C T F A

THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

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E. EDWARD KAVANAUGH
PRESIDENT

August 22, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, Maryland 20857

CITIZEN PETITION: DOCKET 78N-0038

Dear Sir or Madam:

This Citizen Petition is submitted under 21 CFR Sec. 10.30 on behalf of The Cosmetic, Toiletry, and Fragrance Association[1] and The Consumer Healthcare Products Association[2] ("Petitioner"). This Citizen Petition requests the Commissioner of Food and Drugs to take the following action with respect to the Final Monograph for Over-the-Counter Sunscreen Drug Products, 21 CFR Part 352, Subpart C (Final Monograph).

ACTION REQUESTED

The Petitioner requests the Commissioner to reopen the administrative record of the Final Monograph for the purpose of considering the attached information when developing the proposed amendments to the final monograph.

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[1] CTFA is the national trade association representing the personal care products industry. It has an active membership of almost 600 companies that manufacture or distribute the vast majority of finished personal care products marketed in the United States, as well as a large number of OTC drug products and products that are both drugs and cosmetics. CTFA also includes associate member companies from related industries, including manufacturers of raw materials, packaging materials, and research testing laboratories.

[2] CHPA is the national trade association representing the manufacturers and distributors of nonprescription or over-the-counter (OTC) medications. Members of CHPA are responsible for over 90 percent of the retail sales of OTC drugs in the United States. In addition, CHPA members manufacture and distribute some products that are both drugs and cosmetics.

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STATEMENT OF GROUNDS

The agency's regulations recognize that the administrative record of a final monograph may be reopened to consider new data and information, see 21 CFR 330.10 (a)(12)(i), and that the Commissioner may publish a proposed amendment if the Commissioner finds general recognition of safety, effectiveness and labeling under 21 CFR 330.10 (a)(4). In fact, FDA has already indicated its intention to do so in this rulemaking.[3]

On May 21, 1999 FDA published a final rule for OTC sunscreen drug products in Part 352 intended to provide UVB radiation protection, however, the final monograph did not address active ingredients, labeling, and test methods for products intended to provide UVA protection. In addition, CTFA and CHPA petitioned FDA to reconsider a number of decisions regarding SPF claims, anti-aging claims, uses and directions, and labeling to be required under the OTC Drug Labeling Regulation. Accordingly in the Federal Register of June 8, 2000 FDA extended the effective date for all OTC sunscreen drug products in order for the agency to develop a comprehensive sunscreen final monograph that addresses the formulation, labeling, and testing requirements for both UVB and UVA radiation protection under part 352.

Petitioner filed extensive comments on specific information the agency requested when it reopened the administrative record in the June 8 notice. As part of our September 2000 submission, we urged FDA to include additional indications for sunscreen products. The attached document provides further scientific rationale for inclusion of the claim "Helps protect against skin aging caused by the sun" in the Final Monograph for Sunscreen drug products.

Three additional years have now passed, and we feel it is essential that FDA base its decisions on the most current information with respect to anti-aging claims to be permitted. The purpose of this petition is to provide updated scientific literature, and to enable the Agency to decide this issue with all the evidence before it. The information included in the attached materials is directly relevant and essential for the agency to consider in drafting its proposed amendment to the Final Monograph. In particular, it would be inappropriate for FDA to restrict or ban information about the benefits of sunscreens in reducing the effects of the sun without consideration of current scientific information. We are asking the Agency to consider this material as providing new support for actions requested of FDA.

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[3] 66 Fed. Reg. 67485 (December 31, 2001)

In sum, the attached material is directly relevant to the proposed conditions under which sunscreen products may be marketed. Good cause exists for the Commissioner to consider this material because it provides further scientific data and rationale for the need to expand the indications for sunscreen products, at a time when the Agency has raised such questions.

ENVIRONMENTAL IMPACT

According to 21 CFR 25.31(c), this petition qualifies for a categorical exclusion from the requirement that an environmental assessment be submitted.

ECONOMIC IMPACT

According to 21 CFR 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of this petition.

CERTIFICATION

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data know to the Petitioner which are unfavorable to the petition.

Respectfully submitted,

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cc: Charles J. Ganley, M.D. (HFD-560)
Matthew R. Holman (HFD-560)

Attachment

Introduction

These comments are filed on behalf of The Cosmetic, Toiletry, and Fragrance Association (CTFA) and the Consumer Healthcare Products Association (CHPA) in support of the inclusion of additional indications for sunscreen products. As presented in our September 2000 submission[1], we are requesting that the Agency include the following indications for all sunscreen products, to be used individually or in any combination:

- *Helps protect against harmful effects of the sun*
- *Helps protect against (casual) (incidental) (intermittent) (daily) sun exposure*
- *Helps protect against skin damage caused by the sun*
- *Helps protect against skin aging caused by the sun*
- *Regular use helps protect against certain forms of skin cancer caused by the sun*

In addition, we are providing further scientific rationale and evidence to specifically support the claim "*Helps protect against skin aging caused by the sun*" for inclusion in the Sunscreen Drug Products for Over-the-Counter Human Use, Final Monograph[2].

It is the belief of sunscreen manufacturers that limiting scientifically sound indications for sunscreen products will reverse significant gains made by healthcare authorities to establish sensible and practical "sun avoidance" strategies. As presently written, the Final Rule lists *protection against sunburn* as the singular indication for sunscreen products. This clearly suggests that the only benefit of sunscreens is the protection against sunburn. The notion that the only benefit sunscreen products

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[1] Letter from CTFA, Mr. E.E. Kavanaugh, to Docket Management Branch, FDA, Docket No. 78N-0038 Sunscreen Drug Products for Over-the-Counter Human Use (2000) September.

[2] Sunscreen Drug Products for Over-the-Counter Human Use; Final Rule (1999) *Fed. Reg.* **64**:2766, May 21.

provide is a protection against sunburn will, at a minimum, confuse consumers, many of whom purchase such products for protection against the longer-term consequences of incidental or suberythemal exposure to solar ultraviolet (UV). Thus, we respectfully request the Agency consider the evidence and scientific rationale provided herein and include the entire list of indications.

