Comments of the Indoor Tanning Association (ITA) and the American Suntanning Association (ASA)

March 21, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2015-N-1765; General and Plastic Surgery Devices: Restricted Sale, Distribution, and Use of Sunlamp Products

Dear Sir/Madam:

The Indoor Tanning Association (ITA) and the American Suntanning Association (ASA), trade associations of the indoor tanning industry, provide these comments to the Food and Drug Administration (FDA) on issues related to the Agency's proposed rule to establish restrictions on the sale, distribution, and use of sunlamp products. 80 Fed. Reg. 79493 (Dec. 22, 2015).

The proposed restrictions would require that: (1) tanning facility operators restrict the use of sunlamp products to individuals age 18 and older; (2) tanning facility operators provide a copy of the sunlamp product user manual upon request of a user or prospective user; (3) prospective users must sign a risk acknowledgement certification before use and subsequently every six months; and (4) sunlamp product 510(k) holders assure that a user manual accompanies each product and that they provide a copy of the manual upon request of any tanning facility, user, or prospective user. 80 Fed. Reg. at 79495, 79503.

ITA and ASA support the continued availability of indoor tanning to the public, and the provision of clear and accurate information to users and prospective users to assure responsible use of indoor tanning products. But ITA and ASA do not support FDA's proposed restrictions on sale, distribution, and use of sunlamp products, or the requirements that FDA seeks to impose upon tanning facility operators.

If you have any questions about this submission, please contact: (1) John Overstreet, Executive Director, ITA, at (202) 637-1225, or by email at joverstreet@theita.com; and (2) Barton Bonn, President, ASA, by email at bonnbart@gmail.com.

Respectfully submitted,

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DOCKET NO. FDA-2015-N-1765

Comments of the Indoor Tanning Association and American Suntanning Association On FDA's Proposed Rule for the Restricted Sale, Distribution, and Use of Sunlamp Products

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EXECUTIVE SUMMARY

The Indoor Tanning Association (ITA) and American Suntanning Association (ASA) are trade associations of the indoor tanning industry, which currently employs approximately 83,000 people in the United States. ITA and ASA are comprised of hundreds of members, including manufacturers and distributors of sunlamp products, and tanning facility owners and operators who purchase or lease sunlamp products that are used by the public.[1] Our members have extensive expertise and experience in the design, manufacture, use, and operation of sunlamp products. Our members are committed to compliance with safety standards and labeling to assure that providers and consumers understand and conform to appropriate guidelines. Our members have been subject to the special controls promulgated at 21 C.F.R. § 878.4635 and the performance standard promulgated at 21 C.F.R. § 1040.20 that are applicable to sunlamp products.

ITA and ASA submit these comments on issues related to the Agency's proposed rule to require that: (1) tanning facility operators restrict the use of sunlamp products to individuals age 18 and older; (2) tanning facility operators provide a copy of the sunlamp product user manual upon request of a user or prospective user; (3) prospective users must sign a risk acknowledgement certification before use and subsequently every six months; and (4) sunlamp product 510(k) holders assure that a user manual accompanies each product and that they provide a copy of the manual upon request of any tanning facility, user, or prospective user.[2]

ITA and ASA support the continued availability of indoor tanning to the public and the provision of clear and accurate information to users and prospective users to assure responsible use of indoor tanning products. But ITA and ASA do not support FDA's proposed restrictions on sale, distribution, and use of sunlamp products, or the requirements that FDA seeks to impose upon tanning facility operators. ITA and ASA raise the following concerns about FDA's proposed rule:

1. The scientific support provided for the proposed rule fails to reflect the totality of the current scientific evidence;

2. The proposed rule is contrary to law because the restrictions on sale, distribution, and use do not meet the statutory criteria articulated in FDCA § 520(e);

3. The proposal to prohibit the use of sunlamp products by individuals under the age of 18 is unconstitutional and should be replaced with a parental waiver option;

4. The risk acknowledgement certification and user manual provisions are duplicative and overly burdensome; and

5. FDA's economic analysis fails to adequately measure the proposed rule's significant economic impact on small entities.

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[1] The ITA and ASA members are listed in **Exhibit A**.

[2] 80 Fed. Reg. 79493 (Dec. 22, 2015).

Table of Contents

INTRODUCTION

Sunlamp products are currently subject to stringent oversight by FDA. These products are regulated principally and extensively under the Electronic Product Radiation Control provisions of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 360hh-360ss, and implementing regulations, 21 C.F.R. Parts 1002-1010 and § 1040.20. These regulations specify requirements for initial product reports, annual reports, test records, distribution records, product performance standards, protective eyewear, timer systems, and specified labeling statements. In addition, FDA regulates sunlamp products as Class II devices subject to premarket notification and certain special controls.[3] Sunlamp products are also subject to the FDCA's general controls for medical devices, which include requirements related to establishment registration, product listing, good manufacturing practices, adverse event reporting, and labeling.

Prior to June 2014, ultraviolet lamps for tanning purposes were regulated as Class I devices (510(k) exempt), in addition to being regulated as electronic products under the FDCA. In November 2009, FDA announced that the Agency was convening the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee on March 25, 2010 (the March 2010 Panel) to review certain information and "recommend whether changes to current classification or current regulatory controls of UV emitting devices (lamps) used for tanning are needed."[4] ITA submitted comments to the docket for the March 2010 Panel, describing the significant controls already in place to assure the safe and effective use of sunlamp products, and discussing at length the significant limitations in the scientific literature cited and relied upon by FDA.

In May 2013, after Congress enacted the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA issued a proposed order reclassifying sunlamp products and ultraviolet lamps intended for use in sunlamp products from Class I to Class II (special controls) medical devices.[5] ITA and ASA submitted comments that: (1) argued that the proposed order exceeded FDA's authority under FDCA § 513(e); (2) continued to stress the significant controls already in place to assure the safe and effective use of sunlamp products; and (3) underscored the flaws in the scientific literature considered by the March 2010 Panel. Despite these objections, FDA finalized the reclassification order in June 2014.[6]

On December 22, 2015, FDA issued two proposed rules concerning the sunlamp products industry. The comments submitted here focus on issues related to the proposed rule to establish restrictions on the sale, distribution, and use of sunlamp products under FDCA § 520(e).[7] Separate comments are being submitted to the docket for the proposed rule concerning

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[3] 21 C.F.R. § 878.4635(b).

[4] 74 Fed. Reg. 59194 (Nov. 17, 2009).

[5] 78 Fed. Reg. 27117 (May 9, 2013). FDASIA authorized FDA to reclassify devices through an administrative order rather than by regulation following notice-and-comment rulemaking.

[6] 79 Fed. Reg. 31205 (June 2, 2014).

[7] 80 Fed. Reg. 79493 (Dec. 22, 2015).

amendments to the performance standard for sunlamp products and UV lamps intended for use in sunlamp products.[8]

I. The Scientific Evidence Cited and Relied Upon by FDA Fails To Take Into Account More Current Scientific Data and Does Not Support Imposition of the Onerous Requirements of FDA's Proposed Rule.

As noted above, FDA convened an Advisory Panel Meeting in March 2010 to consider certain scientific information about UV radiation and tanning. That was six years ago. Since that time, there have been significant changes in the understanding of the benefits and risks related to sunlamp products. A fuller discussion of the current scientific literature is included in **Exhibit B** to these comments.

In particular, more recent scientific articles do not support FDA's assertion in the proposed rule that children and adolescents who are exposed to UV radiation (including from indoor tanning) may be at higher risk of developing certain types of skin cancer than persons who begin exposure later in life as adults.[9]

In the preamble to the proposed rule, FDA relies upon the 2006 International Agency for Research in Cancer (IARC) report[10] and the follow-up 2012 Boniol study. These studies have been discredited and superseded by the 2014 Colantonio study, which found that there is no statistically significant correlation between indoor tanning before age 25 versus after age 25 and increased risk of melanoma.[11] In addition, FDA fails to acknowledge that the 2010 Lazovich study, published after the meeting of the March 2010 Panel, found that younger individuals are *not* at increased susceptibility to the effects of UV radiation (discussed further in **Exhibit B** to these comments).[12]

A careful review of our scientific submission in **Exhibit B** shows that the totality of the current scientific evidence does not support the restrictions on use of sunlamp products being proposed by FDA.

At the least, we request that FDA convene a new Panel meeting before finalizing this proposed rule. The new Panel meeting should permit the submission of new scientific literature since the meeting of the March 2010 Panel, and a fair opportunity for hearing and discussion of the totality of the scientific evidence concerning UV exposure and indoor tanning, including flaws in the studies relied upon in the IARC report. Then FDA should consider and

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[8] 80 Fed. Reg. 79505 (Dec. 22, 2015).

[9] 80 Fed. Reg. at 79496.

[10] IARC Working Group on Artificial Ultraviolet Light (UV) and Skin Cancer, "The Association of Use of Sunbeds with Cutaneous Malignant Melanoma and Other Skin Cancers: A Systematic Review." *International Journal of Cancer*, 120:1116-1122, 2006.

[11] Colantonio, S., Brakcen, M.B., and Beecker, J., "The Association of Indoor Tanning and Melanoma in Adults: Systematic Review and Meta-Analysis," *Journal of the American Academy of Dermatology*, 70(5):847-857, 2014.

[12] Lazovich, D., Vogel, R.I., Berwick, M., et al., "Indoor Tanning and the Risk of Melanoma: A Case-Control Study in a Highly Exposed Population," *Cancer Epidemiology, Biomarkers & Prevention*, 19(6):1557-1568, 2010.

address the new scientific literature before seeking to impose new and onerous restrictions on the use of sunlamp products for tanning. The Panel should include members specifically qualified to assess UV radiation studies and to assess the safety and effectiveness of sunlamp products and the adequacy of regulatory controls under the electronic product provisions of the FDCA. A consumer representative who understands the use of indoor tanning products and a representative from the indoor tanning industry should also be on the Panel.

II. FDA's Proposal To Impose Restrictions on Sale, Distribution, and Use of Sunlamp Products Does Not Meet the Requirements of FDCA § 520(e).

FDA's authority to restrict the sale, distribution, or use of a device is set forth in FDCA § 520(e). It is highly unusual for FDA to impose such restrictions on a Class I or Class II device, and those restrictions must be imposed by a regulation issued after notice and comment rulemaking.[13]

FDA is now proposing to make sunlamp products subject to restrictions under section 520(e). FDA is making this proposal less than two years after imposing Class II device requirements and special controls on sunlamp products by administrative order. FDA cannot impose section 520(e) restrictions on sunlamp products until the Agency has determined that the existing Class II requirements and special controls, including the applicable performance standard, have not provided reasonable assurance of safety and effectiveness, after allowing a reasonable period of time for assessing the effect of those requirements, controls, and standards.

A. FDA Cannot Impose Restrictions on Sale, Distribution, or Use of Sunlamp Products Because the Criteria of Section 520(e) Are Not Met.

Under FDCA § 520(e), FDA may issue a regulation to require that a device be restricted to sale, distribution, or use:

> "(A) only upon the written or oral authorization of a practitioner licensed by law to administer or use such device, or
>
> (B) upon such other conditions as the Secretary may prescribe in such regulation,
>
> if, because of its potentiality for harmful effect or the collateral measures *necessary to its use*, the Secretary determines that there *cannot otherwise* be *reasonable assurance of its safety and effectiveness*." (Emphasis added.)

These requirements of section 520(e) have not been satisfied.

First, FDA has not satisfied the criterion that restrictions can be imposed only if there "cannot otherwise be reasonable assurance" of the safety and effectiveness of sunlamp products, because the Agency has not allowed an adequate period of time for the current Class II requirements and special controls to be evaluated. The 510(k) requirements and special controls that were imposed by the June 2014 administrative order did not become effective until

[13] FDA can impose restrictions on a Class III device as a condition of approval of a premarket approval application (PMA) pursuant to FDCA § 515(d)(1)(B)(ii), 21 U.S.C. 360e(d)(1)(B)(ii).

August 26, 2015, for existing sunlamp products.[14] FDA proposed this restricted device rule on December 22, 2015. That four months was clearly not adequate time to evaluate whether the existing requirements and controls, which also incorporate by reference the performance standard, provide "reasonable assurance of the safety and effectiveness" of sunlamp products.

Similarly, FDA has not demonstrated that the proposed restrictions for sunlamp products are "collateral measures necessary to its use." In June 2014, FDA had imposed performance testing requirements, a black box warning stating that sunlamp products "should not be used on persons under the age of 18 years," a contraindication for use on persons under the age of 18 years, and several warnings including one about repeated exposure to UV radiation.[15] FDA has not taken the time to evaluate the effectiveness of these requirements. So the Agency cannot satisfy the criterion requiring that restrictions can be imposed on a sunlamp product only if there are additional "collateral measures necessary to its use."

As explained in the scientific submission in **Exhibit B**, the totality of the current scientific evidence does not support FDA's claim that the "potentiality for harmful effect" of sunlamp products cannot otherwise be addressed by the current requirements and special controls. For example, FDA seeks to require tanning facility operators to prohibit use of sunlamp products by anyone under 18 years of age. But the Colantonio study (discussed above) concludes that there is no statistically significant correlation between indoor tanning before age 25 versus after age 25 and increased risk of melanoma. And the Lazovich study (also discussed above) specifically found that younger individuals are not at increased susceptibility to the effects of UV radiation. Given such evidence, the appropriate regulatory controls are the warnings already provided in the current regulation in 21 C.F.R. § 878.4635.

B. Existing Special Controls and Performance Standards Provide Reasonable Assurance of Safety and Effectiveness of Sunlamp Products for Tanning.

ITA and ASA support reasonable labeling requirements, appropriate warnings, and performance standards for sunlamp products. But FDA's proposed device restrictions are overly burdensome, unnecessary, and contrary to law.

Current device special controls[16] and the electronic product performance standards[17] already provide "reasonable assurance of [a sunlamp product's] safety and effectiveness." Additional restrictions, like an age-based prohibition, are unnecessary given the existing special controls and performance standards.

In the preamble to the Final Order reclassifying ultraviolet lamps for tanning from Class I to Class II devices, that special controls in 21 C.F.R. § 878.4635, the Agency asserted: "FDA is designating special controls that are necessary to provide a *reasonable assurance of safety and effectiveness of the device*."[18] This is the same standard articulated in

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[14] 79 Fed. Reg. at 31212.

[15] 21 C.F.R. § 878.4635.

[16] *Id*. at § 878.4635(b).

[17] *Id*. at § 1040.20.

[18] 79 Fed. Reg. at 31205 (emphasis added).

FDCA § 520(e). FDA cannot now claim that the special controls were not enough -- especially after failing to allow adequate time to assess their impact.

The existing special controls require a "black box" warning statement to be permanently affixed or inscribed on the sunlamp product when fully assembled for use, so as to be legible and readily accessible to review by the person who will be exposed to UV radiation immediately before using the product. This warning states: **"Attention: This sunlamp product should not be used on persons under the age of 18 years."**[19] The special controls also stipulate that manufacturers of sunlamp products must provide or cause to be provided in user instructions, as well as all consumer-directed catalogs, specification sheets, descriptive brochures, and Web pages in which sunlamp products are offered for sale, certain contraindication and warning statements, including **"Contraindication: The product is contraindicated for use on persons under the age of 18 years."**[20]

Given these special controls coupled with the electronic product performance standards (explained at length in Section VIII.B), further restrictions on the sale, distribution, or use are excessive and unnecessary for the reasonable assurance of sunlamp products' safety and effectiveness. The "black box" warning on product labeling and the under-18 contradiction on user instructions are more than sufficient to assure the safety and effectiveness of sunlamp products. To our knowledge, FDA has *never* restricted the sale, distribution, or use of a medical device under section 520(e) so as to *prohibit* individuals below a certain age from using or obtaining the benefits of a device.[21] FDA's proposal to prohibit individuals under age 18 from using sunlamp products is unprecedented and unwarranted.

C. FDA Failed To Follow the Statutorily Required Least Burdensome Principle in Its Proposed Rule.

Congress codified the concept of "least burdensome" regulatory requirements when it enacted the Food and Drug Administration Modernization Act of 1997 (FDAMA).[22] The least burdensome principle is intended to reduce regulatory burdens and streamline the regulatory process.[23] Under this principle, FDA is to consider the lowest appropriate level of regulatory control sufficient to provide reasonable assurance of the safety and effectiveness of the device.[24]

As discussed above, the existing regulatory requirements imposed upon sunlamp products already provide reasonable assurance of safety and effectiveness. That was the regulatory finding that FDA made in adopting the special controls in the Final Order. FDA has

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[19] 21 C.F.R. § 878.4635(b)(6)(i)(A) (emphasis added).

[20] *Id*. at § 878.4635(b)(6)(ii)(A) (emphasis added).

[21] We recognize that many devices are labeled as "Not for use in" or "Not studied in" pediatric populations, or as "Not intended for use in children." However, these types of labeling are more in the nature of warnings and contraindications, not bans on availability to or use by someone under 18.

[22] FDCA §§ 513(i)(1)(D) and 513(a)(3)(D)(ii).

[23] FDA, The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, at 1 (Oct. 4, 2002).

[24] *Id*. at 18.

not provided any evidence to show that the existing controls are inadequate. FDA's proposed restricted device rule seeks to impose significant, burdensome, and unnecessary restrictions on the sale, distribution, and use of sunlamp products. Under the least burdensome principle, FDA cannot issue a new regulation under FDCA § 520(e) when the requirements of 21 C.F.R. §§ 878.4635 and 1040.20 are adequate.

III. The Proposal To Prohibit Use by Individuals Under the Age of 18 Is Unconstitutional and Should Be Replaced with a Parental Waiver Option.

A. FDA's Under-18 Prohibition Interferes with the Fundamental Right of Parents to Direct the Upbringing of Their Children.

The Fifth and Fourteenth Amendments to the United States Constitution guarantee that no person shall be deprived of "life, liberty, or property, without due process of law."[25] The U.S. Supreme Court has long recognized that due process "guarantees more than fair process."[26] Due process includes a substantive component that "provides heightened protection against government interference with certain fundamental rights and liberty interests."[27] Government interference includes both state and federal actors.[28]

The oldest fundamental liberty interest recognized by the U.S. Supreme Court is the "interest of parents in the care, custody, and control of their children."[29] The Court has also recognized that due process protects the "*fundamental right* of parents to make decisions concerning the care, custody, and control of their children."[30]

Government interferences with the fundamental right of parents to direct the upbringing of their children should be subject to strict scrutiny.[31] Strict scrutiny is the most stringent standard of judicial review. Generally, the government has the burden of showing that the law infringing the fundamental right is: (1) necessary to achieve a compelling government interest; (2) narrowly tailored to achieve that interest; and (3) the least restrictive means for achieving that interest.[32]

FDA's proposal to prohibit the use of sunlamp products by individuals under 18 years of age is an interference with the fundament right of parents to direct the upbringing of their children. A parent, not a government actor, has the primary right to make decisions concerning the "care, custody, and control of a child." A parent has the decision-making authority to determine whether an adolescent should use sunlamp products, just as the parent

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[25] U.S. Const. amends. V and XIV, § 1.

[26] *Washington v. Glucksberg*, 521 U.S. 702, 719 (1997).

[27] *Id*. at 720.

[28] *Bolling v. Sharpe*, 347 U.S. 497, 499, (1954), supplemented sub nom. *Brown v. Bd. of Educ. of Topeka, Kan.*, 349 U.S. 294 (1955).

[29] *Troxel v. Granville*, 530 U.S. 57, 65 (2000).

[30] *Id*. at 66 (emphasis added).

[31] *Id*. at 80 (Thomas concurring).

[32] *San Antonio Indep. Sch. Dist. v. Rodriguez*, 411 U.S. 1, 16-17 (1973).

has a right to make decisions regarding any activity that might present risks to the child. In addition, there is no rational basis for a rule that would allow a parent to decide the child can utilize sunlamp products at home, but not allow the same parent to let the child use a sunlamp product at a tanning facility -- yet that is what FDA's proposal would do.[33]

In the proposal, FDA has failed to demonstrate a "compelling government interest" to interfere with parental rights.[34] The proposed under-18 prohibition on use of sunlamp products in a tanning facility is neither rational (since the products can be used in the home) nor necessary in protecting the health of young people. Furthermore, FDA has not selected the least restrictive means for achieving whatever interest it might have. For example, warnings, parental waiver (as discussed below in Section III.B), and parental awareness campaigns are less restrictive means than an under-18 prohibition in addressing the asserted "public health" concern, while protecting the fundamental right of parents to direct the upbringing of their children.

B. Any Age-Based Restriction on the Sale, Distribution, or Use of Sunlamp Products Should Include a Parental Waiver Option.

If FDA ultimately decides to implement any age-based restriction on the sale, distribution, or use of sunlamp products, the Agency should include a parental waiver option. In the preamble of the proposed rule, FDA writes: "The age restriction also is necessary because individuals under 18 often fail to appropriately evaluate the significant health risks associated with indoor tanning."[35] This assumption, however, does not recognize that the parental waiver option would transfer the evaluation of health risks associated with indoor tanning from the adolescent to the parent or legal guardian. FDA believes that "[b]y restricting sunlamp product use to individuals 18 and older, we would be protecting a subpopulation that generally tends to discount risk information and favor risk taking." Again, a parental waiver option would permit an adult, not an adolescent, to evaluate any risk information. The parental waiver option, rather than an under-18 prohibition on use, would be the least restrictive, least burdensome means for addressing the Agency's concerns about risk.

FDA claims that an "age restriction is also important because parental awareness of the risks, educational campaigns, and parental consent to the risks, on their own, have been shown to be insufficient in reducing indoor tanning in young age groups."[36] Current literature actually shows the opposite is true (**Exhibit C**). A review of scientific literature reveals that parental awareness, educational campaigns, and parental consent are quite promising and effective in reducing indoor tanning in young adults.[37] Indeed, the States have served as

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[33] 80 Fed. Reg. at 79495.

[34] Even if a court were to review the under-18 ban under the rational basis test, the proposed regulation is not rationally related to a "legitimate government interest" as outlined above.

[35] *Id*. at 79497.

[36] *Id*.

[37] *See* Lazovich, D., Choi, K., Rolnick, C., et al., "An Intervention to Decrease Adolescent Indoor Tanning: A Multi-Method Pilot Study," *Journal of Adolescent Health*, 52(5): S76-S82, 2013 ("A systematic qualitative and quantitative research approach yielded well-received indoor tanning prevention messages for mothers and female adolescents. Enhancing maternal monitoring has potential to decrease adolescent indoor tanning"); Turrisi, R., Hillhouse, J., Robinson, J., et al., "Mediating Variables in a Parent Based (continued...)

laboratories[38] in implementing parental consent. Roughly 60% of States currently offer some form of under-18 use of sunlamp products via parental waiver.

FDA indicated that it "welcomes comment on parental consent and its potential scope."[39] Accordingly, ITA and ASA recommend that an under-18 parental waiver option be recognized and include the following features:

- A parent or legal guardian must sign a one-time form providing consent for that individual to suntan indoors with a particular indoor tanning operator.
- The form must be signed at the indoor tanning facility by the parent or guardian in the presence of the operator.
- The form would include the following information:
    - Acknowledgment that the individual signing the form is the parent or legal guardian.
    - Acknowledgement that the individual agrees to use FDA-approved protective eyewear.
    - An explanation of potential risks of over exposure to ultraviolet light (like natural sunlight, sunlamps can cause eye burn, sunburn, aging of the skin, and skin cancer).
    - A recommendation that a physician be consulted if the individual is taking prescription medication, has a family history of skin cancer, or has any rashes or open wounds.

IV. A Risk Acknowledgement Certification is Unnecessary and Duplicative.

FDA proposes that tanning facility operators would have to provide, and sunlamp product prospective users would have to sign, a risk acknowledgment certification prior to use of any sunlamp product, unless the prospective user has previously signed the certification within the preceding six months. The certification would provide warnings regarding sunlamp products as well as information regarding the proper use of the products. This risk acknowledgement certification fills an entire page.

Intervention to Reduce Skin Cancer Risk in Children," *Journal of Behavioral Medicine*, 30(5): 385-393, 2007 ("[T]he overall emerging picture is a parent-child communication-based skin cancer intervention that shows tremendous promise. The present study supports the notion that parents can be viable change agents for child behaviors and adds to the growing literature that indicates that the quality of the family relationship is critical to the success of such interventions"); Stryker, J., Lazovich, D., Forster, J., et al., "Maternal/Female Caregiver Influences on Adolescent Indoor Tanning," *Journal of Adolescent Health*, 35(6), 528.e1-528.e9, 2004 ("Mothers/female caregivers may be a powerful influence on their teenagers' indoor tanning use, and are an important target for future health promotion efforts...").

[38] *New State Ice Co. v. Liebmann*, 285 U.S. 262 (1932).

[39] 80 Fed. Reg. at 79497.

The content of the risk acknowledgement certification is duplicative of existing instructions and labeling under 21 C.F.R. §§ 878.4635 and 1040.20. Among the statements required in the proposed risk acknowledgement certification are the following: (1) "You must not use this device if you are under 18 years of age"; (2) "Do not use beyond the manufacturer's recommended exposure schedule to avoid burns and over exposure"; (3) "Use appropriate protective eyewear"; and (4) "Do not use if you have any rashes or open wounds." These statements are all currently required on sunlamp product labeling and instructions.

Warning labels -- not written risk acknowledgement certifications -- are used in many other contexts that involve potential risks to consumers. FDA has failed to justify the extraordinary means of imposing a risk acknowledgement certification requirement on users of sunlamp products. In addition to burdening users and prospective users with this paperwork, this proposed requirement would impose a significant paperwork burden on tanning facility operators. Tanning facility operators would be required to maintain these records for one year, or until the prospective user signs a new certification, whichever is earlier.

In additions, FDA has failed to provide any justification for why prospective users have to sign a new risk acknowledgment certification every six months. It is not clear what analysis, if any, the Agency conducted to select the six-month interval. If FDA does finalize the risk acknowledgment certification proposal, we recommend that the Agency only require a prospective user to sign the certification one time with a particular operator, given the extensive existing sunlamp product labeling and instructions.

V. FDA Should Clarify the "User Manual" Requirements.

FDA proposes that tanning facility operators be required to provide a copy of the user manual or the name and address of the manufacturer or distributor who can provide a copy of the user manual to any user or prospective user that requests one. FDA also proposes that 510(k) holders be required to provide user manuals to any tanning facility operator, user, or prospective user that requests one.

Similar to the risk acknowledgement certification, the "user manual" requirements are duplicative and unnecessary. Currently, the electronic product performance standard requires manufacturers to "provide manuals to purchasers and, upon request, to others for the life of the sunlamp product."[40] Indoor tanning users or prospective users, therefore, can acquire a user manual under the electronic product performance standard.

Further, in the preamble to the proposed rule, FDA does not explain how the "user manual" requirements affect discontinued products, products already in the market place, or products for which the manufacturer/distributor is no longer in business. If the Agency proceeds to finalize the proposed rule, FDA should clarify that the "user manual" requirements only apply to products manufactured/distributed *after* the effective date of the final regulation.

[40] *Id*.; *see also* 21 C.F.R. § 1040.20(e).

VI. FDA Should Articulate How the Agency Plans To Enforce Restrictions on the Sale, Distribution, and Use of Sunlamp Products in a Fair and Consistent Manner.

In the preamble of the proposed rule, FDA does not explain in detail how the Agency will fairly and consistently enforce any final rule. The Agency simply states as follows: "FDA expects to cooperate with counterpart agencies at the state level in enforcing the proposed requirements, if they become final. Consumer complaints to FDA and State Agencies would be important in identifying entities that violate the conditions for sale or use of these devices."[41] If the proposed rule becomes final, FDA suggests that restrictions may be enforced by means of seizure of the sunlamp product, a suit for injunction, imposition of civil money penalties, or criminal prosecution.[42]

If FDA issues a final rule imposing restrictions on the sale, distribution, and use of sunlamp products, the Agency should provide greater clarity on how it will process consumer complaints and cooperate with counterpart agencies at the State level. It is not clear that FDA has or will have the personnel and financial resources to appropriately enforce the proposed rules, considering there are an estimated 9,500 indoor tanning salons and 10,000 other facilities that offer indoor tanning services. Further, certain States, like New York and South Carolina, have inappropriately applied federal requirements regarding sunlamp products in the past. There is true concern that an enforcement scheme that relies chiefly on counterpart agencies at the State level will result in an inconsistent patchwork of enforcement actions, practices, and penalties, leading to an unequal application of the law.

VII. FDA's Economic Analysis Fails to Adequately Measure the Proposed Rule's Significant Impact on Small Entities.

Executive Order 12866 requires that any agency promulgating "rules" or "regulations" must, among other things, "tailor its regulations to impose the least burden on society, including individuals, businesses of differing sizes, and other entities..., consistent with obtaining regulatory objectives, taking into account...the costs of cumulative regulations."[43] The Regulatory Flexibility Act also requires agencies to analyze regulatory options that would "minimize any significant impact of a rule on small entities."[44]

In the preamble of the proposed rule, FDA states that the restrictions on the sale, distribution, and use of sunlamp products "would have a *significant* impact on a *substantial number* of small entities chiefly due to the loss of revenue."[45] The Agency recognizes that most,

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[41] 80 Fed. Reg. at 79495.

[42] *Id*.

[43] Exec. Order No. 12866, 58 Fed. Reg. 51735 (Oct. 4, 1993).

[44] 80 Fed. Reg. at 79498.

[45] *Id*. at 79499 (emphasis added).

if not all, indoor tanning operators are small entities[46], but FDA simply states that the impacts on such small entities are "uncertain."[47]

In its more detailed economic analysis submitted to the docket for the proposed rule, the Agency attempts to quantify the uncertainty: "We estimate the loss in revenue from indoor tanning services to range from 15 to 23 percent, the majority of that, almost 70 percent, from the age restriction .... Using the estimate of $278,000 for the average revenue per salon, the loss in sales would range from about $42,000 to $64,000."[48]

We believe that FDA's economic analysis fails to truly comprehend the impact the proposed rule would have on small entities. Losing 15 to 23 percent of revenue--or 70% of these amounts--would affect the bottom line of indoor tanning operators more severely than it would other typical small businesses, and even typical small businesses could not survive a revenue loss of this magnitude. With a service-based industry such as the indoor tanning industry, the "costs of doing business" cannot be reduced in the same manner as would be the case in other retail operations. For example, indoor tanning operators' fixed costs--such as payroll, business loans, rent, insurance, utilities, equipment leases--do not decrease as customers decline. In practical terms for indoor tanning operators, this means 100% of decreased sales comes out of profit. Thus, we estimate that a loss in revenue from indoor tanning services in the range of 10 to 16 percent (70% of 15-23%) would actually turn profits into losses for most tanning salons and put them out of business.

As FDA recognizes, the vast majority of indoor tanning operators are small entities. Therefore, this proposed rule would decimate the indoor tanning industry. Before FDA acts to issue a final rule restricting the sale, distribution, or use of sunlamp products, the Agency should provide a new economic analysis that fully recognizes the impact of the rule on profit reduction for small entities. The economic impact of this proposed rule is anything but "uncertain"--it is devastating and could effectively end the indoor tanning industry.

VIII. Sunlamp Products Are Not Subject to Regulation as "Devices" under the FDCA.

ITA and ASA continue to question FDA's classification of sunlamp products for tanning purposes as medical devices.[49] The electronic product controls of the FDCA apply to both device and non-device products, and those controls and the performance standard applicable to UV lamps and indoor tanning equipment effectively address the potential risks associated with the use of sunlamp products. ITA and ASA believe that FDA's continuing imposition of medical device requirements on sunlamp products for tanning, and now the Agency's proposed restrictions on sale, distribution, and use of sunlamp products, exceed FDA's statutory authority.

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[46] FDA, "Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, Unfunded Mandates Reform Act Analysis" at 47, Docket No. FDA-2015-N-1765 (Dec. 2015).

[47] 80 Fed. Reg. at 79498.

[48] FDA, "Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, Unfunded Mandates Reform Act Analysis," *supra* note 46 at 47.

[49] ITA and ASA submitted detailed comments on this issue to Docket No. FDA-2013-N-0461, the regulatory proceeding which resulted in FDA's administrative order and current 21 C.F.R. § 878.4635.

A. Sunlamp Products are Not Medical Devices.

Although FDA has classified sunlamp products as Class II (special controls) medical devices, its authority to do so is questionable.

Under section 201(h) of the FDCA, a "device" is defined as an article "*intended* for use": (1) to cure, mitigate, or treat disease, or (2) to affect the structure or a function of the body.[50]

FDA defines "intended use" as "the objective intent of the persons legally responsible for the labeling" of the product.[51] Objective intent is determined by the manufacturer's "expressions or may be shown by the circumstances surrounding the distribution of the article."[52] In other words, "[t]he use to which the product is to be put will determine the category into which it will fall .... The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put."[53]

As FDA has acknowledged, virtually all products can affect the structure or function of the body in some way.[54] A product may be regulated as a device, however, only if it is intended (represented) to affect the body in "some medical or drug-type fashion."[55] As FDA has acknowledged, courts "have always read the * * * statutory definitions employing the term 'intended' to refer to specific marketing representations."[56] Sunlamp products generally are not *represented* to affect the structure or function of the body. Rather they are "intended" and represented for tanning purposes, and tanning alters the appearance.

The history of FDA's classification of UV lamps supports the conclusion that sunlamp products are not medical devices. FDA originally proposed in 1982 to classify "dermatologic ultraviolet lamps" as Class II medical devices, including both UV lamps for dermatologic disorders and UV lamps for tanning under the same proposed regulation.[57] When FDA issued the final classification rule in 1988, however, FDA postponed classifying UV lamps for tanning, although it classified UV lamps used for dermatological purposes into Class II.[58] In separating out UV lamps for tanning from UV lamps used for dermatological purposes, FDA highlighted the differences in intended use and the attendant differences in risks between the

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[50] FDCA § 201(h)(2) & (3) (emphasis added).

[51] 21 C.F.R. § 801.4.

[52] *Id*.

[53] S. Rep. No. 74-361, at 4 (1935).

[54] Letter from Daniel E. Troy, Chief Counsel, FDA, to Jeffrey N. Gibbs, Hyman, Phelps, & McNamara, at 3 (Oct. 17, 2002).

[55] *United States v. An Article . . . Sudden Change*, 409 F.2d 734, 742 (2d Cir. 1969) (internal quotation marks omitted).

[56] 68 Fed. Reg. 16520, 16521 n.2 (Apr. 4, 2003) (alteration in original) (internal quotation marks omitted).

[57] 47 Fed. Reg. 2810, 2835, & 2852 (Jan. 19, 1982).

[58] 21 C.F.R. § 878.4630.

two products.[59] With regard to UV lamps for tanning, FDA stated that the performance standard in 21 C.F.R. § 1020.40 "covers the risks to health presented by [the UV lamps for tanning] other than electrical safety hazards."[60]

B. Sunlamp Products Should Be Regulated Only Under the Electronic Product Standards Provisions of the FDCA.

The electronic product standards provisions of the FDCA apply to both device and non-device products. Sunlamp products are comprehensively regulated as electronic products under those statutory provisions and corresponding regulations.

Under the electronic product controls, manufacturers of sunlamp products must submit an initial product report prior to introducing a product into interstate commerce.[61] These reports must include a description of the function, intended and known uses, operational characteristics affecting radiation emissions, and design specifications pertaining to radiation safety (which could include reference to a federal standard). The reports include information on testing methods and quality control procedures, and the results of testing. They also include labels, warning labels, and instructions for installation, operation and use that relate to electronic product radiation safety. [62] Changes to sunlamp products are submitted in supplemental reports.[63]

Manufacturers of sunlamp products must submit annual reports and reports of accidental radiation occurrences.[64] They must maintain records relating to quality control procedures, test results for electronic product radiation safety, complaints, and distribution information.[65] Dealers and distributors of sunlamp products are also subject to recordkeeping requirements.[66] FDA has facility and records inspection authority under the electronic product provisions of the FDCA.[67]

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[59] 53 Fed. Reg. 23856, 23868 (Jun. 24, 1988). In 1990, FDA issued a final rule classifying UV lamps for tanning as Class I devices. *See* 21 C.F.R. § 878.4635.

[60] 53 Fed. Reg. at 23868. In 1994, FDA exempted UV lamps from 510(k) premarket notification requirements, on the ground that such submissions "are unnecessary for the protection of the public health." *See* 59 Fed. Reg. 63005, 63010 (Dec. 7, 1994). The FDA Modernization Act of 1997 ("FDAMA") included a statutory exemption from 510(k) notification requirements for all Class I devices, unless the device is intended for a use that is of substantial importance in preventing impairment of health or "presents a potential unreasonable risk of illness or injury." After FDAMA, FDA confirmed the Class I, 510(k)-exempt status of UV lamps for tanning in 2001. *See* 66 Fed. Reg. 38786, 38803 (July 25, 2001).

[61] 21 C.F.R. § 1002.1(b).

[62] *Id*. at § 1002.10.

[63] *Id*. at § 1002.11.

[64] *Id*. at §§ 1002.13 & 1002.20.

[65] *Id*. at § 1002.30.

[66] *Id*. at § 1002.40.

[67] FDCA § 537.

In addition to all of the above general controls, sunlamp products and UV lamps intended for use in them are subject to the performance standard promulgated at 21 C.F.R. § 1040.20. This performance standard imposes performance requirements, labeling specifications, and user instruction requirements that provide additional assurance of safety in light of the sunlamp product's intended use.

Under the performance requirements in 21 C.F.R. § 1040.20(d), a manufacturer must provide an exposure schedule in the product label.[68] Further, sunlamp products must comply with specified irradiance ratios, incorporate the use of a timer system with multiple settings adequate to implement the recommended exposure limits specified in the product labeling,[69] incorporate a control to manually terminate radiation emission,[70] include protective eyewear,[71] and meet UV lamp compatibility requirements.[72]

FDA's regulation at 21 C.F.R. § 1040.20(d) specifies both the format and content of the required labeling. In particular, sunlamp products must include specific warnings regarding potential risks, including the risk of skin cancer, that may be caused by exposure to UV radiation. The labeling must also specify the following: recommended exposure positions; a recommended exposure schedule, including duration and spacing of sequential exposures; maximum exposure limits; and a statement of the time it may take to achieve the expected results.[73] Instructions must be provided to detail the proper use of the product, as well as "instructions for determining the correct exposure time and schedule for persons according to skin type."[74]

Manufacturers of sunlamp products must certify their compliance with all applicable standards in accordance FDA's regulations at 21 C.F.R. § 1010.2. The tests upon which the certification is based must be made under the operational conditions, voltage, current, and position recommended by the manufacturer and must account for all errors and statistical uncertainties in the process.[75]

The FDCA's electronic product provisions and corresponding regulations provide adequate authority for regulating UV lamps and sunlamp products intended for tanning purposes. These controls provide adequate assurance of safety and effectiveness under the intended conditions of use of sunlamp products.

Congress established the electronic product standards provisions of the FDCA to apply to non-device products. Those statutory and regulatory provisions are the appropriate ones to apply to UV lamps and sunlamp products intended for tanning purposes. FDA has

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[68] 21 C.F.R. § 1040.20(d)(1)(iv).

[69] *Id*. at § 1040.20(c)(1)-(2).

[70] *Id*. at § 1040.20(c)(3).

[71] *Id*. at § 1040.20(c)(4).

[72] *Id*. at § 1040.20(c)(5).

[73] *Id*. at § 1040.20(d). The UV lamps themselves are subject to separate labeling requirements.

[74] *Id*. at § 1040.20(e).

[75] *Id*. at § 1040.20(f).

exceeded its statutory authority in applying the medical device provisions of the FDCA to sunlamp products intended for tanning purposes. Sunlamp products for tanning purposes should be regulated only under the electronic product standards provisions of the FDCA, which provide comprehensive regulatory controls that provide reasonable assurance of the safety and effectiveness of these products.

IX. Conclusion

In sum, FDA must reassess the proposed rule. ITA and ASA believe that FDA should abandon its plan to impose restrictions on sale, distribution, or use of sunlamp products on the ground that the Agency has not satisfied the statutory criteria under section 520(e). If FDA determines to proceed to a final rule nonetheless, FDA must allow a parental waiver for use by individuals under the age of 18, should eliminate the risk acknowledgement certification, and should undertake a new economic impact analysis prior to issuing a final rule to assure that the least burdensome regulations are imposed and the impact on the tanning industry is reasonable.

EXHIBIT A

ITA and ASA Membership Lists

ITA Membership

A Cut Above
All Hours Distribution
Aloha Tan
Aloha Tan, Inc.
Audio Video Media
Bare Necessities Tanning Salon & Day Spa
Belle Fiole Tanning & Spa
Bloom Again European Tanning
Bloom Again Tanning & Vacation/Resort Wear
Bodicare Cosmetics
Body By Design
Body Heat Tanning
BodyBing Tanning
California Tan
Carolina Tan Factory
Club Tan
Coconut Tan
Dreamland Tanning
EJ's Tanning Salon
Electric Sun
Electric Sun Equipment And Supplies
Express Tan, Inc.
Eye Pro, Inc.
Flip Flop Cove Tanning, LLC
Full Throttle Salon
Glo Sun Spa
GoldenSun Tan
Great Tan - Castro
Great Tan - Union
Hawaiian TanFastic
Heartland Tanning Supply
House of Tans
Infusion Tanning
Instatan
Insurtec, Inc
Intelladon
Interlectric Corp
Island Sun Times, Inc.
Island Tanz
Island Tropics Tanning Salon
J. Wagner GmbH
Jill's Beach
Key West Tan
Kool Tan
Light Sources Inc
Lion in the Sun
Malibu Tan, Inc.
Max Tan

Mega Tan
MR International, LLC
Nails by Becky
New Sunshine, Australian Gold, ETS, Helios, Design
Nichesoft, LLC
No Sand Tan Ohio
Oasis Tans
On Track Tanning
Plumeria Spa LLC
Portofino Spas LLC
Power Group Company
Premier Tanning
Private Islands Tanning Salon LLC
ProSun International
R&R Insurance Services
Salon Owner / Taxpayer / Citizen
Shine On Tanning, LLC
Signatures Salon & Day Spa
SOLAR ESCAPE TANNING
Solar Tan
Solartech Inc.
Soleil Tan Spas
Sperti Sunlamp
Suds
Sun City Salon Inc.
Sun Connection
Sun Dial Tanning
Sun Factory Tanning Inc.
Sun Spot Atlantis
Sun Spot Tanning
Sun Spot Tanning Salon
Sun-Kissed Tanning Salon
SunRayz Tannery & Salon
Suns of Intanity, Inc.
Sunsational Tan (PA)
SunSations Tanning Salon, LLC
Suntan Seekers
Suntan Supply
Superior UV Technologies
Supra Brands Group
Supre Inc.
Tahiti Tan
Tan Incorporated
Tan 'N Tone
Tan Seekers
Tan This Inc
Tan Zone
Tanlines Salon LLC
Tanning Bed Inc.
Tanning Oasis
Tanning Salon

Tanning World Of Lewisburg
Tanorama Inc.
Tanpro
The Bronzing Station
The Daniel and Henry Company
The Sun Club
The Sunshine Factory
The Tanning Studio
Time Out
TNG Worldwide
T-N-T Tanning Salon
Tropical Sunsations
Twilight Teeth, Inc.
Ultraviolet Resources Int'l
Verve Tanning
WayTooTan, Inc.
Xclusive Tan
Year Round Brown

ASA Membership

Palm Beach Tan
Sun Tan City
Celsius Franchising
Larry Paul Tanning Spa
Club Tan
Portofino Sun Center
Tan 'N Tone
Body Perfect Tanning Salon
iTan Franchising
Tanning Oasis
Four Seasons Tanning Salon
Beaches Salon
Beach Bum Tanning
Tommy's Tanning, Inc.
Bodies in Heat
Classic Tan
Laundry & Tan Connection
Zoom Tan LLC
Sol Spa Tan
Celebrity Tanning
Solar Dimensions
Sun Seekers By Rosie
Total Tan
South Beach Tans
Beach Body Tanning

EXHIBIT B

STATEMENT OF THE SCIENCE:
SUNLAMP PRODUCTS AND SKIN CANCER

Re: Docket No. FDA-2015-N-1765
Proposed Rule for the Restricted Sale, Distribution, and Use of Sunlamp Products

Submitted by: Indoor Tanning Association
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PO Box 1907
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Date: March 21, 2016

I. Introduction

In 2010, the U.S. Food and Drug Administration (FDA) convened an Advisory Panel Meeting to consider certain scientific information about UV radiation and tanning. That was six years ago. Since that time, there have been two significant new studies that have changed the understanding of the risks related to the use of sunlamp products by persons under the age of 18 [Refs. 1, 2]. Lazovich et al. 2010 [Ref. 1], published after the March 2010 Advisory Panel Meeting, found that younger individuals are not at increased susceptibility to the effects of UV radiation. Colantonio et al. 2014 [Ref. 2] found that there is no statistically significant increased risk of melanoma for use of indoor tanning by persons under age 25 compared to persons age 25 and older, thereby removing any scientific basis for FDA's proposal to ban under-18 indoor tanning. *See* "III. History of Under-18 Science" below.

