 47 patients who were sensitive to chemical sunscreens (7). Listings of active and inactive ingredients are available for sunscreen products sold in the United States to help educate consumers about the composition of the sunscreen product (16, 17). The active and inactive ingredients are listed on the label of each product. Because the ingredients found in a particular sunscreen may change over time, it is important for consumers with allergies to frequently read sunscreen product labels and to become familiar with the different names of their allergen(s) (11, 12).

It is recommended that sunscreen products be applied to the skin at a rate of 2 mg/cm^2 (45). The FDA (1) further recommends that sunscreen products be applied generously before exposure to sunlight and then reapplied at least every 2 h, or after swimming or extreme perspiration. Sunscreens containing up to 6% oxybenzone are recommended for adults and children > 6 months of age (1). Hayden *et al.* (46) reported that oxybenzone was systemically absorbed and excreted in the urine of

healthy participants following the use of an SPF 15+ sunscreen product containing 6% oxybenzone in addition to other sunscreen-active ingredients. They concluded that oxybenzone should not be applied to large portions of the skin for a long period of time and/or for repeated periods of time. However, in Hayden's study, participants were asked to apply 13.0 ± 1.00 g of sunscreen to an area of 1051 ± 60.8 cm², or approximately 12 mg/cm² (46). This is about six times more than the recommended amount of sunscreen needed to prevent sunburn (37, 45, 46).

In addition, most sunscreen products today are formulated with more than one active ingredient, thereby decreasing the amount of each ingredient in the sunscreen product (9). In addition to looking at the concentration of active ingredients used in a particular study or product, it is also important to consider the vehicle in which an active ingredient, such as oxybenzone, is suspended or dissolved (2). Modern vehicles are often developed to retain the sunscreen on the surface of the skin, thus helping to prevent active sunscreen ingredients from absorbing beyond the top layer of the stratum corneum (47). Hayden et al. (46) reported that only 1–2% of the oxybenzone applied was absorbed into the skin during the 12-h application period; these low levels of penetration support the safety of oxybenzone-containing sunscreens (37).

An unpublished, 91-day safety study of a sunscreen product containing 3% oxybenzone was conducted in humans (48). Each participant in the treatment group applied 0.65 ml/kg of the sunscreen product twice a day for 91 consecutive days, covering the arms, legs, back, neck, chest, shoulders, and abdomen. Evaluations included daily recording of skin changes and daily blood collection for hematology and clinical chemistry evaluations. The product was well tolerated, and there were no significant clinical or laboratory findings (48). These observations further support the safety of oxybenzone in sunscreen products.

The scientific literature clearly demonstrates that oxybenzone is an important broad-spectrum sunscreen agent, with significant UV absorbance in both the UVB (290–320 nm) and UVA (320–400 nm) wavebands (1, 10). The literature also shows a low incidence of skin reaction to sunscreens in humans (2, 16, 17, 23, 28, 29, 36, 37), which, combined with the demonstrated benefits of protecting the skin from UV radiation, indicates that there is no cause for significant concern regarding sensitization or irritation from oxybenzone among the general population.

Conclusions

These product-specific data indicate that oxybenzone, at concentrations up to 6%, does not possess a significant sensitization potential for the general population.