ADDITIONAL SUPPORT FOR THE SUNSCREEN INDICATION "*HELPS PROTECT AGAINST SKIN AGING CAUSED BY THE SUN*"

Photoaging is recognized by health care professionals and regulatory authorities around the world as skin damage produced by repeated exposure to solar UV. Reducing exposure to or the cumulative dose of solar UV will diminish such skin damage. There are multiple lines of evidence that support this simple hypothesis. However, in order to comprehend the weight of scientific evidence supportive of the role of sunscreens in diminishing the signs of photoaging, it is essential to understand the effects of UV on the structure and function of the skin, as reducing such effects constitutes the evidence for a chronic benefit. The following sections provide the scientific evidence for the cause-effect relationship between UV exposure and skin aging and the beneficial impact UV filters or sunscreen products have on such events.

I. Regulatory Recognition of *Skin Aging Caused by the Sun*

The etiological basis of skin photoaging is not fully understood although this is not uncommon for complex human diseases and conditions that develop over decades. Nonetheless, what is quite clear and unquestioned is that UV from sunlight plays an essential and critically important role in accelerating the aging process of skin[3]. As

[3] Gilchrest BA (1989) Dermatoheliosis (Sun-Induced Aging). In: Skin and Aging Process, Gilchrest BA Ed., pg 97-116, CRC Press. Lowe NJ, Friedlander J (1998) Sunscreens: Rationale for Use to Reduce Photodamage and Phototoxicity. In: Protection of the Skin Against Ultraviolet Radiations, Rougier A, Schaefer H, Eds., pg 35-58. John Libbey Eurotext, Paris. Kligman LH, Kligman AM. (1998) Ultraviolet Radiation-Induced Skin Aging. In: Protection of the Skin Against Ultraviolet Radiations, Rougier A, Schaefer H, Eds., pg 117-137, John Libbey Eurotext, Paris.

such, it is intuitively logical that reducing the exposure to or the dose of solar UV will mitigate the damage to the skin.

Importantly, the Agency has recognized and continues to acknowledge the causal relationship between *skin aging caused by sunlight* and the potential for sunscreen products to *help protect* against such damage. Specifically, in the Tentative Final Monograph (TFM)[4], the Agency insisted on maintaining this strong association by stating that any variation in the Sun Alert statement ". . . that does not relate skin aging or skin cancer as being 'due to the sun' will cause the [sunscreen] product to be misbranded under section 502 of the act." Section 352.52(e)(7). As well, the final sunscreen rule states ". . . the agency believes that an appropriate statement can be used to inform consumers that sunscreens may reduce the risks of skin aging, skin cancer and other harmful effects from the sun . " This belief has been transformed into prescriptive, regulatory language and may be used to label sunscreen products with the "Sun Alert" statement, which states:

- "Sun alert: Limiting sun exposure, wearing protective clothing, **and using sunscreens may reduce the risks of skin aging,** skin cancer, and other harmful effects of the sun." [emphasis added]

Finally, in the FDA Consumer, it is stated, "...if you use enough, it [sunscreen] helps prevent your skin from taking on that wrinkled, leathery look of photo-aged skin. Best of all, it protects you from the harmful ultraviolet rays that cause skin cancer."[5] In all cases, there is an explicit link between reduction of UV-induced skin aging and use of sunscreens.

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[4] Sunscreen Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (1993) *Fed Reg*, **58**:28194-302.

[5] Thompson L (2000) Trying to look SUNsational? Complexity persists in using sunscreens. *FDA Consumer* **34**:15-21.

We believe that the scientific evidence supportive of the long-term protective benefits of sunscreens has strengthened since publication of the TFM and final rule. Because the statements contained in the "Sun Alert" are accepted as true, limiting anti-aging indications of sunscreen products solely to the prescribed language of the Sun Alert statement unfairly limits truthful product claims.[6] Exclusion of anti-aging claims in the final rule except by meeting a requirement for verbatim use of the "Sun Alert" statement eliminates a potent and effective inducement for many consumers to avoid sun damage. Whereas we have no objection to the voluntary use of the "Sun Alert" statement, we believe the additional indications presented above are scientifically based and truthful and, as such, should be allowed individually or in combination on sunscreen product labels as indications. It is simply inappropriate to condition the use of a truthful anti-aging claim to a requirement that it be made in conjunction with a claim about skin cancer and "other harmful effects of the sun."

In the remainder of this submission, we intend to further support the case for inclusion of the indication "*Helps protect against skin aging caused by the sun*" in the Final Rule. We will present a data based, scientific rationale that establishes the cause and effect relationship between solar UV and accelerated skin aging, and the mechanism(s) for these effects. We will present data linking a reduction in UV and mitigation of accelerated skin aging. Finally, we will present the public health messages from multiple health care associations advocating the use of sunscreens as part of a strategy to reduce photoaging in skin.

II. Solar UV

[6] Indeed FDA's restriction of anti-aging claims runs counter to the First Amendment four-part analysis of allowable government action restricting commercial speech advanced in Central Hudson Gas & Electric Corp. v. Public Service Commission, 447 U.S. 557 (1980). That analysis and its applicability to the laws and regulations administered by the Food and Drug Administration was confirmed by Thompson v. Western States Medical Center, 122 S.Ct. 1497 (2002) ("Western States"). The Supreme Court made clear in Western States that restrictions on commercial speech must directly advance the governmental interest asserted and not be "more extensive than is necessary to serve that interest." Western States at 1504.