In this document, we discuss the current science concerning UV radiation and indoor tanning and refute FDA's numerous incorrect statements of science in the preamble to the proposed rule.

II. The Current State of Science

A. Overview

There are known health benefits of sun exposure, but overexposure can increase the risk of skin cancer. With respect to melanoma, the relationship with UV radiation is not straightforward. Sunburns have been associated with a doubling of risk, while chronic sun exposure has been associated with reduced risk [Ref. 3]. For example, research shows melanoma cases are less frequent in outdoor workers than indoor workers [Ref. 4]. Squamous cell carcinoma (SCC) risk is also doubled by sunburns [Ref. 5] but, unlike melanoma, chronic sun exposure of very high lifetime amounts has been associated with increased risk of SCC [Ref. 6].

Lamps in indoor tanning equipment replicate sun-based UV radiation. FDA's current exposure guidelines as set forth in the 1986 policy letter entitled, "Policy on Maximum Timer Interval and Exposure Schedule for Sunlamp Products," are designed to prevent burning. We are not aware of any evidence that a person who has followed FDA's guidelines has been burned. However, consumers who use sunlamp products at home in an unregulated setting may or may not follow the exposure schedule or even limit themselves to the maximum timer interval. Approximately 25% of indoor tanning occurs at home or in other unregulated settings [Ref. 7]. Studies that have segregated data from home use and tanning salon use have found little risk of melanoma from tanning salons and high risk of melanoma from home use [Refs. 8-10]. Overall, the most recent and most comprehensive meta-analysis [Ref. 2] found a combined risk of melanoma from home use and tanning salon use of 16%, with most of the risk coming from home use.

The purpose of indoor tanning is to receive a tan. A good tan provides significant protection against subsequent sunburn. The protection is provided by increased pigmentation and thickening of the epidermis. It is common knowledge that a tanned person is much less likely to get burned outdoors than a non-tanned person. Scientific studies show that a moderate dose of UV, such as that received from a tanning bed operated in accordance with current FDA

guidelines, produces a moderate tan with an SPF of 3 or 4 [Ref. 11]. This means it takes three to four times as much sun exposure to burn a person with a tan as it does a person without a tan.

By providing a tan, indoor tanning in a commercial tanning salon reduces the risk of sunburn, and studies show that sunburn is associated with a 100% increased risk of melanoma [Ref. 3]. Encouraging persons to obtain their desired tan by using a sunlamp product in a tanning salon rather than at home can also reduce risks from overexposure to UV radiation. The advent of tanning salons in the early 1980's may even be partially responsible for the slight flattening since 2005 in the increase in melanoma incidence, which has been climbing since 1935. *See* Attachment A. Cumulative, lifetime, nonburning UV exposure has been associated with SCC, but the limited studies on the subject indicate that SCC is associated with 20,000 to 50,000 lifetime hours of sun exposure [Ref. 6]. Indoor tanning theoretically adds some amount to the risk of SCC, but with 30 annual sessions and each session being equivalent to approximately 20 minutes of sun exposure, the total lifetime UV exposure from indoor tanning of 150 hours (10 hours per year for 15 years of indoor tanning) is insignificant in comparison with the 20,000 hours associated with the threshold for SCC risk [Ref. 6].[1]

B. Under 18-Ban

FDA's proposal to ban under-18 indoor tanning is based on its stated view that "individuals who begin indoor tanning at ages younger than 18 years are particularly vulnerable to the carcinogenic impact of indoor tanning" [80 Fed. Reg. 79493, 79495 (Dec. 22, 2015)]. This stated view of FDA is incorrect, as shown by Lazovich et al. 2010 [Ref. 1], which found that

[1] Tierney et al. 2015 [Ref. 33] calculated, using a theoretical equation, that a median amount of indoor UV exposure (176 SED/year) for 15 years would increase the risk of SCC for a person age 55 in the Netherlands by 90%. Close examination of Tierney et al. 2015, however, reveals that the same equation shows that incidence of SCC for a person age 55 in the Netherlands is 0.004 per 100,000 as compared to 25 per 100,000 for the Dutch population as a whole, so the increased risk of SCC at age 55 resulting from 15 years of indoor UV exposure is insignificant.

younger individuals are not at increased susceptibility to the effects of UV radiation, and Colantonio et al. 2014 [Ref. 2], which found that there is no statistically significant increased risk of melanoma for use of indoor tanning by persons under age 25 compared to persons age 25 and older. There is no scientific basis for FDA's proposed ban on under-18 indoor tanning.

Burns are equally harmful at all ages, and there is currently an alarmingly-high prevalence of outdoor sunburns in the United States. According to the Centers for Disease Control and Prevention (CDC), the prevalence of sunburns in the United States increased from 32% of all adults in 1999 to 34% in 2004 [Ref. 12] and up to 50% in 2012 [Ref. 13]. Among adolescents aged 12-18 in 1999, 83% reported at least one sunburn in the previous summer, and 36% reported three or more sunburns in the previous summer [Ref. 14]. By providing a tan without burning, commercial indoor tanning salons could help to protect customers from sunburns outdoors. This is especially important for persons under age 18.

Dr. David Hoel, an epidemiologist and member of the Institute of Medicine of the National Academy of Science, has concluded that an under-18 ban may possibly cause additional health problems by leading to an increase in underage tanning at home. *See* Attachment D. Currently, approximately 25% of indoor tanning occurs at home or in other unregulated environments [Ref. 7]. Burning, and thus the risk of melanoma, is far more common at home with self-operation than in a tanning salon with a trained operator. Home users often do not know when to stop. Studies that have separated data from home use and tanning salon use have found little risk of melanoma from tanning salons and high risk from home use [Refs. 8, 9, 10]. The Chen et al. 1998 study [Ref. 8] used in the Colantonio et al. 2014 [Ref. 2] meta analyses found among those first tanning under age 25 that there was a statistically significant melanoma increase in those using sunlamps at home with a odds ratio of 1.79, while for those using commercial tanning had a non-significant odds ratio of 0.63.

III. History of Under-18 Science

The movement to restrict under-18 tanning began with the now-discredited 2006 IARC Report [Ref. 18]. The principal authors of the Report were Peter Boyle, Mathieu Boniol, Philippe Autier, and Sara Gandini. The Report stated: "Epidemiologic studies to date give no consistent evidence that use of indoor tanning facilities in general is associated with the development of melanoma or skin cancer. However, there was a prominent and consistent increase in risk for melanoma in people who first used indoor tanning facilities in their twenties or teen years" [Ref. 32]. The Report concluded: "Based upon 19 informative studies, ever-use of sunbeds was positively associated with melanoma (summary relative risk, 1.15; 95% CI, 1.00-1.31), although there was no consistent evidence of a dose-response relationship. First exposure to sunbeds before 35 years of age significantly increased the risk of melanoma, based on 7 informative studies (summary relative risk, 1.75; 95% CI, 1.35-2.26)]" [Ref. 18]. "Sunbeds" was defined to mean artificial UV devices whether used at home, in beauty salons, in gymnasiums, or in commercial indoor tanning salons. FDA, the CDC, and the media believed that this finding stood for the proposition that use of indoor tanning salons by persons under age 35 increases their risk of melanoma by 75%.

Subsequently, the IARC Report was shown to be flawed. *See* Attachments C and E, Lazovich et al 2010 [Ref. 1], and Colantonio et al. 2014 [Ref. 2]. The CDC eventually removed the Report from its website. However, the Report continued to be quoted by various groups of dermatologists and FDA officials, and it was the basis for enacting the 10% excise tax on indoor tanning salons, which was substituted for the 10% tax on Botox treatments by dermatologists under the Affordable Care Act in 2010. It was also the basis for the lobbying campaign of the American Academy of Dermatology (AAD) to convince various states to ban use of commercial indoor tanning salons by persons under 18.

Lazovich et al. 2010 [Ref. 1] refuted this finding of the IARC Report: "We did not confirm the IARC report's emphasis on an increased risk of melanoma with first exposure to indoor tanning 'in youth', defined as use before the age of 36….Our study was designed to specifically evaluate indoor tanning use initiated at any age. And by simultaneously accounting for duration of use among indoor tanners, our analysis indicates that early age exposure is most likely a marker for cumulative exposure, the reason for an excess risk of melanoma, *not that younger individuals are at increased susceptibility to the effects of UV radiation*" (emphasis added) [Ref. 1]. FDA, the CDC, the media, nor AAD paid any attention to this finding by Lazovich et al. 2010.

In 2009, Boyle, Boniol, and Autier left IARC and started a private company named the International Prevention and Research Institute (IPRI) in Lyon, France. In 2012, Boyle, Boniol, Autier, and Sara Gandini issued a new study stating that the increased risk of melanoma as a result of indoor tanning before age 35 was actually 87% rather than the 75% documented in the IARC Report [Ref. 25]. This study updated the IARC Report to include new studies since 2006 but repeated the IARC Report's flawed analyses. When confronted with one of the incorrect analyses in the study, the authors issued a correction on December 13, 2012 lowering the 87% to 59% but they failed to correct other fatal errors. The CDC subsequently amended its website to eliminate references to the 87% and the 59%.

On March 12, 2013, Dr. Jeffrey Gershenwald of the MD Anderson Cancer Center testified to the Texas Senate on March 12, 2013: "In fact each session in a tanning bed has been estimated to be associated with a 1.8% increased risk. And if people used tanning beds before the age of 35 the risk has been estimated to be almost double by 87%." *See* Attachment F. The Texas Senate relied on this incorrect testimony in passing a ban on under-18 indoor tanning. Dr. Gershenwald failed to mention Lazovich et al. 2010 [Ref. 1], which concluded that younger individuals are not at increased susceptibility to UV radiation from sunbeds. Similar legislation

has been adopted in other states based on comparable testimony by various dermatologists selected by the AADA, the AAD's lobbying arm.

Boniol et al. 2012 [Ref. 25] was superseded and discredited by the Colantonio et al. 2014 [Ref. 2] comprehensive meta-analysis of all prior studies on age at first use of indoor tanning and melanoma. Colantonio et al. 2014 found that there is no statistically significant increased risk of melanoma for use of indoor tanning by persons under age 25 compared to persons age 25 and older, thus removing the last piece of evidence supporting a ban on under-18 indoor tanning. Colantonio et al. 2014 [Ref. 2] and Lazovich et al. 2010 [Ref. 1] represent the current state of the science on the issue of under-18 indoor tanning**.**

Colantonio et al. 2014 was a meta analysis (weighted average of odds ratios) of seven studies which considered separately the risk of melanoma for those first beginning tanning under the age of 25 years with those that began after age 25. The weighted average of the seven odds ratio for melanoma for those under age 25 years was 1.35 with a 95% confidence interval of 0.99 to 1.84. Since the value of 1.0 for the odds ratio was included within the confidence interval, the estimated average of 1.35 is not considered to be statistically different from 1.0. One of the studies in the group of seven (Chen et al. 1998 [Ref. 8]) separated those first exposed before 1970 from those first exposed after 1970. Since the older pre-1970 sunbeds and lamps used a different UVR frequency, it would be more appropriate to use the post-1970 data in the Chen study in the meta analysis. Doing this reduces the meta analysis estimated odds ratio to 1.18 with a confidence interval of 0.80 to 1.74. This is no different than the corresponding estimate for those who first began tanning after the age of 25 of 1.16 with a confidence interval of 0.90 to 1.49. Neither estimate is statistically significant.

IV. Critique of FDA's Statements of the Science

FDA's misstatements of the current state of science in the preamble to the proposed rule are numerous. We address these misstatements in the order in which they appear.

(a) Statement: "In fact, people who have been exposed to radiation from indoor tanning are 59% more likely to develop melanoma than those who have never tanned indoors, according to the American Academy of Dermatology" [FDA, "FDA Proposes New Safety Measures for Indoor Tanning Devices: The Facts" (Dec. 22, 2015), *available at* http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm350790.htm]. Explanation: This statement is incorrect. It is apparently based on the discredited and outdated Boniol et al. 2012 study [Ref. 25]. It is noted that the CDC removed a similar statement from its website after it was challenged by the American Suntanning Association as being incorrect.

(b) Statement: "Skin cancers that have been associated with cumulative repeated UV radiation include melanoma and nonmelanoma skin cancers such as basal cell carcinoma and squamous cell carcinoma" [80 Fed. Reg. at 79495]. Explanation: This statement is incorrect. Melanoma is not associated with cumulative, repeated UV radiation. The opposite is true. Chronic, cumulative, repeated UV radiation is associated with a reduced risk of melanoma [Ref. 3]. For example, it has been shown that the incidence of melanoma is lower for outdoor workers than for indoor workers [Ref. 4]. Some studies have shown SCC to be associated with cumulative lifetime sun exposure of 20,000 hours or more [Ref. 6], but no association between cumulative, repeated UV radiation and basal cell carcinoma has been established.

(c) Statement: "[I]ndividuals who begin indoor tanning at ages younger than 18 years are particularly vulnerable to carcinogenic impact of indoor tanning" [80 Fed. Reg. at 79495]. Explanation: This statement, which is the basis for FDA's proposal to ban under-18 tanning, is based on incorrect analyses. Notably, FDA fails to acknowledge that Lazovich et al. 2010 [Ref.1], the only study specifically designed to determine the risk of indoor tanning for younger persons,

concluded the exact opposite: "We did not confirm the IARC report's emphasis on an increased risk of melanoma with first exposure to indoor tanning 'in youth', defined as use before the age of 36….Our study was designed to specifically evaluate indoor tanning use initiated at any age. And by simultaneously accounting for duration of use among indoor tanners, our analysis indicates that early age exposure is most likely a marker for cumulative exposure, the reason for an excess risk of melanoma, not that younger individuals are at increased susceptibility to the effects of UV radiation" [Ref. 1]. Also, FDA fails to acknowledge that Colantonio et al. 2014 [Ref. 2] found that there is no statistically significant increased risk of melanoma for use of indoor tanning by persons under age 25 compared to persons age 25 and older.

(d) Statement: FDA references two studies (FDA Refs. 10 and 11: Stapleton et al. 2013 and Cokkinides et al. 2009), which found a high level of burning in "indoor tanning" [80 Fed. Reg. at 79495]. Explanation: Stapleton et al. 2013 [Ref. 15] was conducted in two states that do not have laws requiring trained operators in tanning salons. Customer-operated tanning equipment is likely to result in burns. Also, Stapleton et al. 2013 did not differentiate "indoor tanning" in tanning salons and "indoor tanning" with sunlamps and sunbeds in dormitories. Finally, Stapleton et al. 2013 documented reports of "red skin" as being erythema, when it may have been vasodilation caused by heat from the sunlamps. Cokkinides et al. 2009 [Ref. 16] also did not differentiate home tanning from salon tanning and also may have erroneously classified all reports of "getting red" as erythema.

Burning must be avoided in indoor tanning, as well as in outdoor tanning. By condemning all intentional UV radiation whether burning or nonburning, FDA and the CDC dilute the important message of avoiding UV burns. FDA and the CDC should focus on reducing the alarmingly-high incidence of sunburns in the United States as well as reducing the incidence of UV burns in "indoor tanning," primarily by warning the public about the dangers of burns in use of indoor tanning equipment at home and in other unregulated settings.

(e) Statement: "On a cellular level, UV radiation has been known to cause DNA damage" [80 Fed. Reg. at 79496]. Explanation: While this statement is true, it fails to highlight that the human body has DNA-repair mechanisms and other types of mechanisms to protect the body from UV radiation. Additionally, UV radiation is essential for good human health. *See* Attachment B.

(f) Statement: "Although the risks associated with sunlamp products are applicable to all persons, FDA is proposing to restrict the use of this device to persons age 18 and older because children and adolescents who are exposed to UV radiation may be at higher risk of developing certain types of skin cancer than persons who begin exposure later in life as adults (FDA Ref 18 – Autier and Boyle 2008)" [80 Fed. Reg. at 79496]. Explanation: This statement is incorrect. Autier and Boyle 2008 [Ref. 17] is an article by two of the principal authors of the 2006 IARC Report [Ref. 18] repeating the conclusions and errors of the IARC Report. As explained above in "Section III. History of Under-18 Science," the IARC Report is flawed.

(g) Statement: "Published medical evidence demonstrates that there is a direct correlation between sunlamp product use among youths and their developing melanoma skin cancer, as well as other skin cancers (FDA Refs. 25, 26 – Cust et al. 2011 and Balk et al. 2013)" [80 Fed. Reg. at 79496]. Explanation: While it is technically true that there is a correlation between sunlamp product use among youths and their developing melanoma skin cancer, as well as other skin cancers, the same can be said about adults. There is no special risk for persons under 18. Also, the same can be said with respect to sun exposure; there is a direct correlation between sun exposure among youths and their developing melanoma skin cancer, as well as other skin cancers. There is always a risk of burning associated UV exposure, and UV burns have been correlated to melanoma and other skin cancers. With respect to "indoor tanning," studies have shown that most of the risk of melanoma occurs in home tanning, not in commercial tanning salons [Refs. 8-10].

Cust et al. 2011 [Ref. 19] is an Australian study concerning "early-onset" melanoma (diagnosed at ages 18-39) that found: (1) a 41% increased risk of "early-onset" melanoma for ever-use of sunbeds; (2) a 64% increased risk if use began before age 25; and (3) an 88% increased risk if used started before age 20. The study, however, concluded that "after mutual adjustment, the association of earlier age at first use of sunbeds with melanoma was attenuated by about 50%" [Ref. 19]. The failure of this study to include sunburn data in its final models is problematic, since sunburns are the only widely-acknowledged environmental risk factor for melanoma. Notably, Cust et al. 2011 collected data on place of use (home, commercial tanning salon, etc.) but did not present these data in its report. Since Australia had very few commercial tanning salons at the time of this study, this failure to separate home use from commercial tanning salon use renders Cust et al. 2011 unhelpful with respect to the risk of melanoma associated with commercial tanning salons. The authors noted that "a recent study (Lazovich et al 2010 [Ref. 1]) suggested that early age at first use of a sunbed is most likely a marker for cumulative sun exposure, and not an indication of increased susceptibility for younger people" [Ref. 19]. Cust et al. 2011 was taken into consideration in the Colantonio et al. 2014 [Ref. 2] meta-analysis which, as noted above, found no statistically significant increased risk of melanoma for use of indoor tanning by persons under age 25 compared to persons age 25 and older.

Balk et al. 2013 [Ref. 20] is an article (not a study) written by a pediatrician, a dermatologist, and a public health professional, all of whom are well qualified in their fields but are not epidemiological scientists. Their article expresses the widely held, but incorrect, view among dermatologists that all UV exposure is harmful. Neither Cust et al. 2011 nor Balk et al. 2013 provides support for FDA's stated view that persons under age 18 are particularly vulnerable to carcinogenic impact of indoor tanning.

(h) Statement: "Melanoma is a leading cause of cancer death in women ages 15 to 29 years old and there is some evidence that suggests use of sunlamp products is an underlying cause [FDA Refs. 27, 28 – Diffey et al. 2007 and Herzog et al. 2007]" [80 Fed. Reg. at 79496]. Explanation: This statement is incorrect. Melanoma is not a leading cause of cancer death in women ages 15 to 29. Diffey et al. 2007 [Ref. 21] is an editorial endorsing the flawed 2006 IARC Report [Ref. 18]. Herzog et al. 2007 [Ref. 22] is a National Cancer Institute publication on cancer incidence and mortality for adolescents and young adults. It notes that from 1975 to 2000, melanoma was the third most common type of cancer in women ages 15 to 29; but it also notes that melanoma for women ages 15-19 is highly curable, with a five-year survival rate exceeding 95%. Herzog et al. 2007 does not present any data supporting FDA's flawed statement that melanoma is a leading cause of cancer death in women ages 15 to 29. Data from Cancer Research UK show that cancer deaths in women ages 15-24 in the United Kingdom between 2010 and 2013 totaled 124 and that melanoma was not one of the five leading causes. [Cancer Research UK, "Most common causes of cancer deaths by age in females," *available at* http://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/age]. National Cancer Institute SEER data show the same result.

(i) Statement: "There is increasing epidemiological evidence that shows that tanning at ages younger than 18 years increases the risk of developing melanoma (FDA Refs.25, 29 to 32 – Cust et al. 2011, Reed et al. 2012, Boniol et al. 2012, Colantonio et al. 2014, Wehner et al. 2012)" [80 Fed. Reg. at 79496]. Explanation: This statement incorrect. There is increasing epidemiological evidence that demonstrates that tanning at ages younger than 18 years compared to tanning at ages 18 years and older carries no particular risk for melanoma [Refs. 1,2]. That is not to say "indoor tanning" is without risk. As noted above, studies have correlated "indoor tanning" to a 16% increased risk of melanoma for people of all ages, but "indoor tanning" as used in such studies includes home and other unregulated indoor tanning as well as

tanning salon indoor tanning. Home and other unregulated indoor tanning has been correlated with most or all of this 16% risk [Refs. 8-10].

Reed et al. 2002 [Ref. 23] is a Mayo Clinic study of the incidence of melanoma in one county in southeastern Minnesota from 1970 to 2009. It found that the incidence of melanoma in this county is approximately twice the national average and that the increase from 1970 to 2009 is 50% higher than the national average. This study had no data on indoor tanning.

Wehner et al. 2012 [Ref. 24] was a study of non-melanoma skin cancer, not melanoma. Boniol et al. 2012 [Ref. 25] is discussed in Section III above; Colantonio et al. 2014 [Ref. 2] is discussed in Sections I, II and III above; and Cust et al. 2011 [Ref. 19] is discussed in Section IV(g) above.

(j) Statement: "A 2009 IARC report linked UV exposure (including from indoor tanning devices) by individuals under age 35 to higher rates of melanoma as compared to a similar cohort of individuals who had not used sunlamp products, and recommended that minors not use sunlamp products" [80 Fed. Reg. at 79496]. Explanation: This statement is incorrect; the IARC report referred to is the 2006 IARC Report [Ref. 18], not a 2009 IARC report. In 2009, IARC convened 20 scientists from nine countries to review the carcinogenicity of all forms of radiation, including UV radiation. This group reaffirmed the classification of the sun as "carcinogenic to humans" (Group 1) and classified UV-emitting tanning devices in the same category (Group 1). "Carcinogenic," as used by this group of scientists, means capable of causing cancer. These scientists' actions were correct. IARC, however, made it appear that these scientists were also the authors of the statement "the risk of cutaneous melanoma is increased by 75% when the use of tanning devices starts before age 30," which they were not. Dr. David G. Hoel, one of these scientists, affirmed that they made no such finding. This finding was made by

a completely different working group in a report published in 2006 referred to above as the 2006 IARC Report.

(k) Statement: "Similarly, a meta-analysis by Gallagher et al. that evaluated metrics of sunlamp product exposure, including in young adults, indicated a significantly increased risk of cutaneous melanoma subsequent to sunlamp product exposure" [80 Fed. Reg. at 79496]. Explanation: This meta-analysis [Ref. 26] has been superseded by Colantonio et al. 2014 [Ref. 2].

(l) Statement: "Further, a case control study in Connecticut found a relative risk of 1.4 for melanoma diagnosis when individuals are exposed to sunlamp products before the age of 25 (FDA Ref. 35 - Chen et al. 1998)" [80 Fed. Reg. at 79496]. Explanation: This statement is incorrect. Chen et al. 1998 [Ref. 8] found that, for all sunlamp use by persons under age 25, whether at home or in a tanning salon and whether using old sunlamps before 1970 (these old sunlamps had very high UVB and even some UVC and were outlawed) or new sunlamps after 1970, the OR for melanoma risk was 1.38 [Ref. 27]. However, as FDA fails to note, Chen et al. 1998 divided this risk between home use and tanning salon use and found that the OR for home use before age 25 was 1.63 (63% increased risk) and the OR for tanning salon use before age 25 was 0.63 (37% reduced risk) [Ref. 28]. FDA also does not discuss that Chen et al. 1998 divided the risk between use before 1970 and after 1970 and found that the OR for use before 1970 by persons before age 25 was 1.62 (62% increased risk) and the OR for use after 1970 by persons under 25 was 0.54 (46% reduced risk) [Ref. 29].

(m) Statement: "Individuals under 18 who are exposed to UV radiation…are particularly vulnerable to the damaging effects of UV radiation and…are particularly vulnerable to developing skin cancer (FDA Ref. 38 – Whiteman et al. 2001]" [Fed. Reg. at 79496]. Explanation: This statement is incorrect. Whiteman et al. 2001 [Ref. 30] found that "case

control studies differed widely in their findings, and no consistent associations with childhood sun exposure were observed." Also, see discussion in Section IV(c) above.

(n) Statement: "The World Health Organization (WHO) has classified UV radiation from sunlamp products as a class I carcinogen based on the 2009 IARC report that linked sunlamp product use by individuals under age 35 to higher rates of melanoma…" [80 Fed. Reg. at 79496]. Explanation: As previously mentioned, in 2009, IARC convened 20 scientists from nine countries to reassess the carcinogenicity of all forms of radiation. The 2009 Report issued by this group did not link sunlamp product use by individuals under age 35 to higher rates of melanoma, as stated by FDA. The report that purported to link sunlamp product use by individuals under age 35 to higher rates of melanoma is the 2006 IARC Report [Ref. 18]. Dr. David Hoel, who was one of these 20 scientists, has written a paper showing that the 2006 IARC Report is biased and that its finding that use of sunlamp products by persons under age 35 increases their risk of melanoma by 75% is invalid. *See* Attachment C.

(o) Statement: "Restricting use of these devices to individuals 18 and over should reduce future morbidity and mortality from melanoma and other skin cancers and would help to protect the public health, according to both expert advisory opinion and findings from current scientific, medical, and public health policy literature (FDA Ref. 54 – Hirst et al. 2009)" [80 Fed. Reg. at 79497]. Explanation: This statement is incorrect. Restricting use of commercial tanning salons to individuals 18 and over may possibly cause additional health problems by leading to an increase in underage tanning at home. *See* Attachment D. Hirst et al. 2009 [Ref. 31] is a study that begins with the assumption that restricting indoor tanning to persons 18 and older will reduce the incidence of melanoma by 18% for the public and by 49% for persons under age 35. Based on this assumption, the study unsurprisingly concludes that preventing minors from indoor tanning has the potential to reduce the incidence of skin cancers and related costs.

V. Additional Observations

Several dermatologists have filed more-or-less identical docket comments with FDA on the proposed rule. These comments include the following language: "It is estimated that indoor tanning [by this, in context, they are referring to indoor tanning in commercial tanning salons, not tanning at home or in some other unregulated setting] causes upwards of 400,000 cases of skin cancer in the U.S. each year. In fact, using indoor tanning before age 35 can increase your risk of melanoma – the deadliest form of skin cancer – by 59% and the risk increases with each use."

The first sentence quoted above is based on Wehner et al. 2014 [Ref. 34], a study of highly questionable and inaccurate science. *See* Attachment G for a review of this study by Dr. Diana B. Petitti, an epidemiologist and expert on meta-analyses. The second sentence is based on Boniol et al. 2012 [Ref. 25]. As noted under "III. History of Under-18 Science" above, the CDC removed this 59% figure from the CDC's website after it was challenged as being incorrect.

This is the same misinformation that the AADA has used to convince state legislators to enact bans on use of tanning salons by persons under 18. *See* Attachment F. We encourage FDA to carefully scrutinize: (1) comments relying upon this misinformation, and (2) studies potentially sponsored and/or funded by the dermatological, cosmetic, and sunblock industries.

VI. Conclusion

There is no scientific basis for FDA's proposed ban on use of indoor tanning salons by persons under the age of 18.

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Attachments

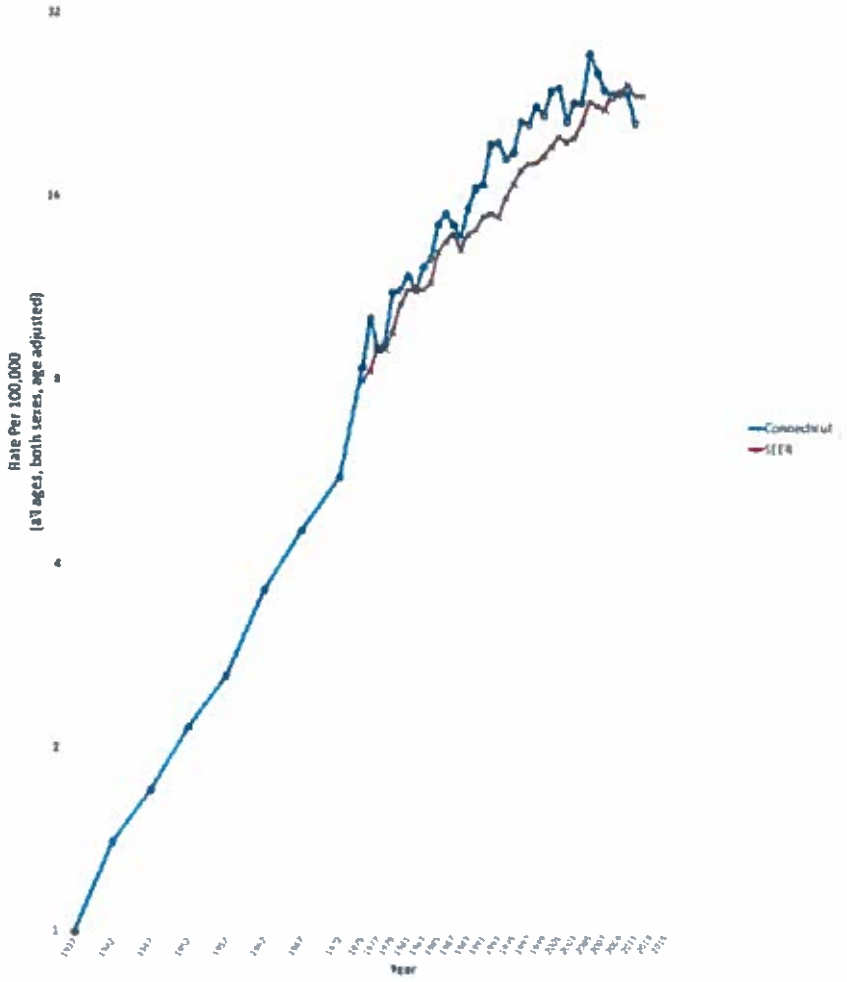
Attachment A	Graph of Melanoma Incidence, 1935 to 2012.
Attachment B	Hoel DG. "Risks and Benefits of Sun Exposure" (2016).
Attachment C	Hoel DG. "IARC's Sunbed and Melanoma Analysis" (Aug. 10, 2011). Curriculum Vitae, David G. Hoel, Ph.D.
Attachment D	Letter of Dr. David G. Hoel to FDA (Mar. 21, 2016).
Attachment E	Schlesselman JJ. "Use of Indoor Tanning Devices and Risk of Melanoma: Review of an Assessment by a Working Group of the International Agency for Research on Cancer" (Aug. 28, 2012). Curriculum Vitae, James J. Schlesselman, Ph.D.
Attachment F	Transcript of Dr. Jeffrey E. Gershenwald's testimony to the Texas Senate, Committee on Health and Human Services (Mar. 12, 2013).
Attachment G	Petitti DB. "Critical Review of Wehner et al. 2014 Estimates of the Prevalence of Ever Exposure to Indoor Tanning in Adults and the Number of Excess Cases of Skin Cancer" (Jan. 19, 2016).

Attachment A

Graph of Melanoma Incidence, 1935 to 2012

Annex I
Melanoma Incidence US 1935-2012

Year	SEER	CT
1935		1
1942		1.4
1947		1.7
1952		2.13
1957		3.6
1962		8.6
1967		4.3
1972		5.5
1975	7.3	8.3
	8.3	10
1977	8.5	8.9
	8.9	9.1
1979	9.5	11
	10.5	11.1
1981	11.1	11.7
	11.2	11.1
1983	11.1	12.1
	11.4	12.3
1985	12.3	14.3
	13.3	14.8
1987	13.7	14.2
	12.9	13.5
1989	13.7	15.1
	13.3	16.3
1991	14.6	16.5
	14.3	19.2
1993	14.6	19.3
	15.7	18.3
1995	16.5	18.6
	17.4	20.9
1997	17.3	20.7
	17.9	22.1
1999	18.3	21.4
	19	21.5
2001	19.7	23.7
	19.3	20.9
2003	19.6	22.4
	20.7	22.4
2005	22.3	24.9
	22.1	25.1
2007	21.5	23.8
	23.2	22.9
2009	23	23.3
	23.9	23.1
2011	22.9	20.7
	22.9	
2013		
2015		



Attachment B

Hoel, DG. Risks and Benefits of Sun Exposure 2016

The Risks and Benefits of Sun Exposure 2016

Introduction

Public health authorities in the United States are advising the public to reduce its sun exposure.[1] At the same time, NHANES data show that 32% of Americans suffer from vitamin D insufficiency.[a]

Here we review the current state of the science on the risks and benefits of sun exposure and suggest that the public health advice should be changed to recommend that all persons obtain enough non-burning sun exposure to maintain their serum 25(OH)D levels at 30 ng/mL year-round.

History

The first scientifically-established health benefit of sun exposure was the discovery in 1919 that sunlight cured rickets, [3, 4, 5] which was followed up by the discovery in 1924 that an inactive lipid in the diet and skin could be converted by ultraviolet light into an antirachitic substance [6] and the identification of vitamin D in 1931. [7] One would have thought that these discoveries would have ignited a sharp increase in scientific investigations of other health benefits of sun exposure, but this did not occur. Instead, for most of the following 80 years, scientific inquiry focused on the health risks of sun exposure, principally melanoma and other types of skin cancer. [8] Chemical sunscreens were developed in 1928. [9] Avoidance of intentional sun exposure and use of chemical sunscreens became and persisted as the standard advice of physicians and public health authorities for reducing the risk of melanoma and other forms of skin cancer. [1, 8] The risks of inadequate sun exposure have been largely ignored.

Risks of Sun Exposure

Melanoma

The cause of melanoma is unknown, but is believed to be linked to genetic factors.[10] The principal identified non-genetic risk factor is ultraviolet radiation (UVR) exposure, and the relationship between melanoma and UVR is two-sided: non-burning sun exposure is associated with a reduced risk of melanoma while sunburns are associated with a doubling of the risk of melanoma.[11] It has long been

[a] The 2010 Institute of Medicine vitamin D report defined vitamin D deficiency as serum 25(OH)D levels of less than 12ng/mL and vitamin D insufficiency as serum 25(OH)D levels of less than 20 ng/mL [2]. NHANES data for 2001-2006 show that 8% of Americans had 25(OH)D below 12 ng/mL and 32% had 25(OH)D below 20 ng/mL. [3]

observed that outdoor workers have a lower incidence of melanoma than indoor workers. [**12-18**] A 1997 meta-analysis found an OR of 0.86 (95% CI: 0.77-0.96) for occupational sun exposure.[**17**]

Biologically, UVB is known to induce DNA damage through the creation of pyrimidine dimers while UVA does so at orders of magnitude less efficiently. [van Schanke **20**] Oxidative damage through the creation of free radicals (singlet oxygen and hydrogen peroxide) occurs at all UVR frequencies. [**20**] However, the human body has many defenses against such damage including DNA repair mechanisms, cell cycle and growth inhibitions, reduced proliferation, enhanced sensitivity to apoptosis, enhancement of cellular differentiation and anti-inflammatory effects, many of which are related to vitamin D produced by exposure to UVB. [**21** IOM Chapter 4, **22** Holick textbook, **23** Endocrine Society 2012, **24** Wacker and Holick, **25** Bikle 2014].

With respect to sunburns, melanocytes are not replicating cells so once DNA damage has taken place it is necessary for cellular replication to occur for the possibility of unrepaired or misrepaired melanocytes to develop into malignant melanoma. [**20**] Sunburns correspond with rare occasions of cell divisions and ensuing vulnerability to mutations in otherwise indolent melanocytes [**20**]. With respect to chronic non-burning sun exposure, it is thought that protection against sunburn and correspondingly melanoma derives from photoadaptation (increased melanisation and epidermal thickening) or from the induction of higher levels of vitamin D, or possibly both [**25** Bikle 2014, **26** Newton-Bishop 2011, **12** Vuong 2014, **27** Reichrath 2013, **28** Dixon 2011]. Vitamin D produced by UVB exposure is converted to the active form of vitamin D by the kidneys and liver and circulated in the bloodstream to the body. Evidence suggests that vitamin D that is produced in the skin can also be converted in the skin to its active form 1,25-dihydroxyvitamin D3. [**25** Bikle 2014, **24** Holick 2013]

The epidemiological studies do not indicate any difference in melanoma risk based on the age at which UVR exposure occurs. [**11** Gandini II 2005, **16** Armstrong 2001, **17** Ellwood 1997] Sunburns appear to be equally risky at any age [**16** Armstrong 2001].

The incidence of melanoma in the United States has increased dramatically from 1 per 100,000 people per year in 1935[b] to 23 per 100,000 per year in 2012 as shown in Appendix I. Various explanations for this phenomenon have been suggested, including diagnostic drift [**29**], depletion of the ozone layer [**30**], the widespread use of artificial UVR devices [**31**], the proliferation of large windows in office buildings [**32**], None of these explanations is particularly satisfactory for the reason that none explain the steady increase in melanoma incidence since 1935. Considering that sunburns have been associated with a doubling of melanoma risk [**11**], chronic non-burning sun exposure and outdoor occupations have been associated with reduced risk of melanoma [**11-18**], indoor occupations such as professional, managerial, clerical, sales and service workers (excluding household and workers) grew from 25% to 75% of total employment between 1910 and 2000 [**33**], 25% of Americans lived on farms in

1930 whereas only 2% do so today [34], indoor attractions such as air conditioning, television, computers and the internet probably have led to Americans spending more of their leisure time indoors, the prevalence of sunburns is high and has been increasing[b], serum 25(OH)D levels of the American public, a likely marker for sun exposure, are low and have been declining[c] a more plausible explanation for the rise in melanoma incidence since 1935 may be the continually-increasing insufficient non-burning sun exposure and related increasing vitamin D insufficiency and the increasing sunburn prevalence experienced by the American public over the same time period[d]. Public health messages during the past 50 years to avoid sun exposure and to use chemical sunscreens may have contributed to the rise in melanoma incidence.

We can find no consistent evidence that use of chemical sunscreens reduces the risk of melanoma. The best study on the subject appears to be Green et al. 2011 [41], which found in a prospective study that there may be an association between sunscreen use and reduced risk of melanoma. However, since the participants knew they were in a skin cancer prevention trial and were questioned periodically during the trial on their use of sunscreen, the likelihood that they were significantly more diligent in applying sunscreen in accordance with manufacturers' instructions than ordinary users of sunscreen cannot be discounted.[e] Use of a placebo sunscreen was barred by ethical concerns.

Sunscreens do, however, reduce acclimatization to UVR and vitamin D production in the skin. [45]. Since public health authorities recommend liberal use of this commercial product for good health, the labeling of sunscreens should be revised to warn consumers about the dangers of vitamin D deficiency that may result from excessive use of sunscreens. Labeling should also notify consumers that sunscreens

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[b] According to the Centers for Disease Control and Prevention, the prevalence of sunburns increased from 32% of all adults in 1999 to 34% in 2004 [35] and up to 50% in 2012 [36]. Among adolescents aged 12-18 in 1999, 83% reported at least one sunburn in the previous summer and 36% reported three or more sunburns in the previous summer. [37 Geller 2002]

[c] Data on temporal trends in vitamin D levels are contained in study by Ginde et al. 2009 [38] who reported that NHANES data on serum 25(OH)D levels show that the prevalence of 25(OH)D of less than 10 ng/mL increased from 2% in 1988-1994 to 6% in 2001-2004 while over the same time period the prevalence of 25(OH)D of less than 20 ng/mL increased from 22% to 36%, and for 25(OH)D of less than 30 ng/mL increased from 55% to 77%.

[d] Such an explanation is not new. White et al. 1988 [39] (published as Garland et al. 1990 [40]) proposed that low levels of vitamin D (either locally available in skin or circulating in plasma) allow melanomas which were previously initiated by sunlight exposure to develop into clinically apparent disease in continually sunlight deprived individuals. This proposal was apparently ignored as precautions against melanoma focused on sun avoidance and liberal use of chemical sunscreens, with inadequate attention paid to the role of sunburns in melanomagenesis and to the role of vitamin D in inhibiting cancer. The first cancer cell line shown in 1980 to be inhibited in growth by $1,25(OH)_2D$ was in fact a melanoma cell line.

[e] Sunscreens are intended to prevent sunburn when used in thickness and frequency recommended by manufacturers or used in setting SPFs. However, studies have shown that the incidence of sunburn is higher or the same in people who almost always use sunscreens compared with those who rarely use sunscreens. [42,43,44]

have not been shown to be effective in reducing the risk of melanoma. Sunscreens have been shown in one study to be effective in reducing the risk of squamous cell, but not basal cell, skin cancer [**46**].

Nonmelanoma Skin Cancer (NMSC)

There are no official registries for basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), and estimates of the prevalence of these carcinomas vary widely. One group of investigators examined Medicare fee-for-service data, extrapolated to the entire United States population, and estimated that 2,152,500 persons were treated for 3,507,693 NMSCs in 2006. [**47** Rogers et al. 2010] Several of the same investigators estimated that 3,315,554 persons were treated for 5,434,193 NMSCs in 2012 and revised the 2006 estimates to 2,463,567 persons and 4,013,890 NMSCs [**48** Rogers et al. 2015]. These latter estimates indicated a 14% increase in Medicare NMSCs over the 6-year period 2006-2012 and a 54% increase in non-Medicare NMSCs over the 6-year period. It is not clear in this analysis that all treatments for NMSCs were in fact treatments for malignancies rather than for non-cancerous lesions, and these investigators found the ratio of BCC to SCC to be 1 to 1 instead of the expected 4 to 1. Another recent study [**49** Asgari 2015], which histologically confirmed all cases but studied only BCCs, calculated based on an analysis of a Kaiser Permanente BCC registry that approximately 2 million BCCs are treated annually in the United States in an undisclosed number of persons. Assuming a 4 to 1 ratio of BCC to SCC, this would indicate that 2.5 million NMSCs are treated annually. This study found that the incidence of BCC increased 17% during the 15-year period from 1998 to 2012.