References

- Food and Drug Administration. Sunscreen drug products for over-the-counter human use. *Fed Regist* 1978; **43**: 38206–38269. Available at: http://www.fda.gov/cder/otcmonographs/Sunscreen/sunscreen_19780825.pdf. Accessed on: August 6, 2007.
- Ang P, Ng SK, Goh CL. Sunscreen allergy in Singapore. *Am J Contact Dermat* 1998; **9**: 42–44.
- Centers for Disease Control and Prevention. Guidelines for school programs to prevent skin cancer. *Morbidity and Mortality Weekly Report* 2002; **51** (RR-4): 1–16.
- Saraiya M, Ganz K, Briss PA, et al. Interventions to prevent skin cancer by reducing exposure to ultraviolet radiation: a systematic review. *Am J Prev Med* 2004; **27**: 422–466.
- The guide to clinical preventive services: recommendations of the US Preventive Services Task Force. Available at: <http://www.ahrq.gov/clinic/uspstf/uspstf.htm>. Accessed on: August 8, 2007.
- Emonet S, Pasche-Koo F, Perin-Minisini M-J, Hauser C. Anaphylaxis to oxybenzone, a frequent constituent of sunscreens. *J Allergy Clin Immunol* 2001; **107**: 556–557.
- Schauder S, Ippen H. Contact and photocontact sensitivity to sunscreens. Review of a 15-year experience and of the literature. *Contact Dermatitis* 1997; **37**: 221–232.
- Sayre RM, Kollias N, Roberts RL, Baqer A, Sadiq I. Physical sunscreens. *J Soc Cosmet Chem* 1990; **41**: 103–109.
- Oakley A. Photodermatitis from sunscreen. *NZ Med J* 1997; **110**: 17–18.
- Collins P, Ferguson J. Photoallergic contact dermatitis to oxybenzone. *Br J Dermatol* 1994; **131**: 124–129.
- Fisher AA. Sunscreen dermatitis: part III—The benzophenones. *Cutis* 1992; **50**: 331–332.
- Knobler E, Almeida L, Ruzkowski AM, Held J, Harber L, DeLeo V. Photoallergy to benzophenone. *Arch Dermatol* 1989; **125**: 801–804.
- Shaaht NA. The encyclopedia of ultraviolet filters. Carol Stream, IL, USA: Allured Publishing Company, 2007; 74–75.
- Nole G, Johnson AW. An analysis of cumulative lifetime solar ultraviolet radiation exposure and the benefits of daily sun protection. *Dermatol Ther* 2004; **17** (Suppl. 1): 57–62.
- Tanaka K, Hasegawa J, Asamitsu K, Okamoto T. Prevention of the ultraviolet B-mediated skin photoaging by a nuclear factor kappaB inhibitor, parthenolide. *J Pharmacol Exp Ther* 2005; **315**: 624–630.
- Funk JO, Dromgoole SH, Maibach HI. Sunscreen intolerance. Contact sensitization, photocontact sensitization, and irritancy of sunscreen agents. *Dermatol Clin* 1995; **13**: 473–481.
- Dromgoole SH, Maibach HI. Sunscreening agent intolerance: contact and photocontact sensitization and contact urticaria. *J Am Acad Dermatol* 1990; **22**: 1068–1078.
- Scheuer E, Warshaw E. Sunscreen allergy: a review of epidemiology, clinical characteristics, and responsible allergens. *Dermatitis* 2006; **17**: 3–11.
- Scheman A. Adverse reactions to cosmetic ingredients. *Dermatol Clin* 2000; **18**: 685–698.
- Thune P. Contact and photocontact allergy to sunscreens. *Photodermatology* 1984; **1**: 5–9.
- Lenique P, Machet L, Vaillant L, et al. Contact and photocontact allergy to oxybenzone. *Contact Dermatitis* 1992; **26**: 177–181.
- DeLeo VA, Suarez SM, Maso MJ. Photoallergic contact dermatitis. Results of photopatch testing in New York, 1985 to 1990. *Arch Dermatol* 1992; **128**: 1513–1518.
- Trevisi P, Vincenzi C, Chierigato C, Guerra L, Tosti A. Sunscreen sensitization: a three-year study. *Dermatology* 1994; **189**: 55–57.
- Bilsland D, Ferguson J. Contact allergy to sunscreen chemicals in photosensitivity dermatitis/actinic reticuloid syndrome (PD/