Any discussion of sunscreens and solar UV would be incomplete without a brief account of the spectrum of sunlight and artificial light sources. Clearly, experts in the Agency and throughout the world are familiar with the solar UV spectrum and recognize the importance of dosimetry when considering biological consequences of exposure. To simplify experimental studies of the solar UV spectrum, i.e., 290 – 400 nm, arbitrary categories have been created and designated as UVB, 290 –320 nm, and UVA, 320 – 400 nm. It is appreciated by most that short wavelengths of UV, i.e. UVB/UVAII, are the most biologically active for producing erythema and the *sequelae* of "sunburn"[7]. In the United States, UVA radiation (320 - 400 nm) has been subdivided into UVA II, 320 – 340 nm, and UVA I, 340 – 400 nm, in recognition of the differences in biological activity and, again, for the convenience of researchers. The longer wavelengths of UV, i.e., > 340 nm, are reported to penetrate more deeply into the skin[8] and, as such, are thought to cause part of the histologic and vascular damage in the dermis.

There is a greater prevalence of UVA radiation in the solar spectrum than UVB. Although UVA radiation is not constant in respect to time of day or season, the changes in shorter wavelengths of UV are more dramatic because of its preferential absorption by the ozone layer, longer path lengths during the winter, and lower sun angles at the beginning and the end of the day.

The most important point of UV, regardless of the source, is that the direct and indirect mechanisms contributing to photoaging of skin are produced by all wavelengths of UV light. As such, reducing the dose of solar UV with the use of

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[7] McKinlay AF, Diffey BL. (1987) A reference action spectrum for ultraviolet induced erythema in human skin. *CIE J* **66**:17-22. Cole CA *et al.* (1983) Comparison of action spectra for acute cutaneous responses to ultraviolet radiation: man and albino hairless mouse. *Photochem Photobiol* **37**:623-631.

[8] Campbell *et al* (1993) Wavelength specific patterns of p53 induction in human skin following exposure to UV radiation. *Cancer Res* **53**:2697-2699. Hoffmann K *et al.* (2000) UV transmission measurements of small skin specimens with special quartz cuvettes. *Dermatol.* **201**:307-311.

sunscreen products will unquestionably diminish both direct and indirect effects causing photodamage.

III. Definition of *Skin Aging Caused by the Sun*

To appreciate the prevention or reduction of photoaging, it is imperative that an understanding of the clinical and histological changes associated with UV-induced skin aging is presented. To be clear, the complex array of structural and functional changes which characterize photodamage of skin is the bridge to acute molecular and biochemical mechanisms and chronic preclinical findings which support a protective/beneficial role of sunscreens and support the claim, "*helps protect against skin aging caused by the sun.*"

As discussed by Gilchrest[9] and Yaar and Gilchrest[10], the aging progression of human skin encompasses two clinically and biologically independent processes that occur simultaneously. Chronological or intrinsic aging is a slow and irreversible process of tissue degeneration. Extrinsic or photoaging results from the exposure of skin to environmental agents, primarily solar UV. In areas chronically exposed to the sun, extrinsic aging is superimposed on the intrinsic aging process. In protected skin, there are remarkably few clinically apparent changes. In contrast, photoaged skin appears wrinkled, rough, and sallow. It is characterized by dryness, roughness, irregular pigmentation (freckling/lentigenes), actinic keratosis, wrinkling, elastosis, inelasticity, sebaceous hyperplasia, mottled dyspigmentation, and telangectasia.

A. Structural features of *skin aging caused by the sun*

1. Stratum Corneum

[9] Gilchrest BA. (1996) A Review of Skin Ageing and Its Medical Therapy. *Br J Dermatol.* **135**:867-875.
[10] Yaar M, Gilchrest BA. (1998) Aging *versus* photoaging: postulated mechanisms and effectors. *J Invest Dermatol Symposium Proceedings* **3**:47-51.

The stratum corneum exhibits clinical signs and histological changes characteristic of photoaging[11]. Clinically, dry and flaky rough skin is noted. Faulty degradation of stratum corneum desmosomes results in a thickening of the stratum corneum, which, in turn, results in a drying of the outer layers due to dehydration. This dehydration leads to a stiffening of the stratum corneum with the development of microfissures, resulting in clumps of stratum corneum cells tearing away. These clumps of cells are clinically noted as flaking.

Sun exposed skin demonstrates a thickening of the epidermis or a hyperproliferative state that has been described as a chronic wound-like condition

2. Epidermis

constantly undergoing repair[12]. A histological hallmark of sun exposure is the formation of sunburn cells, which are actually apoptotic keratinocytes[13]. These are cells that have extensive DNA damage and are now in a 'suicide mode', i.e. they are self destructing before the DNA damage is genetically fixed in daughter cells. Extensive DNA damage in the epidermis can lead to precancerous dysplasia and cancer as well as benign hyperproliferative lesions such as seborrhoic keratosis. The formation of milia or epidermal inclusion cysts has been found to correlate with chronic UV exposure. Another epidermal feature of chronic photodamage appears to be follicular epithelial retention hyperkeratosis and comedone formation[14].

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[11] Warren R *et al.* (1991) Age, Sunlight, and Facial Skin: A Histologic and Quantitative Study. *J Am Acad Dermatol.* **25**:751-760. Bhawan J, *et al.* (1992) Histopathologic differences in the photoaging process in facial versus arm skin. *Am J Dermatopath.* **14**: 224-230.

[12] Kligman LH, Kligman AM (1986) The Nature of Photoaging: Its Prevention and Repair. *Photodermatol.* **3**:215-227.

[13] Sheehan JM, Young AR (2002) The sunburn cell revisited: an update on mechanistic aspects. *Photochem Photobiol. Sci.* **1**:365-377.

[14] Leyden J. (2001) What is Photoaged Skin? *Eur. J Dermatol.* **11**:165-167.

There is an increase in the number of melanocytes and melanocytic hyperplasia found in the epidermis of photoaged skin[15]. Clinically this appears as lentigos or "age spots" and sunburn freckles[12]. Brown pigmented spots called solar lentigines are composed of an increased number of large, hypertrophied, dendritic melanocytes. These foci may be an adaptive effort by the remaining vigorous melanocytes to produce protective melanin[16]. Guttate hypomelanosis are foci of hypopigmentation resulting from loss of functioning melanocytes caused by chronic sun exposure[17].