As with melanoma, sunburns are associated with increased risk of SCC and BCC [**15, 16, 50**]. Cumulative sun exposure, however, which is associated with decreased risk of melanoma, is apparently associated with increased risk of SCC and BCC, although the relationship between cumulative sun exposure and NMSC is not entirely clear. Armstrong and Kricker 2001 [**16**] found that only SCC, not BCC, is related to total sun exposure, and Rosso et al. 1998 [**51**] found no association between cumulative lifetime sun exposure and BCC. Kennedy et al. 2003 [**15**] found a positive association between increasing lifetime sun exposure and the development of SCC and BCC but statistical significance was not always reached after age adjustment. English et al. 1998 [**53**] found that total time spent outdoors was only weakly associated with SCC. Gallagher et al. 1995a [**54**] and Gallagher et al.1995b [**55**] found no association between cumulative lifetime sun exposure and risk of SCC or BCC, but Gallagher et al. 1995b found that occupational sun exposure in the 10 years prior to diagnosis was associated with increased risk of SCC. Many studies have found increased risk of SCC and to a lesser extent BCC from occupational sun exposure [**16, 50, 56, 57**]. Alam et al. 2001 [**58**] found that the risk of SCC, but not BCC, is directly related to cumulative total dose of ionizing radiation from x-rays, that SCC may develop on sun-exposed areas in people with certain genodermatoses, such as oculocutaneous albinism, that chemical agents such

as soot, arsenic and polycyclic hydrocarbons have historically been a major cause of SCC, and that human papillomavirus infection has been associated with SCC. The U.S. Preventive Services Task Force, in its May 2012 Final Recommendation Statement on skin cancer counseling [**59, 60**], stated that studies that measured long-term or total sun exposure had found no association between cumulative sun exposure and either SCC or BCC.

Benefits of Sun Exposure

General

Scientific inquiry into the benefits of sun exposure languished for many decades following the observation in the 1920s that farmers in Europe developed non-melanoma skin cancer on their most sun-exposed areas - their ears, face, nose and backs of their hands [**61** Holick The UV Advantage 2003] - as attention was focused on the risks rather than the benefits of sun exposure. Research on the benefits of sun exposure has accelerated in the past 15 years and particularly in the past 5 years.

Vitamin D

Biological Plausibility

Vitamin D is a hormone and most cells and organs in the human body have a vitamin D receptor which explains the wide variety of diseases and disorders that have been linked to vitamin D insufficiency in epidemiological studies. The production of vitamin D by ultraviolet B radiation, the availability of vitamin D in food and supplements, and the biological plausibility of vitamin D as a mediator for a large variety of favorable health outcomes are well described in the literature and will not be repeated here. [**62** IOM 2010 Vitamin D Report, **22** Holick textbook, **23** Endocrine Society 2012 Vitamin D report, **24** Wacker and Holick 2013, **25** Bikle 2014, **62A** Hossain and Holick 2013]

Recommended Vitamin D Levels

There is considerable controversy within the scientific community regarding optimum 25(OH)D levels for human health. In 2010, the Institute of Medicine defined vitamin D deficiency as 25(OH)D of less than 12 ng/mL and vitamin D insufficiency as 25(OH)D of less than 20 ng/mL. [**2**]. In 2011, The Endocrine Society defined vitamin D deficiency as 25(OH)D below 20 ng/mL and vitamin D insufficiency a 25(OH)D of 21-29 ng/mL. [**63** Holick 2011]. Others have suggested even higher levels.[**22** Holick textbook, **64** Khayznikov 2015, **65** Rosen 2011, **66** Holick 2014]. A letter signed by many respected vitamin D scientists and physicians recommends 40-60 ng/mL [**67** Garland 2009] which is in line with what the Endocrine Society recommended as the preferred range for health – i.e, a

25(OH)D of 40-60 ng/mL. [**63**]. Most reference laboratories have raised the lower boundary of the normal range to 30 ng/mL. [**65** Rosen 2011].

Prevalence of Vitamin D Deficiency/Insufficiency

Ginde et al. 2009 [**38**] reported that NHANES data on serum 25(OH)D levels show that the prevalence of 25(OH)D of less than 10 ng/mL increased from 2% of the U.S. population in NHANES III (1988-1994) to 6% in NHANES 2001-2004, and that over the same period the prevalence of 25(OH)D of less than 20 ng/mL increased from 22% of the U.S. population to 36%[f]. The IOM report did not offer a solution to this problem since that was not its purpose; the IOM was tasked with determining the DRI of vitamin D supplements and found that there was insufficient scientific evidence on the benefits of vitamin D supplementation to support raising the DRI of vitamin D supplements to more than 600 International Units per day[g]. Using the Endocrine Society's definition of vitamin D sufficiency of 30 ng/mL, the level of vitamin D insufficiency increased from 55% of the U.S. population in NHANES III to 77% in NHANES 2001-2004 [**38**], which indicates that the vast majority of Americans have insufficient vitamin D levels.

Mediators other than Vitamin D

Several studies, discussed below, have found that mediators other than vitamin D are or may be involved in the beneficial effects of adequate sun exposure.

Benefits of Vitamin D/Sun Exposure; Risks of Vitamin D Insufficiency/Inadequate Sun Exposure

We next examine the health benefits associated with increasing levels of sun exposure and/or circulating serum 25(OH)D and the health risks associated with inadequate sun exposure and/or inadequate serum 25(OH)D, with particular emphasis on studies published since the 2010 IOM report.

All-Cause Mortality

Chowdhury et al. 2014 [**69**] was a meta-analysis of data from 73 cohort studies with 849,000 participants and 22 randomized controlled trials with 31,000 participants. This study found an inverse association of circulating 25(OH)D with risks of death due to cardiovascular diseases, cancer and other causes (RR 1.35, 95% CI 1.22-1.49 for all cause mortality, bottom third versus top two-thirds of baseline

[f] The differences between NHANES III and NHANES 2001- 2004 may be attenuated by approximately 4 ng/mL after adjustment for improvements in the serum 25(OH)D assay performance from NHANES III to NHANES 2001-2004 [68 Looker 2008].

[g] The Endocrine Society's 2012 review of the nonskeletal effects of vitamin D also found there was insufficient evidence to support a role of vitamin D supplementation in correcting vitamin D insufficiency [**63**].

circulating 25(OH)D distribution), but found that, with respect to possible benefits of vitamin D supplementation, further investigation is required before any widespread supplementation occurs. The prevalence of vitamin D insufficiency (defined as 25(OH)D less than 30 ng/mL) was found to be 69.5% for the United States and 86.4% for Europe. The authors further estimate that 9.4% of all deaths in Europe and 12.8% in the United States could be attributable to vitamin D insufficiency. Other meta analyses include Garland et al. 2014 [70] who pooled the data from 32 studies (30 cohort studies and 2 nested case-control studies) that examined age-adjusted all-cause mortality and serum 25(OH)D levels and found that the overall age-adjusted hazard ratio for all-cause mortality comparing the lowest (0-9 ng/mL) group to the highest (greater than 50 ng/mL) was 1.9 (95% CI 1.6-2.2), indicating that individuals in lowest group had nearly twice the age-adjusted death rate as those in the highest quantile. Schottker et al. 2014 [71]was a meta-analysis of 8 cohort studies with 26,000 participants that found a 1.6-fold higher all-cause mortality in the bottom quintile (25(OH)D approximately <12 ng/mL) compared with the top quintile (25(OH)D approximately > 24 ng/mL) (RR 1.57, 95% CI 1.36-1.81).

Lindqvist et al. 2014 [72] assessed the avoidance of sun exposure as a risk factor for all-cause mortality for 29,518 Swedish women in a prospective 20-year follow-up of the Melanoma In Southern Sweden cohort and found that the population attributable risk for all-cause mortality for those habitually avoiding sun exposure was 3%. As compared to the highest sun exposure group, the all-cause mortality rate was doubled (RR 2.0, 95% CI 1.6-2.5) among avoiders of sun exposure and increased by 40% (RR 1.4, 95% CI 1.1-1.7) in those with moderate exposure. The authors noted that Sweden has national guidelines providing restrictive advice on sun exposure habits in order to lower the risk of skin cancer, and stated that these guidelines may be harmful in terms of overall health of the population.

Afzal et al. 2014 [73] was a mendelian randomization analysis showing that genetically low 25(OH)D levels were associated with increased all-cause mortality, but not with cardiovascular mortality. These results confirm that the measured low 25(OH)D levels in the general population associated with increased mortality as indicated in the above meta-analyses are related to vitamin D rather than simply a consequence of poor health or sequestration of vitamin D in adipose tissue, but indicate that some mediator other than vitamin D may be involved in cardiovascular mortality. Afzal et al. 2014 [73] was the first study with sufficient sample size to investigate the association of genetically low 25(OH)D levels with increased mortality.

Colorectal Cancer

Rebel et al. 2014 [74] experimentally showed for the first time the causality of the relationship between moderate UVR exposure and primary intestinal tumors in mice. The UVR-induced reduction in intestinal cancer in mice could at least in part be attributed to vitamin D. However, the investigators also found a reduced progression to malignancy as a result of UVR exposure which appeared not to be

attributable to vitamin D. Three groups of hairless mice were compared: one on a low-vitamin D diet without vitamin D supplementation or UVR exposure, one on a low-vitamin D diet with vitamin D supplementation but without UVR exposure, and one on a low-vitamin D diet without vitamin D supplementation but with moderate UVR exposure. This permitted the comparison of effects of dietary vitamin D supplementation and UVR exposure. The tumor load (area) was similarly and significantly reduced in both the vitamin D supplementation group and the UVR exposure group, but only the UVR exposure group had a lower percentage of malignant adenocarcinomas. Thus the study provided the first experimental evidence that physiologically relevant, moderate UVR exposure can reduce the load of primary intestinal tumors, which reduction can at least in part be explained by an increase in vitamin D status as a comparable reduction in tumor load was observed in the vitamin D supplementation group that had a similar increase in vitamin D status. However, a reduction in malignant progression and growth of adenocarcinomas could not be attributed to vitamin D as these effects were only observed with moderate UVR exposure and not with dietary vitamin D supplementation. Rebel et al. 2014 [**74**] noted that prior studies had long shown that low exposure to solar UVR is significantly associated with increased risk of colon cancer, and that several recent studies showed that increased risk of colon cancer was significantly associated with prediagnostic low vitamin D status. The 2010 IOM report [**62**] acknowledged that epidemiological studies examining associations between vitamin D status and colorectal cancer incidence generally supported an inverse association, but declined to base vitamin D DRI's on colon cancer outcomes because of the paucity and conflicting findings of prospective randomized controlled trials involving vitamin D supplementation. Notably, the most recent, and only observational, study reviewed in the IOM report found no association of vitamin D supplementation with colon cancer risk, but found that patients in the highest quintile of prediagnostic circulating 25(OH)D concentration (more than 40 ng/mL) had a 42% reduced risk of colon cancer as compared to patients with the lowest quintile (less than 10 ng/mL) [**75** Jenab 2010].

Breast Cancer Incidence and Mortality

Mohr et al. 2014 [**76**] was a meta-analysis of data from five studies [Goodwin 2009 [77], Vrieling 2011 [**78**], Tretli 2012 [**79**], Hatse 2012 [**80**], and Villasenor 2012 [**81**] on the relationship between serum 25(OH)D levels at time of breast cancer diagnosis and breast cancer mortality which found that patients in the highest quintile of 25(OH)D (more than 32 ng/mL) had approximately half the death rate from breast cancer as those in the lowest quintile (less than 14 ng/mL) (HR 0.56; 95% CI: 0.4-0.7). The authors recommended that serum 25(OH)D levels in all breast cancer patients should be restored to the normal range, which the authors defined as 30-80 ng/mL.

Engel et al. 2010 [**82**] found a 27% reduced risk of breast cancer incidence in women in the highest tertile of 25(OH)D (greater than 27ng/mL) as compared to the lowest tertile (less than 19.8

ng/mL) in a nested case-control study (OR 0.73; 95% CI: 0.55-0.96). The authors noted that all six previous case-control studies on the subject have reported a significant inverse association between serum 25(OH)D levels and breast cancer [Abbas 2009 [**83**], Abbas 2008 [**84**], Colston 2006 [**85**], Crew 2009 [**86**], Lowe 2005 [**87**] and Janowsky 1999 [**88**], and that an inverse effect between sun exposure and breast cancer has previously been observed, with John et al. 1999 [**89**] finding that women with higher solar UVB exposure in NHANES III had only about half the incidence of breast cancer as those with lower solar exposure (RR 0.50; 95% CI: 0.33-0.80) and Knight et al 2007 [**90**] finding that increasing sun exposure from ages 10 to 19 reduced breast cancer risk by 35% (OR 0.65, 95% CI 0.50-0.85 for the highest quartile of outdoor activities versus the lowest).

Non-Hodgkins Lymphoma, Colorectal, Prostate and Breast Cancer, and Multiple Sclerosis

Van der Rhee et al. 2013 [**91**] noted that the association between solar radiation and reduced cancer mortality in North America was identified more than 60 years ago [**92** Apperly 1941] and that in 1980 it was hypothesized that vitamin D was the protective factor [**40** Garland 1980] and the authors conducted a systematic review to verify if epidemiological evidence is in line with the hypothesis that the possible preventive effect of sunlight on cancer is more than just the effect of vitamin D. Vitamin D intake studies were excluded from the review and the authors stated that their review presented the sum of epidemiological knowledge on the influence of sun exposure and circulating vitamin D levels on the risk of colorectal cancer, prostate cancer, breast cancer and non-Hodgkin's lymphoma (NHL). They concluded that: there is an inverse association between sun exposure and both colorectal cancer risk [**93** Freedman 2010, 94 Lin 2012] and colon cancer mortality [**95** Freedman 2002] and that 1) there is an inverse association between vitamin D status and both colorectal cancer risk [**96** Ma et al. 2011] (*contra,* Weinstein et al. 2011 [**97**]) and colorectal cancer mortality [**93** Freedman et al. 2010; **98** Fedirko et al. 2012]; 2) there is a negative association between sun exposure and prostate cancer risk [**94** Lin 2012, **99** Bodiwala 2003, **100** John 2003, **101** Gilbert 2009, **102** Kanaan 2012] (*contra*, Nair-Shalliker et al. 2012 **103**) and prostate cancer mortality [**95** Freedman 2002, **104** Rukin 2007], but not between vitamin D status and prostate cancer risk or mortality [**105** Gilbert 2011]; 3) there is a negative correlation between sun exposure and breast cancer risk [**106** Knight 2007, **107** John 2007, **108** Lee 2011] and mortality [**95** Freedman 2002], and possibly between 25(OH)D and breast cancer mortality [**93** Freedman 2010], but studies on the association between 25(OH)D and breast cancer risk are inconclusive; 4) there is a negative association between sun exposure and NHL risk and NHL mortality [**109** Kricker 2008, **110** Freedman 1997, **111** Kane 2010, **112** Kelly 2010, **113** Wong 2012, **114** Kelly 2012, **115** Freedman 2010] but not between vitamin D status and NHL risk or mortality [**112** Kelly 2010, **116** Purdue 2010, **93** Freedman 2010]; 5) there is a negative association between sun exposure and lymphoma risk, but no association between lymphoma risk and vitamin D intake or 25(OH)D levels [**112** Kelly 2010]; and, 6) for multiple

sclerosis, both experimental [**117** Becklund 2010] and epidemiological studies [**118** Lucas 2011] show that the preventative role of sun exposure is independent of vitamin D production. The authors concluded that for colorectal cancer and breast cancer the benefit of sun exposure is mediated by high vitamin D levels produced by sun exposure, whereas for prostate cancer, NHL and multiple sclerosis the benefit of sun exposure is independent of vitamin D. [**91** van der Rhee 2013].

Cardiovascular Disease (CVD)

Liu et al. 2014 [**119**] found that hypertension is reduced by UVR-induced nitric oxide independent of vitamin D. They showed that stores of nitrogen oxides in the human skin are mobilized to the systemic circulation by exposure of the body to UVA radiation, causing arterial vasodilation and a resultant decrease in blood pressure independent of vitamin D, confirming the hypothesis of Feelisch et al. 2010 [**120**]. These results correlate with the findings of Afzal et al. 2014 [**73**] that genetically low 25(OH)D levels were associated with increased all-cause mortality but not with cardiovascular mortality, indicating that a mediator other than vitamin D may be involved in cardiovascular mortality, and with the results of Tunstall-Pedoe et al. 2015 [**121**] challenging vitamin D's alleged role in cardiovascular disease.

Metabolic Syndrome (MetS) and Type 2 Diabetes:

Vitezova et al. 2015 [**125**] found that higher 25(OH)D levels were associated with lower prevalence of metabolic syndrome (OR 0.61, 95% CI 0.49-0.77 for more than 30 ng/mL versus less than 20 ng/mL) in the elderly in an analysis of data from 3240 people (median age 71.2 years) imbedded in the Rotterdam Study, a prospective population-based cohort study of middle-aged and elderly adults. Importantly, after adjustment for body mass index (BMI), higher 25(OH)D levels were still significantly associated with lower odds of MetS. Almost concurrent with Vitezova et al. 2015, Clemente-Postigo et al. 2015 [**126**] showed that low 25(OH)D levels are associated with type 2 diabetes independently of BMI. These findings are important in light of the 2010 IOM report's discounting of the association studies linking low 25(OH)D levels to increased risk of type 2 diabetes on the ground that they may be confounded by obesity, which not only predispose individuals to type 2 diabetes but may also cause lower 25(OH)D levels as a result of sequestration of vitamin D in adipose tissue and possibly other mechanisms. Vitezova et al. 2015 noted that other recent studies [Awad 2012 **127**, Khan 2013 **128**, and Gagnon 2012 **129**] had found an inverse association between vitamin D status and MetS in younger populations, but only one other study of older persons had found the association [**130** Oosterwerff et al. 2011] while another study of older persons had not [**131** Reis et al. 2007]. Neither Vitezova et al. 2015 [**125**] nor Clemente-Postigo et al. 2015 [**126**] cited Geldenhuys et al. 2014 [**132**], which found that UVR exposure levels, not vitamin D supplements or 25(OH)D levels, reduced the risk of obesity and type 2 diabetes, indicating that 25(OH) levels may be to some extent a marker for UVR exposure in this regard.

Afzal et al. 2013 [**133**] measured 25(OH)D levels in 9841 persons of whom 810

developed type 2 diabetes during 29 years of follow-up. The investigators observed an association of low 25(OH)D with increased risk of type 2 diabetes (HR 1.35, 95% CI 1.09-1.66 for lowest (less than 5 ng.mL) vs. highest (more than 20 ng/mL) quartile of 25(OH)D. This finding was substantiated by the authors' meta-analysis of 14 studies representing 16 cohorts with a total of 72,204 participants and 4,877 type 2 diabetes events (HR 1.50, 95% CI 1.33-1.70 for the bottom vs. top quartile of 25(OH)D). A prior 2011 meta-analysis [**134** Mitri 2011] had shown that individuals with 25(OH)D levels above 25 ng/mL had a 43% lower risk of developing type 2 diabetes (95% CI, 24%-57%) compared with individuals with 25(OH)D levels below 14 ng/mL, and that vitamin D supplementation had no effect.

Alzheimer's Disease and Cognitive Decline

Littlejohns et al. 2014 [**135**] studied a group of 1,658 Americans age 65 and older who were able to walk unaided and who were free of dementia. The participants were followed for six years to investigate who went on to develop Alzheimer's disease and other forms of dementia. The investigators found that participants with serum 25(OH)D levels below 10 ng/mL were more than twice as likely to develop Alzheimer's disease than participants with serum 25(OH)D levels greater than 20 ng/mL (HR 2.22, 95% CI 1.02-4.83) and participants with serum 25(OH)D levels of 10 ng/mL to 20 ng/mL were 69% more likely to develop Alzheimer's disease than participants with serum 25(OH)D levels greater than 20 ng/mL (HR 1.69, 95% CI 1.06-2.69). Similar results were obtained for all-cause dementia. According to the authors, this was the first large, prospective, population-based study incorporating a comprehensive adjudicated assessment of dementia and Alzheimer's to examine their relationship with vitamin D concentrations. This study confirms other recent studies linking low vitamin D levels with cognitive decline [**136** Keeney 2013, **137** Annweiler 2013, **138** Balion 2012; **139** Slinen 2012; **140** Llewellyn 2011; **141** Dickens 2011; **142** Llewellyn 2010.]

Keeney et al. 2013 [**136**] manipulated vitamin D status in middle-age to old-age rats by dietary supplementation with low, moderate and high levels of vitamin D. The results suggested that dietary vitamin D deficiency contributes to significant nitrosative stress in the brain and may promote cognitive decline in middle-age and elderly humans.

Annweiler et al. 2013 [**137**] was a systematic review and meta-analysis finding that 25(OH)D levels were lower in Alzheimer's cases than in controls (summary random effect size 1.40, 95% CI 0.26-2.54), which means that the probability is about 140% that an individual without Alzheimer's would have a higher 25(OH)D level than an individual with Alzheimer's if both individuals were chosen at random from a population.

Multiple Sclerosis (MS), Type 1 Diabetes, Rheumatoid Arthritis

Wang et al. 2014 [**143**] found that UVR suppressed experimental autoimmune encephalomyelitis (EAE - an animal model of MS), independent of vitamin D production, confirming the conclusions of van

der Rhee et al. 2013 [**91**] and the findings of Becklund et al. 2010 [**117**]. The investigators showed that UVB irradiation did not suppress immune response in the periphery, but suppressed EAE by blocking selectively the infiltration and binding of inflammatory cells into the central nervous system. These findings support the long-held view that the incidence of MS is inversely related to UVR exposure. [**144** Knippenberg 2014, **145** Correale 2013, **146** Simpson, **147** Ponsonby 2005, **148** Acheson 1960].

Baarnhielm et al. 2012 [**149**] was an association study finding that persons with low UVR exposure had a significantly increased risk of MS compared with those who reported the highest exposure (OR 2.2, 95% CI 1.5-3.3), and that this association persisted after adjustment for vitamin D status. Wang et al. 2014 [**143**] and Baarnhielm et al. 2012 [**149**] confirmed the conclusions of van der Rhee et al. 2013 [**91**] that sun exposure reduces the risk of MS through pathways independent of vitamin D.

Ponsonby et al. 2005 [**147**] stated that genetic factors appear to be involved in MS, but the low concordance among identical twins for MS [**150** Hogancamp 1997] and trends of increasing incidence of MS over time [**151** Bach 2002] suggest environmental factors are also important determinants, and that UVR exposure may be one factor that can attenuate MS through several mechanisms and that some the pathways are independent of vitamin D. The authors concluded that it was critical to consider the benefits of sun exposure as well as the risks, and to provide information to the public on the minimum sun exposure required for beneficial health effects as well as the maximal sun exposure to avoid the adverse health effects associated with excessive sun exposure. Ponsonby et al. 2005 [**147**] made similar conclusions about two other autoimmune diseases, type 1 diabetes and rheumatoid arthritis. Also Mokry et al. 2015 [**152**] was a mendelian randomization analysis showing that genetically low 25(OH)D levels were associated with increased risk of MS.

Psoriasis

Gisondi et al. 2012 [**153**] found that the prevalence of 25(OH)D of less than 20 ng/mL was 57.8% in patients with psoriasis vs. 29.7% in healthy controls, and that in a logistic regression analysis, vitamin D deficiency was associated with psoriasis independently of other factors (OR 2.50, 95% CI 1.18-4.89) . The investigators noted that topical vitamin D derivatives and UVB radiation are used in the treatment of psoriasis. Vitamin D status was found to be unrelated to levels of self-reported sun exposure, but the measure used for sun exposure, which was minutes per day of sun exposure from March to September, may not have been appropriate for vitamin D production since it apparently did not include the time of day or the area of skin exposed.

Liver Disease

Gorman et al. 2015 [**154**] in a review stated that a large number of studies in recent

years [**132** Geldenhuys 2014, **155** Gorman 2012, **156** Nakano 2011] have shown that exposure to UVR has the potential to curtail the development of non-alcoholic fatty liver disease (NAFLD) through vitamin D dependent and vitamin D independent mechanisms. The authors noted that most observational studies support an inverse association between serum 25(OH)D levels and NAFLD [**157** Barchetta 2011, **158** Bhatt 2013, **159** Bril 2015, **160** Dasarathy 2014, **161** Hao 2014, **162** Jablonski 2013, **163** Kasapoglu 2013, **164** Kucukazman 2014, **165** Li 2013, **166** Liangpunsakul 2011, **167** Rhee 2013, **168** Seo 2013, **169** Black 2014, **170** Katz 2010, **171** Malespin 2015, **172** Nobili 2014, **173** Pirgon 2013, **174** Eliades 2013], but that vitamin D supplementation did not produce the same results. [**175** Sharifi 2014]. The authors further stated that circulating vitamin D levels may represent a proxy for bodily exposure to sunlight [**176** Feelisch 2014], explaining the observation that mediators induced by sun exposure other than vitamin D may play important roles in curtailing NAFLD.

Statin Intolerance and Muscle Pain, Weakness:

Khayznikov et al. 2015 [**64**] found that statin intolerance because of myalgia, myositis, myopathy, or myonecrosis associated with serum 25(OH)D less than 23 ng/mL can be resolved with vitamin D supplementation raising serum 25(OH)D to 53 ng/mL. Aleksic et al. 2015 [**177**] found that low vitamin D levels are a potentially significant and correctible risk factor for statin-related myopathy, especially in African-Americans.

Macular Degeneration

Millen et al. 2015 [**178**] observed a 6.7-fold increased risk of age-related macular degeneration (AMD) among women with serum 25(OH)D levels less than 12 ng/mL who also had genetic risk for AMD, and noted that previous studies had found that decreased odds of AMD are associated with high compared to low concentrations of 25(OH)D [**179** Graffe 2012, **180** Millen 2011, **181** Parekh 2007]

Reverse Causation

Autier et al. 2014 [**182** Autier 2014] suggested that low serum 25(OH)D levels may be the result rather than the cause of diseases associated with low serum 25(OH)D levels in observational studies (reverse causation). The authors offer little evidence to support such a hypothesis, and it is contraindicated by the prospective nature of many of the studies linking serum 25(OH)D levels with health outcomes, by Mendelian randomisation studies [**73, 152**], and by the body of knowledge concerning the bioactivity of vitamin D, particularly its cancer-inhibiting properties.

Obesity

Geldenhuys et al. 2014 [**132**] suggests that UVR exposure may be an effective means of suppressing the development of obesity and metabolic syndrome through mechanisms that are independent of vitamin D but dependent on other UVR-induced mediators such as nitric oxide. This study investigated whether UVR and/or vitamin D supplementation had an effect on the development of

obesity and type 2 diabetes in mice fed a high-fat diet, and found that UVR significantly suppressed weight gain but vitamin D supplementation did not. These results indicate that low vitamin D status in obese persons may only be a marker for low UVR exposure or a result of sequestration of vitamin D in adipose tissue, and provide a new view of previous studies showing a consistent association between increasing body mass index and lower serum 25(OH)D levels. [**183**]

Myopia

French et al. 2015 [**184**] was a review stating that recent epidemiological evidence suggests that children who spend more time outdoors are less likely to be or to become myopic, irrespective of how much near work they do or whether their parents are myopic. The likely mechanism for this protective effect is visible light stimulating release of dopamine from the retina, which inhibits increased axial elongation, the structural basis of myopia. The authors describe the effect of time outdoors on the risk of myopia as robust. The prevalence of myopia in the U.S. in persons 12 to 54 years old increased 66% between 1971-1972 and 1999-2004, from 25.0% to 41.6%, according to the National Eye Institute of the National Institutes of Health. [**185, 186**] For African Americans, the increase was 157.7%. [**186**] This high prevalence of myopia presents a major public health problem since, in addition to requiring corrective lenses, myopia poses substantially increased risk of retinal detachment, glaucoma, macular degeneration, amblyopia and cataracts.[**187, 188**]

Serotonin

Lambert et al. 2002 [**189**] suggested that the prevailing amount of sunlight affects brain serotonergic activity. Deficiencies in serotonin and brain serotonergic activity have been linked to sudden infant death syndrome [**190** Duncan 2010], seasonal affective disorder [**189** Lambert], depression [**191** Svenningsson 2006], schizophrenia [**192** Abi-Dargham 1997], Alzheimer's disease [**193** Cross 1990], and migraine headaches [**194** Hamel 2007].

Beta-Endorphin

Beta-endorphin, a neuorohormone that acts as an analgesic, has been known for many years to be released in the human body by exercise, producing a feeling of wellbeing similar to the feeling of wellbeing induced by sun exposure. [**195**] A recent study [**196** Fell 2014] showed that UVR exposure significantly raised circulating plasma beta-endorphin levels in a UV-exposure mouse model, leading to suggestions that UVR exposure is addictive [**196** Fell 2014]. Alternatively, the release of beta-endorphins by sun exposure could be a natural reward mechanism encouraging sun exposure.

Vitamin D Supplements vs. Sun Exposure

In light of the studies discussed in this review that found health outcomes related to sun exposure independent of vitamin D, health outcomes dependent on serum 25(OH)D levels but not vitamin D supplementation, and health outcomes dependent on mediators other than vitamin D, it is apparent that vitamin D supplements are not an effective substitute for adequate sun exposure.

Balancing the Risks of Moderate Non-Burning Sun Exposure Against the Risks of Inadequate Sun Exposure

The only identified risk associated with the amount of non-burning sun exposure needed to achieve serum 25(OH)D levels of 30 ng/mL is some possible increased risk of nonmelanoma skin cancer. The amount of sun exposure required to produce this level of vitamin D varies among individuals and according to time of year, time of day and latitude. White people with Type II skins[h] at 40 degrees latitude can obtain their annual requirements of vitamin D by spending about 15 minutes in the sun with face, arms and legs exposed (half that time if in a bathing suit) two to three times a week between 11 am and 3 pm during the months of May through October [**197** Holick MF, The Vitamin D Solution, Hudson Street Press 2010]. In comparison, nonmelanoma skin cancer is associated with many thousands or tens of thousands of cumulated hours of lifetime sun exposure. [**15** Kennedy 2003, **53** English 1998, **51** Rosso 1996]. Moreover, inadequate acclimatization to UVR in daily life carries the risk of sunburn and corresponding increased risk of both nonmelanoma skin cancer and melanoma.

The risks of inadequate non-burning sun exposure include increased risks of all-cause mortality, colorectal cancer, breast cancer, non-Hodgkins lymphoma, prostate cancer, pancreatic cancer, hypertension, cardiovascular disease, metabolic syndrome, type 2 diabetes, obesity, Alzheimer's disease, multiple sclerosis, type 1 diabetes, rheumatoid arthritis, psoriasis, non-alcoholic fatty liver disease, statin intolerance, macular degeneration and myopia.

People with darker skins require more time in the sun to produce their requirements of vitamin D but also have lower risks of nonmelanoma skin cancer, and people with Type I skins, who are unable to tan, require less time in the sun but have higher risks of nonmelanoma skin cancer. All persons should

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[h] There are 6 categories of skin on the Fitzpatrick Scale: Type I Very Fair White - always burns, never tans;Type II Fair White - usually burns, tans minimally; Type III Cream White – sometimes mild burn, gradually tans; Type IV Brown – rarely burns, tans with ease; Type V Dark Brown – very rarely burns, tans very easily; Type VI Black – never burns, tans very easily.

avoid sunburns, which are associated with substantial increased risk of melanoma and nonmelanoma skin cancer.

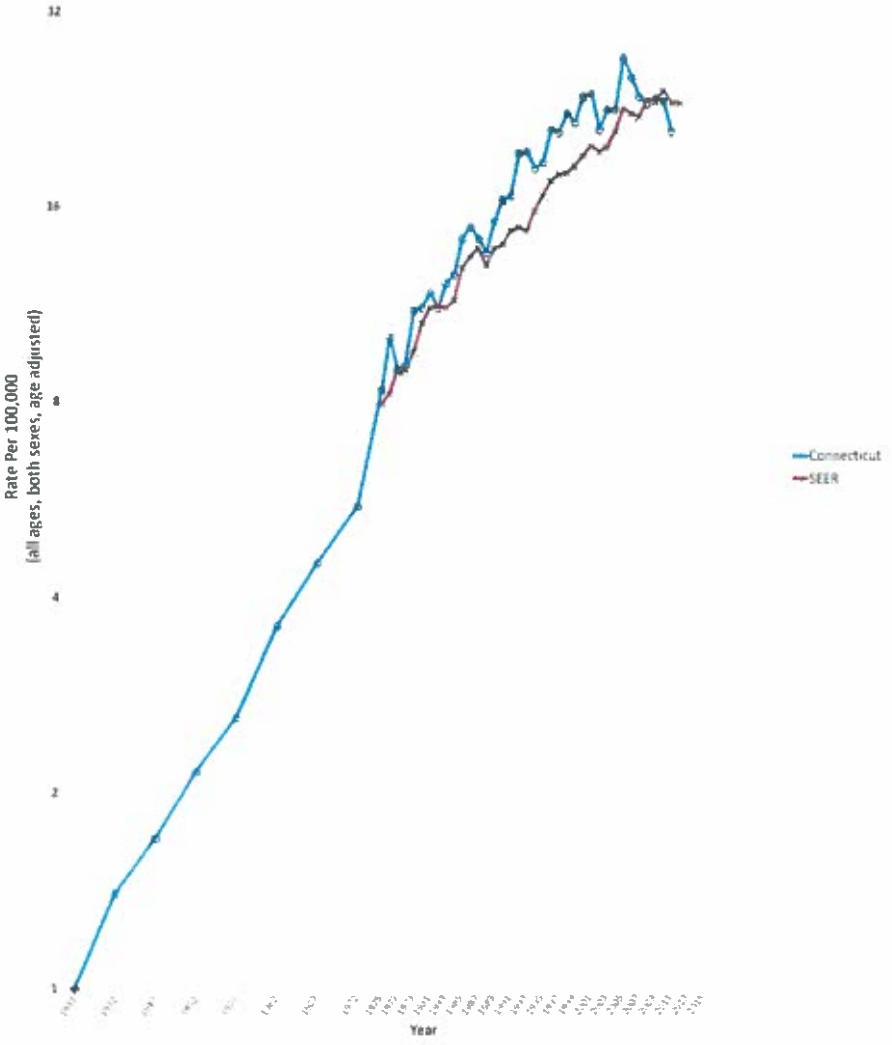
Conclusions

Insufficient sun exposure has become a major public health problem, demanding an immediate change in the current sun-avoidance public health advice. The degree of change needed is small but critically important. The public should be advised to obtain enough sun exposure to maintain a serum 25(OH)D level of 30 ng/mL. The amount of sun exposure required depends on skin pigmentation, latitude, time of day and time of year. Warnings on the dangers of sunburn at any age should be strengthened. Periodic testing of serum 25(OH)D levels is also indicated.

END

Annex I
Melanoma Incidence US 1935-2012

Year	SEER	CT
1937		1
1942		1.4
1947		1.7
1952		2.15
1957		2.6
1962		3.4
1967		4.5
1972		5.5
1975	7.9	8.3
	8.2	10
1977	8.9	8.9
	8.9	9.1
1979	9.5	11
	10.5	11.1
1981	11.1	11.7
	11.2	11.1
1983	11.1	12.1
	11.4	12.5
1985	12.8	14.2
	13.3	14.8
1987	13.7	14.2
	12.9	13.5
1989	13.7	15.1
	13.9	16.3
1991	14.6	16.5
	14.8	19.2
1993	14.6	19.3
	15.7	18.2
1995	16.5	18.6
	17.4	20.9
1997	17.8	20.7
	17.9	22.1
1999	18.1	21.4
	19	23.5
2001	19.7	23.7
	19.3	20.9
2003	19.6	22.4
	20.7	22.4
2005	22.5	26.9
	22.1	25.1
2007	21.8	23.4
	23.2	22.9
2009	23	23.3
	23.9	23.1
2011	22.9	20.7
	22.9	
2013		
2015		



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Attachment C

Hoel DG. IARC's Sunbed and Melanoma Analysis (Aug. 10, 2011)

IARC's 2006 Sunbed and Melanoma Analysis

Hoel DG*

IARC convened a working group to systematically review the epidemiological and experimental literature on the possible relationship between the use of indoor tanning devices and skin cancer. A summary of the working group's findings and conclusions was subsequently published in 2006 in the International Journal of Cancer (120:116-1122). The basic results reported by the working group were values obtained from a statistical meta-analysis of 19 epidemiological studies that they considered to be appropriate. The studies were case-control studies, except for one, of melanoma and the use of artificial UV radiation. The working group concluded that "Based upon 19 informative studies, ever-use of sunbeds was positively associated with melanoma (summary relative risk, 1.15; 95% CI, 1.00-1.31), although there was no consistent evidence of a dose-response relationship." The relative risk of 1.15 is very small and marginally significant (i.e. CI, 1.00-1.31). The removal of just one of the more questionable studies would result in the result no longer being statistically significant. The individual studies used by the IARC working group and the summary relative risk is given in Table I.

The working group did report that in 7 studies the age of first use of tanning beds was given and subset analyses were carried out for those first using tanning beds before age 35. Using these 7 subset analyses the summary relative risk was stated to be increased to 1.75; 95% CI, 1.35-2.26). The working group based on these subset analyses recommended that "Young people should be discouraged from using indoor tanning equipment and restricted access to sunbeds by minors should be strongly considered." IARC in 2009 convened another cancer working group that focused on both UV and all forms of ionizing radiation with a summary published later that year in Lancet Oncology (10:751-2). The subset analysis finding from the 2006 working group was repeated in the Lancet article which generated renewed concern about the use of sun tanning by minors.

In meta-analysis work there is the fundamental concern of publication bias. Basically studies with positive effects are more likely to be published than those with negative findings. This would also apply to subset analyses of studies. If a study has no overall findings then it is less likely that the researchers would also conduct a subset analysis and report an additional negative finding. This is illustrated in Table 2 where the 19 studies are divided into two groups; the 7 studies with a subset analysis of those under age 35 for first use and the remaining 12 studies that did not report an age subset analysis. What we observe is that those studies with a higher overall relative risk were more likely to carry out and report a subset analysis. The 12 studies without a separate subset analysis had a summary relative risk of 1.01; 95% CI, 0.88-1.17 while the 7 studies with a reported subset analysis had a summary relative risk of 1.30; 95% CI, 1.05-1.59. Thus if all 19 studies had reported a subset analysis it is very likely that the summary relative risk for those first exposed before age 35 would be considerably smaller than what is quoted for the 7 studies. So we conclude that the use of a relative risk value of 1.75 for those first exposed before age 35 is not valid.

We have not addressed the individual studies with regard to confounding factors and the various sources of the study subjects UV exposures

*Medical University of South Carolina
August 10, 2011

TABLE 1

Studies from the IARC meta analysis

Year	Study	RR	95% CI
1981	Adam	2.93	(1.16-7.40)
1986	Holman	1.10	(0.60-1.80)
1988	Osterlind	0.73	(0.53-1.01)
1988	Swerdlow	2.94	(1.41-6.17)
1988	Zanetti	0.90	(0.40-2.00)
1989	MacKie (males)	1.30	(0.20-7.90)
1989	MacKie (females)	1.20	(0.50-3.00)
1993	Dunn-Lane	1.16	(0.54-2.47)
1993	Garbe	1.50	(0.90-2.40)
1994	Autier	0.97	(0.71-1.32)
1994	Westerdahl	1.30	(0.90-1.80)
1995	Holly	0.94	(0.74-1.20)
1998	Chen	1.13	(0.82-1.54)
1999	Walter	1.54	(1.16-2.05)
2000	Naldi	0.78	(0.45-1.37)
2000	Westerdahl	1.20	(0.90-1.60)
2001	Kaskel	1.00	(0.60-1.80)
2003	Veierod	1.55	(1.04-2.32)
2004	Bataille	1.19	(0.84-1.68)
2005	Bataille	0.90	(0.71-1.14)
	Summary	**1.14**	**(1.00-1.30)**

TABLE 2

Studies without a subset analysis

Year	Study	RR	95% C.I.
1981	Adam	2.93	(1.16-7.40)
1986	Holman	1.10	(0.60-1.80)
1988	Osterlind	0.73	(0.53-1.01)
1988	Zanetti	0.90	(0.40-2.00)
1989	MacKie (males)	1.30	(0.20-7.90)
1989	MacKie (females)	1.20	(0.50-3.00)
1993	Dunn-Lane	1.16	(0.54-2.47)
1993	Garbe	1.50	(0.90-2.40)
1994	Autier	0.97	(0.71-1.32)
1995	Holly	0.94	(0.74-1.20)
2000	Naldi	0.78	(0.45-1.37)
2001	Kaskel	1.00	(0.60-1.80)
2004	Bataille	1.19	(0.84-1.68)
	Summary	**1.01**	**(0.88-1.17)**

Studies with a subset analysis

1988	Swerdlow	2.94	(1.41-6.17)
1994	Westerdahl	1.30	(0.90-1.80)
1998	Chen	1.13	(0.82-1.54)
1999	Walter	1.54	(1.16-2.05)
2000	Westerdahl	1.20	(0.90-1.60)
2003	Veierod	1.55	(1.04-2.32)
2005	Bataille	0.90	(0.71-1.14)
	Summary	**1.30**	**(1.05-1.59)**

February 2015

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1993 - 1997	Professor and Chairman, Department of Biometry and Epidemiology and Associate Director for Epidemiology, Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina
1981 - 1993	Director, Division of Biometry and Risk Assessment, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina
1990 - 1991	Acting Director, National Institute of Environmental Health Sciences and also the National Toxicology Program, Research Triangle Park, North Carolina
1984 - 1986	Associate Director, Radiation Effects Research Foundation, Hiroshima, Japan
1979 - 1980	Visiting Scientist, Epidemiology Department, Radiation Effects Research Foundation, Hiroshima, Japan
1977 - 1979	Acting Scientific Director, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina
1973 - 1981	Chief, Biometry Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina
1970 - 1973	Mathematical Statistician, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

1970 - 1993 Adjunct Professor, Department of Biostatistics, University of North Carolina, Chapel Hill

1968 - 1970 Statistician, Oak Ridge National Laboratory, Oak Ridge, Tennessee

1967 - 1968 Senior Mathematician, Westinghouse Research Laboratories, Pittsburgh, Pennsylvania

Honors and Other Scientific Recognition:

Fellow, American Statistical Association, 1974-present
NIH Director's Award, 1977
Mortimer Spiegelman Gold Medal Award, American Public Health Association, 1977
Public Health Service Superior Service Award, 1980
Senior Executive Service Award, 1983, 1987 - 1991
Citation Classic, Institute for Scientific Information (Hoel et al. "Estimation of risks of irreversible delayed toxicity" J. Toxicol. Env. Health 1:133-51, 1975).
Member, Council of Fellows, Collegium Ramazzini, 1987-present
Member, Institute of Medicine, National Academy of Sciences, 1988-present
Council Member, National Council on Radiation Protection and Measurements (NCRP), 1992-1998 and 1999-2005
Westinghouse Distinguished Scientist, 1993-2004
Ramazzini 1994 Award Recipient for "Contributions to scientific knowledge on the oncogenic effects of nuclear radiation"
Fellow, American Association for the Advancement of Science, 1997- present
National Associate, National Academy of Sciences and National Research Council, 2001-

Editorial - Books:

Methods for Estimating Risk of Chemical Injury: Human and Nonhuman Biota and Ecosystems, SCOPE /SGOMSEC 2, Proceedings of Workshop on Quantitative Estimation of Risk to Human Health from Chemicals, Rome, Italy, 1982 (co-editor with VB Vouk, GC Butler and DB Pekall).