- AR) and polymorphic light eruption (PLE). *Contact Dermatitis* 1993; **29**: 70–73.
25. Szczurko C, Domp Martin A, Michel M, Moreau A, Leroy D. Photocontact allergy to oxybenzone: ten years of experience. *Photodermatol Photoimmunol Photomed* 1994; **10**: 144–147.
 26. Gonalo M, Ruas E, Figueiredo A, Gonalo S. Contact and photocontact sensitivity to sunscreens. *Contact Dermatitis* 1995; **33**: 278–280.
 27. Journe F, Marguery M-C, Rakotondrzafy J, Sayed FE, Bazex J. Sunscreen sensitization: a 5-year study. *Acta Derm Venereol* 1999; **79**: 211–213.
 28. Cook N, Freeman S. Report of 19 cases of photoallergic contact dermatitis to sunscreens seen at the skin and cancer foundation. *Australas J Dermatol* 2001; **42**: 257–259.
 29. Thompson G, Maibach H, Epstein J. Allergic contact dermatitis from sunscreen preparations complicating photodermatitis. *Arch Dermatol* 1977; **113**: 1252–1253.
 30. Camarasa JG, Serra-Baldrich E. Allergic contact dermatitis to sunscreens. *Contact Dermatitis* 1986; **15**: 253–254.
 31. Green C, Norris PG, Hawk JLM. Photoallergic contact dermatitis from oxybenzone aggravating polymorphic light eruption. *Contact Dermatitis* 1991; **24**: 62–63.
 32. Torres V, Correia T. Contact and photocontact allergy to oxybenzone and mexenone. *Contact Dermatitis* 1991; **25**: 126–127.
 33. Cook N, Freeman S. Photosensitive dermatitis due to sunscreen allergy in a child. *Australas J Dermatol* 2002; **43**: 133–135.
 34. Landers M, Law S, Storrs FJ. Contact urticaria, allergic contact dermatitis, and photoallergic contact dermatitis from oxybenzone. *Am J Contact Dermat* 2003; **14**: 33–34.
 35. Nedorost ST. Facial erythema as a result of benzophenone allergy. *J Am Acad Dermatol* 2003; **49**: S259–S261.
 36. Langan SM, Collins P. Photocontact allergy to oxybenzone and contact allergy to lignocaine and prilocaine. *Contact Dermatitis* 2006; **54**: 173–174.
 37. Agin P, Anthony FA, Hermansky S. Oxybenzone in sunscreen products. *Lancet* 1998; **351**: 525.
 38. Robinson MK, Stotts J, Danneman PJ, Nusair TL. A risk assessment process for allergic contact sensitization. *Food Chem Toxicol* 1989; **27**: 479–489.
 39. Kimber I, Basketter DA, Berthold K, et al. Skin sensitization testing in potency and risk assessment. *Toxicol Sci* 2001; **59**: 198–208.
 40. Gerberick GF, Robinson MK. A skin sensitization risk assessment approach for evaluation of new ingredients and products. *Am J Contact Dermat* 2000; **11**: 65–73.
 41. Zhang X-M, Nakagawa M, Kawai K, Kawai K. Erythema-multiforme-like eruption following photoallergic contact dermatitis from oxybenzone. *Contact Dermatitis* 1998; **38**: 43–44.
 42. Bryden AM, Ferguson J, Ibbotson SH. Milia complicating photocontact allergy to absorbent sunscreen chemicals. *Clin Exp Dermatol* 2003; **28**: 668–669.
 43. Nixon RL, Frowen KE, Lewis AE. Skin reactions to sunscreens. *Australas J Dermatol* 1997; **38** (Suppl. 1): S83–S85.
 44. Foley P, Nixon R, Marks R, Frowen K, Thompson S. The frequency of reactions to sunscreens: results of a longitudinal population-based study on the regular use of sunscreens in Australia. *Br J Dermatol* 1993; **128**: 512–518.
 45. Gonzalez HG, Farbroth A, Larkö O. Percutaneous absorption of benzophenone-3, a common component of topical sunscreens. *Clin Exp Dermatol* 2002; **27**: 691–694.
 46. Hayden CGJ, Roberts MS, Benson HAE. Systemic absorption of sunscreen after topical application. *Lancet* 1997; **350**: 863–864.
 47. Chatelain E, Gabard B, Surber C. Skin penetration and sun protection factor of five UV filters: effect of the vehicle. *Skin Pharmacol Appl Skin Physiol* 2003; **16**: 28–35.
 48. Data on file. Schering-Plough HealthCare Products, 1981.