3. Dermis

In the dermal matrix, the hallmark of photoaging is elastosis[18]. The normal dermal matrix of collagen, elastin, and glycosaminoglycans (GAGs) is replaced by large bundles of coarse elastic fibers and decreased collagen. The initial clinical sign is wrinkling which proceeds to a yellowish cobblestone appearance with pronounced sagging of the skin. Elastosis is accompanied by a neutrophilic infiltrate that is referred to as heliodermatitis or dermatoheliosis[19]. A histological marker of heliodermatitis is the presence of numerous mast cells that are partially degranulated. Release of inflammatory substances from mast cells and the appearance of other immune cells produce a chronic inflammation in photoaged skin. Elastases from neutrophils may damage elastin and play a part in the wrinkling or sagging. Solar-

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[15] Bhawan J, *et al.* (1995) Photoaging versus intrinsic aging: a morphologic assessment of facial skin. *J Cutan Pathol* **22**:154-159.

[16] Gilchrest BA *et al.* (1996) Mechanisms of Ultraviolet Light-Induced Pigmentation. *Photochem Photobiol.* **63**:1-10. Schallreuter K. *et al.* (1998) What controls melanogenesis? *Exp Dermatol.* 7:143-150.

[17] Lober CW, Fenske NA. (1990) Photoaging and the skin: differentiation and clinical response. *Geriatrics* **45**: 36-40, 1990. Castanet J, Ortonne JP (1997) Pigmentary changes in aged and photoaged skin. *Arch Dermatol.* **133**:1296-1299.

[18] Wlaschek M. *et al.* (2001) Solar UV irradiation and dermal photoaging. *J Photochem. Photobiol.* **63**:41-51.

[19] Boyd AS *et al.* (1995) The effects of chronic sunscreen use on the histologic changes of dermatoheliosis. *J Am Acad Dermatol* **33**:941-946.

simulated UV has been shown to increase the activity of metalloproteinases, a family of 14 proteinases that can degenerate surrounding collagen[20].

The vasculature in the dermis can be affected in two ways. Loss of the papillary plexus, flattening of the rete ridges, and loss of papillary dermis results clinically in a sallow washed out appearance. In some individuals, there may be a proliferative response resulting in dilated and enlarged vessels in the papillary and mid-dermis clinically presenting as telangiectasis[10,13,14].

Finally, chronic sun exposure results in sebaceous gland enlargement, which is clinically manifested by small yellowish nodules. This may advance to a thick coarsening of the skin with large follicular openings[10,13,14]. Stellate pseudoscars are lesions that occur on the habitually sun-exposed skin of the lateral arms and neck.

B. Functional changes in photoaged human skin

Clinical observations have demonstrated that the process of photoaging aggravates most of the age associated functional losses of the skin such as epidermal turnover rate, barrier function, sensory perception, Vitamin D production, immunosurveillance, inflammatory responses, thermoregulation, and mechanical protection[21]. Non-invasive measurements of cutaneous properties such as electrical conductance have pointed to the accentuation of normal skin aging by chronic exposure to UV radiation (UVR). The presence of actinic elastosis has been associated with a thickening of the subepidermal non-echogenic band as assessed by ultrasound[22]. Full-skin thinning, loss of extensibility and elasticity, and color heterogeneity have been reported to be cumulative effects of chronic sun exposure of women in their late

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[20] Kang S *et al.* (1997) Photoaging and topical tretinoin. therapy, pathogenesis and prevention. *Arch Dermatol* **133**:1280-1284.
[21] Gilchrest BA. (1989) Skin aging and photoaging: An overview. *J Am Acad Dermatol* **21**:610-613.
[22] Herschenfeld RE, Gilchrest BA. (1998) The cumulative effects of ultraviolet radiation on the skin: Photoageing. *In: Photodermatology* (Hawk JLM, Ed.):69-87,. Chapman & Hall, London. Gnadecka M (2001) Effects of ageing on dermal echogenicity. *Skin Res Technol.* 7:204-207.

70's and 80's. Finally, immunologic changes, primarily diminished function or capacity, have been implicated as part of the overall photoaging process.

IV. Models of "*Skin Aging Caused by the Sun*"

A. A molecular model of skin aging: Acute exposure repeated over a lifetime

The most comprehensive information on molecular mechanisms in human skin photoaging has come from the work of Fisher[23], Uitto[24], and Gilchrest[25].

Fisher, *et al,* 1996[23], conducted a series of experiments on the buttock (not normally exposed to UVR) skin of human volunteers. Assays were performed on biopsies taken after exposure to an artificial light source, predominantly short wavelength UV. In these studies, UV upregulated AP1-1 and NF-κB binding to DNA. These are known stimulators of matrix metalloproteinase (MMP) genes. Metalloproteinase messenger RNA's, proteins, and activities in the skin were all

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[23] Fisher GJ *et al.* (1996) Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature* **379**:335-339. Fisher GJ *et al.* (1997) Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med* **337**:1419-1428. Fisher GJ, Voorhes JJ (1998) Molecular mechanisms of photoaging and its prevention by retinoic acid: ultraviolet irradiation induces MAP kinase signal transduction cascades that induce Ap-1-regulated matrix metalloproteinases that degrade human skin *in vivo*. *J Invest Dermatol Symposium Proceeding* **3**:61-68. Fisher GJ *et al.* (2001) Ultraviolet irradiation increases matrix metalloproteinase-8 protein in human skin *in vivo*. *J Invest Dermatol* **117**:219-226.