Banbury Report 19: Risk Quantitation and Regulatory Policy, Proceedings of the Banbury Conference on Risk Quantitation and Regulatory Policy, (co-editor with R Merrill and F Perera). Cold Spring Harbor Laboratory, 1985.

Statistical Methods in Cancer Epidemiology, Proceedings of a Conference of the U.S.-Japan Cooperative Cancer Research Program, 1985 (co-editor with W Blot and T Hirayama).

Trends in Cancer Mortality in Industrial Countries, (co-editor with D Davis), New York Academy of Sciences, 1990.

Biostatistics in Cancer Risk Assessment, (co-editor with T Yanagawa), Scientist, Inc. Tokyo, 1991.

2-Amino-N^6-hydroxyadenine: A collaborative study on the genetic toxicology of 2-amino-N^6-hydroxyadenine, (co-editor with FJ de Serres), Mutation Research, Vol. 253, 1991.

International Case Studies in Risk Assessment and Management, (co-editor with L Mohr and W Nixon), The Medical University of South Carolina Press, 1998.

Multimedia Modeling and Risk Assessment, (co-editor with J Regens and C Travis), The Medical University of South Carolina Press 1999.

Extrapolation of Radiation-Induced Cancer Risks from Nonhuman Experimental Systems To Human, (Chairman) Members included B Carnes, R Dedrick, RJ M Fry, D Grahn, W Griffith, P Groer, RJ Preston) National Council on Radiation Protection and Measurements, NCRP Report No. 150, 2005.

Editorial - Journals:

Associate Editor, Journal of Statistical Computation and Simulation, 1972 - 1978
Associate Editor, Journal of the American Statistical Association, 1973 - 1979
Member, Editorial Board of the Journal of Toxicology and Environmental Health, 1975 - 1979
Member, Editorial Board of Communications in Statistics, Part B - Simulation and Computation, 1977 - 1979
Member, Editorial Board of the Journal of Environmental Pathology and Toxicology, 1979 - 1980
Member, Editorial Board of Fundamental and Applied Toxicology, 1981 – 1986
Member, Editorial Board of Environmental Health Perspectives, 1973 - 2000
Member, Editorial Advisory Board of Journal of Statistical Computation and Simulation, 1978 -
Member, Editorial Board of the IMA Journal of Mathematics Applied in Medicine and Biology, 1983 – 1988
Member, Editorial Advisory Board of Environmental and Occupational Health Sciences: A Series, 1986 -
Section Editor, Journal of Environmental Pathology, Toxicology and Oncology, 1986 -
Associate Editor, American Journal of Industrial Medicine, 1987 - date
Associate Editor, Environmental Research, 1987 - date
Member, Editorial Board of Risk Analysis, 1987 - 1990
Associate Editor, Journal of Communications in Statistics, 1987 -
Associate Editor, Biological Monitoring: An International Journal, 1988 - 1990
Member, International Advisory Board, Journal of Environmental Statistics, 1992 - 1995
Section Editor, Encyclopedia of Biostatistics, 1996 - 1997
Advisory Board, Environmental and Ecological Statistics, 2004 - date

Societies:

American Statistical Association
Biometric Society
Society for Risk Analysis
Collegium Ramazzini
American Association for the Advancement of Science
Radiation Research Society
Health Physics Society
Society for Epidemiological Research

Society Appointments:

Member, Regional Committee of the Biometric Society (ENAR), 1973 - 75, 1978 - 80

Biometrics Section Representative on the Council of the American Statistical Association, 1975 - 76
Secretary, Biometrics Section, American Statistical Association, 1979
Representative of the Institute of Mathematical Statistics to the Biology Section of the AAAS, 1978 - 1981
Program Chairman, Biometric Society Spring Meetings, 1977
Member, Council of the Society for Risk Analysis, 1982-85
Member/Chairman, American Statistical Association Awards Committee, 1991-93

National Academy of Sciences Committees:

Member, Subcommittee on Margin of Safety and Extrapolation of the Safe Drinking Water Committee, 1976 - 77
Member, Panel on Low Molecular Weight Halogenated Hydrocarbons of the Coordinating Committee for Scientific and Technical Assessments of Environmental Pollutants, 1976-77
Chairman, Risk Assessment Subcommittee, Safe Drinking Water Committee, 1978 - 79
Member, Committee on Chemical Environmental Mutagens, 1980 - 83
Member, Board on Toxicology and Environmental Health Hazards, 1982 - 85
Member, Committee on the Biological Effects of Ionizing Radiation (BEIR V), 1986 - 9
Member, Committee to Provide Interim Oversight of the DOE Nuclear Weapons Complex, 1988 - 90
Member, Committee on Environmental Epidemiology, 1990 - 92
Member, Committee on Epidemiology and Veterans Follow-up Studies, 1990 -
Member, Committee on Applied and Theoretical Statistics, 1991 - 94
Member, Committee on The Health Effects of Mustard Gas and Lewisite, 1991-92
Chairman, Committee to Study the Mortality of Military Personnel Present at Atmospheric Tests of Nuclear Weapons, 1993-94
Member, National Toxicology Program's Science Advisory Board 1994-96
Chairman, Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam, 1996 – 2002
Member, Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, 1997 – 2003
Chairman, Board of the Medical Follow-up Agency, 1996 –2001
Member, Commission on Life Sciences, 1999-2000
Advisor, Division on Earth and Life Studies (DELS), 2001-
Chairman, Medical Follow-up Agency, Patterns of Illness and Care before Deployment to the Persian Gulf War, 2001-3
Member, Defense Threat Reduction Agency (DTRA), Committee to Review the Dose Reconstruction Program, 2002-3
Member, Committee on California Agriculture Res. Priorities - Pierce's Disease, 2003-4
Member, Committee on Evaluation of Radiation Shielding for Space Exploration 2006-8
Member, Committee on Beryllium Alloy Exposures 2006-8
Chairman, Committee on Health Effects of Depleted Uranium 2007-8
Scientific Councilor, Radiation Effects Research Foundation (Hiroshima) 2006-2016
Member, Board on Nuclear and Radiation Studies 2008-2011
Member, Committee on the Evaluation of Space Radiation Cancer Risk Models 2011-12
Member, Committee on the Research Directions in Human Biological Effects of Low

Level Ionizing Radiation 2013-14.
Member, Committee on Ethics, Principles and Guidelines for Health Standards for Long Duration and Exploration Spaceflights, 2013-14.

World Health Organization and Other International Activities:

Member, International Agency for Research on Cancer Working Group on the Use of Mechanistic Data to Evaluate the Carcinogenicity of Chemicals to Humans, 1991
Member, International Agency for Research on Cancer Working Group on the Evaluation of the Carcinogenic Risks to Humans, 1977, 1981, 1982
Consultant, Subcommittee of International Commission for Protection against Environmental Mutagens and Carcinogens (ICPEMC) 1977 - 1982
Member, Environmental Mutagenesis and Carcinogenesis Panel, US-Japan Cooperative Medical Science Program, NCI; 1987-1992
Member, Advisory Committee on The Radiation Protection of the Public from Radioactive Residues in Kazakhstan, International Atomic Energy Agency United Nations 2003 - 2005
Contributor to United Nation's UNSCEAR Report 2006
Member, International Agency for Research on Cancer Working Group on the Evaluation of the Carcinogenic Risks to Humans, Vol. 100D Ionizing Radiation 2009

U.S. Environmental Protection Agency Advisory Committees:

Ex-officio member, Administrator's Pesticide Policy Advisory Committee, EPA, 1976
Advisor, Carcinogen Assessment Group, EPA, 1977
Member, Work Group on Health Effects Risks of the EPA Science Advisory Board's Committee on Research Strategies, 1987 – 1988
Member, EPA's FIFRA (pesticide) Science Advisory Panel 1993-
Member, EPA's Science Advisory Board's Radiation Advisory Committee 1993-1995
Chairman, EPA's Expert Panel Review of Benzene Risk Assessment, 1997
Consultant, EPA's Science Advisory Board's Radiation Advisory Committee, 1996-
Member, EPA's Science Advisory Board's Environmental Health Committee, 1997-2004
Member, EPA's Science Advisory Board's Environmental Health Committee, TCE Health Risk Assessment: Synthesis and Characterization Review Panel, 2002
Member, EPA's Expert Panel Review of Perchlorate, 2002
Member, EPA's Expert Panel Review of Asbestos, 2003
Member, EPA's Expert Panel Review, Supplemental Guidance for Assessing Cancer Susceptibility from early-life Exposure to Carcinogens" (SGACS), 2003
Member, Board of Scientific Counselors' Subcommittee on Human Health Research 2008-
Member, EPA's Science Advisory Board's Environmental Health Committee, TCE Health Risk Assessment: Synthesis and Characterization Review Panel, 2010
Consultant, Radiation Advisory Committee (RAC) of EPA's Science Advisory Board's review of the draft report "EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population, Dec. 2008". 2009-2010.
Member, EPA's Science Advisory Board's Perchlorate Maximum Contaminant Level Goals Approaches Review Panel, 2012-3

Other Advisory Committees:

Chairman, Subcommittee on Estimation of Risks of Irreversible, Delayed Toxicity of the DHEW Committee to Coordinate Toxicology and Related Programs, 1975

Member, Scientific Advisory Board of the National Center for Toxicological Research, 1977 - 1980

Member, Ad Hoc Working Group to Develop Radioepidemiological Tables, NIH, 1984

Member, Interagency Staff Group for Development of OSTP Carcinogen Document, Office of Science and Technology Policy, 1983 - 1984 (Report: Chemical Carcinogens: A Review of Science and Its Associated Principles, Environmental Health Perspectives, Vol. 67, pp 201-282, 1986).

Chairman, Research Needs Subcommittee of the Committee to Coordinate the Environment and Related Programs, U.S. Public Health Service, 1990 - 1991

Chairman, Committee to Study the Extrapolation of Radiation Risks from Animals to Humans, National Council on Radiation Protection and Measurements (NCRP), 1991-2005

Member, Office of Technology Assessment's Advisory Panel on Aging Nuclear Power Plants: Life Attainment, License Renewal, and Decommissioning. Congress of the United States, 1992.

Member, Scientific Advisory Committee of the Electric Power Research Institute's (EPRI) Environmental Risk Analysis Program, 1994-1995

Member, Scientific Committee 89 (non-ionizing radiation), National Council on Radiation Protection and Measurements (NCRP), 1994-1995

Member, Scientific Advisory Board, Environmental Health Foundation (EHF), 1994-8

Member, DOD's Breast Cancer Research Program Integration Panel, 1995-1996

Panel Member, NIH Consensus Development Conference on Breast Cancer Screening in Women Ages 40-49, 1997

Member, Health Effects Institute (HEI) Diesel Epidemiology Project, 1998-1999

Member, U.S. Consumer Product Safety Commission's Chronic Hazard Advisory Panel 1999-

Member, FDA's Transmissible Spongiform Encephalopathies Advisory Committee, 1997-2000

Consultant, FDA's Center for Biologics Evaluation and Research (CBER), 2004-2008

Chairman, NCRP's Report Committee 150: Extrapolation of Radiation-Induced Cancer Risks from Nonhuman Experimental Systems to Humans (2005)

Member, Electric Power Research Institute's committee report Evaluation of Updated Research on the Health Effects and Risks Associated with Low-Dose Ionizing Radiation (2009)

Member, NCRP's Report Committee: Guidance on Radiation Dose Limits for the Lens of the Eye (2014-2015)

International Conferences Organized:

"Methods for Estimating Risk of Chemical Injury: Human and Non-Human Biota and Ecosystems" in Rome, Italy, July 12-16, 1982 (with G. Butler, D. Peakall, and N. Nelson)

"Conference on Risk Assessment and Statistical Methods" in Kyoto, Japan, August 30-31, 1984 (with A. Kudo and K. Wakimoto)

"The Third Japan-U.S. Conference on Biostatistics in the Study of Human Cancer" in Hiroshima, Japan, November 11-13, 1988 (with K. Aoki and T. Yanagawa)

"Trends in Cancer Mortality in Industrial Countries" in Carpi, Italy, October 21-22, 1989 (with D. Davis, J. Fox, and A. Lopez)

"International Biostatistics Conference in the Study of Toxicology" in Tokyo, Japan, May 23-25, 1992 (with A. Sakuma and T. Yanagawa)

"The Fourth Japan-US Biostatistics Conference in the Study of Human Cancer" in Tokyo, Japan, November 9-11, 1992 (with R. Miller, H. Sugano, and T. Yanagawa)

"The Role of Environmental Factors in Breast Cancer: Collaborative Workshop" in Washington, DC, December 6-8, 1992 (with D. Davis)

"International Conference in Immunogenetic Risk Assessment in Human Disease" (MUSC) in Charleston, March 6-8, 1994 (with J. Pandey)

"The International Forum on Risk Assessment and Risk Management" (MUSC) in Charleston, March 5-7, 1996 (with L. Mohr and W. Nixon)

Congressional Testimony:

Senate Committee on Appropriations: Subcommittee on Labor, Health and Human Services, Education, and Related Agencies (Sen. Harkin) - March 14, 1991

House Committee on Appropriations: Subcommittee on Labor, Health and Human Services, Education, and Related Agencies (Cong. Natcher)- April 16, 1991

House Committee on Energy and Commerce: Subcommittee on Oversight and Investigations (Cong. Dingell) - May 8, 1991

Senate Committee on Appropriations: Subcommittee on Labor, Health and Human Services, Education, and Related Agencies (Sen. Specter) - February 5, 1997.

Senate Committee on Environment and Public Safety (Sen. Boxer) – May 6, 2008.

House Committee on Science and Technology: Subcommittee on Investigations and Oversight (Cong. Miller) - June 12, 2008.

Bibliography:

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2. Hoel DG: Sequential testing of sample size. Technometrics 10: 331-341, 1968.

3. Hoel DG: Closed sequential tests of an exponential parameter. Biometrika 55: 387-391, 1968.

4. Hoel DG and Mazumdar M: An extension of Paulson's selection procedure. Annals of Mathematical Statistics 39: 2067-2074, 1968.

5. Hoel DG: Discussion of engineering analysis of experimental data by Robert P. Benedict. ASME Trans. 91: 130, 1969.

6. Hoel DG and Mazumdar M: A class of sequential tests for an exponential parameter. Journal of American Statistical Association 64: 1549-1559, 1969.

7. Crump KS and Hoel DG: Some applications of renewal theory on the whole line. Journal of Applied Probabilty 7: 734-746, 1970.

8. Gaver Jr. DP and Hoel DG: Comparison of certain small-sample Poisson probability estimates. Technometrics 12: 835-850, 1970.

9. Hoel DG: On the Monotonicity of the OC of an SPRT. Annals of Mathematical Statistics 41: 310-314, 1970.

10. Hoel DG: A simple two-compartmental model applicable to enzyme regulation. Journal of Biological Chemistry 245: 5811-5812, 1970.

11. Hoel DG: Some modifications and applications of Wald's OC formula. Annals of the Institute of Statistical Mathematics 22: 65-75, 1970.

12. Kastenbaum MA, Hoel DG and Bowman KO: Sample size requirements: One-way analysis of variance. Biometrika 57: 421-430, 1970.

13. Kastenbaum MA, Hoel DG and Bowman KO: Sample size requirements: Randomized block designs. Biometrika 57: 573-577, 1970.

14. Hoel DG: A method for the construction of sequential selection procedures. Annals of Mathematical Statistics 42: 630-642, 1971.

15. Hoel DG and Mitchell TJ: The simulation, fitting, and testing of a stochastic cellular proliferation model. Biometrics 27: 191-199, 1971.

16. Hoel DG and Sobel M: Comparisons of sequential procedures for selecting the best binomial population. Proceedings of the Sixth Berkeley Symposium on Probability and Statistics 4: 53-69, 1971.

17. Hoel DG: A representation of mortality data by competing risks. Biometrics 28: 475-488, 1972.

18. Hoel DG: An inverse stopping rule for play-the-winner sampling. Journal of American Statistical Association 67: 148-151, 1972.

19. Hoel DG, Sobel M and Weiss GH: A two-stage procedure for choosing the better of two binomial populations. Biometrika 59: 317-322, 1972.

20. Hoel DG and Walburg Jr. HE: Statistical analysis of survival experiments. Journal of the National Cancer Institute 49: 361-372, 1972.

21. Hook GER, Bend JR, Hoel DG, Fouts JR and Gram,TE: Preparation of lung microsomes and a comparison of the distribution of enzymes between subcellular fractions of rabbit lung and liver. Journal of the Pharmocology Experimental Therapeutics182: 474-490, 1972.

22. Beauchamp JJ and Hoel DG: Some investigations and simulation studies of canonical analysis. J. Stat. Comput. Simul. 2: 197-209, 1973.

23. Hoel DG and Crump KS: Estimating the generation time distribution of an age-dependent branching process. Biometrics 30: 125-135, 1973.

24. Patel KM and Hoel DG: A generalized Jonckheere K-sample test against ordered alternatives when observations are subject to arbitrary right censorship. Communication in Statistics 2: 373-380, 1973.

25. Patel KM and Hoel DG: A nonparametric test for interaction in factorial experiments. Journal of American Statistical Association 68: 615-620, 1973.

26. Chand N and Hoel DG: A comparison of models for determining safe levels of environmental agents. In Proschan F and Serfling RJ (Eds.): Reliability and Biometry. Philadelphia, SIAM, 1974, pp. 681-700.

27. Crump KS and Hoel DG: Mathematical models for estimating mutation rates in cell populations. Biometrika 61: 237-252, 1974.

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29. Hoel DG: Some statistical aspects of experiments for determining the teratogenic effects of chemicals. In Pratt J (Ed.): Statistical and Mathematical Aspects of Pollution Problems. New York Marcel Dekker, Inc., 1974, pp. 375-381.

30. Hoel DG: Statistical models for estimating carcinogenic risks from animal data. In Proceedings of the Fifth Annual Conference on Environmental Toxicology. AMRL-TR-74-125 Washington, D.C., GPO, 1974, pp. 285-291.

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35. Hoel DG, Sobel M and Weiss GH: A survey of adaptive sampling for clinical trials. In Elashoff RM (Ed.): Perspectives in Biometrics. New York, Academic Press, 1975, pp. 29-61.

36. Hoel DG, Sobel M and Weiss GH: Comparisons of sampling methods for choosing the best binomial population with delayed observations. J. Stat. Comput. Simul. 3: 299-313, 1975.

37. Hoel DG and Weiss GH: A clinical trial design with a fixed maximum number of failures. Communication in Statistics 4: 429-436, 1975.

38. Simon R, Weiss GH and Hoel DG: Sequential analysis of binomial clinical trials. Biometrika 62: 195-200, 1975.

39. Crump KS, Hoel DG, Langley CH and Peto R: Fundamental carcinogenic processes and their implications for low dose risk assessment. Cancer Research 36: 2973-2979, 1976.

40. Hoel DG: Statistical extrapolation methods for estimating risks from animal data. Annals of New York Academy Sciences 271: 418-420, 1976.

41. Hoel DG, Weiss GH and Simon R: Sequential tests for composite hypotheses with two binomial populations. Royal Statistical Society 38: 302-308, 1976.

42. Guess HA and Hoel DG: The effect of dose on cancer latency period. Journal of Environmental Toxicology 1: 279-286, 1977.

43. Hoel DG: Some problems in low dose extrapolation. In Hiatt HH, Watson JD and Winsten JA (Eds.): Origins of Human Cancer, Vol. 4, Book C. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, 1977, pp. 1391-1396.

44. Hoel DG and Weiss GH: Properties of noise emitted by vehicular queues. Transportation Research 11: 39-44, 1977.

45. Simon R, Hoel DG and Weiss GH: The use of covariate information in the sequential analysis of dichotomous response experiments. Communication in Statistics (A-Theory and Methods) 6: 777-788, 1977.

46. Haseman JK and Hoel DG: Statistical design of toxicity assays: Role of genetic structure of test animal population. Journal of Toxicology Environmental Health 5: 89-101, 1979.

47. Hogan MD, Chi P, Hoel DG and Mitchell TJ: Association between chloroform levels in finished drinking water supplies and various site-specific cancer mortality rates. J. of Journal of Environmental Pathology and Toxicology 2: 873-887, 1979.

48. Hoel DG: Animal experimentation and its relevance to man. Proceedings from US-Japan Conference on Biostatistics in the Study of Human Cancer, May 1978. Environmental Health Perspective 32: 25-30, 1979.

49. Hoel DG: Low-dose and species-to-species extrapolation for chemically induced carcinogenesis. In McElheny VK and Abrahamson S (Eds): Banbury Report 1: Assessing Chemical Mutagens: The Risk to Humans. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, 1979, pp. 135-145.

50. Hoel DG: Sequential methods in genetic risk assessment. Genetics 92: s195-s198, 1979.

51. Hoel DG: Statistical approaches to toxicological data. Proceedings, 5th Symposium on Statistics and the Environment, NAS. Environmental Health Perspective 32: 267-271, 1979.

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53. Anderson MW, Hoel DG and Kaplan NL: A general scheme for the incorporation of pharmacokinetics in low dose risk estimation for chemical carcinogenesis: Example--vinyl chloride. Toxicology Applied Pharmacology 55: 154-161, 1980.

54. Hoel DG: Incorporation of background in dose-response models. Proceedings, Symposium on Extrapolation of Laboratory Toxicity Data to Man: Factors Influencing the Dose-Toxic Response Relationship, April 1979. Federation Proceedings 39: 73-75, 1980.

55. Yanagimoto T and Hoel DG: Comparisons of models for estimation of safe doses using measures of the heaviness of tail of a distribution. Annals of the Institute of Statistical Mathematics, Part B, 32: 465-480, 1980.

56. Yanagimoto T and Hoel DG: Measures of the heaviness of tail of estimation of safe doses. In Matusita K (Ed.): Recent Developments in Statistical Inference and Data Analysis. New York, North Holland Publishing Company, 1980, pp. 347-357.

57. Gaylor DW and Hoel DG: Statistical analysis of carcinogenesis data from chronic animal studies. In Sontag JM (Ed.): Carcinogens in Industry and Environment. New York, Marcel Dekker, 1981, pp. 97-111.

58. Haseman JK, Hoel DG and Jennrich RI: Some practical problems arising from the use of the gamma multi-hit model for risk estimation. Journal of Toxicology Environmental Health 8: 379-386, 1981.

59. Hogan MD and Hoel DG: Estimated cancer risk associated with occupational asbestos exposure. Risk Analysis l: 67-76, 1981.

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62. Hoel DG: Statistical issues in toxicology. Selected Papers, Society for Industrial & Applied Mathematics. Environmetrics 81: 248-257, 1981.

63. Hoel DG and Crump KS: Waterbourne Carcinogens: A Scientist's View. In Crandell R and Lave L (Ed.): The Scientific Basis of Health in Safety Regulations. The Brookings Institute, 173-195 1981.

64. Hoel DG: Extrapolation of laboratory data to human health effects. Environmental Science Research 25: 521-526, 1982.

65. Hoel DG: Statistical measures of risk. Drug Metabolic Reviews 13: 829-838, 1982.

66. Hogan MD and Hoel DG: Extrapolation to man. In Hayes AW (Ed.): Principles and Methods of Toxicology. New York, Raven Press, 1982, pp. 711-731.

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69. Brown KG and Hoel DG: Multistage prediction of cancer in serially dosed animals with application to the ED_{01} study. Fundamental Applied Toxicology 3: 470-477, 1983.

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71. Hoel DG, Kaplan N and Anderson MW: Implication of nonlinear kinetics on risk estimation in carcinogenesis. Science 219: 1032-1037, 1983.

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75. Portier C and Hoel DG: Low-dose rate extrapolation using the multistage model. Biometrics 39: 897-906, 1983.

76. Poon AH and Hoel DG: Nonparametric estimation of the survival function when cause of death is uncertain. Biometrics 40: 1151-1158, 1984.

77. Portier C and Hoel DG: Design of animal carcinogenicity studies for goodness-of-fit to multistage models. Fundamental Applied Toxicology 4: 949-959, 1984.

78. Portier C and Hoel DG: Type I error of trend tests in proportions and the design of cancer screens. Communication in Statistics (A-Theory and Methods) 13: 1-16, 1984.

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81. Hoel DG: Mathematical dose-response models and their application to risk estimation. In Vouk VB, Butler GC, Hoel DG and Pekall DB (Eds.): Methods for Estimating Risk of Chemical Injury: Human and Nonhuman Biota and Ecosystems, Scope 1985/SGOMSEC 2. New York, J. Wiley and Sons, 1985, pp. 347-359.

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84. Hoel DG: The impact of occupational exposure patterns on quantitative risk estimation. In Hoel DG, Merrill RA and Perera FP (Eds.): Risk Quantitation and Regulatory Policy,

Banbury Report 19, 1984. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, 1985, pp. 105-118.

85. Hoel DG: Dose-response in radiation carcinogenesis: Animal studies. In Castellani A (Ed.): Epidemiology and Quantitation of Environmental Risk in Humans from Radiation and Other Agents: Potential and Limitations. London, Plenum Press, pp. 93-103, 1985.

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88. Hoel DG: The incorporation of pharmacokinetics in low-dose risk estimation. In Clayton D, Krewski D and Munro I (Eds.): Toxicological Risk Assessment (Volume I). Boca Raton, Fla., CRC Press, 1985, pp.205-214.

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91. Brown KG and Hoel DG: Statistical modeling of animal bioassay data with variable dosing regimens: Example--vinyl chloride. Risk Analysis 6: 155-166, 1986.

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2. Book Chapter on Ionizing Radiation in: "Casarett & Doull's Toxicology: The Basic Science of Poisons", Eighth Edition; Curtis Klaassen (Editor) McGraw Hill, New York, 2013.

3. Book Chapter on Radiation in: "Oxford Textbook of Children's Environmental Health" Phillip Landrigan and Ruth Etzel (Editors) Oxford University Press, 2014.

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Attachment D

Letter of Dr. David G. Hoel to FDA (Mar. 21, 2016)

DAVID G. HOEL, PH.D.
36 SOUTH BATTERY
CHARLESTON, SOUTH CAROLINA 29401

TELEPHONE: 843-723-1155 EMAIL: DGHOEL@GMAIL.COM

March 21, 2016

Neil R. P. Ogden
Center for Devices and Radiological Health
Food and Drug Administration

Re: Docket No. FDA-2015-N-1765
Proposed Rule for the Restricted Sale, Distribution, and Use of Sunlamp Products

Dear Mr. Ogden:

There is no real credible scientific evidence that persons under age 18 are at increased susceptibility to the effects of indoor tanning than older individuals. Lazovich et al. 2010 [Ref. 1] expressly found that younger individuals are not at increased susceptibility to the effects of UV radiation, and Colanatonio et al. 2014 [Ref. 2] found that there is no statistically significant correlation between the use of sunbeds before age 25 and increased risk of melanoma. Colantonio et al. 2014 was a meta analysis (weighted average of odds ratios) of 7 studies which considered separately the risk of melanoma for those first beginning tanning under the age of 25 with those that first began after age 25. The weighted average of the 7 odds ratio for melanoma for those under age 25 years was 1.35 with a 95% confidence interval of 0.99 to 1.84. Since the value of 1.0 for the odds ratio was included within the confidence interval the estimated average of 1.35 is not considered to be statistically different from 1.0. One of the studies in the group of 7 (Chen et al. 1998 [Ref. 3]) also separated those first exposed before 1970 from those first exposed after 1970. Since the older pre 1970 sunbeds and lamps used a different UVR frequency it would be more appropriate to use the post 1970 data in the Chen study in the meta analysis. Doing this reduces the meta analysis estimated odds ratio to 1.18 with a confidence interval of 0.80 to 1.74. This is no different than the corresponding estimate for those who first began tanning after the age of 25 of 1.16 with a confidence interval of 0.90 to 1.49. Neither estimate is statistically significant.

Studies that have separated out data from home use and tanning salon use of sunlamp products have found little risk of melanoma from tanning salons and high risk of melanoma from home use of sunlamp products [Refs. 3, 4]. Chen et al. found among those first tanning under age 25 that there was a statistically significant melanoma increase in those using sunlamps at home with an odds ratio = 1.79 while for those using commercial tanning had a non significant odds ratio of 0.63. This is probably because of the increased risk of UV burns in home use of

sunlamp products. The relationship between UV exposure and melanoma risk is not straightforward. Sunburns have been associated with increased risk of melanoma, but nonburning chronic sun exposure has been associated with reduced risk of melanoma [Ref. 5].

FDA's statements in the Federal Register indicate that FDA has not evaluated the health risks involved with banning use of commercial tanning salons by persons under 18. In my opinion, FDA's proposed rule to restrict use of commercial indoor tanning salons to persons age 18 and older may possibly cause additional health problems by leading to an increase in underage tanning at home.

The FDA also ignores the health benefits of UV exposure for both the need for sufficient vitamin D levels as well as the cardiovascular benefits, which specifically involve UV but not vitamin D. For the protective health effects of UV exposure that is obtainable through commercial sun tanning especially during the cold winter months and also for protection against summer vacation sunburns are ignored by the FDA.

Sincerely yours,

David G. Hoel

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[1] Lazovich D, Vogel RI, Weinstock MA, Anderson KE, Warshaw MA. Indoor Tanning and Risk of Melanoma: A Case-Control Study in a Highly Exposed Population. Cancer Epidemiol Biomarkers Prev 2010; 19:1557-1568.

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Attachment E

Schlesselman JJ. "Use of Indoor Tanning Devices and Risk of Melanoma: Review of an Assessment by a Working Group of the International Agency for Research on Cancer" (Aug. 28, 2012).

Curriculum Vitae, James J. Schlesselman, Ph.D.

James J. Schlesselman, PhD

Use of Indoor Tanning Devices and Risk of Melanoma: Review of an Assessment by a Working Group of the International Agency for Research on Cancer

This review conveys my comments on the report entitled "Exposure to Artificial UV Radiation and Skin Cancer," [1] which was prepared by a Working Group convened under the auspices of the International Agency for Research on Cancer (IARC).[a] The report was published in abbreviated form as an article in the International Journal of Cancer. [2] The Working Group's conclusions with respect to cutaneous melanoma were also summarized by IARC staff in a special policy report published in 2009. [3] Although the Working Group's report [1] on skin cancer in relation to the use of indoor tanning devices included epidemiologic studies of basal-cell and squamous-cell skin cancers, my discussion is focused on the more serious of these conditions: cutaneous malignant melanoma, hereafter called *melanoma*.

The occasional use of the phrase *indoor tanning* in my review, as opposed to *indoor tanning devices*, represents a shorthand expression for the use of sunlamps and/or sunbeds without regard to the specific devices involved, which have changed over time, and without regard to the circumstances of use: at home (sunlamps) or in commercial tanning facilities (sunbeds), both situations in which regulatory standards for use may or may not be followed.

My review proceeds as follows: Section 1 summarizes the background of the IARC report. Section 2 discusses its major findings concerning a purported increased risk of melanoma arising from the use of indoor tanning devices, especially when used before age 35. Section 3 discusses the Working Group's interpretation of their analyses. There I point out inconsistencies between the Working Group's conclusions and statements made in their report. [1] I also point out that the IARC's analyses do not provide a scientifically reliable basis to infer that harm arises from indoor tanning by teens and young adults when they use commercially-operated facilities in the USA that adhere to FDA regulations and guidance.[b] Section 4 provides a summary of my review.

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[a] For convenience of expression, I refer occasionally to the *IARC* as shorthand for its Working Group.

[b] *See* Performance standards for light-emitting products (21CFR1040.20); Required reports for the sunlamps and sunlamp products manufacturers or industry; and Industry Guidance - other documents of interest: http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/HomeBusinessandEntertainment/ucm116447.htm

1. Background

The origin of the IARC Working Group's report and their remit were stated as follows: [1 (p. ix)]

> "The concern that there may be an association between exposure to artificial UV radiation and skin cancer was reactivated in 2003-4 when the 10th Report on Carcinogens published by the National Toxicology Program in the USA classified UVA radiation as a "Known Carcinogen to Humans".
>
> "In October 2004, the French Ministry of Health contacted the Director of the International Agency for Research on Cancer (IARC), Dr Peter Boyle, raising a particular concern about the continuous increase in incidence of melanomas in France and in the world. Since the last IARC Monograph on ultraviolet (UV) radiation in 1992, a large number of epidemiological and experimental studies have been conducted on the risks associated with exposure to UV radiation. The Ministry therefore requested IARC to investigate the possibility of reevaluating the carcinogenic risk associated with this radiation, particularly concerning artificial UV sources and the use of indoor tanning facilities.
>
> "A Working Group and a Secretariat were gathered by Dr Peter Boyle to this end. The Secretariat met in January to prepare for the meeting of the Working Group in June 2005. The Working Group met on 27–29 June 2005 to compile the present document."

1.1 Overview of the IARC report. To provide context for the Working Group's meta-analyses [c] of epidemiologic studies of skin cancer in relation to the use of indoor tanning devices, and to aid in their assessment of potential risk, the Working Group:

- Summarized the physical characteristics and sources of exposure to natural and artificial ultraviolet (UV) radiation, particularly UVA and UVB. [1 (pp. 1-5), d]

- Reviewed European and international positions regarding artificial sources of UV radiation, including standards for tanning devices, national and international policies regarding UV-emitting

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[c] ***Meta-Analysis***. "A collection of techniques whereby the results of two or more independent studies are statistically combined to yield an overall answer to a question of interest. The rationale behind this approach is to provide a [statistical] test with more power than is provided by the separate studies themselves. The procedure has become increasingly popular in the last decade or so but it is not without its critics particularly because of the difficulties of knowing which studies should be included and to which population final results actually apply." *See* Everitt BS. The Cambridge Dictionary of Statistics, third edition. Cambridge: Cambridge University Press, 2006, p. 256.

[d] According to the classification of the Commission Internationale de l'Eclairage (CIE, International Commission on Illumination), ***UVA*** is the region between 315 and 400 nm; ***UVB*** is 280-315 nm; and ***UVC*** is 100-280 nm. Visible light is the region between 400 nm and 780 nm. [1 (p. 1), 4 (p. 43)]

devices used for purpose of tanning, and regulations and recommendations by health authorities [1 (pp. 5-6, Appendix)]

- Presented an overview of the biological effects of UV radiation studied in various experimental systems, such as cells, tissue, and laboratory animals. [1 (pp. 7-10).]

- Reported findings from a number of surveys concerning the prevalence of indoor tanning and compliance with regulations by the customers and operators of commercial tanning facilities. [1 (pp. 11-19)]

The Working Group's overview of the biological effects of UV-radiation exposure mentioned above drew upon three prior reviews, [4, 5, 6] one of which was by an IARC Working Group in 1992. [4]

The IARC's 2006 report acknowledged that "no valid animal model of human melanoma or other skin cancers exists." [1 (p. 20)] Thus, with respect to assessing the magnitude of skin cancer risk possibly associated with the use of indoor tanning devices, the Working Group necessarily relied on epidemiologic studies (observational studies in humans), while pointing out some of the deficiencies of that evidence: [1 (p. 20), e]

> "As no valid animal model of human melanoma or other skin cancers exists, evidence of an association between indoor tanning facility exposure and skin cancer must be sought predominantly from epidemiological studies. Few studies have addressed this topic specifically, but most skin cancer studies have included one or more items about use of indoor tanning facilities. We systematically analysed the summary statistics compiled from the relevant studies in a meta-analysis. The results have also been discussed qualitatively, to allow for the large differences in study populations and study quality."

[e] As noted by the Working Group, "Since melanoma and other skin cancers differ somewhat in their aetiology, studies of melanoma were analysed separately from those of basal and squamous cell cancers." [1 (p. 20)]

1.2 Major findings by the IARC. With respect to melanoma, a succinct but somewhat inaccurate expression of the Working Group's findings appears in their published article: [2 (Abstract)]

> "Based on 19 informative [epidemiologic] studies, ever-use of sunbeds was positively associated with melanoma (summary relative risk, 1.15; 95% CI, 1.00–1.31), although there was no consistent evidence of a dose–response relationship. First exposure to sunbeds before 35 years of age significantly increased the risk of melanoma, based on 7 informative studies (summary relative risk, 1.75; 95% CI, 1.35-2.26)."

A somewhat different summary was published in a special policy report by IARC staff:

> "A comprehensive meta-analysis concluded that the risk of cutaneous melanoma is increased by 75% when use of tanning devices starts before 30 years of age." [3 (p. 752)]

The inaccuracy in the first quotation above concerns the Working Group's referral to "sunbeds." Their analyses were not specific to sunbeds, much less to use of sunbeds in compliance with regulatory standards: all types of tanning devices, including sunlamps used at home, were conflated in the Working Group's analyses of indoor tanning devices. [f] The importance of this point concerns the intensity of the UV exposures involved, and the opportunity for UV burns, the latter being a major risk factor for melanoma. Section 2.4 and section 3.1 discuss these matters further.

In the second quotation above, the IARC staff refers to first use of indoor tanning devices before age 30, as opposed to age 35, which appears in the first quotation above, and which was likewise stated by the IARC Working Group in their report: [1 (p. 30)]

> "When "first exposure [to sunlamps/sunbeds] before age 35 years" was analysed, a [statistically] significant 75% increase in risk was detected … " [g]

The Working Group also noted, however, that their analysis of age at first use refers to age "less than approximately 30 years," [1 (p. 50)] probably because most of the data used in the analysis was based on age at first use < 30 years: see Figure 1 in section 2.1 below.

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[f] Figure 1 in Chen et al. (1998) provides examples of different types of sunlamps and sunbeds. [10 (p. 760)]

[g] ***Statistically significant***: *informally*, the probability that the result observed is unlikely to be due to chance; i.e., the probability is less than 5% that a result as extreme as that observed will occur. Calculations of statistical significance do not account for study bias, or other multiple sources of error.

The Working Group emphasized their summary estimate of relative risk 1.75 [h] in partial justification of their conclusion that use of indoor tanning devices, particularly before age 35 years, involves a carcinogenic hazard for melanoma:

> "there is convincing evidence to support a causal relationship, particularly with exposure before the age of 35 years." [1 (p 50)]

In view of the importance of this assertion, and the claim by the IARC that use of indoor tanning devices before age 30 or 35 confers a 75% increased risk of melanoma, section 2 below reviews the IARC's meta-analysis of melanoma in relation to initial use of indoor tanning devices before age 35. [i]

2. IARC Meta-Analysis: First Use of Indoor Tanning Devices Before Age 35 [j]

2.1 The epidemiologic studies involved. Figure 1 on the following page reproduces Table 9 from the IARC report. It shows information concerning the estimates of relative risk from the 7 epidemiologic studies that formed the basis of the Working Group's summary estimate 1.75. [7, 8, 9, 10, 11, 12, 13] With one exception, a cohort study in Norway and Sweden,[12] the studies were of case-control design. [14]

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[h] ***Relative risk***: "The ratio of the risk of an event among the exposed to the risk among the unexposed." ***Risk***: "The probability that an event will occur, e.g., that an individual will become ill or die within a stated period of time or before a certain age." *See* Porta M. A Dictionary of Epidemiology, fifth edition. New York: Oxford, 2008, p. 213 & p. 217. For example, in year 2004 melanoma was diagnosed in U.S. white females age 20-54 at an annual rate of 22.6 cases per 100,000 women. As a hypothetical, if this rate were truly increased 1.75-fold from indoor tanning initiated before age 35, then melanoma would occur at the rate of 39.5 cases per 100,000 annually (1.75 × 22.6) in women who had initiated indoor tanning before age 35.

[i] A graphical summary of the Working Group's meta-analysis, presented in Figure 3 of their report [1 (p 31)] and reproduced as Figure 2 in their publication, [2 (p 1120)] refers to Walter et al. (1999). The correct citation is the article by Walter et al. (1990).

[j] Many of the problems of meta-analysis discussed in this section apply equally to the IARC's other summary estimate of relative risk, 1.15 (95% CI: 1.00–1.31), corresponding to ever-use of indoor tanning devices.

Figure 1. Table 9 from the IARC report. [1]

Table 9. Estimates included in the evaluation of an association of first use of indoor tanning facility in youth and risk for melanoma

Reference	Definition	Relative risk (95% CI)	Adjustment
Swerdlow *et al.* (1988)	Age at first exposure <30 years *vs* never	3.8 (0.9–16.5)	Naevi, skin type, hair and eye colour, sun exposure
Walter *et al.* (1990)	Age at first use <30 years *vs* never	1.67 (1.17–2.39)	Age
Westerdahl *et al.* (1994)	Ever use of sunbed at age younger than 30 years	2.7 (0.7–9.8)	Sunburns, hair colour, naevi, sunbathing
Chen *et al.* (1998)	Age at first use of sunlamp < 25 years *vs* never	1.35 (0.88–2.08)	Sex, age, phenotype index, recreational sun exposure
Westerdahl *et al.* (2000)	Age at first exposure ≤ 35 years *vs* never	1.6 (0.9–2.9)	Sunburns, hair colour, skin type, naevi
Veierod *et al.* (2003)	Exposure at age 20–29: ≥ 1 time/month *vs* never	2.58 (1.48–4.50)	Age, region of residence, sunburns, summer vacations
Bataille *et al.* (2005)	Ever sunbed use before age 15 years *vs* never	1.82 (0.92–3.62)	Age, sex, skin type

The title of Table 9 refers to "first use of indoor tanning facility in youth." This is a mischaracterization in two respects. As shown above, age at first use was not limited to *youth*, unless one includes 20-year olds and 30-year olds (≤ 35 years) in the definition. What is not evident from Table 9, however, is that none of the estimates of relative risk relates specifically to indoor tanning *facilities*.

Figure 2 (following page) shows that in every instance except perhaps one, *exposure* represented a person's use of either sunlamps and/or sunbeds: in other words, exposure was not defined by tanning in a facility.

Figure 2 also provides other pertinent information on the studies involved: the years in which the cases of melanoma were diagnosed, the pathologic entities considered to be melanoma, the age ranges of the cases, and the locations in which the studies were conducted. This information is based on the material and methods sections in the published articles with one minor exception: for the study reported by Chen et al. (2008), the age range is based on an initial report by Berwick et al. (1996),[15] which was cited by Chen et al. for further information on their study's design. [k]

[k] In 4 of the 6 case-control studies, response rates ranged from 85% to 90% for the cases, and from 70% to 80% for the controls. Two studies, by Swerdlow et al. (1998) and Bataille et al. (2005), did not report response rates.

Figure 2. Study characteristics.