[24] Bernstein, EF *et al.* (1995) Ultraviolet radiation activates the human elastin promoter in transgenic mice: a novel *in vivo* and *in vitro* model of cutaneous photoaging. *J Invest Dermatol* **105**:269-273. Bernstein EF *et al.* (1996) Chronic sun exposure alters both the content and distribution of dermal glycosaminoglycans. *Br J Dermatol.* **135**:255-262. Bernstein, EF *et al.* (1997) Evaluation of sunscreens with various sun protection factors in a new transgenic mouse model of cutaneous photoaging that measures elastin promoter activation. *J Am Acad Dermatol* **37**:725-729.
Uitto J, Bernstein EF. (1998) Molecular Mechanisms of Cutaneous Aging: Connective Tissue Alterations in the Dermis. *J Invest Dermatol Symposium Proceedings* **3**:41-44

[25] Garmyn M. *et al* (1992) Effect of aging and habitual sun exposure on the genetic response of cultured human keratinocytes to solar-simulated irradiation. *J Invest Dermatol* **99**:743-748. Garmyn M *et al.* (1995) The effect of acute and chronic photodamage on gene expression in human keratinocytes. *Dermatol.* 190:305-308. Hadshiew IM *et al.* (2000) Skin aging and photoaging: the role of DNA damage and repair. *Am J Contact Derm.* **11**:19-25.

induced within hours of exposure. Since metalloproteinases are known to degrade collagen and elastin in the skin, it was hypothesized that induction of MMPs may be the primary mechanism mediating cutaneous photoaging. Moreover, this repeated injury, reported to occur at suberythemal doses of UV, if occurring over a lifetime, would be expected to produce the clinical signs of photodamaged skin.

Berneburg, *et al*[26] have postulated that the induction of metalloproteinases as well as damage to mitochondrial DNA (mtDNA) play a substantial role in photoaging of the skin. Exposure to UV light induces a wide variety of MMPs. MMPs proteolytically degrade proteins, each MMP affecting a specific component. For example, MMP1 degrades collagen type I, II, and III while MMP-9 degrades collagen types IV, V, and gelatin. Exposure to low level UV radiation (0.1 MED) induces the expression of transcription factors AP-1 and NF-κB within minutes. As noted above, AP-1 and NF-κB are known stimulatory factors of MMP genes leading to the expression of MMPs within hours of UV exposure. These studies provide independent support and replication of the work of Fisher *et al.*[19]

Beyond induction of MMPs, it has been demonstrated that the accumulation of elastotic material in human photodamaged skin is a result of increased synthesis of elastin and fibrillin, and that there is a steady state increase in elastin mRNA. In the studies by Uitto and colleagues[24], it was found that activation of elastin gene expression, with enhancement of transcriptional activity of other extracellular matrix genes, is an early event in photoaging.

Finally, there is substantial evidence that free radical damage is intrinsic to the normal aging process of the skin. Free radical damage may also play an important additional role in photoaging. Gilchrest and coworkers[25] have proposed the following construct: "UV irradiation produces free radicals in the skin; sufficiently high UV

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[26] Berneburg M. (2000) Photoaging of human skin. *Photodermatol. Photoimmunol. Photomed.* **16**:239-244.

doses produce enough free radicals to overwhelm antioxidant defenses; these excessive free radicals then damage proteins, lipids, and DNA; this damage finally leads to the observed chronic changes in the skin."

Collectively, the work of Fisher, Uitto and Gilchrest serve as a molecular and biochemical basis for experimentally studying skin photoaging. In any case, these investigative teams have either demonstrated experimentally or in discussion of their work the belief that reduction of UV exposure as occurs with sunscreens will diminish the molecular events, which lead to skin photoaging. Although prospective, decades long human studies have not been performed, this hypothesis is supported by animal findings.

IV. Animal Models of Skin Aging Caused by UV

As with many human diseases such as cancer that develop over a lifetime, i.e., decades separate initiating events from clinical manifestation, prospective studies of photoaging in human skin have not been conducted. As such, the scientific evidence supporting the etiology is based on careful clinical observations, short-term mechanistic studies and animal models. The mouse has been used since the late 1950s as a model to study the biological effects of UV. More specifically, the SKH1 albino hairless mouse has been used for the past 30 years as a model for human photoaging because 1) changes can be studied in relatively short periods of time, i.e., less than a year, 2) UV dosimetry can be accurately measured and 3) evidence of skin damage can be readily observed and quantitated. Most important, the clinical, histological and molecular events produced by solar-simulated UV in hairless mouse skin appear to reflect those observed in human skin. There are several excellent reviews on this subject[27].

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[27] Bissett DL *et al.* (1987) An animal model of solar-aged skin: histological, physical, and visible changes in UV-irradiated hairless mouse skin. *Photochem Photobiol* **46**:367-378. Bissett DL *et al.* (1989) The hairless mouse as a model of skin photoaging: its use to evaluate photoprotective materials.

For 30+ years, Kligman and co-workers have used the hairless mouse as a model to study human skin photoaging. For example, in human skin one of the first signs of photodamage/photoaging is elastic fiber hyperplasia an observation Kligman, *et al.*[28] showed in hairless mouse skin after 9 or 10 weeks of UVR exposure. In these studies, there was a continuous accumulation of elastic tissue, which became more damaged over time. Inflammatory infiltrate was associated with elastosis. In the deep dermis there was evidence of stimulation of elastic tissue caused by low-grade chronic tissue reactions. In the dermis of irradiated mice, a second population of fibroblasts appeared, again, akin to the increase in secondary fibroblasts observed in photodamage/photoaged human skin. In the dermal matrix there was also a loss of collagen, greatly enhanced acid muco-polysaccharides (AMPS) and massive damage to the basement membrane. Collectively, these data and other work by Kligman, Bissett, Kiss, and Moloney[27], all support the utility of the hairless mouse as a model to study human skin photoaging.

V. Prevention of Photoaging

A. Rationale for sun avoidance behavior and use of sunscreens

As presented in the preceding sections, repeated exposure to solar UV damages the skin leading to changes that are collectively known as photoaging. If exposure to solar UV produces photoaging, then reducing solar UV exposure will reduce the signs of photoaging.

1. Evidence supporting the protective benefit of sunscreens against UV-induced photoaging of skin

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Photodermatol **6**:228-233. Kligman LH. (1991) The hairless mouse and photoaging. *Photochem Photobiol* **54**:1109-1118. Kiss I *et al.* (1991) The effect of high and low ultraviolet-B dose exposure on the degree of hairless mouse skin wrinkling. *Photochem Photobiol* **53**:109-112 Moloney SJ *et al.* (1992) The hairless mouse model of photoaging: evaluation of the relationship between dermal elastin, collagen, skin thickness and wrinkles. *Photochem Photobiol* **56**:505-511.

[28] Kligman LH, *et al* (1982) Prevention of Ultraviolet Damage to the Dermis of Hairless Mice by Sunscreens. *J Invest Dermatol* **78**:181-189.

Snyder and May[29] reported actinic damage to hairless mouse skin in a study of the photocarcinogenic effects of short wavelength UV, i.e., 290 – 320 nm. In this study, the mice were pretreated with 9,10-dimethyl benz-[a]-anthracene and then exposed to artificial UVR three times weekly for 29 weeks. One group of mice was treated with a sunscreen containing 5% PABA prior to UVR exposure. The mice treated with PABA appeared grossly normal in protected areas but developed cutaneous lesions, i.e., horns, in the head area that was unprotected. Two months after cessation of UVR exposures, unprotected mice showed elevated levels of DNA synthesis as well as a hyperplastic epidermis and hypergranulosis. Mice protected showed levels of DNA synthesis at the high end of the normal range and milder hyperplasia and hypergranulosis. Elastotic material was deposited in a dose dependent manner with untreated mice showing low levels, unprotected UVR exposed mice showing large amounts, and PABA protected mice demonstrating an intermittent level. Therefore in this experiment, PABA, a sunscreen that absorbs primarily in the shortwave UV range afforded protection against photoaging.

The seminal work of Kligman[30] demonstrated the ability of hairless mouse skin to repair itself following exposure to artificial UV radiation and the effects of sunscreen use on that repair process. First, the authors demonstrated that skin photoaging, *per se*, is a reversible phenomenon. Hairless mice kept alive for 15 weeks following exposure to UVR for 30 weeks were found to have a new band of dermis formed in the subepidermal region. This band tended to push downward the elastotic material produced during the 30 weeks of UVR exposure. The collagen in this area appeared normal with delicate elastic fibers and a sparse amount of ground substance. Although the severely damaged portion of the upper dermis did not undergo complete recovery, it was pushed down by the newly forming dermis. Ultrastructurally, normal

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[29] Synder DS, May M (1975) Ability of PABA to protect mammalian skin from ultraviolet light-induced skin tumors and actinic damage. *J Invest. Dermatol.* **65**:543-546.

[30] Kligman LH, *et al.* (1983) Sunscreens promote repair of ultraviolet-induced dermal damage. *J Invest Dermatol.* **81**:98-102. Kligman LH. (1987) Connective tissue photodamage in the hairless mouse is partially reversible. *J Invest Dermatol.* **88**:12s-17s.

collagen bundles in a horizontal and parallel array characterize the subepidermal recovery zone. The authors noted that although the skin cannot be returned to a pristine condition, damage can be halted and even reversed if UV exposure is reduced or eliminated.

Similarly, the use of sunscreen after chronic UVR exposure could halt the damage and permit the formation of an overlying band of healthy dermis. In mice treated for 10 or 20 weeks with UVR, fibroblasts begin to synthesize a normal matrix. If an SPF 7 or 15 sunscreen is applied to the skin and UVR continued, the same repair is seen. This study clearly demonstrated that protection with the sunscreen after 10 weeks of unprotected UV exposure arrested the development of further damage. Damage was limited to mild elastic fiber hyperplasia and moderately increased levels of GAGs. Unprotected animals exposed for 20 weeks demonstrate severe hyperplasia of elastic fibers, collagen damage, and maximally increased levels of GAGs. Protection with the sunscreen for the last 10 weeks of exposure yielded distinct repair despite continued UV exposure. Repair included deposition of new, normal collagen, and compressed elastic fibers that were pushed down by a new zone of reconstruction. Although higher at 30 weeks, GAG levels returned to normal by the end of a 15-week period of non-UV exposure. Thus, the use of a sunscreen promotes repair of photodamaged skin even after such damage is present.

Harrison, *et* al[31] studied the effects of sunscreens with low SPF (2%, 2-ethylhexyl 4′-methoxycinnamate or octyl methoxycinnamate) alone and with the addition of either 0.75 or 2% of a UVA filter (butyl methoxy dibenzoylmethane [avobenzone]) on skin damage produced by chronic UV exposure. Chronological aging (32-weeks, no UVR exposure) was characterized by thicker and shorter elastic fibers, a coarsening and increase in dermal collagen and a thickening of the dermis due to an increase of dermal cysts. Exposure to UVA radiation for 32 weeks enhanced all

[31] Harrison JA *et al.* (1991) Sunscreens with low sun protection factor inhibit ultraviolet B and A photoaging in the skin of the hairless albino mouse. *Photodermatol Photoimmunol Photomed* **8**:12-20.

of these effects of chronological aging along with a modest increase in elastic tissue. Exposure of mice to solar simulated radiation (UVB + UVA) for up to 16 weeks produced profound photoaging including: epidermal thickening and hyperplasia, increased cellularity of the dermis with a proliferation of fibroblasts, increased number and size of dermal cysts resulting in a thickening of the dermis, an inflammatory infiltrate with an increase in mast cells, thickened and highly compressed collagen bundles, and elastic fiber hyperplasia. The use of 2% octyl methoxycinnamate markedly reduced the severity of the alterations to skin morphology produced by solar-simulated radiation. The addition of 0.75% avobenzone to octyl methoxycinnamate had no additive effect to that seen with octyl methoxycinnamate alone. However when the level of avobenzone was increased to 2%, there was a clear enhancement of the photoprotective action of octyl methoxycinnamate. The authors concluded that the daily use of even a low broad spectrum SPF sunscreen can significantly attenuate solar radiation induced photoaging, and ultimately, photocarcinogenesis.