Reference	Years of Dx	Endpoint	Age Range	Exposure	Location
Swerdlow et al. (1988)	1979-84	CMM	15 - 84	UV lamps & sunbeds	Glasgow, Edinburgh & West Scotland
Walter et al. (1990)	1984-86	CMM [1]	20 - 69	sunlamps & sunbeds	Southern Ontario, Canada
Westerdahl et al. (1994)	1988-90	CMM [2]	15 - 75	sunlamps & sunbeds	Southern Sweden
Chen et al. (1998) *	1987	CMM	18 to >70	sunlamps & sunbeds	Connecticut, USA
Westerdahl et al. (2000)	1995-97	CMM [2]	16 - 80	sunbeds **	Southern Sweden
Veierød et al. (2003) †	1991-99	CMM [3]	30 - 59	sunlamps & sunbeds	Norway and Sweden
Bataille et al. (2005)	1998-2001	CMM [4]	18 - 49	sunlamps & sunbeds #	Sweden, The Netherlands, UK, Belgium, France

CMM primary cutaneous malignant melanoma.

CMM [1] included Hutchison's melanotic freckle, lentigo maligna, and melanoma in situ.

CMM [2] restricted to invasive disease.

CMM [3] among the 187 incident cases, 183 were primary invasive disease; 4 cases involved a "second cancer diagnosis."

CMM [4] excluded lentigo maligna and melanoma in situ.

* Age range and response rate in cases based on Berwick et al. 1996.

** Sunlamps may have been included: see authors' Discussion section, which characterizes results from their prior study in terms of "sunbed use," when both sunlamps and sunbeds were used to define exposure.

† Study was based on a cohort of women in which exposure was determined prior to diagnosis of melanoma.

Authors' tabulations refer to "sunbed use," but this included mercury lamps and portable UV units for tanning the face.

Three additional points are worth noting, [1] all in connection with the two studies reported by Westerdahl et al. [9, 11]

First, the estimate of relative risk cited by the IARC in connection with the study by Westerdahl et al. (1994), relative risk = 2.7 (95% CI 0.7 – 9.8) in Figure 1 above, refers only to melanoma occurring *before* 30 years of age, not thereafter. [9 (Table 1)] Although cases ranging in age from 15 to 75 years were

[1] A review of the methods, strengths and weaknesses of the 7 epidemiologic studies involved in the IARC's meta-analysis falls beyond my objective, which is to discuss the IARC's analysis and conclusions. Thus, I only note issues arising from studies insofar as they are pertinent to my review of the IARC's report [1] and published article. [2]

included for study in Westerdahl et al. (1994), see Figure 2 above, their estimate of relative risk 2.7 does not refer to, or apply to, a purportedly increased risk of melanoma occurring at age 30 years or older, a time when the majority of melanomas are diagnosed. This point bears on the interpretation of every estimate of relative risk cited by the IARC in their Table 9, as well as their summary estimate: the values of relative risk in Table 9 do not refer to melanoma occurring within any consistent range of age, such as before age 50, or from age 20 to 60, etc. In consequence, the meaning of the IARC's summary estimate of relative risk 1.75 based on the data in Table 9 (Figure 1 above) is ambiguous at best, and its numerical value 1.75 cannot be interpreted without making a number of assumptions about a hypothetical effect of indoor tanning exposure.

The second issue concerns the study reported by Westerdahl et al. in year 2000. Age at first use of indoor tanning devices was defined by the age cutpoint ≤ 35 years, in contrast to the age cutpoint < 30 years used by Westerdahl et al. in 1994. With respect to that earlier study, the investigators stated the following: [9 (p. 694)]

> "We decided to focus the study on persons younger than age 30 years because exposure to sunbeds or sunlamps has been shown to be particularly common among young persons (13)."

If exposure to sunbeds and sunlamps was "particularly common among young persons" as of 1988-1990, the time of case ascertainment in Westerdahl et al.'s 1994 article (see Figure 2 above), then surely such exposure was at least as common if not more so in 1995-1997, the time of case ascertainment in Westerdahl et al.'s 2000 article. Thus, what was the reason for changing the age cutpoint to ≤ 35 years in the later study? Was this done to avoid reporting inconsistent findings between the two studies? One cannot tell, because no discussion of the age cutpoint ≤ 35 years appears in Westerdahl et al. (2000). [m]

The third point concerns the investigators' inclusion of cases of *in situ* melanoma when they intended to study *invasive* disease. As background on this point, Westerdahl et al. (2000) state that:

> "The study identified 709 persons, aged 16–80 years, in the South Swedish Health Care Region with a first histopathological diagnosis of cutaneous *invasive* malignant melanoma between 1 January 1995 and 30 June 1997, according to the population-based Regional Tumour Registry." [11 (p. 1593)] [authors' emphasis in italics]

The investigators then note that 13 of the 709 cases (2%) were incorrectly reported as invasive disease, because in situ melanoma was subsequently established. [11 (p. 1594)] These 13 cases should have been

[m] There were more cases of melanoma in Westerdahl et al. (2000) than in Westerdahl et al. (1994): 517 versus 400, respectively. Thus, a sufficient number of cases age <30 should have been available for analysis by Westerdahl et al. (2000).

excluded from the study. The investigators' only rationale, such as it is, for inclusion of in situ melanoma is their statement that:

> "Furthermore, when the 13 cases with in situ melanoma were excluded from the analyses the results were unaltered."

If this is true, then there was no reason to include these cases. Furthermore, the results referred to are not made clear … do the investigators mean every result reported? One should be somewhat skeptical that the investigators' assurance, quoted above, applies to their estimate of relative risk corresponding to first use of indoor tanning devices at age ≤ 35 years.

2.2 Estimates of relative risk. Using the data shown in Figure 1 (IARC Table 9), the Working Group calculated a summary estimate of the relative risk of melanoma to be 1.75 (95% CI: 1.35–2.26).[n] My own calculation based on these data, which employs random effects meta-analysis, [16] the method used by the IARC, yields a summary estimate of relative risk equal to 1.74 (95% CI: 1.41–2.15). Putting aside the question whether these summary estimates of relative risk actually have any meaning, a point discussed on pages 7-8 above, the numerical difference between my calculation and that reported by the IARC is not of great consequence. I mention the difference because my calculation differs slightly from that by the IARC and, more importantly, because there is an error in the Working Group's tabulated data, which I correct, and because of the additional analyses I report below.

The error in the IARC's tabulated data concerns the estimate of relative risk from the study by Westerdahl et al. (2000). As shown in Figure 1, the Working Group used the value 1.6 (95% CI: 0.9 – 2.9). This estimate of relative risk, however, refers to age at first exposure > 35 years.[o] The correct value corresponding to age at first exposure ≤ 35 years is 2.3 (95% CI: 1.2 – 4.2). [11 (Table 2)] With this correction, the summary estimate of relative risk by my calculation is 1.82 (95% CI: 1.47 – 2.25), which is slightly larger than the summary estimate 1.75 reported by the IARC.

A further adjustment to the Working Group's analysis should also be made which takes into account the updated estimate of relative risk from the study by Veierød et al. (2003). Whereas the Working Group used the value RR = 2.58, Veierød et al. reported in 2010, based on 5 additional years of follow-up data, that RR = 1.53 (95% CI: 0.99 – 2.38). [17 (Table 5)]

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[n] The IARC used PROC MIXED in SAS (version 8.02) for their meta-analysis. [1 (p. 30)]

[o] The error arose in extracting the data from Table 2 in Westerdahl et al. (2000).

Incorporating the updated information shown in Figure 3 below (bold font), the resulting summary estimate of relative risk by my calculation is 1.67 (95% CI: 1.37 – 2.05), which is slightly smaller than the summary estimate 1.75 reported by the IARC.

Figure 3. Correction to IARC's Table 9, with Updated Results from Veierød et al.

Study	RR	L95	U95
Swerdlow et al. (1988)	3.80	0.90	16.50
Walter et al. (1990)	1.67	1.17	2.39
Westerdahl et al. (1994)	2.70	0.70	9.80
Chen et al. (1998)	1.35	0.88	2.08
Westerdahl et al. (2000)	**2.30**	**1.20**	**4.20**
Veierød et al. (2010)	**1.53**	**0.99**	**2.38**
Bataille et al. (2005)	1.82	0.92	3.62

RR = estimated relative risk.
L95 & U95: lower and upper 95% confidence limits.

One additional point should be noted: the estimate of relative risk 1.82 from Bataille et al. (2005), see Figure 3 above, was essentially repudiated by the study investigators in an article appearing in the same issue of the journal which published the initial report:

> "Whilst we cannot rule out the possibility that sunbed use is not a risk factor for melanoma and may even be protective, the indications for potential biases in recruitment and recall make it impossible to rely on risk estimates derived from our analyses [Bataille et al. (2005)]." [See de Vries et al. (2005) [18 (p. 2153)]]

If one accepts the judgment of the study investigators, quoted above, then the estimate of relative risk 1.82 from Bataille et al. (2005) should not have been included in the IARC's meta-analysis. [P] This is of little consequence in the present instance: if one omits Bataille et al. (2005), the resulting summary estimate of relative risk by my calculation is 1.66 (95% CI: 1.34 – 2.05).

[P] Three co-authors (Drs. Boniol, Doré, and Autier) of the report by deVries et al.,[18] which essentially repudiated Bataille et al.'s estimates of the relative risk of melanoma in relation to indoor tanning,[13] were members of the IARC Working Group. Despite this, and inexplicably to me, the IARC's meta-analysis included Bataille et al.'s estimates of relative risk.

2.3 Additional analyses conducted by the IARC. The discussion above in section 2.2 concerns the IARC's meta-analysis of melanoma in relation to *first use* of indoor tanning devices before age 35.

The Working Group also performed meta-analyses concerning other aspects of indoor tanning exposure: *ever use* of indoor tanning devices, regardless of when first use began; *duration of use*; use *distant-in-time*; and use *recent-in-time*. [q] Various analyses were also performed by the IARC in which some epidemiologic studies were dropped from consideration, with essentially the same results as those from their meta-analysis based on all of the studies having available information, although the resultant studies represented only a fraction of the 19 studies involved (see below). [1 (Tables 11-15)]

Results from 19 epidemiologic studies were used in the Working Group in their primary meta-analysis of *ever use* of indoor tanning devices. [1 (Table 11, Figure 2)] Only 5 of these studies, however, were included in their analysis of melanoma risk in relation to indoor tanning *distant-in-time* and *recent-in-time*. [1 (Table 10)] The Working Group's meta-analysis of *duration of use* was limited even further: only 4 of the 19 epidemiologic studies were included. [1 (Table 15)] Thus, the opportunity for bias arising from meta-analysis based on few among many studies is noteworthy. [r] The Working Group attempted to assess whether *publication bias* might account for their summary estimates of increased relative risk, [1 (pp. 35 & 35)] but the method they employed is neither sensitive nor specific for detecting publication bias. [19 (pp. 114-5), 20 (p. 66)]

2.4 Limitations of meta-analysis. The Working Group's claim that use of indoor tanning devices increases the risk of melanoma relied extensively on their meta-analysis. They did not, however, discuss the limitations of the method they employed.

One major deficiency of the IARC's meta-analysis arises from the epidemiologic studies that were involved: few studies had detailed information on tanning behaviors, such as a person's age at start, the number of times indoor tanning had been used per year, the devices that had been used, whether burns had occurred from use of indoor tanning devices, and whether the assessment of use was restricted to

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[q] Use distant-in-time and use recent-in-time were not assessed reliably by the IARC: few studies recorded details of indoor tanning, and only 5 studies were involved in the meta-analysis of distant vs. recent exposure. [1 (Table 10)]

[r] ***Bias*** refers to a "deviation of results or inferences from the truth, or processes leading to such deviation; any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth." *See* Last JM. A Dictionary of Epidemiology, fourth edition. New York: Oxford University Press, 2001, p.14.

modern fluorescent lamps in commercial facilities that followed regulatory guidance by the FDA or other national standards.

Another deficiency of many studies is that important potential confounders, [s] such as a person's skin type, number of nevi, family history of melanoma, and whether burns had occurred from outdoor UV exposure, were not assessed or taken into account in the analyses of the original study data. [1 (pp. 20-25 & Tables 8-10)] Thus, the IARC's meta-analysis, which was based on the reported results of these studies, did not and could not remediate these deficiencies of study design and analysis.

Finally, many studies did not consider latency, i.e., the period of time required before the effect of some agent, such as a drug, device or other exposure, becomes manifest.

In view of the above, the IARC's summary estimates of relative risk, 1.15 for *ever use* of indoor tanning devices, and 1.75 for *first use* at age ≤ 35 years, are not scientifically reliable estimates of the effect, if any, of indoor tanning on melanoma occurrence. The IARC's estimates of relative risk moreover, do not relate to the use of modern sunbeds, whether as a teenager, or as a young adult or older person, in commercially-operated facilities that follow FDA regulations and guidance, or other national standards.

A few additional points should be mentioned. The first concerns the 95% confidence intervals on the IARC's summary estimates of relative risk. These confidence intervals do not represent the full extent of uncertainty about the relative risk of melanoma.[21, t]

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[s] ***Confounding*** refers to the situation in which underlying factors give rise to an apparent association between an exposure and putative outcome, where no cause-and-effect exists. For example, as stated by the IARC Working Group: "Users of indoor tanning facilities have been shown to have a greater-than-average propensity to engage in intentional sun exposure (Autier et al., 1991), and may have characteristics of inherited sun sensitivity different from the rest of the population (see [IARC's] page 9). Hence, a possible association between exposure to tanning appliances and risk for melanoma could in fact be due to greater sun exposure than average, or to greater use of indoor tanning facilities by subjects naturally more prone to melanoma." [1 (pp. 34-36)]

[t] ***Confidence interval***. "A range of values, calculated from sample observations, that is believed, with a particular level of probability, to contain the true parameter value. A 95% confidence interval, for example, implies that were the estimation process repeated again and again, then 95% of the calculated intervals would be expected to contain the true parameter value." *See* Everitt BS. The Cambridge Dictionary of Statistics, third edition. Cambridge: Cambridge University Press, 2006, p. 93.

For example, for first use of indoor tanning devices at age ≤ 35, the IARC reports the following summary estimate of relative risk and 95% confidence interval (CI): 1.75 (95% CI: 1.35 – 2.26). Although the lower 95% confidence limit 1.35 exceeds 1.0, the "no effect" value, the actual effect of indoor tanning at age ≤ 35 on the risk of melanoma could be vanishingly small or nonexistent. In other words, the true (but unknown) relative risk may lie below 1.35, and could even be 1.0, i.e., correspond to no increased risk whatsoever. [u] Why is this so? Some reasons in general are the following:

> "No meta-analysis can compensate for the inherent limits of nonexperimental data for making inferences about causal effects. … The meta-analyst should remember that even if the variations across studies appear to be no more than random, it remains possible that all studies suffered similar systematic error, or have net error in the same direction." [22 (p. 654)]

> "Like large epidemiologic studies, meta-analyses run the risk of appearing to give results that are more precise and conclusive than warranted (Egger et al., 1998). The large number of subjects contributing to a meta-analysis will often lead to very narrow confidence intervals for the effect estimate [e.g., the estimate of relative risk]. It is thus crucial to remember that these intervals take no account of average bias across studies, and take account of between-study variation in effect or bias only under restrictive assumptions. When uncertainties about bias sources are included, interval estimates will expand dramatically (Greenland 2005b; see Chapter 19)." [22 (p. 677)]

> "Systematic errors [v] can be and often are larger than random errors, and failure to appreciate their impact is potentially disastrous. The problem is magnified in large studies and pooling projects [such as meta-analyses], because in those studies the large size reduces the amount of random error. In such studies, a focus on "statistical significance" or even on confidence limits may amount to nothing more than a decision to focus on artifacts of systematic error as if they reflect a real causal effect." … "A discomforting aspect of these analyses [to assess systematic error in studies] is that they reveal the highly tentative and subjective nature of inference from observational data, a problem that is concealed by conventional statistical analysis." [23 (pp. 346-7)]

The first paragraph quoted above refers to potential systematic errors and bias. These are discussed in section 2.5 and section 2.6 which follow.

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[u] Similar remarks about uncertainty of possibly increased relative risk apply to the upper 95% confidence limit: 2.26.

[v] Such as those arising from residual confounding, biased selection of study subjects, or biased information.

2.5 Bias from surveillance and detection. The possibility of biased *surveillance for* and *detection of* melanoma in persons who use indoor tanning devices was not discussed or addressed by the IARC. [1, 2] To my knowledge, this matter has not been addressed by any epidemiologic study of indoor tanning reported to date.

There are several reasons why methods of detecting melanoma are important. To begin, melanoma is not like a myocardial infarction or a stroke, which routinely lead to a trip to an emergency room, a stay in hospital, and eventual diagnosis. Melanoma has no symptoms of early disease, only signs: the appearance of a new lesion, i.e., a nevus or pigmented mole, or a change in the size, elevation or pigmentation of an existing lesion occurring on one's skin. [w] To be diagnosed with melanoma, one must therefore notice its signs, then seek an exam, receive a biopsy, and then have that biopsy specimen examined by a pathologist, preferably one experienced with skin cancer. [24, 25, 26, 27, 28]

Skin examinations for melanoma are not routinely done,[x] and if done tend to be targeted to individuals thought to be at increased risk of melanoma, which presumptively includes persons with a history of indoor tanning. [y] Furthermore, public-health activities such as skin-cancer screening initiatives in Scotland [29] and unfavorable media attention to indoor tanning in Australia, [30 (p. 2433)] will increase the likelihood of detecting melanoma in persons who tan indoors, while missing the detection of melanoma in those who do not. With regard to the USA, the Centers for Disease Control and Prevention (CDC) and the FDA, to name two U.S. federal agencies, emphasize the presumptive hazards of indoor tanning. [31, 32] The U.S. American Academy of Dermatology (AAD), moreover, has been a long-standing advocate of screening for skin cancer, with programs in place since the mid-1980s. [33] Like the CDC and the FDA, the AAD alerts persons to the presumptive hazard of indoor tanning devices.[34]

With respect to the IARC's meta-analysis, which included epidemiologic studies worldwide, the Working Group noted the following: [1 (p. 3)]

> "In the 1980s and 1990s, amid growing concern about the carcinogenic potential of UVB, the UV output of low-pressure fluorescent lamps was shifted towards UVA, allowing so-called "UVA tanning"."

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[w] Bleeding and ulceration, which can arise later, are indicative of *late-stage* disease. This represented at most 16% of melanoma cases diagnosed in the USA between 2002 and 2008: http://seer.cancer.gov/statfacts/html/melan.html .

[x] http://www.cdc.gov/cancer/skin/basic_info/screening.htm

[y] http://www.cdc.gov/cancer/skin/basic_info/risk_factors.htm

Thus, concerns about skin cancer in relation to indoor tanning have apparently been expressed for many years.

An Australian case-control study of melanoma in relation to indoor tanning, reported by Cust et al. in 2011, refers explicitly to that study's avoidance of selection bias arising from media coverage. [30 (p. 2433)] Such concern complements earlier remarks by de Vries et al. on their European population-based study, reported in 2005:[17 (p. 2153)]

> "the indications for potential biases in recruitment and recall make it impossible to rely on risk estimates derived from our analyses. The data presented here highlight the need to be aware of potential recall and selection biases when studying an exposure for a disease in a well educated and informed population."

Another concern related to biased surveillance for and detection of melanoma is that persons who use indoor tanning devices may be more aware of the condition of their skin, and thus more likely to notice any changes on their body. The importance of this possibility is reinforced by a study of 471 patients newly diagnosed with melanoma between 1995 and 1998: 57% of patients detected their own melanoma; only 16% of melanomas were detected by physicians. [35]

With respect to screening for melanoma, Terushkin and Halpern note the following: [36 (p. 487)]

> "Despite the lack of official guidelines, numerous screening programs have been performed in an effort to diagnose earlier forms of melanoma. Screening efforts in the United States were initiated as early as 1985 by the American Academy of Dermatology (AAD) and continue to this day. In a survey of participants with suspected melanomas in the 1992 to 1994 programs, Koh and colleagues [33] showed that more than 90% of melanomas detected measured less than 1.5 mm in depth. Melanomas at a less advanced stage were found during screenings, in comparison to the 1990 Surveillance, Epidemiology and End Result Registry (SEERR) data."

Thus, persons who are preferentially screened for melanoma are expected to have earlier-stage disease and, as discussed above, persons with a history of indoor tanning may be more likely to have melanoma detected and diagnosed.

From an analysis of incidence data for melanoma in the Surveillance, Epidemiology and End Results Registry (SEER) , and skin biopsy rates from Medicare claims in the USA, Welch et al. concluded that for the period 1986 to 2001: [37 (Abstract)]

> "The incidence of melanoma is associated with biopsy rates. That the extra cases diagnosed were confined to early stage cancer while mortality remained stable suggests over diagnosis – the increased incidence being largely the result of increased diagnostic scrutiny and not an increase in the incidence of disease."

The implication of surveillance and detection bias is that epidemiologic studies may be destined to find a spuriously increased relative risk of melanoma in relation to indoor tanning, even if there is no recall bias or self-selection bias involved.

If surveillance and detection bias were present, then one would expect cases of melanoma with a history of indoor tanning to be more likely to have smaller tumor size (T), less nodal involvement (N), and less metastatic (M) disease at diagnosis as compared to cases of melanoma with no history of indoor tanning. Comparisons of TNM stage for the cases exposed to indoor tanning, versus the cases with no history of this, would not rule out the possibility that differential biopsy rates led to more cases of melanoma being detected in persons with a history of indoor tanning. Comparisons of TNM stage would, however, provide the first step to address an important issue that should have been addressed by the IARC. [z]

In summary, conducting epidemiologic studies in populations with haphazard screening for and detection of melanoma, or which target individuals thought to be at high risk of melanoma, increases the likelihood of biased results. A meta-analysis of biased results does not resolve the problem. Analyses which consider study participants' answers to questions about skin exams and melanoma detection could possibly address some of the issues discussed above. It is far preferable, however, to perform epidemiologic studies in non-contaminated environments, rather than attempt to account for biased surveillance and detection by post-hoc statistical analyses of the resulting data.

2.6 Bias from self-selection and recall in case-control studies. [aa] As a matter of good study design and implementation, the method employed to contact cases and controls, such as by letter, telephone-screening interview, or nurse-interview, should not reveal the study's main purpose.

2.6.1 Self-selection bias. One reason for masking the purpose of study and the hypothesis involved is to avoid biased self-selection into the study. For example, one wants to avoid conducting a study in which persons with melanoma who happened to have tanned indoors are more likely to agree to participate, which would result in estimates of relative risk that were biased toward values >1.0. Likewise, one wants to avoid having potential controls who tanned indoors decline participation, perhaps thinking mistakenly

[z] TNM stage has long been the de-facto standard of pathologic diagnosis of melanoma and other cancers. The International Union Against Cancer (http://www.uicc.org/node/7735) describes TNM as "the globally accepted method of describing the anatomical extent of cancer."

[aa] The considerations discussed in this section do not apply to cohort studies, such as that by Veierød et al.,[12, 17] in which exposure information is collected before the occurrence of disease.

that because they don't have melanoma the study has nothing to do with them, which would likewise bias estimates of relative risk toward values > 1.0.

If all study-eligible cases and all study-eligible controls agree to participate, then there would be no possibility of bias from self-selection, although major bias could still arise from other sources (see section 2.5 above).

With regard to first use of indoor tanning devices before age 35, the IARC Working Group relied on 7 epidemiologic studies, 6 of which were case-control studies. Four of these studies reported the rates of participation for cases and controls. These ranged from 85% to 90% for study-eligible cases, and from 70% to 80% for study-eligible controls.[8, 9, 10, 11, 15] Swerdlow et al. and Bataille et al. did not report this information.[7, 13, 18]

The standard argument used to dismiss self-selection bias is the absence of direct evidence for it, despite the fact that there is rarely any reliable evidence at all ... either for, or against, self-selection bias. Although one could perform sensitivity analyses in which various assumptions are made about exposure in the non-participating cases and controls, this is rarely done, and it was not done for the case-control studies upon which the IARC relied.

One reason for not performing a sensitivity analysis of self-selection bias is that the results often lead to a very wide range of estimates of relative risk. Another reason is that one doesn't know whether the assumptions used in a sensitivity analysis are close to the facts, which cannot be determined. In any event, the IARC Working Group gave no consideration to self-selection bias, and they did not report the response rates for the case-control studies involved in their analyses.

As noted above on page 10, the investigators for the case-control study reported by Bataille et al. [13] essentially repudiated [18 (p. 2153)] their finding no increased risk of melanoma in relation to indoor tanning, in part because of possible bias in recruiting controls:

> "High percentages of sunbed use among controls indicated possible recruitment bias: eligible controls who were sunbed users were probably more likely to accept the invitation to participate than non-users, possibly due to a feeling of 'guilt' or 'worry' about their habits. Such selective participation may have strongly influenced the risk estimates of sunbed use in our study." [18 (Abstract)]

The argument quoted above is not only indirect, but also speculative. [bb] The investigators' motivation for questioning their results arose from finding no association between melanoma and sunlight exposure, including sunburns, or between melanoma and the use of tanning beds. [cc]

An editorial comment [38] on the articles by Bataille et al. [13] and by de Vries et al. [18] expressed the widely-held opinion that indoor tanning is a well-established hazard for melanoma, because it involves increased exposure to UV radiation. [39] Neither the editorial nor the analyses reported by Bataille et al. and by de Vries et al., however, addressed the two major hypotheses in this regard: (1) that an increased risk of melanoma arises from *excessive* UV radiation exposure, represented for example by burns; and (2) that increased risk arises from *intermittent exposure,* which itself could be a correlate of burns. [27] None of the IARC's meta-analyses [1, 2] addressed either one of these important issues.

2.6.2 Recall bias. A second reason for masking the purpose of study and its underlying hypothesis is to ensure that the information collected by self-administered questionnaires and interviews, either in person or by telephone, is not biased. For example, one wants to avoid having some of the cases claim that they had used indoor tanning devices when in fact they had not, or deny the use of indoor tanning when in fact they had done this. Furthermore, to avoid prompting persons to give replies in the direction expected under the hypothesis which motivates a study, e.g., the hypothesis that indoor tanning is harmful, one should ideally mask the purpose of study and its underlying hypothesis from the staff who conduct the telephone and/or personal interviews. This is often impossible to achieve in practice. Having a well-structured interview procedure, interview form, and good training of study interviewers may serve the purpose of masking the study personnel involved.

Swerdlow et al. and Chen et al. mention the use of a structured interview in their studies, but otherwise omit discussion of other important aspects of recall bias. [7, 10] Walter et al. paid great attention to recall bias, and offered evidence that it was not responsible for finding an association between melanoma and use of indoor tanning devices. [8]

[bb] The investigators did not report the participation rates (response rates) for the cases and controls in their study, and they did not perform a sensitivity analysis of their estimates of relative risk.

[cc] The term ***association*** is used in biomedical sciences as a synonym for correlation or relationship. Thus, an association refers to a statistical connection, not a causal dependence, between two or more factors. *See* Last JM. A Dictionary of Epidemiology, fourth edition. New York: Oxford University Press, 2001, p.7.

Westerdahl et al. used different lines of reasoning to support their belief that recall bias did not result in either one of their two studies reporting a spurious association between melanoma and the use of indoor tanning devices. In their 1994 article, Westerdahl et al. state that:

> "without knowing our hypothesis, a large percentage of the cases and controls answered the comprehensive [self-administered] questionnaire, which asked about a variety of different epidemiologic variables. At the time when cases and controls answered the questionnaire (1988-1990), the general population was unaware of a possible relation between the use of sunbeds or sunlamps and the development of malignant melanoma." [9 (p. 698)]

In their follow up study reported in 2000, Westerdahl et al. used a different line of reasoning, which suggests that some of the cases and the controls were aware of the study hypothesis:

> "We used identical procedures of data collection for cases and controls. In addition, information from cases was collected close in time to the diagnosis in order to avoid the influence, which the diagnosis of melanoma may have on recall of sunbed use. Nevertheless, it can not be solely ruled out that awareness of the diagnosis of malignant melanoma and the hypothesis of an association between sunbed use and melanoma occurrence may have perverted the answers to the questions on sunbed use. However, in the present study the estimated risks were virtually the same as those obtained when the general population was unaware of the hypothesis (Westerdahl et al, 1994). Moreover, a higher rate of both cases and controls reported exposure to sunbeds in the present study (cases: 44%; controls: 41%) compared to our previous study (cases: 29%; controls: 24%)." [11 (p. 1598)]

From Westerdahl et al.'s reasoning, quoted above, they essentially argue that when results *agree* with expectation, then recall bias is unlikely. This complements the reasoning by de Vries et al., quoted below, who dismiss finding no association between melanoma and use of indoor tanning devices, because some of their results *disagree* with expectation:

> "negative associations were found between sun exposure and melanoma risk (adj. OR 0.87 (95% CI: 0.65–1.18)) and in cases between sun exposure and naevus count. These observations led us to speculate that cases may have underreported their sun exposure and, most likely, their sunbed exposure." [18 (Abstract)]

In summary, reasoning from the belief that indoor tanning devices represent a carcinogenic hazard, without considering whether the devices are used properly or not, the investigators for two studies judged whether their results were subject to bias. If agreement with belief is the standard for ruling in or ruling out study bias, and accepting or dismissing results that are found, then there is no need to conduct a scientific investigation: belief suffices.

3. The IARC Working Group's Conclusions

The results of the Working Group's meta-analysis were said to support their conclusions:

> "On balance, the evidence pertaining to the strength, consistency, dose-response and temporal sequence of the association of the use of indoor tanning equipment with melanoma risk, and of the coherence and biologic plausibility of the association, leads us to conclude that ***there is convincing evidence to support a causal relationship, particularly with exposure before the age of 35 years. This evidence is strongly suggestive*** and further studies could clarify our understanding of this association and allow more definitive conclusions." [1 (p.50), 2 (p. 1121)] [my emphasis]

The Working Group did not parse the distinction they had in mind between "convincing evidence" and "strongly suggestive" evidence of cause-and-effect. [dd]

The IARC Working Group also did not resolve the inherent contradiction expressed in the Executive Summary of their report: [1 (p. xi)]

> "We have assessed the available evidence relating to possible detrimental health effects of exposure to artificial ultraviolet radiation through use of indoor tanning facilities, in particular whether their use increases the risk for skin cancer. ***Epidemiologic studies to date give no consistent evidence that use of indoor tanning facilities in general is associated with the development of melanoma or skin cancer. However, there was a prominent and consistent increase in risk for melanoma in people who first used indoor tanning facilities in their twenties or teen years. … Although the available findings are therefore not conclusive***, the strength of the existing evidence suggests that policymakers should consider enacting measures, such as prohibiting minors and discouraging young adults from using indoor tanning facilities, to protect the general population from possible additional risk for melanoma and squamous cell carcinoma." [1 (Executive Summary, p. xi)] [my emphasis]

As discussed above in section 2 and explained below, the Working Group's call for policymakers to prohibit minors and discourage young adults from using indoor tanning facilities is based on unreliable evidence concerning melanoma in relation to indoor tanning. Furthermore, the imprimatur of the IARC was used to lend credence to policy recommendations that some members of the Working Group evidently had in mind years before they met under the auspices of the International Agency for Research on Cancer. [40]

[dd] Perhaps what they meant is that the evidence is "convincing" to them, but that it might be only "strongly suggestive" to others. For reasons explained in my report, the evidence is neither convincing nor strongly suggestive that proper use of indoor tanning devices is a cause of melanoma.

In view of more recent commentary about policy concerning indoor tanning, [41, 42] one wonders whether the Working Group was fully capable of being objective in reaching conclusions, and whether the IARC's report was strongly influenced by prior opinions and beliefs of several of its members that indoor tanning is a melanoma hazard. [ee]

3.1 Exposure. As noted in section 1.2, the Working Group's meta-analysis made no distinction between the use of indoor tanning *facilities* and the use of indoor tanning *devices*. Indoor tanning devices represent not only sunbeds, which are used commercially, but also sunlamps which are used at home. (See for example Figure 1 in Chen et al. (1998). [10]) Some of the earlier tanning devices employed mercury lamps, which were "banned in most countries around 1980." [1 (p. 3)] Sunlamps and sunbeds now used for tanning employ UV-emitting fluorescent tubes, earlier versions of which were introduced in the 1960s. The IARC pointed out that the intensity and spectrum of UV radiation (UVA, UVB, UVC) emitted by fluorescent tubes used for tanning have varied greatly over time. [1 (pp. 3-5)]

While indoor tanning facilities (commercial tanning salons) use sunbeds, some facilities may not adhere to FDA regulations and guidance, or other national standards. The IARC's analyses took no account of proper versus improper use of tanning devices, modern sunbeds in particular. Likewise, the IARC did not consider the intensity of the UV-radiation exposures involved, or whether burns had occurred from improper use.

Although use of indoor tanning devices had been studied epidemiologically, deficiencies of those studies prevented the IARC from estimating the relative risk of melanoma in relation to the devices involved, their proper use (e.g., without burns or excessive exposure), and the UV-radiation doses incurred. Consequently, the IARC's estimates of increased relative risk based on meta-analysis cannot be interpreted as evidence of a melanoma hazard incurred from indoor tanning, whether as a teenager, young adult or as an older person, in commercially-operated facilities that follow FDA regulations and guidance, or other national standards.

[ee] Drs. Autier, Boniol, Boyle, Doré, and Green, who were co-authors of the cited commentaries on policy, [40, 41, 42] were members of the IARC Working Group. [1 (p. v)] Two other members, Dr. Westerdahl and Dr. Walter, had authored articles reporting that indoor tanning is associated with an increased risk of melanoma.

3.2 Criteria for assessment. The Working Group said their conclusion of cause-and-effect was based on the "strength, consistency, dose-response and temporal sequence of the association of the use of indoor tanning equipment with melanoma risk, and of the coherence and biologic plausibility of the association." [1 (p.50), 2 (p. 1121)] These considerations are widely accepted for the review of epidemiologic studies and forming judgments based upon them. [43, 44, 45] However, before the Working Group expressed their opinion that use of indoor tanning devices is a cause of melanoma, [ff] they should have considered the nature of the exposures involved (see section 3.1 above) and, equally important, whether bias, confounding, or chance [gg] were plausible explanations for the results they reported.[45] The latter three explanations (bias, confounding, and chance) were considered to some extent by the IARC, but evidently not thoroughly: see section 2.5 and section 2.6.

Consider now each of the criteria mentioned by the IARC … strength, consistency, dose-response, temporal sequence, coherence, and biologic plausibility – with additional reflection on bias, confounding, and chance.

3.2.1 Strength and consistency. The *strength* of association concerns the Working Group's summary estimate of relative risk in relation to first use of indoor tanning devices before age 35: [1 (p.50)]

> "Our systematic review of published studies, conducted mainly in North America and Europe, of the association of indoor tanning ***facility use*** with melanoma revealed an association of early age at first use (less than approximately 30 years) with melanoma risk. These studies consistently indicated a ***moderate strength*** of association, with a summary relative risk of 1.75 (1.35–2.26)." [my emphasis; the reference to "facility use" is mistaken]

[ff] The term ***cause*** refers to something that produces an effect. In biomedical investigations, the concept of cause denotes "a significant, effectual, relationship between an agent and an associated disorder or disease in the host." *See* Advisory Committee to the Surgeon General of the Public Health Service. Smoking and Health. U.S. Department of Health, Education, and Welfare, Public Health Service. Washington, DC: GPO, 1964, pp. 19-21 and pp. 123-257. In the natural or practical sciences, the cause of an event is considered to be "something among its temporal antecedents such that if it had not been present, the event would not have occurred." *See* Nowell-Smith PH. Causality *in* Encyclopedia Britannica, 14th ed, Chicago: Encyclopedia Britannica, 1973, pp. 104-7.

[gg] ***Chance***: the occurrence of events in an unpredictable, non-deterministic, or probabilistic manner. *See* H.T. David & W. Morris. Chance [I], pp. 403-5; and D.H. Mellor. Chance [II], pp. 405-11. *In* Encyclopedia of Statistical Sciences. Volume 1, Kotz S, Johnson NL (Eds.) New York: Wiley, 1982.

> "The association with ***ever use*** of these facilities [summary relative risk 1.15 (95% CI, 1.00–1.31)], or use more than 15 to 20 years prior to diagnosis of melanoma, ***was weak***, and evidence regarding a dose-response relationship was scanty." [1 (p.50)] [my emphasis]

With respect to "early age at first use," the lower 95% confidence limit 1.35 [hh] nominally rules out *chance* as a plausible explanation for the summary estimate of increased relative risk 1.75, [ii] but it fails to account for the fact that this summary estimate was derived from a meta-analysis based on only 7 of the 19 different studies that were used by the IARC to estimate the relative risk of melanoma in relation to *ever use* of indoor tanning devices. [1 (Table 8 & 11)]

Although each one of the 7 studies concerning *first use* of indoor tanning devices before age 35 reported a relative risk greater than 1.0, [jj] yielding results that are *consistent* in that respect, the individual estimates of increased relative risk could simply be a reflection of residual confounding, selective reporting, or other sources of bias, discussed above in section 2, surveillance bias and detection bias in particular, which were not considered by the IARC. [kk]

[hh] The standard interpretation of a 95% confidence interval (confidence limits) is that one is "95% confident" that the true but unknown value of relative risk lies within the interval reported. An important caveat, however, should be kept in mind: confidence intervals (confidence limits) do not account for bias, confounding, or errors of study conduct. This caveat also applies to results that are said to be "statistically significant."

[ii] The standard interpretation of a 95% confidence interval (confidence limits) is that one is "95% confident" that the true but unknown value of relative risk lies within the interval. An important caveat, however, should be kept in mind: confidence intervals (confidence limits) do not account for bias, confounding, or errors of study conduct. This caveat also applies to results that are said to be "statistically significant."

[jj] See Figure 1 and Figure 3 in section 2.1 above.

[kk] As noted above in section 2.3, the Working Group attempted to assess whether publication bias might account for their summary estimates of increased relative risk, but the method they employed is neither sensitive nor specific for that purpose. The Working Group also acknowledged that the evidence concerning indoor tanning is limited by potential confounding by sun exposure and other variables. [1 (p. 50)]

3.2.2 Dose response. The Working Group states the following:

> "On balance, the evidence pertaining to the strength, consistency, ***dose-response*** and temporal sequence ***of the association of the use of indoor tanning equipment with melanoma risk***, and of the coherence and biologic plausibility of the association, leads us to conclude that there is convincing evidence to support a causal relationship, particularly with exposure before the age of 35 years." [1 (p 50), 2 (p 1121)] [my emphasis]

As quoted above, the IARC Working Group seems to imply that there is evidence of a dose-response relationship between the occurrence of melanoma and the use of indoor tanning devices. This needs to be considered in light of what the Working Group also stated:

> "***There was no consistent evidence for a dose–response relationship*** between indoor tanning exposure and risk for melanoma." [1 (p. 40)] [my emphasis]

> "***A dose-response model was not considered*** for this meta-analysis because of the heterogeneity among the categories of duration and frequency of exposure used by different authors. [1 (p 26)] [my emphasis]

Figure 4 shows the Working Group 's evidence concerning dose response.

Figure 4. Table 15 from the IARC report. [1]

Table 15. Duration of exposure to indoor tanning facilities and risk for melanoma in selected case–control studies[1]

Reference Place & years of study Numbers of cases/control		Duration of exposure	Cases	Controls	Estimated risk	95% CI
Autier *et al.* (1994)		Never used	310	327	1.00	Ref.
Belgium, France, Germany,	Exposure starts	< 10 hours	36	45	0.75	0.46–1.25
1991–92	≥ 1980	≥ 10 hours	19	18	0.99	0.49–2.00
420/447[2]	Exposure starts	< 10 hours	16	15	1.00	0.47–2.13
	< 1980	≥ 10 hours	18	7	2.12	0.84–2.12
Westerdahl *et al.* (1994)		Never used	282	479	1.0	Ref.
Sweden, 1988-90		1–3 sessions/year	44	67	1.1	0.7–1.9
400/640		4–10 sessions/year	30	55	1.1	0.7–1.9
		>10 sessions/year	41	33	1.8	1.0–3.2
Chen *et al.* (1998)		Never used	483	417	1.00	Ref.
Connecticut, USA, 1987–89		< 10 sunlamp uses	76	50	1.25	0.84–1.84
624/512		≥ 10 sunlamp uses	63	40	1.15	0.60–2.20
Westerdahl *et al.* (2000)		Never used	319	538	1.0	Ref.
Sweden, 1995–97		1–125 uses	22	32	2.8	1.0–7.8
571/913		126–250 uses	34	31	3.1	1.3–7.1
		> 250 uses	31	37	1.5	0.7–3.2

[1] Duration of exposure, relative risk, and 95% confidences as in published reports. All estimated risks are adjusted for age, sex, natural sun sensitivity and recreational sun exposure.

[2] The 21 cases and 35 controls who were exposed to sunlamp or sunbed for non-tanning purposes are not reported in this Table.

With respect to Table 15, the Working Group wrote the following:

> "Table 15 presents adjusted relative risks for melanoma associated with exposure to tanning appliances, showing some statistically significant dose–effect relationship for two studies (Autier *et al.*, 1994; Westerdahl *et al.*, 1994), a borderline statistically significant dose–effect relationship in one study (Chen *et al.*, 1998), and one study with a non-significant dose–effect relationship (Westerdahl *et al.*, 2000). [1 (p 36)]

Contrary to the Working Group's claim, the study by Autier et al. (1994) does not show a statistically significant dose-effect relationship: there is no progressive increase in relative risk with increasing hours of use, and the confidence limits on the estimates of relative risk substantially overlap each other.

Likewise, the study by Westerdahl et al. (1994) does not show a statistically significant dose-effect relationship. Only among persons who were classified as having "> 10 sessions per year" was there a suggestion of increased risk (see Figure 4 above). Furthermore, Westerdahl et al. did not define what they meant by "> 10 sessions per year." Neither did they define what they meant by 1-3 and by 4-10 sessions per year. For example, does "> 10 sessions per year" refer to a person's having >10 indoor tanning sessions for every year beginning at age 15? … for every year beginning at age 20? … Or does "> 10 sessions per year" refer to an individual's typical use of indoor tanning over some (unspecified) period of time prior to interview? In brief, the results reported by Westerdahl et al. (1994), shown in Figure 4, are not interpretable.

As quoted above, the Working Group states that there was "a borderline statistically significant dose-effect relationship in one study (Chen *et al.*, 1998)." This statement is a misrepresentation: Figure 4 shows that an increased number of sunlamp uses, ≥10 versus <10, was not associated with an increased estimate of relative risk, much less a statistically significant increase.

The Working Group also states that "one study [reported] a non-significant dose-effect relationship (Westerdahl *et al.*, 2000)." Figure 4 shows that Westerdahl et al. (2000) reported a *smaller* estimate of relative risk for ">250 uses" of indoor tanning devices, as compared the estimates of relative risk corresponding to "1-125 uses" and "126-250 uses."

As noted in section 3.1, the Working Group did not address the *intensity* of UV exposure from indoor tanning devices, such as the doses of UV radiation involved and the cumulative exposure resulting therefrom. A surrogate endpoint that would be relevant to this issue is the number of burns resulting from indoor tanning, which was not considered by the IARC, or by any of the studies included in the IARC's meta-analysis. Equally important is that none of Working Group's analyses of "dose response" was

directed to first use of indoor tanning devices, sunbeds in particular, before age 35, which was the foundation of the IARC's claim concerning the "strength" of evidence for increased risk. Likewise, the Working Group's analyses of exposure to indoor tanning devices distant in time and recent in time, which concern *latency*, were not based on first use of indoor tanning devices before age 35.

In summary, one may quote the IARC Working Group, recognizing that they conflate indoor tanning facilities with indoor tanning devices:

> "The association with ever use of these facilities, or use more than 15 to 20 years prior to diagnosis of melanoma, was weak, and evidence regarding a dose-response relationship was scanty." [1 (p.50)]

3.2.3 Temporal sequence. With respect to *temporal sequence*, the fact that use of indoor tanning devices preceded the diagnoses of melanoma does not indicate or imply that indoor tanning was the cause of any of the cases studied. For example, although an infant's breast feeding precedes the occurrence of autism, cancer, stroke, cardiovascular disease, and senile dementia, breast feeding is not a cause of those conditions in a mother's child.

3.2.4 Coherence and biological plausibility. Despite the Working Group's claim that there is *coherence* [II] and *biologic plausibility* for an association between melanoma and indoor tanning, the Working Group performed no analyses of epidemiologic data to address the two major hypotheses involved: intense, intermittent UV-radiation exposure from use of indoor tanning devices; and burns resulting from indoor tanning devices. Concern about intermittent exposure to solar UV radiation and burns from the sun have been repeatedly expressed, and were well known to the Working Group. [46, 47, 48]

> "29 epidemiological studies have consistently shown that intermittent sun exposure (eg, sunbathing, boating, swimming in the open air) is the essential environmental risk factor for melanoma." [Autier et al. 1998 [40]]

> "Sunburn during childhood or during adulthood is a risk factor for melanoma, and the risk increases with increasing number of sunburns (IARC, 1992)." [IARC 2006 [1 (p. 11)]]

As stated in the review by Berwick et al.: [49]

> "Ultraviolet radiation (UVR) is the major known etiologic agent associated with melanoma. Many individuals however do not know that different patterns of sun exposure have different effects in the development of

[II] ***Coherence***: "the extent to which a hypothesized causal association fits with preexisting theory and knowledge." *See* Porta M. A Dictionary of Epidemiology, fifth edition. New York: Oxford University Press, 2008, pp. 21 & 44.

melanoma. For example, chronic sun exposure, that which one receives during outdoor work on a daily basis, does not increase risk for melanoma and is even associated with inhibition of melanoma.[9–11] On the other hand, intermittent sun exposure, large blasts of UVR, received on weekends or holidays, is the major form of UVR promoting the development of melanoma.[12]"

With regard to biological plausibility, the Working Group states that: [1 (p.20)]

> "As ***no valid animal model of human melanoma or other skin cancers exists***, evidence of an association between indoor tanning facility exposure and skin cancer must be sought predominantly from epidemiological studies." [my emphasis]

As discussed above, the IARC's meta-analyses of epidemiologic study results are not a reliable basis for inferring harm from proper use of indoor tanning devices.

3.3 Summary. The IARC Working Group's assertion that "there is convincing evidence to support a causal relationship" between melanoma and use of indoor tanning devices [1 (p.50), 2 (p. 1121)] is scientifically unjustified by their analyses. Numerous statements by the IARC, quoted throughout section 3 above, are inconsistent with their opinion about causation.

The IARC's meta-analysis and their estimates of increased relative risk in relation to indoor tanning cannot be interpreted as scientifically reliable evidence of a melanoma hazard incurred from indoor tanning, whether as a teenager, young adult or as an older person, in commercially-operated facilities that follow FDA regulations and guidance, or other national standards. In this regard, the IARC's report and publication are uninformative because the issue was not addressed.

The IARC's claim that persons who initiate use of indoor tanning devices before age 30 or 35 incur a 75% increased risk of melanoma (see section 1.2) is not supported by reliable science.

4. Summary of Review

4.1 Strengths of the IARC report.

The Working Group assembled for the review of skin cancer in relation to artificial UV radiation was comprised of members with long-standing, wide-ranging expertise in melanoma research, including epidemiologic studies of melanoma and other skin cancers.

The Working Group provided an excellent synopsis of background information on UV radiation and issues related to the use of indoor tanning devices.

The Working Group employed well established statistical methods in their meta-analysis of epidemiologic studies, and they performed a variety of subsidiary analyses to assess the extent to which their summary estimates of relative risk (based on meta-analysis) were affected by their choice of studies to analyze.

4.2 Limitations of the IARC report.

The epidemiologic studies upon which the Working Group relied had limited information on indoor tanning devices, their circumstances of use, and potential confounding variables, thereby compromising the Working Group's analyses and limiting the inferences that justifiably might be made.

The possibility that biased surveillance for and detection of melanoma might account for the estimates of increased relative risk was not considered by the Working Group.

The exposure studied by the Working Group, i.e., use of indoor tanning devices, made no distinctions among tanning devices used at home, in unregulated or poorly-regulated commercial environments, and in commercially-operated facilities that adhere to FDA regulations and guidance, or other national standards.

The Working Group did not perform a proper assessment of dose response, in part because of limitations of the epidemiologic studies available.

The Working Group's meta-analysis, and their estimates of increased relative risk, do not provide scientifically reliable evidence of a melanoma hazard incurred from the use of modern indoor tanning devices, whether as a teenager, young adult or as an older person, in commercially-operated facilities that follow FDA regulations and guidance, or other national standards.

The IARC's claim that persons who initiate use of indoor tanning devices before age 30 incur a 75% increased risk of melanoma (see section 1.2) is not supported by reliable science.

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August 28, 2012

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Curriculum Vitae: October 2014

James J. Schlesselman, Ph.D.

Professor Emeritus, Department of Biostatistics
University of Pittsburgh Graduate School of Public Health

Education

Princeton University

Ph.D. Statistics, 1971
M.A. Statistics, 1968
M.A. Psychology, 1968

Michigan State University

B.S. *With High Honor* (Psychology major, Mathematics minor), 1966

Membership in Professional & Scientific Societies

American Association for the Advancement of Science
American Statistical Association
Institute of Mathematical Statistics

Awards and Honors

The Kenneth E. Schuit Award (University of Pittsburgh School of Medicine Dean's Award for Master Educator), 1997
Fellow of the American College of Epidemiology, 1983
Psychometric Fellowship, Princeton University, 1966-1969
Honors College, Michigan State University, 1963-1966
Valedictorian, Lake Park High School, 1963

Research Interests

Role of statistics in scientific inference. Statistical methods for planning, monitoring, and analyzing data from clinical trials. Statistical methods for the design and analysis of epidemiologic studies.

Employment

2004 - 2009	Professor, Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, and Director, Biostatistics Facility, University of Pittsburgh Cancer Institute; *retired on 31 July 2009.*
1997 - 2004	Professor, Department of Epidemiology and Public Health, University of Miami School of Medicine, and Chief, Division of Biostatistics, Sylvester Comprehensive Cancer Center
1992 - 1997	Professor and Chief, Division of Biostatistics, Department of Family Medicine and Clinical Epidemiology, University of Pittsburgh School of Medicine
1985 - 1992	Professor, Department of Preventive Medicine and Biometrics, F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences (USUHS)
1981 - 1985	Associate Professor, Department of Preventive Medicine and Biometrics, F. Edward Hebert School of Medicine, USUHS
1976 - 1981	Chief, Biometry Branch, National Institute of Child Health and Human Development NIH/NICHD
1973 - 1976	Mathematical Statistician, Biometry Branch, NIH/NICHD
1971 - 1973	Senior Staff Fellow, Biometry Branch, NIH/NICHD
1969 - 1971	Commissioned Officer, United States Public Health Service, Epidemiology and Biometry Branch, NIH/NICHD

Appointments

2009 - *present*	Professor Emeritus of Biostatistics, University of Pittsburgh
1993 - 2005	Adjunct Professor, Department of Preventive Medicine & Biometrics, Uniformed Services University of the Health Sciences
1992 - 1997	Professor, Department of Biostatistics, University of Pittsburgh Graduate School of Public Health – *secondary appointment*
1996 - 1997	Professor, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh School of Medicine – *secondary appointment*
1996 - 1997	Director, Biostatistics Core, General Clinical Research Center, University of Pittsburgh Medical Center
1989 - 1996	Senior Associate, Department of Epidemiology, The Johns Hopkins University

Military Service Commissioned Officer, United States Public Health Service, 1969-1971

National & International Service

International Atomic Energy Agency (IAEA). Invited participant in a Technical Meeting concerning data-management and statistics related to clinical trials: Applied Radiation Biology and Radiotherapy Section . Vienna, Austria, May 30 - June 2, 2011.

National Cancer Institute, National Institutes of Health. Epidemiology of Cancer Study Section, Health of Populations Integrated Review Group. Chair of Special Emphasis Panel. Hendon Virginia, May 19, 2010.

National Institute on Drug Abuse (NIDA). Protocol Review Board (PRB) for NIDA's National Drug Abuse Treatment Clinical Trials Network: CTN protocol 0037 (Exercise as a Treatment for Substance Abuse Disorders). Member of PRB, July 2008 – present. Chair of Data and Safety Monitoring Board, May 2009 – 2013.

National Cancer Institute, National Institutes of Health. Epidemiology of Cancer Study Section, Health of Populations Integrated Review Group. Annapolis, MD, June 5-6, 2008.

Canada Foundation for Innovation. Reviewer for Research Hospital Fund Large-Scale Institutional Endeavours Competition. November 20, 2007.

National Cancer Institute, National Institutes of Health. Epidemiology of Cancer Study Section, Health of Populations Integrated Review Group. Baltimore, MD, June 14-15, 2007.

National Cancer Institute, National Institutes of Health. Epidemiology of Cancer Study Section, Health of Populations Integrated Review Group. Washington DC, June 29-30, 2006.

National Cancer Institute, National Institutes of Health. Epidemiology of Cancer Study Section, Health of Populations Integrated Review Group. Washington DC, June 23-24, 2005.

National Institute on Drug Abuse (NIDA). Data and Safety Monitoring Board for NIDA's National Drug Abuse Treatment Clinical Trials Network: CTN protocol 03-005 (A Two Phase Randomized Controlled Clinical Trial of Buprenorphine/Naloxone Treatment plus Individual Drug Counseling for Opioid Analgesic Dependence). Member of DSMB, April 2005 – April 2010.

National Institutes of Health. Biostatistical Methods and Research Design Study Section. Health of Populations Integrated Review Group. Washington DC, October 29, 2004.

Department of Social Medicine, University of Bristol, UK. Meeting to develop reporting guidelines for cohort, case-control, and cross-sectional studies. September 1-3, 2004.

National Cancer Institute, National Institutes of Health. Cluster review of applications in the Population Based Prevention Studies P01 Review Cluster. Bethesda, June 28-30, 2004.

Centers for Disease Control, National Immunization Program, Anthrax Vaccine Safety Activity. Meeting to advise on the design of an epidemiologic study of long-term safety of AVA vaccine. Atlanta, May 2002.

World Health Organization. Meeting on the relationship between steroid hormone contraceptive use, HPV infection and cervical cancer. Geneva, March 2002.

National Vaccine Advisory Committee, Centers for Disease Control, DHHS. Invited background paper by J. Schlesselman. Intussusception in relation to immunization with rhesus rotavirus vaccine: primer on study design. November 2001.

National Vaccine Program Office, Centers for Disease Control, DHHS. Workshop on Intussusception, Rotavirus, and Oral Vaccines. Invited presentation by J. Schlesselman: Critique of six epidemiologic studies' design, strengths, and weaknesses. Washington DC, September 2001.

UC Davis Medical Center, M.I.N.D. Institute. Scientific Advisory Panel for Epidemiology of Autism in California Study. Sacramento, November 2000.

World Health Organization. WHO Temporary Advisor for meeting on Improving Access and Quality of Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use. Geneva, March 2000.

National Institute of Child Health and Human Development, NIH. Scientific Advisory Committee for the Network for Contraceptive Research. Member, 1999 - 2006.

World Health Organization. WHO Scientific Group on Oral Contraceptives and Cardiovascular Disease. Geneva, November 1997.

University of Zimbabwe and The Johns Hopkins University. Data and Safety Monitoring Committee for a randomized clinical trial of high dose vitamin A to prevent maternal-fetal transmission of HIV. Member, 1997 - 2000.

National Institute of Child Health and Human Development, NIH. Science Advisory Committee to the NICHD Women's Contraceptive and Reproductive Experiences (CARE) Study. Member, 1996 - 1998.

National Heart, Lung, and Blood Institute, NIH. Data and Safety Monitoring Board for A Case Control Etiologic Study of Sarcoidosis (ACCESS). Member, 1996 - 2002.

National Institute of Child Health and Human Development, NIH. Advisory Committee on Steroid Contraceptives and HIV Transmission: Recommendations for Research. Bethesda, June 1996.

World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction: Steering Committee of the Task Force on Epidemiological Research on Reproductive Health. Geneva: Member, 1991 - 1997.

National Institute of Child Health and Human Development, NIH. Special Review Committee for proposed clinical trial of treatment of mitochrondial myopathies with dichloroacetate. Bethesda, August 1993.

American Society for Reproductive Immunology. Special consultant for worldwide collaborative study and meta-analysis of allogeneic leukocyte immunotherapy for recurrent spontaneous abortion. Washington DC, July 1993.

International Conference on Beta-Agonists. Statistical consultant to the Department of Epidemiology and Biostatistics, McGill University School of Medicine. Montreal, January 1992.

World Health Organization. Advisory Committee on the Evaluation of Antenatal Care in Developing Countries. Geneva, November 1991.

Visiting Professor. McGill University School of Medicine, Department of Epidemiology and Biostatistics, November 1991.

World Health Organization. Workshop on Vasectomy in Relation to Cancer of the Prostate and Testis. Geneva, October 1991.

Food and Drug Administration. Workshop on Critical Issues in Medicine: Contrast Media Safety. Rockville, Maryland, June 1990.

World Health Organization. WHO Scientific Group on Oral Contraceptives and Neoplasia. Geneva, December 1990.

World Health Organization. WHO Task Force on the Safety and Efficacy of Contraceptive Methods. Geneva, October 1988.

Food and Drug Administration. Fertility and Maternal Health Drugs Advisory Committee. Rockville, Maryland: Member, 1986 - 1992.

National Research Council. Food and Nutrition Board: Subcommittee on Vitamin A. Washington DC: Member, 1986.

University of Trondheim, Department of Community Medicine and General Practice. Statistical consultant on epidemiologic studies of occupational health and prenatal care. Trondheim, Norway, September 1985.

Nutrition Center of the Philippines. Statistical consultant on a community intervention study of iron and food supplementation. Manila: June 1983, March 1984 and May 1985.

National Institute of Child Health and Human Development, NIH. Statistical consultant on vaccine field trials. Bethesda: 1981 - 1991.

Postgraduate Institute of Medical Education and Research. WHO invited lecturer in biostatistics. Chandigarh, India, October 1979.

Agency for International Development. Statistical consultant on a sample survey and clinical trial of vitamin A supplementation to treat and prevent xerophthalmia. Jakarta, Indonesia, June 1979.

Institute of Nutrition of Central America and Panama. Statistical consultant on a community intervention study of protein/calorie supplementation and mental development. Guatemala City, Guatemala: June 1976 and July 1978.

Chulalongkorn University Institute of Health Research. WHO Special Adviser on epidemiologic and clinical studies of hormonal contraception. Bangkok, Thailand: October 1975, November 1976 and November 1979.

Centers for Disease Control, Division of Reproductive Health, Epidemiologic Studies Branch. Statistical consultant on epidemiologic studies of contraceptive methods, 1979 - 1985.

Institute of Mother and Child. Statistical consultant on a follow-up study of sequelae of induced abortion. Warsaw, Poland, October 1976.

National Institute of Child Health and Human Development, NIH. Chief of Biometry Branch: design, coordinate, and analyze collaborative clinical trials conducted by the NICHD. Bethesda: 1974 - 1981.

Gerontology Research Center. Statistical consultant on longitudinal study of human aging in males. Baltimore, Maryland: 1969 - 1974.

Editorship

American Journal of Epidemiology. Associate Editor, 1982-1988.

Peer Reviews

American Journal of Epidemiology, Archives of Pediatrics & Adolescent Medicine, Biometrical Journal, British Medical Journal, Cancer Causes and Control, Controlled Clinical Trials, Clinical Trials, European Journal of Cancer, Human Reproduction, Journal of the American Medical Association, Journal of Clinical Epidemiology, Journal of Clinical Oncology, Lancet, Obstetrics & Gynecology, Preventive Medicine, Statistics in Medicine.

Books

Schlesselman, JJ. *Case-Control Studies: Design, Conduct, Analysis.* New York: Oxford University Press, 1982, xv + 354 pp. (in Japanese translation, 1985)

Articles

Raez LE, Papadopoulos K, Ricart AD, Chiorean EG, Dipaola RS, Stein MN, Rocha Lima CM, Schlesselman JJ, Tolba K, Langmuir VK, Kroll S, Jung DT, Kurtoglu M, Rosenblatt J, Lampidis TJ. A phase I dose-escalation trial of 2-deoxy-D-glucose alone or combined with docetaxel in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2013 Feb;71(2):523-30.

Mehta DR, Foon KA, Redner RL, Raptis A, Agha M, Hou JZ, Duggal S, Luong TM, Schlesselman JJ, Boyiadzis M. Fludarabine and cytarabine in patients with acute myeloid leukemia refractory to two different courses of front-line chemotherapy. *Leuk Res* 2011 Jul;35(7):885-8. Epub 2011 Feb 18.

McHayleh W, Foon K, Redner R, Sehgal R, Raptis A, Agha M, Luong TM, Schlesselman JJ, Boyiadzis M. Gemtuzumab ozogamicin as first-line treatment in patients aged 70 years or older with acute myeloid leukemia. *Cancer* 2010 Jun 15;116(12):3001-5.

McHayleh W, Sehgal R, Redner RL, Raptis A, Agha M, Natale J, Luong TM, Schlesselman JJ, Foon KA, Boyiadzis M. Mitoxantrone and etoposide in patients with newly diagnosed acute myeloid leukemia with persistent leukemia after a course of therapy with cytarabine and idarubicin. *Leuk Lymphoma* 2009 Nov;50(11):1848-53.

Brell JM, Matin K, Evans T, Volkin RL, Kiefer GJ, Schlesselman JJ, Dranko S, Rath L, Schmotzer A, Lenzner D, Ramanathan RK. Phase II study of docetaxel and gefitinib as second-line therapy in gemcitabine pretreated patients with advanced pancreatic cancer. *Oncology*. 2009; 76(4):270-274. Epub Mar 4.

Epperly MW, Dixon T, Wang H, Schlesselman J, Franicola D, Greenberger JS. Modulation of radiation-induced life shortening by systemic intravenous MnSOD-plasmid liposome gene therapy. *Radiat Res*. 2008 Oct;170(4):437-43.

Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; for the STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. *Ann Intern Med* 2007 Oct 16;147(8):W163-94. *Note: this article was also published in Epidemiology 2007;18:805-835; PLoS Medicine 2007;4:e297; Gaceta Sanitaria [in Spanish] 2009 Mar-Apr;23(2):158. Epub 2009 Feb 26.*

Schlesselman JJ. The emerging case-control study: lung cancer in relation to tobacco smoking. *Prev Med.* 2006 Oct;43(4):251-5. Epub 2006 Sep 25.

Schlesselman JJ, Reis IM. Phase II clinical trials in oncology: strengths and limitations of two-stage designs. *Cancer Invest.* 2006 Jun-Jul;24(4):404-12.

Singal R, Das PM, Manoharan M, Reis IM, Schlesselman JJ. Polymorphisms in the DNA methyltransferase 3b gene and prostate cancer risk. *Oncol Reports* 2005; Aug;14(2): 569-73.

Singal R, Ferdinand L, Das PM, Reis IM, Schlesselman JJ. Polymorphisms in the methylenetetrahydrofolate reductase gene and prostate cancer risk. *Int J Oncol* 2004; 25(5):1465-71.

Singal R, Ferdinand L, Reis IM, Schlesselman JJ. Methylation of multiple genes in prostate cancer and relationship with clinicopathological features of disease. *Oncol Reports* 2004; 12:631-7.

Raez LE, Cassileth PA, Schlesselman JJ, Sridhar K, Padmanabhan S, Fisher EZ, Baldie PA, Podack ER. Allogeneic vaccination with a B7.1 HLA-A gene-modified adenocarcinoma cell line in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2004; 22:2800-7.

Burkman R, Schlesselman JJ, Zieman M. Safety concerns and health benefits associated with hormonal contraception. *Am J Obstet Gynecol* 2004;190:S5-22.

Raez LE, Cassileth PA, Schlesselman JJ, Padmanabhan S, Fisher EZ, Baldie PA, Sridhar K, Podack ER. Induction of CD8 T-cell-Ifn-γ response and positive clinical outcome after immunization with gene-modified allogeneic tumor cells in advanced non-small-cell lung carcinoma. *Cancer Gene Therapy* 2003; 10:850-8.

Schlesselman JJ, Collins JA. Evaluating systematic reviews and meta-analyses. *Seminars in Reproductive Medicine* 2003; 21:95-105.

Sofer M, Hamilton-Nelson KL, Schlesselman JJ, Soloway MS. Risk of positive margins and biochemical recurrence in relation to nerve-sparing radical prostatectomy. *J Clin Oncol* 2002; 20:1853-58.

Walker GR, Schlesselman JJ, Ness RB. Family history of cancer, oral contraceptive use, and ovarian cancer risk. *Am J Obstet Gynecol* 2002; 186:8-14.

Collins JA, Schlesselman JJ. Perimenopausal use of reproductive hormones: effects on breast and endometrial cancer. *Obstet Gynecol Clin North Am* 2002; 29:511-25.

Ness RB, Grisso JA, Klapper J, Schlesselman JJ, Silberzweig S, Vergona R, Morgan M, Wheeler JE, and the SHARE Study Group. Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. *Am J Epidemiol* 2000;152:233-241.

Mies C, Schlesselman JJ. Detection of "occult" lymph node metastasis in breast cancer: Should pathologists go the extra mile? *Adv Anatomic Pathol* 2000;7:149-152.

Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, Morgan M, Schlesselman JJ. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology* 2000;11:111-117.

Collins JA, Schlesselman JJ. Hormone replacement therapy and endometrial cancer. *In* Lobo R ed. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects, 2nd edition*. New York: Lippincott-Raven, 1999: 503-511.

Farley TMM, Collins J, Schlesselman JJ. Hormonal contraception and risk of cardiovascular disease: an international perspective. *Contraception* 1998; 57:211-230.

Zimmerman RK, Schlesselman JJ, Mieczkowski TA, Medsger AR, Raymund M. Physician concerns about vaccine side effects and potential litigation. *Arch Pediatr Adolesc Med* 1998; 152:12-19.

WHO Scientific Group (includes J. Schlesselman). Cardiovascular Disease and Steroid Hormone Contraception. WHO Technical Report Series 887. Geneva: World Health Organization, 1998, 89 pp.

Schlesselman JJ, Collins JA. The influence of steroids on gynecologic cancers. *In* Fraser IS, Jansen RPS, Lobo RA, Whitehead MI, eds. *Estrogens and Progestogens in Clinical Practice.* London: Churchill Livingstone, 1998: 831-864.

Schlesselman JJ. Risk of endometrial cancer in relation to use of combined oral contraceptives. A Practitioner's Guide to Meta-analysis. *Hum Reprod* 1997;12:1851-1863.

Zimmerman RK, Schlesselman JJ, Baird AL, Mieczkowski TA. A national survey to understand why physicians defer childhood immunizations. *Arch Pediatr Adolesc Med* 1997;151:657-664.

Schlesselman JJ. Biostatistics in epidemiology: a view from the faultline. *J Clin Epidemiol* 1996;49:627-629.

Mishell, Jr. DR, Carr BR, Comp PC, Kaunitz AM, Ory HW, Schlesselman JJ, Sulak PJ. Estrogen Doses of Oral Contraceptives: What Are the Choices? *Dialogues in Contraception* 1996;4:1-12.

Expert Panel (includes J. Schlesselman). Principles for Evaluating Epidemiologic Data in Regulatory Risk Assessment. Washington DC: Federal Focus, 1996, 124 pp.

Schlesselman JJ. Net effect of oral contraceptive use on the risk of cancer in women in the United States. *Obstet Gynecol* 1995;85:793-801.

The Recurrent Miscarriage Immunotherapy Trialists Group (writing committee: Coulam CB, Clark DA, Collins J, Scott JR, Schlesselman JJ). Worldwide collaborative observational study and meta-analysis on allogeneic leukocyte immunotherapy for recurrent spontaneous abortion. *Amer J Reprod Immunol* 1994;32:55-72.

Gross TP, Schlesselman JJ. The estimated effect of oral contraceptive use on the cumulative risk of epithelial ovarian cancer. *Obstet Gynecol* 1994;83:419-24.

Gross TP, Schlesselman JJ, Stadel BV, Yu W, Lee NC. The risk of epithelial ovarian cancer in short-term users of oral contraceptives. *Am J Epidemiol* 1992;136:46-53.

Schlesselman JJ, Stadel BV, Korper M, Yu W, Wingo PA. Breast cancer detection in relation to oral contraception. *J Clin Epidemiol* 1992;45:449-59.

WHO Scientific Group (includes J. Schlesselman). Oral Contraceptives and Neoplasia. WHO Technical Report Series 817. Geneva: World Health Organization, 1992, 46 pp.

Greenland S, Maclure M, Schlesselman JJ, Poole C, Morgenstern H. Standardized regression coefficients: a further critique and review of some alternatives. *Epidemiology* 1991;2:387-92.

Schlesselman JJ. Oral contraceptives and neoplasia of the uterine corpus. *Contraception* 1991;43:557-79.

Speroff L, Haney A, Lippman M, Schlesselman JJ. Role of hormones in breast cancer risk. *Contemporary OB/GYN* 1991;36:80-95.

Schlesselman JJ. Oral contraceptives and breast cancer. *Am J Obstet Gynecol* 1990;163:1379-87.

Schlesselman JJ. Breast cancer and the contraceptive pill: What is the current thinking? *Medical Dialogue* 1990;283:1-4.

Wingo PA, Lee NC, Ory HW, Layde PM, Webster LA, Rubin GL, Sattin RW, Stadel BV, Schlesselman JJ. Oral contraceptives and the risk of breast cancer. *In* Mann RD, ed. *Oral Contraceptives and Breast Cancer*. Carnforth: Parthenon 1990:67-84.

Schlesselman JJ. Oral contraceptives in relation to cancer of the breast and reproductive tract: an epidemiological review. *Br J Fam Planning* 1989;15:23-33.

Westin S, Schlesselman JJ, Korper M. Long-term effects of a factory closure: unemployment and disability during ten years' follow-up. *J Clin Epidemiol* 1989;42:435-41.

Schlesselman JJ. Cancer of the breast and reproductive tract in relation to use of oral contraceptives. *Contraception* 1989;40:1-38.

Murray PP, Stadel BV, Schlesselman JJ. Oral contraceptive use in women with a family history of breast cancer. *Obstet Gynecol* 1989;73:977-83.

Grimes DA, Mishell DR, Schlesselman JJ, Stadel BV. OCs and breast cancer: a roundtable discussion. *Dialogues in Contraception* 1989;2:1-8.

Stadel BV, Lai SH, Schlesselman JJ, Murray P. Oral contraceptives and premenopausal breast cancer in nulliparous women. *Contraception* 1988;38:287-99.

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Schlesselman JJ, Stadel BV, Murray P, Lai SH. Breast cancer in relation to early use of oral contraceptives: no evidence of a latent effect. *J Am Med Assoc* 1988;259:1828-33.

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Schlesselman JJ. Power families: a note on the Box and Cox transformation. *J Royal Stat Soc, Series B*, 1971;33:307-11.

Book Reviews

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Letters

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Stadel BV, Rubin GL, Wingo PA, Schlesselman JJ. Oral contraceptives and breast cancer in young women. *Lancet* 1986;1:436.

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Invited Courses

Schlesselman JJ. Phase II clinical trials: the bridge to pivotal studies. 2nd International Biometric Society Conference of the Eastern Mediterranean Region. Antalya, Turkey, January 12, 2003.

Schlesselman JJ. Design of Clinical Trials. Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, June 4-12, 1998.

Caritis S, Ness R, Schlesselman JJ. Clinical Epidemiology Applied to Maternal-Fetal Medicine. Magee-Womens Hospital, Pittsburgh, April 14 - June 2, 1994.

Schlesselman JJ. The Conduct and Interpretation of Case-Control Studies. The University of Michigan School of Public Health. International Graduate Summer Session in Epidemiology, July 7-26, 1991.

Schlesselman JJ. Statistical Methods for Epidemiologic Studies. Children's Castle Hospital, Helsinki, Finland, June 8-12, 1987.

Schlesselman JJ. Design and Analysis of Epidemiologic Studies. Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing, China, April 15-19, 1985.

Schlesselman JJ. Design and Analysis of Medical Investigations in Clinical Practice. University of Oslo, Norway, October 3-4, 1983.

Schlesselman JJ. Case-Control Studies. University of Trondheim, Norway, September 25-30, 1983.

Invited Talks *(since 1990)*

Statistical perspective on disease screening and treatment effectiveness. Osher Lifelong Learning Institute at Carnegie Mellon University, Pittsburgh. September 13, 2011 & May 9, 2012.

Biostatistics in Observational and Experimental Studies. Summer Institute for Training in Biostatistics. University of Pittsburgh Graduate School of Public Health, Pittsburgh, June 23, 2011.

Statistical Methods in Medical Research: Does Treatment Help or Harm? Osher Lifelong Learning Institute at Carnegie Mellon University, Pittsburgh. November 17, 2010 & May 11, 2011.

Multiple Comparisons in Epidemiology. Peking Union Medical College, Beijing, China. May 30, 2007.

Clinical Trials in Translational Research - The Bridge from Laboratory-Based Science to Clinical Applications. The 1st Asian-Pacific Summit on Emerging Healthcare Strategy. (Organized by the Chinese Academy of Medical Sciences, Peking Union Medical College, and Mayo Clinic College of Medicine.) Beijing, China. May 26-29, 2007.

Cytochlor - protocol development for a phase I study. Fox Chase Cancer Center, Philadelphia, June 12, 2003.

Screening for HPV infection in women seeking oral contraception: estimated effects on cervical cancer, unintended pregnancies, and maternal mortality in countries worldwide. 2nd International Biometric Society Conference of the Eastern Mediterranean Region. Antalya, Turkey, January 14, 2003.

The Story of C. Mayo Clinic. Rochester, MN. September 24, 2002.

Statistics in Biomedical Inference. Mayo Clinic. Rochester, MN. September 23, 2002.

Neoplastic Effects of Hormonal Contraceptives. National Institute of Child Health and Human Development, NIH, Bethesda, MD. Symposium on Preventing Unintended Pregnancy: Advances in Hormonal Contraception, June 11-12, 2001.

Statistics in Biomedical Inference. American Statistical Association, Princeton-Trenton Chapter, Princeton University, June 16, 2000.

Study Designs in Clinical Research. Mount Sinai Medical Center, Miami Beach, FL, September 14, 1999.

Biostatistics in Clinical Research. Center for Clinical Pharmacology, University of Pittsburgh Medical Center, November 24-25, 1997.

Randomized Clinical Trials. Biometry Facility, University of Vermont, November 19, 1996

Case-Control Studies. St. Margaret's Hospital, Residency Program in Family Medicine, Pittsburgh, PA, August 8, 1996.

Meta-Analysis of Cancer Risk Associated with Use of Oral Contraceptives in U.S. Women. Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA, March 18, 1995.

Use of Statistics in Planning Biomedical Studies. Department of Mathematics and Statistics, University of Pittsburgh, Pittsburgh, PA, November 11, 1993.

Net Effect of Oral Contraceptives on Cancer of the Breast and Reproductive Tract. International Symposium on Reproductive Epidemiology and Social Science Research, Chengdu, China, October 11-13, 1993.

Biostatistics in Epidemiology. Pittsburgh Statistical Society Annual Meeting, Pittsburgh, PA, May 13, 1993.

Oral Contraceptives and Breast Cancer. Eastern Virginia Medical School, Current Topics in Reproductive Endocrinology and Gynecology Conference, Falls Church, VA, April 3-4, 1992.

Is There Biased Detection of Breast Cancer in Women Using Oral Contraceptives? U.S. Food and Drug Administration, Center for Drug Evaluation Research, Rockville, MD, April 1, 1992.

Biostatistics in Epidemiology: A View from the Faultline. Society for Epidemiologic Research, 24th Annual Meeting, Buffalo, NY, June 11-14, 1991.

Oral contraceptives and Breast Cancer: Issues Related to Age, Duration of Use, Dose, and Latent Effects. The Institute of Medicine. Conference on the Relationship Between Oral Contraceptives and Breast Cancer, Irvine, California, May 3-4, 1990.

Breast Cancer and the Contraceptive Pill. Georgetown University Medical Center, Vincent T. Lombardi Cancer Research Center, Washington, DC, Sept 14, 1990.

Multivariate Analysis. The Johns Hopkins University, Department of Epidemiology, April 16, 1990.

Ph.D. Committees

Phyllis A. Wingo. Five-year survival in women with breast cancer according to prior use of oral contraceptives. Member, Dissertation Committee for PhD in Biostatistics, Emory University School of Public Health, 1992-1993.

Daniel Feaster. The effect of attrition on estimated parameters of a model of CD4 cell count decline in HIV infection. Co-chair, Dissertation Committee for PhD in Biostatistics (Inter-Departmental Program), University of Miami, 1998 - 2000.

Hong Lai. Clinical Implications of Mutations in the p53 Tumor Suppressor Gene in Female Patients with Breast Cancer. Member, Dissertation Committee for PhD in Epidemiology, University of Miami, Department of Epidemiology and Public Health, 2000 - 2001.

Fengchao Ma. Cancer Incidence and General Mortality in a Cohort of Florida Firefighters. Member, Dissertation Committee for PhD in Epidemiology, University of Miami, Department of Epidemiology and Public Health, 1999 - 2003.

Master's Degree Committees

Ahmad A. Tarhini, MD. Safety and Immunogenicity of Vaccination with Multi-Epitope Peptide Vaccine Containing MART-1, gp100, and Tyrosinase Peptides given with the Combination of GMCSF and CpG Oligonucleotide (CpG 7909) in ISA-Oil Adjuvant for Patients with Recurrent Inoperable Stage III or Stage IV Melanoma. Member, Thesis Committee for MSc in Clinical Research, University of Pittsburgh School of Medicine, 2005-2006.

Mentoring of Graduate Students

Ahmad A. Tarhini MD, MSc, doctoral candidate in Clinical and Translation Science, University of Pittsburgh School of Medicine, 2008 – 2009.

The-Minh Luong, doctoral candidate in Biostatistics, University of Pittsburgh Graduate School of Public Health (GSPH), University of Pittsburgh, 2006 – 2009.

Yongyun Zhao, doctoral candidate in Biostatistics, GSPH, University of Pittsburgh, 2005 – 2006.

Beth Zamboni, doctoral candidate in Biostatistics, GSPH, University of Pittsburgh, 2004 – 2006.

Courses Taught

Clinical Trials: Methods and Practice. Developed and taught a spring-semester 2006 course on clinical trials (BIOST 2062) in the Department of Biostatistics, University of Pittsburgh Graduate School of Public Health. This course presents principles that underlie the design of clinical trials, and statistical methods and computer software that can be used in planning such studies and analyzing data from them. To achieve its aims, the course uses lectures, case studies, classroom discussions, written assignments, and problems for solution. Students learn design principles for phase I, phase II, and phase III clinical trials, including cross-over studies, bioequivalence studies, and community intervention trials. Through classroom discussion of written protocols and published clinical trials, students learn how to write a protocol for a clinical trial, justify the design and sample size for these investigations, present plans for the statistical analysis of the resulting data, and propose how study progress should be monitored. Students also learn basic methods for the analysis of cross-over studies and survival analysis for parallel-group studies, some of the requirements for sound data management, and ethical considerations that arise in planning and conducting human investigations. Active participation in classroom discussions, timely completion of assigned problems, well-prepared presentations in class, and the development of a brief protocol for a clinical trial (term paper) are required for successful completion of the course.

Clinical Trials. Developed and taught in Winter Term a three-credit course (EPH604) for graduate students in epidemiology and biostatistics. Students learned principles that underlie the design of clinical trials, practical and ethical problems that arise in human investigations, and statistical methods and computer software for planning clinical trials and analyzing data from them. The course covered the design and analysis of phase I, phase II, and phase III clinical trials, including cross-over studies, bioequivalence studies, and community intervention trials. Students critiqued study protocols and published studies, planned clinical trials, and analyzed data from them. Students also developed a protocol for a clinical trial within their area of interest. Department of Epidemiology and Public Health, University of Miami School of Medicine, 1999-2004.

Design of Clinical Trials. Developed and taught a one-credit short course for graduate students in biostatistics. Students learned statistical methods and computer software for planning clinical trials. The course covered the design f phase III clinical trials, cross-over studies, bioequivalence studies, and community intervention trials. Students critiqued study protocols and they wrote a statistical section for a clinical trial of their choice. Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, June 1998.

Planning Biomedical Studies. Developed and taught a three-credit course for graduate students in epidemiology and biostatistics. Students learned to apply statistical methods and use computer software for planning clinical trials (parallel groups, cross-over, community intervention, bioequivalence), cohort studies, case-control studies, sample surveys, and cross-sectional studies. Previously written grant proposals and problems developed by the Instructor served as case studies in the course. Students worked as members of teams in planning studies, and articulated through written and oral presentations, the statistical issues involved in study design and analysis. Students wrote statistical sections of study proposals to learn how to present the design of a study, its major scientific objectives, and the proposed analysis of its data. Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, 1997.

Clinical Epidemiology and Biostatistics. Planned and organized this first-year medical student course involving over 140 medical students and 80 faculty as part of the new curriculum at the University of Pittsburgh School of Medicine. Served as Course Director, lectured on Biostatistics, conducted reviews for all exams, and wrote all examinations. University of Pittsburgh School of Medicine, 1992-1997.

Case-Control Studies. Invited lecturer on the analysis of case-control studies. Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, 1992-1997.

Clinical Epidemiology and Biostatistics Prematriculation Course. Course Director and lecturer in epidemiology and biostatistics for this prematriculation course for medical students. University of Pittsburgh School of Medicine, 1993-1997.

Preventive Medicine. Led small-group discussions on the design, interpretation and analysis of epidemiologic studies in this second-year medical-student course. F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, 1983-1986.

Epidemiology and Biostatistics. Lectured on probability and survival analysis, wrote exams, and advised students in this first-year medical-student course. F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, 1988-1992.

Microcomputer Applications. Organized and team-taught this one-quarter graduate student course. F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, 1983-1992.

***Service for* University of Pittsburgh Cancer Institute (2004 – 2009)**

Standing Committees

Cancer Informatics Services Advisory Committee, 2007 - 2009

Clinical Research Oversight Committee, 2004 - 2009

Clinical Research Committee, 2005 - 2009

Clinical Research Services Task Force, 2005 - 2006

Data and Safety Monitoring Committee, 2004 - 2007

Independent Data and Safety Monitoring Committee, 2004 - 2009

Protocol Review Committee B, 2004 - 2009

***Service for* University of Pittsburgh Medical Center (2008 – 2012)**

Institutional Data and Safety Monitoring Board

Subcommittee *for* Study of MUC1 Peptide-MPL Adjuvant in Subjects with Advanced Colorectal Adenomas, 2008 - 2012.

***Service for* University of Miami (1997 – 2004)**

Standing Committees

Executive Committee, Sylvester Comprehensive Cancer Center, 1997 - 2004

Scientific Steering Committee, Sylvester Comprehensive Cancer Center, 1997 - 2004

Protocol Review Committee, Sylvester Comprehensive Cancer Center, 1997 - 2004

Data and Safety Monitoring Committee, Sylvester Comprehensive Cancer Center, 2003 - 2004

Audit Committee, Sylvester Comprehensive Cancer Center, 2002 - 2003

Teaching Executive Policy Committee, Department of Epidemiology and Public Health, 1998 - 2001

Research Committee, Department of Epidemiology and Public Health, 2000

Ad Hoc Committees

Research Committee, Department of Epidemiology and Public Health, 1998

Search Committee (for leader of a new University of Miami Center for Research Design and Clinical Outcomes), University of Miami School of Medicine, 2003

***Service for* University of Pittsburgh (1992 – 1997)**

Standing Committees

Medical Student Promotions 1994 - 1997

Ad Hoc Committees

Fact-Finding Committee for the Performance Review of George M. Bernier, Jr., M.D., Dean of the School of Medicine, 1994

Advisory Committee on the Management of the Biostatistical Center of NSABP, 1994

Search Committee for Director, NSABP Biostatistical Center (Chair), 1994

Appointment Committee for Professor of Biostatistics (GSPH), 1995

Prematriculation Program Planning Committee, 1995

MD/MPH Steering Committee, 1995-1997

Promotion and Tenure Committees

Thomas E. Rudy (Medicine), 1994

Joseph P. Costantino (Biostatistics), 1995

Michael E. Thase (Psychiatry), 1995

Carol J. Coffee (Biochemistry), 1995

Attachment F

Transcript of Dr. Jeffrey E. Gershenwald's testimony to the Texas Senate, Committee on Health and Human Services (Mar. 12, 2013).

Jeffrey E. Gershenwald, M.D.
MD Anderson Cancer Center

Testimony before Texas Senate Committee on Health and Human Services, March 12, 2013, as recorded at www.senate.tx.us. - News and Media; Archived Video; March 12, 2013, Part I.

Senate Bill 329 Under-18 Tanning Ban

Transcript:

Madame Chairman and the Committee: My name is Jeff Gershenwald. I am a professor and certified oncologist at MD Anderson and also medical director of the melanoma and skin cancer and I am happy to entertain any questions and serve as a resource on senate bill 329.

Sure so I am a certified oncologist so I am a trained surgeon who then did additional fellowship training in cancer surgery and my specialty is melanoma. We see between melanoma and non-melanoma skin cancer and other dermalogic conditions over 5,000 new patients and consultations in our center. My particular focus is in melanoma.

Sure, so melanoma when caught early is very treatable and often curable but we learned as well that in its advanced stages it is very very difficult and challenging to cure. Unlike many cancers where there has been a decreased incidence in this country and in the state of Texas melanoma has been associated with an increased risk - about 3-4% a year.

And we've learned as well over many years but in particular from the last couple of years when there have been several important studies that have demonstrated the significant risk associated with indoor tanning and the risk of melanoma. People who have ever used a tanning bed compared to people who have never used a tanning bed risk an increase of about 20%. In fact each session in a tanning bed has been estimated to be associated with a 1.8% increased risk. And if people used tanning beds before the age of 35 the risk has been estimated to be almost double by 87%. Being under 18 years of age when initiating indoor tanning compared to never tanning in another recent study that was well controlled it was associated with an increased melanoma risk of 85% and so there is really has become clear and compelling data of late that embraces a lot of modern approaches to these kinds of difficult analyses that have really provided a strong impetus for us to help to educate on the importance of minimizing tanning exposure.

Attachment G

Petitti DB. "Critical Review of Wehner et al. 2014 Estimates of the Prevalence of Ever Exposure to Indoor Tanning in Adults and the Number of Excess Cases of Skin Cancer" (Jan. 19, 2016).

Critical Review of Wehner et al. 2014 Estimates of the Prevalence of Ever Exposure to Indoor Tanning in Adults and the Number of Excess Cases of Skin Cancer

Diana B. Petitti, M.D., M.P.H.
January 19, 1016

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Funding Source: This review was conducted for the American Suntanning Association. Dr. Petitti was compensated for her time in preparing the review. The American Suntanning Association did not have rights to modify the final report. Dr. Petitti is solely responsible for the content of the report and its conclusions.