In 1994, Kligman and Zheng[32] summarized the accumulating evidence that full spectrum UV exposure induces dermal connective tissue damage. These changes include elastic fiber hyperplasia, increases in glycosaminoglycans (GAGs) of the ground substance, and a change in the susceptibility of collagen to enzymatic digestion. A sunscreen containing the UV filter oxybenzone was found to prevent elastic fiber hyperplasia and increase GAGs in the skin of hairless mice exposed to solar-simulated UVR. However, the same UV filter provided no protection in a study using an artificial light source filtered to emit UVA. The authors then studied the effects of a broad spectrum sunscreen against UVA I irradiation (340 – 400 nm). Exposures to up to 100 J/ cm^2 three times per week for 32 weeks were used. Erythema was avoided in these animals. Unprotected mice had thickened, yellow, sagging skin at the end of the exposure period. The sunscreen protected against these gross effects

[32]Kligman LH, Zheng P. (1994) The protective effect of a broad-spectrum sunscreen against chronic UVA radiation in hairless mice: a histologic and ultrastructural assessment. *J Soc Cosmet Chem* **45**:21-33.

with the mice showing slightly thickened pale skin. Histologically, the sunscreen protected against a loss of order, atypia, and parakeratosis in the dermis. There was protection against elastic fiber hyperplasia and an increase of dermal GAGs. UVA I radiation was found to have severe effects on the cutaneous vasculature. There was an increase in the basement membrane surrounding vessels of up to 14 layers. Extensive vesiculation of the cytoplasm and mitochondrial swelling was noted in vascular endothelial cells. Thus, sunscreens affording broad spectrum UV protection essentially blocked this damage.

Although an SPF 15 sunscreen can block about 93% of UVR, small amounts of UVA and UVB can penetrate to the viable layers of the skin. Whereas, sunburn may be prevented, photodamage could still occur from chronic exposure to the UV radiation transmitted through the UV filters. To test this hypothesis, Kligman *et al.*[33] studied the effects of three sunscreens on connective tissue damage in hairless mice following exposure to solar-simulated radiation (SSR). They determined a dose of SSR that would produce a 50% increase in elastic fibers over a period of 9 weeks in mice. This exposure provided a cumulative dose of approximately 1 J/ cm^2 of UVB and approximate 170 J/ cm^2 of UVA. Over the course of the study, three groups of mice received 16 times this dosage, each group treated with one of the experimental sunscreens: SPF 7 containing a UVB/UVA-II absorber, octyl methoxycinnamate (OMC); SPF 16 containing OMC with oxybenzone as a shortwave UVA-II absorber or SPF 18 containing OMC, oxybenzone, and an additional UVA-I absorber, avobenzone. Although all three sunscreens blocked erythema, varying amounts of photodamage were observed. The SPF 7 sunscreen allowed the greatest amount of damage while the SPF 18, broad spectrum sunscreen, afforded the greatest protection. The authors concluded that the addition of a UVA I absorber (avobenzone) reduces all aspects of UVR induced photoaging and support the concept of using sunscreens with UVA I

[33]Kligman LH, *et al.* (1996) Broad-spectrum sunscreens with UVA I and UVA II absorbers provide increased protection against solar-simulating radiation-induced dermal damage in hairless mice. *J Soc Cosmet Chem* **47**:129-155.

protection to modulate the accumulation of photodamage to humans following years of sun exposure.

This limited sampling of published experimental studies demonstrates the protective benefit of sunscreens against chronic UV-induced skin damage, specifically photoaging. It is noteworthy that similar studies have been performed in which the protective benefit of sunscreens against UV-induced skin tumor formation was shown. As reviewed by Gasparro *et al.*[34] sunscreens have been shown to reduce UV-induced skin tumor formation in virtually every study, i.e., 30+ independent studies. Only now are chronic human studies being conducted and, in limited cases, showing similar promise[35]. As such, the protective benefits shown in chronic mouse studies are seemingly and arguably predictive of what would be observed in humans.

VI. Support of Government Agencies and Professional Societies

Photoaging/chronic skin damage is recognized as a consequence of solar UV exposure by government agencies and numerous professional organizations. Such groups recommend strategies to reduce solar UV exposure, which include daily use of sunscreen.

A. American Academy of Dermatology

The American Academy of Dermatology's Guidelines/Outcomes Committee has developed "Guidelines of care for photoaging/photodamage"[36]. In these guidelines the committee states "No credible scientific evidence contradicts the relation of sun

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[34] Gasparro, FP *et al.* (1998) A review of sunscreen safety and efficacy. *Photochem Photobiol* **68:**243-256.

[35] Green A *et al.* (1999) Daily sunscreen application and beacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomized controlled trial. *The Lancet* **354**:723-729.

[36] Bergfeld WF *et al.* (1997) Executive summary of the national partners in prevention skin cancer conference: American Academy of Dermatology and Centers for Disease Control and Prevention. *J Am Acad Dermatol* **36**:798-801. Drake LA *et al.* (1996) Guidelines of Care for Photoaging/Photodamage. *J Am Acad Dermatol* **35**:462-464.

exposure to the development of skin cancer and the undesirable results of photoaging and photodamage". The committee contends that a significant portion of the approximately $14 billion spent on cosmetics in the US in 1996 was specifically spent to conceal the effects of photoaging and photodamage. An additional significant amount of money is spent on surgical and medical procedures. The committee believes that early recognition and treatment of photo damaged and photoaged skin will lead to a decrease in the incidence of premalignant and malignant skin lesions. Photodamage and photoaging are at least partially reversible with photoprotection and the use of sunscreens that protect against solar UV is encouraged.