Table of Contents

Summary

Overview of Reviewed Publication

This report is a critical review of the Wehner et al. (2014) publication titled "International Prevalence of Indoor Tanning: a Systematic Review and Meta-analysis." The Wehner et al. (2014) publication presents estimates of the prevalence of ever exposure to indoor tanning and exposure to indoor tanning in the past year among adults, adolescents, and university students in the United States, Northern and Western Europe, and Australia. The publication also presents the results of a model that uses the meta-analytically-derived summary estimates of the prevalence of ever exposure to indoor tanning in adults based on the studies identified in the systematic review in conjunction with other data (described in more detail below) to estimate of the number of squamous cell skin cancers, basal cell cancers and malignant melanomas attributable each year to indoor tanning in the United States, Northern and Western Europa, and Australia.

Based on their systematic review and meta-analysis, Wehner et al. (2014) conclude that the prevalence of ever exposure to indoor tanning is 35% in adults in the United States, 42% in adults in Northern and Western Europe and 11% in adults in Australia. Using these prevalence estimates and other data, Wehner et al. (2014) conclude that 419,245 skin cancers, including 6,199 melanomas, are attributable each year to indoor tanning in the United States; that 26,484 skin cancers, including 4,874 melanomas, are attributable each year to indoor tanning in Northern and Western Europe; and that 18,441 skin cancers, including 301 melanomas, are attributable each year to indoor tanning in Australia.

Estimates of the number of skin cancers attributable each to indoor tanning in the United States are presented as facts about the effects of indoor tanning at the Centers for Disease Control and Prevention (CDC) website http://www.cdc.gov/cancer/skin/basic_info/indoor_tanning.htm (access 11/14/2015) . They are featured in a 2015 CDC grand rounds that is available at the CDC website www.cdc.gov/cdcgrandrounds/pdf/archives/2015/april2015.pdf. The prevalence estimate for ever exposure to indoor tanning in adults in the United States and the estimates of the number of skins cancer attributable to tanning in the United States are cited in a December 18, 2015 New York times article about indoor tanning (http://www.nytimes.com/2015/12/19/health/fda-proposes-ban-on-indoor-tanning-for-minors-to-fight-skin-cancer.html)

Scope of Comments in the Report

My comments about the Wehner et al. (2014) publication pertain to the systematic review and meta-analysis that identified the studies that were used to derive summary estimates of the prevalence of ever exposure to indoor tanning in adults in the United States, Northern and

Western Europe, and Australia and to the use of these prevalence estimates to derive an estimate of the number of skin cancers attributable each year to indoor tanning in the United States, Northern and Western Europe, and Australia.

My Conclusions

United States

None of the studies reporting the prevalence of ever exposure to indoor tanning in adults that Wehner et al. 2014 identified in their systematic review provide data representative of the general adult population of the United States. Several of the studies are from haphazard samples. For example, one study, *Mawn and Fleischer 1993 (*Wehner et al. reference 23) collected data using self-administered questionnaires distributed to "477 persons in a shopping mall, at a social gathering, and on a vacation cruise ship." Another study, *Hoerster et al. 2007* (Wehner reference 40) collected data about the prevalence of ever exposure to indoor tanning in adults in the United States from a telephone survey of households that were selected because they had a high likelihood of having a child 14, 15, 16, or 17. Responses about ever exposure to indoor tanning in adults pertain to households with an adult who had a child age 14, 15, 16, or 17 years. One study, *Lazovich et al. 2008* (Wehner reference 36), collected data about the prevalence of ever exposure to indoor tanning in adults in the United States using an interviewer-administered questionnaire given to a 26 adults recruited from an undergraduate psychology seminar and a convenience sample of adult staff and friends in Virginia and from flyers, announcements, and advertisements in Massachusetts. One study *Cohen et al. 2013* (Wehner reference 29) collected data about the prevalence of ever exposure to indoor tanning in adults in the United States using a self-administered questionnaire given to a "convenience" sample of 100 parents of children being seen in three pediatric practices in Chicago.

One study, *Mawn and Fleischer 1993 (*Wehner et al. reference 23), collected data in 1992, more than two decades before 2014, the year for which the estimate of the prevalence of ever exposure to indoor tanning in adults was made. Several other studies collected data more than a decade before 2014.

The meta-analytically derived estimate of the prevalence of ever exposure to indoor tanning for adults in the United States based on the studies identified by Wehner et al. (2014) is meaningless; the estimate of the number of skin cancers attributable to indoor tanning in the United State based on this meaningless estimate is meaningless.

Northern and Western Europe

The Wehner et al. (2014) systematic review identified studies of the prevalence of ever exposure to indoor tanning adults that were done in the United Kingdom, Ireland, France, Germany, Denmark, and Sweden. Only one study, Borner et al. (2009) had a sampling frame that could have yielded data representative of Germany but the r response rate was very low (13%). Germany is not representative of all of Northern and Western Europe. Austria, Belgium, Luxembourg, the Netherlands, Estonia, Finland, Iceland, Latvia, Lithuania, Norway and Switzerland are countries in Northern and Western Europe for which no prevalence data were identified.

One study, *Bränstrom et al. 2004 (*Wehner reference 28), collected data about the prevalence of ever exposure to indoor tanning in adults based on population-based sample limited to adults age 18-37 years in Stockholm County, Sweden One study, *Pertl et al. 2010* (Wehner reference 37), collected data about the prevalence of ever exposure to indoor tanning in adults using an interviewer-administered questionnaire given to "convenience sample" of adults between age 16 and 27 recruited in "various locations around Ireland (e.g., schools, sports clubs, universities and train stations."

One study, *Jackson et al. 1999*, (Wehner reference 33) collected data in 1995, nineteen years before 2014, the year for which the estimate of prevalence was made. Several other studies collected data more than a decade before 2014.

The meta-analytically derived estimate of the prevalence of ever exposure to indoor tanning for adults in Northern and Western Europe based on the studies identified by Wehner et al. (2014) is meaningless; the estimate of the number of skin cancers attributable to indoor tanning in Northern and Western Europe based on this meaningless estimate is meaningless.

Australia

The Wehner et al. (2014) systematic review identified one study (Francis et al. 2010) that reported a measure of the prevalence of ever exposure to indoor tanning adults in Australia that is probably "in the ball park." The prevalence measure based on data collected in 2007/2008 is reasonably current considering 2014 as the year for which the estimate was made. The sources of data on the annual number of incident melanoma and non-melanoma skin cancers in Australia is credible and I was able to verify the accuracy of these estimates.

Summary of the Systematic Review and Meta-analysis

Wehner et al.'s state (p. 391) that their systematic review sought to obtain prevalence estimates "representative of the general population." Specifically excluded as non-representative (page 391) were "studies of groups recruited based on factors that could be related to indoor tanning (e.g., studies of indoor tanners, skin cancer screening participants, dermatology clinic patients, and patients with skin cancer)." Also excluded (page 391) were case-control studies.

Wehner et al. (2014) do not specify the criteria used to define an estimate of prevalence as representative of the general population other than by applying these exclusions.

The systematic review identified 17 studies reporting on the prevalence of ever exposure to indoor tanning in adults that the authors concluded met the eligibility criterion as representative of the general population. (Mawn and Fleisher 1991; Moore et al. 2003; Lazovich et al. 2005; Woodruff et al. 2006; Hoerster et al. 2007; Lazovich et al. 2008; Cohen et al. 2013; Jackson et al. 1999; Boldeman et al. 2001; Bränstrom et al. 2004; Ezzedine et al. 2008; Börner et al. 2009; Schneider et al. 2009; Pertl et al. 2010; Køster et al. 2011; Schneider et al. 2013; Lawlor et al. 2006; Francis et al. 2010. These studies reported 22 estimates of the prevalence of ever exposure to indoor tanning in adults. The estimates of prevalence of ever exposure to indoor tanning in adults in these 17 studies are shown in Wehner et al.'s Figure 2 forest plot (page 393).

Seven studies (Mawn and Fleisher 1991; Moore et al. 2003; Lazovich et al. 2005; Woodruff et al. 2006; Hoerster et al. 2007; Lazovich et al. 2008; Cohen et al. 2013) met the Wehner et al. (2104) eligibility criterion as representative of ever exposure to indoor tanning in United States adults. These studies yielded seven estimates of prevalence of ever exposure to indoor tanning in adults in the United States.

Nine studies identified in the systematic review (Jackson et al. 1999; Boldeman et al. 2001; Bränstrom et al. 2004; Ezzedine et al. 2008; Börner et al. 2009; Schneider et al. 2009; Pertl et al. 2010; Køster et al. 2011; Schneider et al. 2013) met the Wehner et al. (2014) eligibility criterion as representative of the prevalence of ever exposure to indoor tanning in adults in Northern and Western Europe. These studies yielded 13 estimates of prevalence of ever exposure to indoor tanning in adults in Northern and Western Europe.

Two studies identified in the systematic review (Lawlor et al. 2006; Francis et al. 2010) met the Wehner et al. (2104) eligibility criterion as representative of the prevalence of ever exposure to indoor tanning in Australia adults;. These studies yielded three estimates of prevalence of ever exposure to indoor tanning in adults in Australia.

Measures of Exposure Prevalence Representative of the General Population

Exposure prevalence is the proportion of individuals in a defined population that have been exposed to a factor that affects or might affect disease or health. Exposure prevalence is measured in relation to a specified point in time (point prevalence) or during a specified period of time (period prevalence). For indoor tanning, possible measures of exposure prevalence include ever exposure in a lifetime and exposure in the last day, month, year, or some other time period.

Exposure prevalence is usually measured by collecting information directly from potentially exposed individuals using surveys or questionnaires, although for some conditions that are considered exposures (e.g., obesity, low hemoglobin), exposure prevalence might be measured using physical examination or laboratory measurement of blood or bodily fluids. For indoor tanning, exposure prevalence has been measured by collecting information directly from potentially exposed individuals.

Measures of exposure prevalence that represent exposure in the general population are often of public health interest. They are used to guide policies that seek to mitigate the adverse effects of the exposure on health with the aim of improving health and well-being.

It is difficult to obtain measures of exposure prevalence that are representative of the general population. To accomplish this aim requires drawing samples (generally large samples) that are representative of the general population (or drawing samples that can be made to represent the general population, such as stratified samples and appropriate weighted analysis); collecting data systematically with scrupulous attention to quality control in data collection; obtaining high response rates or obtaining responses that are representative of those asked to provide data; and appropriately analyzing data.

To be useful for making policy pertinent to the general population of a country or a region or the world, exposure prevalence data must be reasonably current.

Several on-going periodic surveys—e.g., the National Health Interview Survey (NHIS) and the Behavioral Risk Factor Surveillance System (BRFSS) in the United States and comparable surveys in other countries—collect information on the current prevalence of various exposures using methods that attempt to assure that exposure prevalence is representative of the general population.

Description of Studies in the Systematic Review and Meta-analysis Considered Representative of the General Population

Summary

The description of the studies considered to be eligible as representative of the prevalence of ever exposure to indoor tanning in adults appears in Wehner et al.'s (2014) e-Appendix. Absent from this e-Appendix description are statements about the survey method (e.g., self-administered questionnaire, interviewer administered questionnaire, phone survey, mailed survey, web survey), detail about the methods for selecting potential participants and/or the sampling frame, and response rates.

I read the full text of each of 16 of the 17 publications that Wehner et al. (2014) identified as yielding an estimate of the prevalence of ever exposure to indoor tanning in adults representative of the general population. The full text of one study (Mawn and Fleischer 1993) could not be obtained but the abstract presented detail on the study methods. I prepared a table (Table 1) that describes the survey method, the sampling frame / data collection method, and the response rate from the 17 publications. The exact wording from the methods section of several papers is presented in the table in several instances. Table 1 provides information on the year of data collection, which appears also in the Wehner et al. (2014) e-Appendix.

My Table1 includes my comments on the representativeness of the data for the country/region for which the data are meant to be representative and delineates other concerns about using the data to draw conclusions about the prevalence of ever exposure to indoor tanning in adults for the general population of the United States, Northern and Western Europe, and Australia. A summary of the studies and my comments on each study considering the representativeness of the data for the general population is summarized below.

United States

Mawn and Fleischer 1993 (Wehner reference 23) collected data about the prevalence of ever exposure to indoor tanning in adults in 1992 using self-administered questionnaires distributed to "477 persons in a shopping mall, at a social gathering, and on a vacation cruise ship." The response rate was not reported in the abstract.

Comment. The data are not current. The sample is haphazard. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in the United States.

Moore et al. 2003 (Wehner reference 25) collected data about the prevalence of ever exposure to indoor tanning in adults in 2002 using a self-administered questionnaire "distributed randomly by nursing staff to patients over the age of 18 who had a routine appointment" in a single primary care clinic in rural northeaster North Dakota. The response rate was not reported.

Comment. The data are not current. The sample is a convenience sample, not a representative sample. The data on the prevalence of exposure to indoor tanning reported in this study are not representative of the general population of adults in the United States.

Lazovich et al. 2005 (Wehner reference 24) collected data about the prevalence of ever exposure to indoor tanning in adults in 2002 using a telephone survey of adults from randomly selected households in Minnesota. The response rate was 45%.

Comment: The data are not current. The response rate is probably high enough to yield a sample that is representative of adults in Minnesota. Minnesota is not, however, representative of the entire United States. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in the United States.

Woodruff et al. 2006 (Wehner reference 40) collected data in 2004 about the prevalence of ever exposure to indoor tanning in adults in the United States in a telephone survey of households in Columbia, South Carolina and New Haven Connecticut that were selected because they had a high likelihood of having a child age 14, 15, 16, or 17. Responses about ever exposure to indoor tanning in adults pertain to adults living in households that had a child age 14, 15, 16, or 17 years. The response rate was 50% with an introductory letter and 45% without. This study was a pilot study for the study reported by Hoerster et al. (2007).

Comment: The data are not current. The response rate is probably high enough to yield a sample that is representative of adults in Columbia, South Carolina and New Haven, Connecticut living in households that have a child age 14-17 years. Data on the prevalence of exposure to indoor tanning in adults living in households that have a child in the age range 14-17 years are not representative of all adults. Data from adults in Columbia, South Carolina and New Have Connecticut are not representative of adults in the entire United States. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in the United States.

Hoerster et al. 2007 (Wehner reference 40) collected data in 2005 about the prevalence of ever exposure to indoor tanning in adults in the United States from a telephone survey of households that were selected because they had a high likelihood of having a child 14, 15, 16, or 17. Responses about ever exposure to indoor tanning in adults pertain to households with an adult who had a child age 14, 15, 16, or 17 years. The sampled households in this study were in the 100 largest cities in the United States. The response rate was 75%.

Comment: The data are not current. The response rate is high enough to yield a sample that is representative of adults in the 100 largest cities in the United States living in households that have a child age 14-17 years. Data about adults living in the 100 largest cities would approximate data from adults living in the entire United States only if a very high proportion of all adults in the United States live in these 100 cities; the proportion of the United States adult population living in these 100 cities is not discussed. Data on the prevalence of exposure to

indoor tanning in adults living in households that have a child in the age range 14-17 years are not representative of all adults. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in the United States.

Lazovich et al. 2008 (Wehner reference 36) collected data in 2006 about the prevalence of ever exposure to indoor tanning in adults in the United States using an interviewer-administered questionnaire given to a 26 adults recruited from an undergraduate psychology seminar and a convenience sample of adult staff and friends in Viriginia and from flyers, announcements, and advertisements in Massachusetts. The response rate was not reported.

Comment: The data are reasonably current. The sample is haphazard. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in the United States.

Cohen et al. 2013 (Wehner reference 29) collected data in 2010 about the prevalence of ever exposure to indoor tanning in adults in the United States using a self-administered questionnaire given to a "convenience" sample of 100 parents of children being seen in three pediatric practices in Chicago. The response rate was not reported.

Comment: The data are reasonably current. Data on the prevalence of ever exposure to indoor tanning in parents of children being seen in a pediatric practice in Chicago are not representative of adults in Chicago. Data on the prevalence of ever exposure to indoor tanning in adults in Chicago is not representative of adults in the entire United States. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in the United States.

Northern and Western Europe

Jackson et al. 1999 (Wehner reference 33) collected data about the prevalence of ever exposure to indoor tanning in adults in 1995 using a self-administered questionnaire given to randomly selected patients age 16+ years being seen for a GP consultation in 18 randomly selected group practices in Crewe and Macclesfield Health Districts in Cheshire, United Kingdom. The response rate was 89% for practices asked to participate. The response rate was 69% in patients asked to respond.

Comment: The exposure prevalence data are not current. The response rate for both practices and patients is high enough to yield a sample that is representative of adults who are being seen for a GP consultation in this area of the United Kingdom. It is not certain whether adults being seen by a GP in these health districts are representative of all adults in these health districts. Adults in this area of the UK are not representative of all adults in the UK. The UK is not representative of all of Northern and Western Europe. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in Northern and Western Europe.

Boldeman et al. 2001 (Wehner reference 26) collected data about the prevalence of ever exposure to indoor tanning in adults in 1999 using a questionnaire mailed to a random sample of adults age 20-50 years in Stockholm County, Sweden The response rate was 68%.

Comment: The exposure prevalence data are not current. The response rate is high enough to yield a sample that is representative of adults age 20-50 years in Stockholm County, Sweden. Adults age 20-50 years in Stockholm County are not representative of all adults in Sweden. Sweden is not representative of all of Northern and Western Europe. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in Northern and Western Europe.

*Bränstrom et al. 2004 (*Wehner reference 28) collected data about the prevalence of ever exposure to indoor tanning in adults in 2001 using a questionnaire mailed to a "random population-based sample" of adults age 18-37 years in Stockholm County, Sweden The response rate was 55%.

Comment: The exposure prevalence data are not current. The response rate is high enough to yield a sample that is representative of adults age 20-37 years in Stockholm County, Sweden. Adults age 20-37 years in Stockholm County are not representative of all adults in Sweden. Sweden is not representative of all of Northern and Western Europe. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in Northern and Western Europe.

Ezzedine et al. 2008 (Wehner reference 30) collected data about the prevalence of ever exposure to indoor tanning in adults in 2001 using a questionnaire—the "sun survey"--mailed to 12,741 participants in a French cohort study that was assembled in 1994-1995. The response rate to the "sun survey" among cohort members was 57%.

Comment: The exposure prevalence data are not current. The response rate is probably high enough to yield data that representative of all cohort members. While the original cohort was assembled to be representative of French adults in 1994-1995, the representativeness of the cohort of French adults in 2001 is uncertain. France is not representative of all of Northern and Western Europe. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in Northern and Western Europe.

Börner et al. 2009 (Wehner reference 27) collected data about the prevalence of ever exposure to indoor tanning in adults in 2007 using a telephone survey of a nationally representative sample of Germans age 14+ years contacted using random digit dialing. The response rate was 13%.

Comment: The exposure prevalence data are reasonably current. The response rate is very low and the data may not be representative of Germans 14+ years of age given the low

response rate. Germany is not representative of all of Northern and Western Europe. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in Northern and Western Europe.

Schneider et al. 2009 (Wehner reference 39) collected data about the prevalence of ever exposure to indoor tanning in adults in 2007 using a telephone survey of households in Mannheim, Germany. Households with an adult 18-45 years were identified and one adult per household provided a response to the survey. The response rate was 38%.

Comment: The exposure prevalence data are reasonably current. The response rate is marginal and the data may not be representative of adults in Mannheim, Germany age 18-45 given the low response rate. Even if the data are representative of adults 18-45 years in Mannheim, Germany, adults 18-45 years are not representative of all adults in Mannheim, Germany. Mannheim, Germany is not representative of all of Germany. Germany is not representative of all of Northern and Western Europe. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in Northern and Western Europe.

Pertl et al. 2010 (Wehner reference 37) collected data about the prevalence of ever exposure to indoor tanning in adults in late 2007 and early 2008 using an interviewer-administered questionnaire given to "convenience sample" of adults between age 16 and 27 recruited in "various locations around Ireland (e.g., schools, sports clubs, universities and train stations)." The response rate was not reported.

Comment: The exposure prevalence data are reasonably current. The sample is haphazard. The data pertain to adults between 16 and 27 years of age in Ireland and adults 16-27 years of age are not representative of all adults in Ireland. Ireland is not representative of all of Northern and Western Europe. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in Northern and Western Europe.

Køster et al. 2011 (Wehner reference 34) collected data about the prevalence of ever exposure to indoor tanning in adults in March 2007, August 2007, August 2008, and August 2009 using web and telephone surveys of a nationally representative sample of residents of Denmark. Reported analyses of the prevalence of exposure to indoor tanning excluded adults age 60+ years. The response rates varied by survey year and ranged from 26% in 2009 to 47% in August 2007.

Comment: The exposure prevalence data are reasonably current. The response rates are marginal and the respondents may not be representative of Danish adults age <60 years. Adults age <60 years are not representative of all Danish adults. Denmark is not representative of all of Northern and Western Europe. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in Northern and Western Europe.

Schneider et al. 2013 (Wehner reference 38) collected data about the prevalence of ever exposure to indoor tanning in adults in 2012 using a telephone survey of households Germany. Using a multistage sampling strategy, households with an adult 14-45 years were identified and one adult per household provided a response to the survey. The response rate was 28%.

Comment: The exposure prevalence data are current. The response rate is low and the data may not be representative of adults in Germany age 18-45 given the low response rate. Even if the data are representative of adults age 18-45 years in Germany, adults 18-45 years are not representative of all adults in Germany. Germany is not representative of all of Northern and Western Europe. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in Northern and Western Europe.

Australia

Lawlor et al. 2006 (Wehner reference 35) collected data about the prevalence of ever exposure to indoor tanning in adults in 2004 using a telephone survey of residents of Queensland, Australia age 20-75 years. Households with a landline were identified using a stratified random sampling method. The analysis accounted for the stratified nature of the sample. The response rate was not reported.

Comment: The exposure prevalence data are not current. The lack of information about the response rate is a limitation when judging representativeness. The sampling frame is an appropriate one for generating data that are representative of adults in Queensland, Australia. Queensland is not representative of all of Australia. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not representative of the general population of adults in Australia.

Francis et al. 2010 (Wehner reference 31) collected data about the prevalence of ever exposure to indoor tanning in adults in 2003/2004 and again in 2007/2008 using a telephone survey of residents of Australia age 18-69 years. A representative sample of households with a landline were identified and contacted. The response rate was 24% in 2003/2004 and 18% in 2007/2008.

Comment: The exposure prevalence data for 2003/2004 data are not current. The exposure prevalence data for 2007/2008 are reasonably current. The sampling frame is an appropriate one for generating data that are representative of adults age 18-69 in Australia. The response rate for both 2003/2004 and 2007/2008 is low. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not assured to representative of the general population of adults in Australia in 2004 given the low response rates. The restricted age range for the sample is a limitation when generalized to all adults in Australia. The Francis et al. (2010) study is the only study identified in the Wehner et al. (2014) systematic review that provides information about the prevalence of ever exposure to indoor tanning in adults in a country (Australia) that is probably "in the ballpark."

Conclusion

None of the seven studies that provide data on the prevalence of ever exposure to indoor tanning in adults in the United States yielded prevalence estimates representative of the general population of adults in the United States. Two studies (Mawn and Fleischer 1993; Lazovich et al. 2008) are based on samples that are haphazard and one of these (Mawn and Fleischer 1993) presents data that is obsolete. Two studies (Moore et al. 2003; Cohen et al. 2013) use "convenience" samples of patients being seen in highly selected clinical practices in a small and unrepresentative region of the United States. Of the studies, only the study by Lazovich et al. (2005) had a sampling frame—randomly selected households in Minnesota—that is appropriate for drawing conclusions about the general population of adults in Minnesota but Minnesota adults are not representative of all adults in the United States.

None of the nine studies that provide data on the prevalence of ever exposure to indoor tanning in adults in Northern and Western Europe yielded prevalence estimates representative of the general population of adults in Northern and Western Europe. Only one study done in a country in Northern/Western Europe, the Borner et al. (2007) study, was based on nationally representative sample of German adults of all ages but this study had a response rate of only 13%.

One study (Frances et al. 2010) provides data on the prevalence of ever exposure to indoor tanning in adults in Australia (Frances et al. 2010) for two different periods—2003/2004 and 2006-2007—that is based on a nationally representative sample of adults 18-69 years. The response rate was only 24% in 2003/2004 and 18% in 2006/2007 and this is a limitation. This study is the only study identified in the Wehner et al. (2014) systematic review that provides information about the prevalence of ever exposure to indoor tanning in adults in a country (Australia) that is probably "in the ball park."

The Model Used to Estimate the Number of Skin Cancers Attributable Each Year to Indoor Tanning

Description of the Model

Wehner et al.'s Figure 2 forest plot (page 393) shows the estimates of the prevalence of ever exposure to indoor tanning in adults for the seventeen studies that were considered to provide prevalence estimates representative of the general population (23 estimates) along with a summary estimate of the prevalence of ever exposure to indoor tanning for each region and overall based on a random effects meta-analysis. Wehner et al. (2104) used the meta-analytically derived summary prevalence estimates to derive an estimate of the number of incident (new) skin cancers attributable each year to indoor tanning in the United States, in Northern and Western Europe, and in Australia. The estimates of the number of incident skins cancers attributable each year to indoor tanning were made in two steps.

Step 1. The first step was to estimate the population proportional attributable risk of skin cancer (separately for squamous cell carcinoma, basal cell carcinoma and malignant melanoma in each of the three regions) based on the following formula:

population proportional attributable risk =
(prevalence of exposure x [RR – 1.0]) / 1 + (prevalence of exposure x [RR – 1.0])

where RR is the relative risk of the skin cancer (squamous cell carcinoma, basal cell carcinoma and malignant melanoma in those with ever exposure to indoor tanning.

Step 2. The next step was to apply the estimate of the population proportional attributable risk of skin cancer calculated in Step 1--again separately for squamous cell carcinoma, basal cell carcinoma and malignant melanoma in each of the three regions--to estimates of the annual number of incident cases of each type of skin cancer in the United States, Northern and Western Europe, and Australia. This step yielded an estimate of the number of incident skin cancers of each type attributable to ever exposure to indoor tanning for each region. These estimates were summed to yield an estimate of the total number of incident skin cancer of all types attributable each year to indoor tanning.

Data Sources

Estimates of the Relative Risk of Skin Cancer for Individuals Ever Exposed to Indoor Tanning

Estimates of the relative risks (RR) for the three types of skin cancer were based on two published systematic reviews and meta-analyses (Boniol et al. 2012; Wehner et al. 2012). The meta-analytically derived summary RR of malignant melanoma for ever exposure to indoor tanning in the Boniol et al. (2012) meta-analysis was 1.25. The meta-analytically derived summary RR of basal cell carcinoma for ever exposure to indoor tanning in the Wehner et al. (2012) systematic review was 1.29; the summary RR of squamous cell carcinoma was 1.67.

Comment: I identified two other published systematic reviews that presented summary estimates of the RR of malignant melanoma in ever users of indoor tanning were identified (Colantonio, Bracken and Bleecker 2014; IARC 2007). The summary RR of malignant melanoma in ever users of indoor tanning was 1.16 (95% CI 1.05-1.28) in Colantonio, Bracken and Beecker 2014; it was 1.15 (95% CI, 1.00-1.31) in IARC 2007.

I did not identify any other systematic reviews that calculated estimates of the RR of basal cell carcinoma or squamous cell carcinoma.

Wehner et al. (2014) state that they used the Boniol et al. 2012 systematic review as the source of their summary estimate of the RR of malignant melanoma in ever users of indoor tanning because it was “rigorous” had been published in the “last year.” The Colantonio, Bracken and

Beecker (2014) systematic review of melanoma and ever exposure to indoor tanning was equally rigorous and was published later than the Boniol et al. (2012) systematic review. It is possible, however, that the Colantonio, Bracken, and Beecker (2014) systematic review was not known to Wehner et al. (2014). The difference in the summary estimates of the RR of malignant melanoma in ever users of indoor tanning comparing Boniol et al. (2012) and Colantonio, Bracken and Bleecker (2014) is negligible—1.25 and 1.15 respectively.

Estimates of the Prevalence of Ever Use of Indoor Tanning in Adults

United States

Comment: None of the studies reporting the prevalence of ever exposure to indoor tanning in adults that Wehner et al. 2014 identified in their systematic review provide data representative of the general population of the United States. Several of the studies are from haphazard samples.

The prevalence data for the seven studies that were meta-analyzed in order to derive a summary estimate of the prevalence of ever exposure to indoor tanning were extremely heterogeneous ($I^2 = 96.5\%$; $p < .001$), which is not surprising given the heterogeneous nature of the studies contributing to the estimate. In the face of such extreme statistical and methodologic heterogeneity, the validity of a meta-analytically derived summary measure of prevalence is highly questionable. The summary estimate of prevalence of ever exposure to indoor tanning in adults in the United States based on the studies identified by Wehner et al. (2014) is meaningless.

The estimates of prevalence of ever exposure to indoor tanning from the seven studies that Wehner et al. (2014) used to estimate prevalence are based on samples that are younger than the United States population. More than 80% of all melanoma and about 70% of non-melanoma skin cancers in the United States occur in people who are age 65 years or more. (Rogers et al. 2010;http://seer.cancer.gov/csr/1975_2012/browse_csr.php?sectionSEL=18&pageSEL=sect_18_table.07.html accessed 1/1/2016.) Applying a prevalence estimate that pertains to younger adults to estimates of the number of skin cancers occurring in adults of all ages, influenced prominently by adults 65+ years, yields a grossly upwardly biased estimate.

Northern and Western Europe

Comment: The Wehner et al. (2014) systematic review identified studies of the prevalence of ever exposure to indoor tanning adults that were done in the United Kingdom, Ireland, France, Germany, Denmark, and Sweden. Only one study, Borner et al. (2009) had a sampling frame that could have yielded data representative of Germany but the r response rate was very low (13%). Germany is not representative of all of Northern and Western Europe.

Austria, Belgium, Luxembourg, the Netherlands, Estonia, Finland, Iceland, Latvia, Lithuania, Norway and Switzerland are countries in Northern and Western Europe for which no prevalence data were identified.

The prevalence data for the studies that were meta-analyzed in order to derive a summary estimate of the prevalence of ever exposure to indoor tanning were extremely heterogeneous (I^2 = 99.9%; p < .001), which is not surprising given the heterogeneous nature of the studies contributing to the estimate. In the face of such extreme statistical and methodologic heterogeneity, the validity of a meta-analytically derived summary measure of prevalence is highly questionable.

Australia

Comment: The Wehner et al. (2014) systematic review identified one study (Francis et al. 2010) that reported a measure of the prevalence of ever exposure to indoor tanning adults in Australia that is probably "in the ball park." The measure for 2007/2008 is reasonably current. The source of data on the annual number of incident melanoma and non-melanoma skin cancers in Australia is credible and the accuracy of the estimates were verified.

Wehner et al. (2014) report that the data on prevalence of ever exposure to indoor tanning that were used to derive a summary estimate of the prevalence of ever exposure to indoor tanning were extremely heterogeneous (I^2 = 99.9%; p < .001). This is surprising since the three estimates of prevalence for Australia are identical with narrow and virtually identical:

Lawler et al. 2006	0.11 (95% CI 0.10-0.11)
Francis et al. 2010	0.11 (95% CI 0.10-0.12)
Francis et al. 2010	0.11 (95% CI 0.10-0.11)

I conclude that a mistake was made in calculating I^2.

Estimates of the Number of Incident Cases of Cancer in the United States, Northern and Western Europe and Australia

United States

Malignant Melanoma

Data on the annual number of incident melanomas in the United States in 2012 were obtained from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program (US National Cancer Institute 2013; Wehner et al. reference 94).

Comment: SEER is a credible source of data on the annual number of malignant melanomas in the United States. I was able to verify that the number cited in Wehner et al. (2014) is as the number was reported in SEER.

Non-melanoma Skin Cancer

The number of incident non-melanoma skin cancers in the United States was based on a complex analysis by Rogers et al. (2010) that used census data, the Centers for Medicare and Medicaid Services 2007 Trustee's report and three different databases--the Centers for Medicare and Medicaid Services Fee-for-Service Medicare physician/supplier procedure summary master file (the "Total Claims Data Set"), the CMS Medicare Limited Data Set Standard Analytic File 5% Sample Physician Supplier Data (the "5% Sample Data Set"), and the National Ambulatory Medical Care Service database. The methods section of the Rogers et al. (2010) publication that explains how these data sources were used to obtain an estimate of the number of non-melanoma skin cancers is reproduced in the Appendix.

Roger's et al. (2012) estimated that the total number of non-melanoma skin cancers treated in 2006 in the United States was 3,507,693. In Rogers et al. (2010), 2,482,801 of the non-melanoma skin cancers (71%) were ascribed to patients 65 years of age or older. Based on a ratio of skin cancers treated per affected patient of 1.63, Rogers et al. estimated that 2,152,500 people were treated for non-melanoma skin cancer in the United States in 2006.

Comment: The claims data pertain to procedures used to treat possible non-melanoma skin that also have an ICD-9-CM code for cancer. The problem of upcoding in claims databases is well-known. The large increase in the number of claims for procedures to treat skin cancer in the Medicare fee-for-service population that Rogers et al. (2012) document—from 1,158,298 in 1992 to 2,048,517 in 2006—raises questions about the data.

In estimating the number of non-melanoma skin cancers attributable to indoor tanning, Wehner et al. (2014) allocated 75% of the 3,507,693 skin cancers to basal cell carcinoma (n=2,630,770) and 25% to squamous cell carcinoma (n=876,923) without citing a source for this allocation ratio, which does not appear in Rogers et al.'s.

Northern and Western Europe

Malignant Melanoma

Wehner et al. (2014) estimated the number of incident cases of malignant melanoma in Northern and Western Europe by multiplying the incidence of melanoma in Northern and Western Europe reported for 2008 in the IARC GLOBOCAN database (IARC GLOBOCAN database; Wehner et al. reference 93) by 285,763,000, which was the size of the adult population of Northern and Western Europe in 2008. The estimated incidence rate for melanoma used was 18.1 per 100,000. Thus,

$$18.1 \text{ per } 100{,}000 \times 285{,}763{,}000 = 51{,}740$$

Comment: I was not able to locate an estimate for the incidence of malignant melanoma of 18.1 per 100,000 for the countries that comprise Northern and Western Europe at the IARC GLOBOCAN website. The countries that comprise Northern and Western Europe are: Austria,

Belgium, Denmark, Estonia, Finland, France, Germany, Iceland, Ireland, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Sweden, Switzerland, UK. I was able to determine an average crude rate of malignant melanoma for these 17 countries for 2012 based on data on the individual crude rates of malignant melanoma per 100,000 for these 17 countries and a population-weighted rate of malignant melanoma for the whole of Northern and Western Europe. These estimates are shown in Table 2 of this report.

Based on the data I was able to obtain from the GLOBOCAN database, the estimated malignant melanoma incidence rate for Northern and Western Europe is 20.4 per 100,000 (average crude rate for all 17 countries) or 20.9 per 100,000 (population weighted). The use of the estimate 18.1 per 100,000 by Wehner et al. (2014) seems reasonable.

Non-Melanoma Skin Cancer

Overview

Wehner et al. cited a systematic review of the incidence of non-melanoma skin cancer by Lomas et al. 2012 (Wehner reference 95) as the source of the estimate of the number of incident cases of basal cell carcinoma and squamous cell carcinoma that they used in their model to estimate the number of non-melanoma skin cancer attributable to indoor tanning.

Basal Cell Carcinoma

For basal cell carcinoma incidence was (page 397, footnote e to Table 2):

> "calculated using a yearly incidence rate of 50 per 100,000 (lower-bound conservative estimate from Lomas et al. for 2000-2005) multiplied by the 2008 Northern and Western European population of 285,762,000"

Comment: The Lomas et al. (2012) systematic review presented estimates of the age-standardized incidence of basal cell carcinoma per 100,000 in European males from 1968-2005 from studies in Denmark, Finland, Germany, Italy, Netherlands, Scotland, South Wales, Slovakia, Switzerland, UK, and Wales (page 1076, Figure 3). These rates varied from 20 per 100,000 in Finland in 1968 to 130 per 100,000 (interpolated) in South Wales in 2002 (interpolated).

On page 1074, in Table 2, Lomas et al. (2012) present data on directly standardized annual incidence for non-melanoma skin cancer, basal cell carcinoma, and squamous cell carcinoma in the UK for 2000-2006. Estimates of the standardized incidence of basal cell carcinoma in the UK ranged from 0.24 per 100,000 (London) to 121.29 per 100,000 (South-West England).

No data reporting on the incidence of basal cell carcinoma for the period 2000-2005 could be identified in the Lomas et al. (2012) publication. A value for the incidence of basal cell carcinoma of 50 per 100,000 could not be located anywhere in the Lomas et al. (2012) publication. The terms "lower-bound" and "conservative" could not be found in a search of the PDF file of the full text of the Lomas et al. (2012) publication.

Squamous Cell Carcinoma

For squamous cell carcinoma, incidence was (page 397, footnote f to Table 2):

> "calculated using a yearly incidence rate of 10 per 100,000 (lower-bound conservative estimate from Lomas et al. for 2000-2005) multiplied by the 2008 Northern and Western European population of 285,762,000"

Comment: The Lomas et al. (2012) systematic review presented estimates of the age-standardized incidence of squamous cell carcinoma per 100,000 in European males from 1958-2003 from studies in Denmark, Finland, Germany, Italy, Netherlands, Scotland, South Wales, Slovakia, Sweden, Switzerland, UK, and Wales (page 1076, Figure 4). These rates varied from 4 per 100,000 in Finland in 1958 (interpolated) to 32 per 100,000 in Germany in 1988 (interpolated).

Estimates of the standardized incidence of squamous cell carcinoma in the UK ranged from 14.98 per 100,000 (London) to 33.02 per 100,000 (South-West England).

No data about the incidence of squamous cell carcinoma pertaining to the period 2000-2005 could be identified in the Lomas et al. publication.

On page 1075, column 2, lines 18-19, Lomas et al. (2012) state that "Denmark reported very low rates of SCC [squamous cell carcinoma] of less than 10/100,000 person-years." This is the only place in the Lomas et al. publication that the figure 10/100,000 for the incidence of squamous cell carcinoma could be found.

The terms "lower-bound" and "conservative" could not be found in a search of the PDF file of the full text of the Lomas et al. (2012) publication.

Australia

Data on the annual number of incident non-melanoma skin cancers for Australia were obtained from the Australian Institute of Health and Welfare. (Cancer Australia & AIHW 2008; Wehner et al. reference 91. Data on the annual number of melanoma skin cancer for Australia were obtained from the Australian Institute for Health and Welfare. (Australian Institute of Health and Welfare; Wehner et al. reference 92).

Comment: I compared the number of incident non-melanoma and melanoma skin cancers reported in Wehner et al. (2014) with the data reported in sources cited and was able to confirm that the numbers of melanoma and non-melanoma skin cancer reported in Wehner et al. (2014) match the source data.

Conclusion

Estimates of the number of melanoma and non-melanoma skin cancers attributable to indoor tanning each year in the United States and in Northern and Western Europe, which are based on a model that uses meaningless prevalence estimates and poor data on non-melanoma skin cancer, are not credible. The publication that presents the meaningless data on the prevalence of ever exposure to indoor tanning in adults in the United States should be removed from the CDC website. The data about the number of melanoma and non-melanoma skin cancers in the United States attributable each year to indoor tanning should not be cited by the CDC or any other agency because these numbers are based on a meaningless estimate of prevalence and a poor estimate of the total number of non-melanoma skin cancers.

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Table 1. Information about Methods from Studies of the Prevalence of Exposure to Indoor Tanning Cited in the Systematic Review and Meta-analysis by Wehner et al. 2014, Figure 2 with Comments

Reference Number in Wehner	First Author and Year of Publication	Year of Data Collection	Method of Data Collection	Response Rate	N of Respondents	Methods for Obtaining Responses / Sampling Frame
United States						
23	Mawn and Fleischer 1993	1992	Self-administered questionnaire	NR	477	"A written, anonymous questionnaire was distributed to a sample of 477 persons in a shopping mall, at a social gathering, and on a vacation cruise ship"
COMMENT The data were collected in 1992 and are not current. The prevalence of exposure in 1992 is not representative of current or recent exposure. The non-response rate is unknown. Responses from people in shopping malls, social gatherings, and a vacation cruise ship are not representative of the general US adult population. The sample is haphazard.						
25	Moore et al. 2003	2002	Self-administered questionnaire	NR	106	A questionnaire was distributed randomly by the nursing staff to patients over the age of 18 who had a routine appointment at a local primary care clinic in rural northeastern North Dakota
COMMENT The data were collected in 2002 and are not current. The response rate is unknown. Responses from primary care clinic attendees in rural northeastern North Dakota are not representative of the general US adult population.						
24	Lazovich et al. 2005	2002	Telephone survey	45%	802	Adults from randomly selected households in Minnesota
COMMENT The data were collected in 2002 and are not current. The response rate is reasonable. Responses from residents of Minnesota are not representative of the general US adult population.						
40	Woodruff et al. 2006	2004	Telephone survey	50% with letter of introduction 45% without letter	94	Pilot study for Hoerster. Data collected in two cities not scheduled to be included in Hoerster study (reference 32) (Columbia, South Carolina and New Haven, Connecticut). Households were selected by a professional survey research organization as having a high probability of an adolescent 14, 15, 16 or 17 years of age living in the

						household. Parents in households that had an adolescent in the targeted age range provided information on their own use of indoor tanning.
COMMENT The data were collected in 2004 and are not current. The response rate is reasonable. Adults in households that have children age 14-17 years are not representative of all adults. Adults from residents of Columbia, South Carolina and New Haven, Connecticut are not representative of the general US adult populations.						
32	Hoerster et al. 2007	2005	Telephone survey	75%	5274	Data collected in the 100 largest cities in the United States. Methods as described in Woodruff (reference 40)
COMMENT The data were collected in 2005 and are not current. Adults in households that have children age 14-17 years are not representative of all adults. Adults from residents of the 100 largest cities in the United States cannot be certain to be representative of the general US adult populations without knowing what proportion of the US adult population resides in cities this size. .						
36	Lazovich et al. 2008	2006	Interviewer administered questionnaire	NR	24	"In Virginia, participants were recruited from an undergraduate psychology seminar and a convenience sample of young adult staff and friends. In Massachusetts, flyers posted in community businesses, announcements in online classified sites, and advertisements on the University of Massachusetts Medical School employee intranet were used. Participants in Tennessee were drawn from the Psychology Department Research Subject pool, while in New Hampshire, high school age girls were recruited through posters placed in their school. Individuals who had either used sunless tanning products or indoor tanning devices in the past were targeted for interviews."
COMMENT The data were collected in 2010 and are reasonably current. The response rate is unknown. The sample is haphazard. The study responses are not representative of the general population of adults in the United States.						
29	Cohen et al. 2013	2010	Interviewer administered questionnaire	NR	300	"Convenience sample" of 100 parents of children being seen in 3 pediatric practices in Chicago
COMMENT The data are current. The response rate is unknown. Adults with children being seen in pediatric clinics are not representative of all adults. Adults from Chicago are not representative of the general US adult populations.						
Europe						

33	Jackson et al. 1999	1995	Self-administered questionnaire	89% practices 69% patients	3105	18 randomly selected group practices in Crewe and Macclesfield Health Districts in Cheshire United Kingdom were asked to participate. In the 16 cooperating practices, randomly selected patients aged 16 years and over who attended their surgery for a GP consultation for any reason during a one-week period between September and November 1995 were invited by the reception staff to complete a questionnaire at the time or to return it by post after subsequent completion.
COMMENT The data were collected in 1995. The prevalence of exposure in 1995 is not representative of current or recent exposure. The response rate is reasonable both for practices and patients. The representativeness of attendees at a GP clinic for all patients seeing a GP is unknown. Attendees in a GP clinic in Cheshire United Kingdom are not representative of GP attendees in the entire UK. Cheshire UK is not representative of the general population of the UK or of the general population of Northern and Western Europe.						
26	Boldeman et al. 2001	1999	Mailed questionnaire	68%	2684	A random sample of 4000 adults age 20-50 years in Stockholm County were selected from the national census registry and sent a mailed questionnaire with two reminders.
COMMENT The data were collected in 1999. The prevalence of exposure in 1999 is not representative of current or recent exposure. The response rate is reasonable. The sample frame is appropriate for a question pertaining to adults in the restricted age range 20-50 years. Responses in this age range are not representative of all adults in Stockholm County. Stockholm County is not representative of all of Sweden. Stockholm county is not representative of all of Northern and Western Europe.						
28	Branstrom et al. 2004	2001	Mailed questionnaire	55%	1752	"A random population-based sample (n = 3200, 18–37 years of age) in the Stockholm County, Sweden, stratified by gender and age (in four age strata; 18–22, 23–27, 28–32 and 33–37), was selected from the Swedish census registry. In May 2001, they were mailed a questionnaire" with one reminder.
COMMENT The data were collected in 2001. The prevalence of exposure in 2001 is not representative of current or recent exposure. The response rate is reasonable. The sampling frame is appropriate for a question pertaining to adults in the restricted age range 18-37 years. Responses in this age range are not representative of all adults in Stockholm County. Stockholm County is not representative of all of Sweden. Stockholm county is not representative of all of Northern and Western Europe.						
30	Ezzedine et al. 2008	2001	Mailed questionnaire	57%	7303	12,741 participants in a French cohort study originally recruited in 1994-1995 were asked to complete a special "sun survey" in 2001.
COMMENT The data were collected in 2001. The prevalence of exposure in 2001 is not representative of current or recent exposure. The response rate is reasonable. The representativeness of the original cohort for all French adults is not established. France is not representative of all of Northern and Western Europe.						