B. American Cancer Society

In its efforts to educate the American public about the importance of prevention and early detection of skin cancer, the American Cancer Society discusses on its website the damage that UV can cause to skin and eyes, including the effects of photoaging:

> **What Damage Does UV Cause?**
>
> The short-term results of unprotected exposure to UV rays are tanning and sunburn. ...
>
> The long-term effect of sunburn is more serious.
>
> UV exposure that is intense enough to cause sunburn clearly increases a person's risk of developing skin cancer. And UV exposure can increase skin cancer risk even without causing sunburn.
>
> Long-term exposure can also cause premature changes in skin including:
>
> - Aging
> - Wrinkles
> - Loss of elasticity
> - Dark patches (lentigos, that are sometimes called "age spots" or "liver spots"
> - Actinic keratoses

C. Skin Cancer Foundation

The Skin Cancer Foundation recently updated its brochure, "Simple Steps to Sun Safety", which states:

> Your skin is an excellent recordkeeper. Every moment in the sun adds up, accumulating like money in the bank. The payoff, however, is damage to the skin and possibly skin cancer. ...Sunlight also causes wrinkling, blotching, drying, and leathering of the skin, making you look old before your time. The best defense, now and for the future, is to limit time in the sun and protect yourself whenever you go outdoors.

D. American Society of Photobiology

The American Society for Photobiology (ASP) is also "concerned with the interaction of light and living things" including the harmful effects of UV on humans. In its publication The Light and Life brochure published "to inform government officials, students and the general public about the science of photobiology", the ASP states:

> *Harmful effects of light.* Sunlight is implicated in several skin diseases, including premature aging of the skin and skin cancer. Skin sensitivity to sunlight is controlled by the genetic ability of an individual to produce melanin, the pigment that helps protect the skin from light-induced injury.
>
> *Photoprotection.* Both topical and systemic sunscreen agents prevent the acute and chronic effects of sunlight. They enable people to work outdoors and enjoy outdoor activities with reduced risk of sun-induced injury. The damage that absorbed light creates in the skin, such as the changes recognized as aging of the skin, is preventable by using new types of water- and sweat- resistant sunscreens.

E. Centers for Disease Control and Prevention (CDC)

The Centers for Disease Control and Prevention (CDC) has educational programs and recommendations that are targeted to apply "disease prevention and control, environmental health, and health promotion and education activities designed to improve the health of the people of the United States." On its web site Choose Your Cover, it specifically states:

excessive and unprotected exposure to the sun can result in premature aging and undesirable changes in skin texture. Such exposure has been associated with various types of skin cancer, including melanoma, one of the most serious and deadly forms.

F. National Institutes of Health (NIH)/Environmental Protection Agency

In addition to the CDC, other government agencies including the National Institutes of Health (NIH) and the Environmental Protection Agency (EPA) have reiterated concern about the effect of UVA on the skin. The "MEDLINEplus Health Information" service of the U.S. National Library of Medicine and the National Institutes of Health, states that "[s]unscreens help to prevent sunburn and reduce the harmful effects of the sun such as premature skin aging and skin cancer.

The Environmental Protection Agency has related materials on its website to promote greater public awareness of the impact of UV exposure:

> Exposure to ultraviolet radiation from the sun can seriously harm human health. Mild exposure can lead to sunburn. More extended exposure to the sun may result in premature aging and discoloration of the skin and, ultimately, skin cancer. These health effects have only been made more acute by the destruction of the ozone layer which protects the earth from the sun's ultraviolet radiation. ... The EPA and other agencies also promote awareness of the dangers of sun exposure and the safety precautions such as minimizing exposure and using sunscreen.
>
> ******
>
> UV radiation from the sun can seriously threaten human health.
>
> The most obvious result of too much sun is sunburn, which involves skin
> redness and sometimes tenderness, swelling, blistering, fever, and nausea.
> Although some skin types prevent individuals from burning, everyone is at risk for other UV-related health effects.
>
> Premature wrinkling

In the long run, too much exposure to the sun can change your skin's texture, giving it a tough, leathery appearance. The sun also can cause discolorations in skin tone including red, yellow, gray, or brown spots.

VII. Conclusions

The conclusions are clear:

- Exposure to solar UV damages human skin,
- repeated exposure to solar UV manifests as photoaging after many years,
- molecular mechanisms of photoaging have been developed using human skin and are operative in animal models,
- use of sunscreens protects against short-term markers of UV-induced skin damage, and
- sunscreens or UV filters reduced molecular, biochemical and clinical events associated with photoaging in animal models.

This evidence together with the public health policy recommendations of the leading dermatological and cancer societies and government agencies overwhelmingly support the view that sunscreen products *help protect against skin aging caused by the sun.*

VIII. Recommendations

As the Agency itself has recognized, there are a wide variety of products marketed for sun protection use, several of which include cosmetic properties and other attributes of importance to the consumer. Given the expanding conditions of use of sunscreen drug products, to the recognized health benefit of all, it is imperative that these products be labeled appropriately for their use. Consumers use sunscreen products for more than just prevention of sunburn. The Agency has acknowledged this fact as well. A compelling reason for sun avoidance beyond sunburn and skin cancer

prevention is the benefit of maintaining a youthful appearance by actively preventing sun-induced aging through the use of products containing sunscreens. Such a driving force can propel a public health benefit which is supported by the logic of scientific evidence even if decades long prospective clinical trials do not exist. We therefore urge FDA to permit the following labeling indications, each of which allows communication of truthful information about the benefits of using sunscreens:

- *Helps protect against harmful effects of the sun*
- *Helps protect against (casual) (incidental) (intermittent) (daily) sun exposure*
- *Helps protect against skin damage caused by the sun*
- *Helps protect against skin aging caused by the sun*
- *Regular use helps protect against certain forms of skin cancer caused by the sun*

We strongly urge FDA to reevaluate its decision in the Final Monograph for OTC sunscreen drug products and permit these labeling indications in light of substantial and credible scientific evidence as well as in the context of the First Amendment.