27	Borner et al. 2009	2007	Telephone survey	13%	1419	A nationally representative sample of German age 14+ years was contacted using a random digit dial procedure to access households and then selecting the respondent according to the so-called "last birthday" method (selecting the household member age 14 or over who has had the last birthday).
COMMENT The data were collected in 2007 and are reasonably current. The response rate is very low. The sample frame is appropriate for estimating prevalence in Germany. Germany is not representative of all of Northern and Western Europe.						
39	Schneider et al. 2009	2007	Telephone survey	38%	500	A two stage sampling procedure was used. Households in Mannheim, Germany were selected using the official telephone register. Households with at least one member age 18-45 were asked to participate, selecting the respondent according to the "last birthday" method (selecting the household member age 18-45 who had the last birthday)
COMMENT The data were collected in 2007 and are reasonably current. The response rate is somewhat low. The sampling frame is appropriate for a question pertaining to adults in the restricted age range 18-45 years. Responses in this age range are not representative of all adults in Mannheim, Germany. Mannheim, Germany is not representative of all of Germany. Mannheim, Germany is not representative of all of Northern and Western Europe.						
37	Pertl et al. 2010	12/2007-1/2008	Interviewer administered questionnaire (some uncertainty if interviewer administered or self-administered)	NR	590	"Convenience sampling was used to recruit young adults, between the ages of 16 and 26 years, from the general public. Potential participants were approached by research assistants in various locations around Ireland (e.g. schools, sports clubs, universities and train stations) and a recruitment script was used to ensure that all participants were approached in the same way."
COMMENT The data were collected in 2007-2008 and are reasonably current. The non-response rate is not known. Responses from people in various locations in Ireland are not representative of the entire Irish population. Responses in the restricted age range 16 to 26 years are not representative of all Irish adults. Responses from adults in Ireland are not representative of all adults in Northern and Western Europe. The sample is haphazard.						
34	Koster et al. 2011	March 2007	Web/telephone	30%	3356	A nationally representative sample of residents of Denmark was identified using random digit dialing with data collected using interviews and the web in 2007, replaced by a web-only survey in 2008 and 2009. Analysis of sunbed use excluded residents age 60+ years
34	Koster et al. 2011	August 2007	Web/telephone	47%	3497	See above
34	Koster et al. 2011	August 2008	Web survey	36%	3915	See above
34	Koster et al. 2011	August	Web survey	26%	3746	See above

		2009				
COMMENT The data were collected in 2007-2009 and are reasonably current. The response rate is marginal. The study results are likely to be representative of adults less than 60 years in Denmark but not of all adults in Denmark. Denmark is not representative of all of Northern and Western Europe.						
38	Schneider et al. 2013	2012	Telephone survey	28%	4851	"The study included German residents aged 14 to 45 years. A multistage sampling process was used to randomly select study participants….. A pool of telephone numbers was generated and a telephone number was selected using a random algorithm, and the corresponding household was contacted by phone. If there was more than 1 person from the target population in that household, the person with the next birthday was chosen to participate."
COMMENT The data were collected in 2012 and are current. The response rate is low. The sample frame is appropriate for a question pertaining to adults in the restricted age range 14-45 years. Responses in this age range are not representative of all adults in Germany. Germany is not representative of all of Northern and Western Europe.						
Australia						
35	Lawler et al. 2006	2004	Telephone survey	NR	9298	English speaking adults age 20-75 years and residing in Queensland Australia were eligible. Households with a landline (95% in Queensland at the time of the study) were selected using a stratified random sampling method. Results were weighted to reflect stratified design.
COMMENT The data were collected in 2003/2004 and are not current. The response rate is unknown. The sample frame is appropriate for a question pertaining to adults in the age range 20-75 years. Responses are likely to be generally representative of adults in Queensland. Queensland is not representative of all of Australia						
31	Francis et al. 2010	2003/2004	Telephone survey	24%	5073	A representative sample of Australian adults (age 18–69 years) were recruited via weekly cross-sectional telephone calls to randomly selected households with a landline telephone.
31	Francis et al. 2010	2006/2007	Telephone survey	16%	5085	Same as above.
COMMENT Data were collected in 2003/2004 and in 2006/2007. The 2003/2004 data are not current. The sampling frame is an appropriate one for generating data that are representative of adults age 18-69 in Australia. The response rate for both 2003/2004 and 2007/2008 is low. The data on the prevalence of ever exposure to indoor tanning in adults reported in this study are not assured to representative of the general population of adults in Australia in 2004 because of the low response rate. The restricted age range for the sample is a limitation. This study is the only study identified in the Wehner et al. (2014) systematic review that provides credible information about the prevalence of ever exposure to indoor tanning in adults in a country—Australia.						

Table 2. Incidence of Malignant Melanoma in Countries Comprising Northern and Western Europe. IARC GLOBOCAN Database. 2012.

		2012	2012
Country	Population in 2010	Crude Rate per 100,000	Population Weighted
Austria	8,374,290	15.8	0.46
Belgium	10,839,905	18.0	0.68
Denmark	5,534,738	28.5	0.55
Estonia	1,340,127	12.4	0.06
Finland	5,351,427	22.4	0.42
France	62,791,000	15.6	3.41
Germany	81,802,257	20.6	5.86
Iceland	317,630	15.5	0.02
Ireland	4,467,854	18.8	0.29
Latvia	2,248,374	10.1	0.08
Lithuania	3,329,039	8.4	0.10
Luxembourg	502,066	16.4	0.03
Netherlands	16,574,989	28.7	1.65
Norway	4,858,199	30.4	0.51
Sweden	9,340,682	30.7	1.00
Switzerland	7,785,806	32.1	0.87
UK	62,026,962	23.0	4.96
All Countries	287,485,345	20.4	20.94

IARC. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. On-line calculator. http://globocan.iarc.fr/Pages/summary_table_site_sel.aspx

Appendix

Methods Section Reproduced From Rogers et al. 2010

DATA SOURCES

Our analyses were based primarily on 2 distinct Medicare databases and on national survey data. The Medicare physician/ supplier procedure summary master file (hereinafter, Total Claims Data Set) was analyzed for the years 1992 and 1996 to 2006 (available years).[18] For our primary approach to the estimation of NMSC, the 2006 Total Claims Data Set was used to provide total numbers of approved fee-for-service Medicare claims categorized by Current Procedural Terminology (CPT) procedure code number.[19] However, the Total Claims Data Set does not contain information relating to patient age or *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis, associated with each procedure code.[20] The Medicare Limited Data Set Standard Analytic File 5% Sample Physician Supplier Data (hereinafter, 5% Sample Data Set) was available for 2002 to 2006.[21] This nationally sampled Medicare database contains information on claims filed for approved procedures with their associated *ICD-9-CM* diagnosis codes, patient age stratification, and counts of unique persons receiving the services. Hence, the 5% Sample Data Set allowed estimation of the proportion of procedures for skin cancer that were for NMSC, the proportion of procedures that were conducted on enrollees older than 65 years, and the mean number f procedures per enrollee with any procedures.

The National Ambulatory Medical Care Survey (NAMCS) is a cross-sectional survey system of ambulatory-based physicians wherein participating physicians complete a questionnaire for patient visits during a random 1-week period of the year.[22] These visit observations are then used to provide a national estimate of physician visits and limited characteristics of these visits for that year. The NAMCS allowed estimation of the proportion of visits for NMSC in the United States that were conducted in the population older than 65 years.

ESTIMATION OF THE TOTAL NUMBEROF NMSCs IN 2006

For this study, we define NMSC incidence in 2 ways: as newly diagnosed NMSCs and as persons with a newly diagnosed NMSC, with the latter as our primary definition, although we present both. The number of skin cancers in the fee-for-service Medicare population was estimated in this study as the total of approved skin cancer treatment procedures (malignant destructions, malignant excisions, and Mohs micrographic surgical procedures) for that year from the Total Claims Data Set. Thus, the crude number of skin cancers for a claims for skin cancer procedure code series (11600-11606, 11620-11626, and 11640-11646 for malignant excisions; 17260-17266, 17270-17276, and 17280-17286 for malignant destructions, 17304 for Mohs surgical procedures). The total specific to NMSC was determined by multiplying the estimated crude number of skin cancers by the proportion of skin cancer procedure code claims associated with

the *ICD-9-CM* diagnoses for invasive non-melanoma cutaneous malignancy (173.0-173.9) and in situ malignancy (232.0-232.9) from the 5% Sample Data Set. The number of procedures per affected individual and the number of unique persons that underwent at least 1 procedure were also derived from the 5% Sample Data Set.

Based on our *ICD-9-CM* code definition of NMSC, almost all of the skin cancers measured in this study were keratinocyte carcinomas (ie, BCC, invasive SCC, or SCC in situ). However, other varieties of skin cancer are also included in our totals, such as Merkel cell carcinoma, adnexal carcinomas, and malignant melanoma in situ. These cancers are relatively uncommon compared with BCC and SCC, and because of the imprecise nature of *ICD-9-CM* coding, we cannot separate procedures for these diagnoses. Excluded from our count were some forms of NMSC, such as cutaneous lymphoma and genital skin cancers that have separate *ICD-9-CM* codes. Therefore, although some malignant melanomas in situ are included in our estimates, and some NMSCs are excluded, the overall number of keratinocyte carcinomas is so much larger that these inclusions and exclusions should have a small effect on our overall estimate. For example, analysis of the Surveillance, Epidemiology, and End Results (SEER) database for 2006 estimates 49 710 new US cases of malignant melanoma in situ (1.4% of our total NMSC estimate).[23] For this article, we will use the common but admittedly imprecise term *NMSC*.

The number of NMSCs in the Medicare population 65 years or older was established from the Total Claims Data Set and the 5% Sample Data Set. The proportion of the entire US population (>=65 years) covered under Medicare was derived from the Center for Medicare and Medicaid Services 2007 Trustee's report and US census data, allowing estimation of the number of NMSCs in the entire population segment that was 65 years or older.[24,25] The proportion of total office visits for NMSC *ICD- 9-CM* codes (173.0-173.9 and 232.0-232.9) that were for the segment of the population that was 65 years or older in 2006 was obtained from the NAMCS. The number of NMSCs in the US population (_65 years old) was then divided by the proportion of office visits for NMSC in that group, allowing estimation of the total number of skin procedures for NMSC in the United States. The total number of persons in the United States diagnosed as having NMSC in that year was calculated from the skin cancer procedure totals and the number of NMSCs per affected Medicare patient. More detailed representation of the calculation described in this section is available at the Skin Cancer Center Web site.[26]

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EXHIBIT C

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Original article

An Intervention to Decrease Adolescent Indoor Tanning: A Multi-Method Pilot Study

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A B S T R A C T

Purpose: Indoor tanning usually begins during adolescence, but few strategies exist to discourage adolescent use. We developed and tested a parent–teenager intervention to decrease indoor tanning use.

Methods: Through focus groups, we identified key messages to enhance parent–teenager communication about indoor tanning, and then developed a pamphlet for parents and postcards for adolescents to use in a direct mail experiment with randomly selected households. Two weeks after the mailing, we asked intervention parents (n = 87) and adolescents (n = 69) and nonintervention parents (n = 31) and adolescents (n = 28) about intervention receipt and content recall, parental concern, monitoring, parent–teenager conversations, and indoor tanning intention.

Results: In intervention households, 54% of mothers and 56% of girls recalled receipt and reported reading materials, but few boys and no fathers did. Among mothers, 57% in intervention households indicated concern about daughters' indoor tanning, and 25% would allow daughters to tan indoors, whereas 43% of nonintervention mothers had concerns and 46% would allow indoor tanning. Fewer girls in intervention households than in nonintervention households thought parents would allow indoor tanning (44% vs. 65%), and fewer intended to tan indoors (36% vs. 60%). Most mothers and daughters who read the intervention materials also reported discussions about indoor tanning. Moreover, the less likely girls were to think that their mothers would allow indoor tanning, the less likely it was that they intended to tan indoors, a relationship mediated by perceptions of maternal monitoring.

Conclusions: A systematic qualitative and quantitative research approach yielded well-received indoor tanning prevention messages for mothers and female adolescents. Enhancing maternal monitoring has potential to decrease adolescent indoor tanning.

IMPLICATIONS AND CONTRIBUTION

Effective strategies are needed to curb indoor tanning by adolescent girls. This study developed and pilot-tested an intervention to enhance mothers' influence over daughters' use of indoor tanning by encouraging informed conversations between mothers and daughters. Preliminary results support this approach, but further evaluation in a randomized controlled trial is needed.

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Melanoma is one of the fastest increasing cancers in the U.S. and accounts for 75% of all skin cancer deaths [1]. Furthermore, melanoma is the second and third most common cancer among women and men under age 40 years, respectively [2]. Solar ultraviolet radiation is an established risk factor for melanoma [3], and recently, artificial ultraviolet radiation obtained from indoor

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tanning devices was declared to be carcinogenic to human skin [4]. In particular, use of indoor tanning at a young age is widely believed to confer increased risk of melanoma [5]. This is especially concerning because indoor tanning typically starts during adolescence and is more commonly practiced by younger than older adults [6–8]. Recent studies offer evidence to support two different mechanisms by which early onset of indoor tanning affects melanoma risk. Initiation of the behavior at a young age may increase the cumulative exposure, leading to greater likelihood of melanoma [9,10]. For a subset of persons genetically predisposed to melanoma, earlier use of indoor tanning may accelerate melanoma development and cause it to occur at a younger age [10].

Although 16% of high school students overall and 25% of high school girls report indoor tanning [11], and the median age of initiation among girls is 17 years (interquartile range, 16–18 years) [12], the problem of indoor tanning among adolescents has yet to become an active area for intervention. Altogether, just four intervention studies targeting indoor tanning use, all of college-aged females, have been reported: a pilot study of a 30-minute individual counseling session versus a personalized feedback sheet [13], a pilot study that used ultraviolet photography to show skin damage [14], a pilot study that compared narrative with statistical messages [15], and a randomized controlled trial that tested the efficacy of a booklet that encouraged alternatives to enhance appearance other than indoor tanning [16]. Given the dearth of research on interventions in this area for the adolescent population, we conducted a study that incorporated qualitative and quantitative methods for the purpose of developing an intervention to prevent adolescent indoor tanning. Because parents' indoor tanning has been consistently and strongly predictive of adolescents' indoor tanning [17–20], and family interaction has been identified as an important influence on the health behavior of children and adolescents, including sun protection [21–24], we included both parents and adolescents in the project with the goal of developing an intervention that enhanced family communication on this topic. Here, we present the findings from our research endeavor.

Methods

Overview

As described in detail below, we conducted focus groups with parents and teenagers to inform the content of our parent–teenager indoor tanning intervention, pretested the intervention with parents and teenagers via a semistructured in-depth telephone interview, and pilot-tested the intervention to determine its reach into the target population. We recruited participants from the membership of HealthPartners, a large integrated health system of more than 800,000 residents in the Minneapolis–St. Paul, Minnesota, metropolitan area with similar characteristics to the state as a whole, and from two area suburban high schools. At each stage, parents provided consent for themselves and their adolescents, whereas we asked adolescents for their assent. Institutional Review Boards at the University of Minnesota and HealthPartners approved the study.

Focus groups

From March through June 2008, we conducted six focus groups with adolescents aged 14–16 years, and two with mothers or fathers of adolescents in the 14- to 16-year age range (one of these included parents related to adolescents who also participated in a focus group). We restricted three focus groups for adolescents to girls who tanned indoors (n = 13), one to girls who had not tanned indoors (n = 6), and two to boys regardless of their indoor tanning experience (n = 13; one indoor tanner). Twenty-five adolescents were non-Hispanic white, four were African-American, two were Hispanic, and one was Native American. Among 10 parents (nine female and one male), eight were non-Hispanic white, one was African-American, and one was Hispanic. Parents ranged in age from 46 to 53 years. Of the 10 parents, seven had at least some college education.

We gathered viewpoints regarding knowledge and attitudes about indoor tanning, preferred media for message delivery, barriers to parent–teenager conversations, and parental roles regarding adolescent indoor tanning. We transcribed and analyzed audio recordings from the focus group discussions using a thematic approach [25]. From these data, we derived a set of themes and worked with a graphic designer and science writer to create the intervention materials.

Pretest

After we created draft versions of intervention materials in fall 2008, we sent them to 10 parents of adolescents ages 14–16 years and 10 adolescents of the same age in December 2008 to January 2009. After giving each participant about a week to review, we then conducted in-depth telephone interviews for a detailed assessment of relevance, appearance, and comprehension of the intervention materials.

Pilot test

The pilot test took place in April to June 2009. From 500 randomly selected households that were HealthPartners members with an adolescent (boy or girl) aged 15 or 16 years, and that had not participated in our focus groups or pretest, we randomized 70% to receive the intervention materials and 30% to serve as a comparison group. Before sending the intervention materials, we sent a letter to all households informing the parents that they and their adolescent could be selected for a telephone interview on skin health and behavior, and that they might receive some mailed information on that topic. We planned to interview approximately 100 parents and 100 adolescents (limited to one parent and one adolescent per household) while maintaining the 7:3 ratio of intervention to comparison households to ensure an adequate number of participants from intervention households likely to recall receiving the materials. Telephone interviews were completed by 87 parent–teen dyads, 31 parents only, and 10 adolescents only. Altogether, we interviewed 87 parents and 69 adolescents in intervention households and we interviewed 31 parents and 28 adolescents in nonintervention households (70.7% of eligible households contacted by telephone). The primary purpose of the interview was to determine whether the interviewee recalled receiving the intervention materials, and if so, whether the materials were read. We asked these questions of both intervention and comparison groups to determine the possibility of biased recall. Among those who indicated having read the materials, we assessed the accuracy with which they recalled the content and inquired about their satisfaction with the materials. From all study participants, we also collected information about indoor

Table 1
Themes and quotes from focus group discussions: pilot test of intervention to reduce indoor tanning by teenagers, 2009

Themes	Quotes
Topics of Interest	
Health effects	"Risk of skin cancer or what kind of diseases—what could they get? What do they get besides the tan?" *Female parent* "Consequences … like disease, skin cancer or something." *Male teenager* "Problems it does to your skin and your health, because some people don't really understand all that." *Female teenager, tanner*
Appearance	"An interesting thing would be to give me a 'this is what someone who's tanned for 10 years—for 20 years—for 30 years—looks like.'" *Female parent* "Yeah, like, is that true [that indoor tanning gives you wrinkles]? I don't know if it's true or not." *Female teenager, tanner*
Possible benefits	"It's a good source of vitamin D …" *Female parent* "[People] go tanning so that when they get to where they're going [for vacations in the winter], they don't burn. Does that work?" *Female parent* "Like, helps appearance, helps confidence, how it relaxes …" *Female teenager, tanner*
Personal story	"It would be interesting to follow a story of someone … just see if they have a higher incidence of skin cancer or something." *Female parent* "Well, like if you really want to, like, go scare somebody, you could tell someone, like, a disaster story." *Female teenager, tanner*
Safer than the sun	"I guess one of the other topics would be, is tanning worse than the sun? Is tanning better than the sun?" *Male parent* "Is it health[ier than tanning outdoors] that I should do it?" *Male teenager*
Regulations	"I don't know about the law." *Female parent* "I was not aware of a law—it's nothing we've ever had to think about." *Female parent*
Barriers to parent-teenager conversation	
Not important/relevant	"They're not asking to tan to get it, so it must not be that important to them." *Female parent* "I don't know. I never really thought of indoor tanning in my life. Maybe I'm just used to my mom saying pale skin, fair skin is nice. I don't know." *Female teenager, nontanner* "We basically just both agree how stupid it is…" *Male teenager*
Need for conversation triggers	"We have a discussion about it—I mean, for prom, I'm sure you've heard that—they all wanna be tan, they all—they can't be white-looking." *Male parent* "I just ask her if I can go [tan indoors], and she'll say, 'Yeah.'" *Female teenager, tanner* "[How we started the conversation was that] we got some things in the mail—this new place opened by our house, and you can get, like, a free—3 tans in a row." *Male teenager*
Lack of credible information	"I've never researched it … I guess I would have to do some research if she expressed interest in it." *Female parent* "I didn't really know [anything about tanning]." *Female teenager, tanner*

tanning-related knowledge, attitudes, and behavior using measures reported in prior studies [17,18,20,26,27].

In descriptive analyses, we compared responses from parents and adolescents who were mailed the intervention materials with the responses of those who were not mailed the materials, testing for differences using chi-square statistics. We also conducted a mediation analysis using structural equation models to understand hypothesized mechanisms by which the intervention could affect adolescents' intention to tan indoors. We restricted this analysis to dyads in which both the parent and adolescent were female (n = 60). Among these dyads, 43% of mothers and 38% of daughters reported reading the intervention materials. The outcome, daughters' intention to tan indoors, was a factor score derived from three items similar to a validated measure used to assess intention to smoke [28] (will try indoor tanning soon, will try if offered by friends, or will try in next 12 months). We estimated standardized regression coefficients to represent changes in daughters' intention to tan indoors (in standard deviation) that correspond to one standard deviation increase in the predictor in each hypothesized path. We conducted the mediation analysis using Mplus, version 5.0 (Los Angeles, CA) [29].

Results

Focus groups

Table 1 lists themes and quotes from the focus groups. Both parents and adolescents expressed interest in the adverse consequences of indoor tanning on health and appearance. Girls who tanned indoors were particularly interested in how likely and how quickly these consequences occurred. Participants also inquired about the benefits of indoor tanning (e.g., getting vitamin D or preventing sunburn), and some wondered whether indoor was safer than outdoor tanning. Participants indicated that they were not aware of state regulations pertaining to indoor tanning by minors.

Indoor tanning appeared to be an infrequent topic of conversation among parents and adolescents. Some parents thought it was not a relevant topic because their teenagers had not expressed interest in tanning indoors. Adolescents, particularly boys, also thought that indoor tanning was not a topic that they would discuss with their parents. Conversations related to indoor tanning were triggered by upcoming school dances or receiving indoor tanning advertisements in the mail. Both parents and adolescents commented that their lack of accurate knowledge about the topic was a barrier to discussion.

The intervention

We created a pamphlet and postcard for delivery via U.S. mail for parents. Content included information about health risks associated with indoor tanning, common misperceptions (e.g., a base tan prevents sunburn), parental influences (e.g., parents' own use of indoor tanning), industry tactics, and tips for talking to teenagers about indoor tanning. We created three postcards for adolescents to be delivered about 2 weeks apart. Topics included health risks, common misperceptions, and industry

tactics, as well as alternatives to indoor tanning (e.g., makeup). Opportunities to encourage parent–teenager conversation about indoor tanning were incorporated into the intervention. The first teenager postcard was embedded in the parent's pamphlet, which required the parent to then share the information with her child. The second teenager postcard included a quiz that teenagers were encouraged to use to test their parents' knowledge. In addition, the pamphlet and all postcards included the address of a website where parents and teenagers could together learn more about the topic, view videos, and access additional resources (e.g., material from the American Cancer Society).

Pretesting

Adolescents and parents who participated in pretesting the intervention materials correctly described the key messages and found the materials to be age appropriate and informative. Based on their feedback, we modified the content (e.g., we placed more emphasis on the parenting tips) and images (e.g., we reduced the number of images on some of the postcards). Final versions of the pamphlet and postcards can be accessed as supplemental data **here**.

Pilot study findings

Characteristics of interviewed parents and teenagers in intervention and nonintervention households were similar. Among parents, 62% reported light or extremely light skin; 60% had a college or advanced degree. About 23% of adolescents and 15% of parents had tanned indoors during the previous year. Nearly all survey respondents among parents and about three quarters of survey respondents among adolescents were female (Table 2). Among those randomly assigned to receive the intervention materials, no fathers and fewer than half of boys recalled receiving the pamphlet or postcards, whereas 71% of mothers and 88% of girls recalled receiving them. A substantial proportion of interviewed mothers and girls in intervention households reported reading the materials, for a total reach into the target population of 54% of mothers and 56% of girls. Whereas a small percentage of mothers, boys, and girls in the comparison group reported receipt of the materials, none reported reading the materials. Because mothers and girls were the primary beneficiaries of the intervention, we restricted subsequent analyses to females.

Among female participants who had read the intervention materials (45 mothers and 28 girls), a high proportion correctly recalled information about the risk of melanoma associated with indoor tanning use (Table 3). Girls were more likely than mothers to recall information about burns and wrinkles, and alternative ways to enhance appearance or to obtain vitamin D. Although mothers appeared to receive the message related to industry practices targeting teenagers, only a small proportion recalled content regarding state laws against teenager use of indoor tanning. Only a small percentage (2%–7%) of both the mothers and girls recalled information that was not included (e.g., weight loss). Satisfaction with the intervention materials was high among both mothers and girls; 80% of mothers and 68% of girls reported talking with each other about intervention content.

We performed an intent-to-treat analysis to compare indoor tanning-related knowledge, attitudes, perceived norms, and behavior between mothers and girls who were or were not mailed the intervention materials (Table 4). Even though only a few differences were statistically significant, mothers who were sent the intervention materials tended to report higher knowledge, less favorable attitudes, and a lower normative perception about indoor tanning than those who were not sent the intervention materials. Among mothers, 57% in intervention households and 43% in nonintervention households indicated concern about their daughters' indoor tanning; 25% of intervention mothers would allow daughters to tan indoors, but 46% of nonintervention mothers would allow it. Compared with mothers, daughters had fewer differences in knowledge and attitudes between those who were and were not mailed the intervention material, except for perception of peer use of indoor tanning, which was statistically significantly lower among girls in intervention households. In addition, a lower proportion of girls in intervention households than girls in nonintervention households thought their parents would allow indoor tanning (44% vs. 65%) and expressed an intention to tan indoors (36% vs. 60%).

Table 2
Percentage of parents and teenagers who recalled receiving or reading pamphlet or postcards: pilot test of intervention to reduce indoor tanning by teenagers, 2009

	Mailed pamphlet or postcards							
	Yes				No			
	Parents		Teenagers		Parents		Teenagers	
	N	%	N	%	N	%	N	%
Total respondents	87	100.0	69	100.0	31	100.0	28	100.0
Female	83	95.4	50	72.5	28	90.3	20	71.4
Male	4	4.6	19	27.5	3	9.7	8	28.6
Recalled receipt								
Female	59	71.1	44	88.0	3	10.7	1	5.0
Male	0	0.0	8	42.1	0	0.0	2	25.0
Read materials (if receipt recalled)								
Female	45	76.3	28	63.6	0	0.0	0	0.0
Male	N/A		3	37.5	N/A		0	0.0
Total reached (if receipt recalled and read)								
Female	45	54.2	28	56.0	0	0.0	0	0.0
Male	0	0.0	3	15.8	0	0.0	0	0.0

N/A = Questions were not asked or not applicable.

Table 3
Accuracy of content recall and satisfaction with intervention among mothers and girls who reported reading pamphlet or postcards: pilot test of intervention to reduce indoor tanning by teenagers, 2009

	Mothers (n = 45)	Girls (n = 28)
Percentage who correctly recalled content		
Indoor tanning and …		
Melanoma risk	71.1	75.0
Burns and wrinkles	48.9	78.6
Weight loss (bogus item)	2.2	7.1
Other ways to look good	26.7	71.4
Other ways to get vitamin D	53.3	60.7
Beauty queen with melanoma	N/A	71.4
Base tan not protective	64.4	N/A
State laws for parental permission	20.0	N/A
Industry targets teenagers	80.0	N/A
Tips for talking with teenagers	66.7	N/A
Agree or strongly agree materials meant for them (%)	63.6	89.3
Learned some or a lot (%)	77.8	85.7
Liked materials some or a lot (%)	93.3	92.9
Talked with each other about intervention content (%)	80.0	67.9
Retained pamphlet (%)	42.4	N/A
Retained postcards (%)	71.2	50.0

N/A = Questions were not asked or not applicable.

Table 4
Comparison of indoor tanning knowledge, attitudes, perceived norms, and behavior between mothers and girls who were and were not mailed pamphlet or postcards: pilot test of intervention to reduce indoor tanning by teenagers, 2009

	Mailed pamphlet or postcards			
	Mothers		Girls	
	Yes (n = 83)	No (n = 28)	Yes (n = 50)	No (n = 20)
Knowledge				
Percentage who agreed or were correct that …				
Skin cancer is common	98.8	89.3[a]	98.0	95.0
Tanned skin is damaged	92.8	85.7	88.0	95.0
Melanoma is increasing	86.8	89.3	90.0	90.0
Indoor tanning is safer than sun	1.2	3.6	0	4.0
Indoor tanning could cause cancer	94.0	96.4	100.0	100.0
Base tan protects from sun	21.7	25.0	36.0	45.0
Alternatives to look good exist	N/A	N/A	90.0	85.0
Laws exist for parental consent	18.1	0[a]	28.0	5.0
Attitudes				
Percentage who agreed that …				
People with tans are more attractive	77.1	88.9	49.0	70.0
Chances of skin cancer are small	24.1	37.0	32.0	30.0
Tanned skin looks healthier	78.6	66.3	34.0	40.0
Industry markets to teenagers	96.1	96.4	90.0	100.0
Industry targeting teenagers is serious	92.2	85.7	N/A	N/A
One gets compliments on tanned skin	80.0	67.9	90.0	100.0
Indoor tanning lifts spirits	59.5	84.6[a]	57.1	50.0
Indoor tanning is relaxing	46.3	61.5	59.2	83.3
Perceived norms				
Percentage who believed that …				
>50% of peers use indoor tanning	48.8	63.0	55.1	79.0[a]
Behavior				
Percentage who …				
Talked to teenager or parent about indoor tanning	43.4	N/A	38.0	N/A
Think parent would allow indoor tanning	N/A	N/A	44.0	65.0
Would use indoor tanning if friend offered free session	N/A	N/A	56.0	65.0
Were concerned if teenager tanned indoors occasionally	56.6	42.7	N/A	N/A
Were concerned if teenager tanned indoors regularly	96.4	96.4	N/A	N/A
Would allow teenager to tan indoors	25.3	46.4[a]	N/A	N/A
Intend to tan indoors soon	N/A	N/A	36.0	60.0
Intend to tan indoors in next 12 months	14.5	25.0	44.0	55.0

N/A = Questions were not asked or not applicable.
[a] Difference between groups was statistically significant at $p < .05$.

Figure 1 shows results of the mediation analysis. Although mothers' reading the intervention materials was positively associated with knowledge of state laws, higher knowledge of state laws was statistically significantly correlated with lower likelihood that mothers would disallow daughters to tan indoors. However, a greater likelihood of mothers' disallowing daughters to tan indoors was associated with a lower intention to tan indoors among daughters, both directly (path A; standardized regression coefficient [SRC] = −.40, $p = .01$) and indirectly through daughters' perception that parents would allow indoor tanning (path B*G; SRC = −.18, $p = .02$). Daughters who read the materials also reported lower intention to tan indoors than did daughters who had not read the materials (sum of paths C, D*G, and E*F; SRC = −.36, $p = .02$). About 39% of the effect of reading the materials on daughters' intention to tan indoors was through the daughters' perception that mothers would allow indoor tanning, and the daughters' disagreeing with the idea that a tan was attractive (total indirect effect, the sum of paths D*G and E*F; SRC = −.14, $p = .04$).

Discussion

Through a formal and systematic approach that involved the end user, we created messages about indoor tanning that were salient to parents and adolescents and served as triggers for conversation between them about the topic. Because no interventions for indoor tanning have been reported for adolescents, focus groups were critical to define the messages. Our pretest of the intervention materials with both parents and adolescents led to modifications to improve the relevance of the messages and the visual presentation, and it confirmed our planned mode of delivery. We considered reaching more than half of mothers and girls with our mailed messages to be a success. Given today's electronic and social media environment, and that print media accounts for only 38 minutes of the total average time (7 hours 38 minutes) that children or adolescents aged 8–18 years spend with media in a day [30], results from our pilot test suggest that a mailed intervention to adolescents may be a novelty that cuts through the myriad of electronic media.

Although we randomized households to be mailed the intervention materials, our pilot test was not a true randomized trial. We did not collect baseline information before mailing the intervention materials from experimental or comparison households; thus, we could not assess change in knowledge, attitudes, or intention to tan indoors. Also, because indoor tanning is a seasonal behavior, and we asked only about indoor tanning use in the previous year, the short interval (about 2 weeks) between receipt of the final intervention mailing and

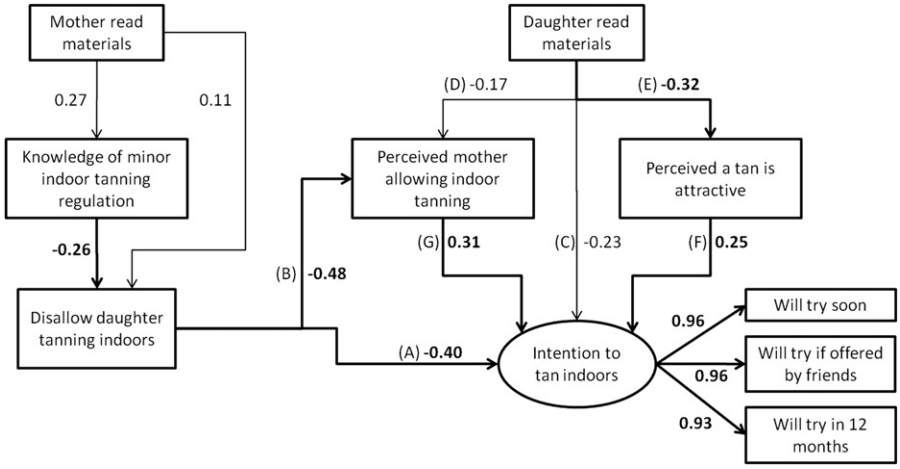

Figure 1. Results of the mediation analysis: pilot test of intervention to reduce indoor tanning by teenagers, 2009. The total effect of mothers' disallowing daughters to tan indoors on daughters' susceptibility to indoor tanning is the sum of the direct [Path A] and indirect effects [Path B*G]. The total effect of daughters' reading the materials on susceptibility to indoor tanning is the sum of the direct effect [Path C] and indirect effects through the perception that mother allows indoor tanning [Path D*G] and that a tan is attractive [Path E*F]. Bolded paths and standardized regression coefficients are statistically significant ($p < .05$).

the interview eliminated the possibility of assessing whether our intervention had any effect on actual indoor tanning. In addition, our sample size for the pilot test was small. Therefore, we were able to perform only crude data analyses and our results may be subject to selection bias.

Another limitation is that we used the same messages for adolescents whether or not they had tanned indoors. An argument could be made that strategies for prevention of the behavior may differ from those needed to help adolescents refrain from indoor tanning use. However, in a previous study, we found that associations were similar between knowledge and attitudes and the likelihood of intention to initiate or continue indoor tanning among adolescents [26]. Our approach allows for greater dissemination because it does not require knowledge of indoor tanning status. Still, more formative work may be necessary to develop strategies to help adolescents quit tanning indoors.

Although girls and young women are primary users of indoor tanning [8,11], we included boys and fathers at every step of our intervention development, to meet federal guidelines against gender bias in research. Our data provide clear support for focusing future interventions to prevent indoor tanning use by adolescent girls. The fact that no fathers recalled seeing the parent pamphlet is consistent with mothers typically taking responsibility for their family's health and spending more time with their children, a pattern that has persisted over recent decades in the U.S. despite some changes [31]. Boys clearly showed only limited interest in the information, as indicated by the fact that a small proportion recalled receipt and reported reading the materials. Therefore, targeting girls for intervention is a more efficient use of resources. Furthermore, interventions could incorporate messages and images that would be more appealing to girls than boys, and thus be potentially more effective in changing the behavior in the target population.

We and others have previously shown that maternal influences such as the mother's use of indoor tanning (role modeling), allowing her adolescent to tan indoors (permissiveness), concern about her adolescent's indoor tanning use, and knowledge and attitudes are strong predictors of adolescent indoor tanning use [17–20]. Of these possible mechanisms, we were able to examine only parental permissiveness because there was limited variation in our small sample and because of the inability to assess change in indoor tanning just 2 weeks after the intervention mailing. We found that the parental permissiveness pathway explained a considerable proportion of the likelihood of daughters' intention to tan indoors. Future interventions that persuade parents to be less permissive about adolescent indoor tanning use could be especially effective. As posited by the Protection Motivation Theory [32], individuals are motivated to perform a protective behavior, such as disallowing their teenagers to tan indoors, when they perceive the consequences of not performing the protective behavior to be risky (in terms of severity and susceptibility), that they are capable of performing the protective behavior (self-efficacy), and that performing the protective behavior would prevent the risk (response efficacy). Because our data suggested that parents already recognized indoor tanning as harmful to health, interventions that enhance parental self-efficacy (e.g., coaching parents to discuss indoor tanning with their children) and response efficacy (e.g., emphasizing the importance of parental monitoring of teenagers' indoor tanning use) may motivate parents to disallow and thereby prevent their adolescents from tanning indoors.

Future directions also include expanding the intervention and testing its efficacy to prevent indoor tanning by the target population. In light of the importance of interpersonal ties and connections as a venue for public health interventions [33,34], fruitful next steps for interventions (such as the one we describe here) could be to provide mothers with the information needed to discuss indoor tanning with their daughters (via pamphlets and postcards), offer mothers resources to enhance parenting skills and promote mother–daughter conversations (e.g., via an interactive website), prime daughters to be receptive to their mothers' conversations (via mailed postcards), and cue mothers to have a conversation with their daughters (e.g., via text messaging) [35,36]. Whereas this approach addresses intrapersonal and interpersonal influences of the socioecological model [37], reducing indoor tanning by adolescents also lends itself to intervention at organizational and environmental levels. For example, schools could be enlisted to refuse advertising or event sponsorship from indoor tanning salons [38,39], health care

providers could be encouraged to advise mothers and daughters against indoor tanning use (consistent with the most recent American Academy of Pediatrics policy statement on protecting children from ultraviolet radiation [40]), and state and federal laws could be strengthened to prohibit indoor tanning by minors (as California has recently done and as is currently under review by the Food and Drug Administration).

In conclusion, we developed and demonstrated the feasibility of a low-cost and technologically simple intervention to encourage parent–teenager conversations about indoor tanning and to discourage indoor tanning by adolescents. Use of both qualitative and quantitative methods ensured a relatively thorough understanding of the strengths and weaknesses of our product. We now need large-scale trials to assess whether engaging both mothers and daughters in conversation about the risks of indoor tanning and enhancing parental influences via permissiveness and role modeling will be effective in preventing, discontinuing, or reducing a behavior that begins during adolescence and puts girls at increased risk of melanoma.

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Supplementary Material

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jadohealth.2012.08.009

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Mediating Variables in a Parent Based Intervention to Reduce Skin Cancer Risk in Children

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Abstract The present study examined theoretical mediators of a parent-based intervention on sunbathing tendencies and sunburn frequencies based on the work of Turrisi et al. [Turrisi, R., Hillhouse, J., Heavin, S., Robinson, J., Adams, M., & Berry, J. (2004). *Journal of Behavioral Medicine, 27*, 393–412.]. Three hundred and forty parents in two regions of the United States were educated about the dangers of risky sun behavior and how to convey information about skin cancer prevention to their children. Attitudes toward sunbathing, health beliefs, appearance beliefs, and social normative beliefs were examined and found to be significant mediators of program effects on sunbathing tendencies and sunburn frequencies. The findings are discussed with respect to maximizing the effectiveness of future skin cancer interventions with children.

Keywords Skin cancer prevention · Parents · Children · UV exposure · Sun exposure

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Introduction

The dramatic increase in the incidence rate of skin cancer is a major concern for health-orientated researchers (American Academy of Dermatology 2005). Over the past two decades, researchers and medical practitioners have suggested that skin cancer rates could be lowered through behavioral changes such as the use of sun protection and avoidance of intentional UV exposure (e.g., Stern et al. 1986; Thieden et al. 2005; Thompson et al. 1993; Vail-Smith and Felts 1993; Wang et al. 2001; Westerdahl et al. 2000). Despite these warnings, more than one million cases of skin cancer are diagnosed each year (American Cancer Society 2005) and skin cancer is among the five most expensive cancers to treat (Housman et al. 2003). Research has shown some efficacy in changing young individuals' behaviors (e.g., Buller et al. 1996; Glanz et al. 2006). Notwithstanding, studies consistently report widespread rates of intentional UV exposure and low sun protection among young people (e.g., Cokkinides et al. 2001; Coogan et al. 2001; Demko et al. 2003; Ellis 1992; Hall et al. 1999; Lazovich et al. 2004; Livingston et al. 2003; Robinson et al. 1997a). These accounts suggest a continued need to develop and disseminate evidence-based skin cancer prevention programs that can reach large audiences with minimal effort in terms of time and cost.

A recent skin cancer intervention designed with these parameters in mind utilized a parent-based approach in an attempt to reach children while at home via their parents (Turrisi et al. 2004). The intervention provided a handbook to 340 parents of children ages 9–12 prior to summer that summarized strategies for positive parenting practices, developing good communication patterns, and initiating conversations with children. The handbook also provided in-depth coverage on methods parents can use to: (1) teach

their children how to avoid sun-related risk behaviors and increase sun-safe behaviors, (2) make children more resistant to external social and media influences that encourage high-risk UV behaviors, and (3) reinforce existing school-based educational efforts. Turrisi et al. (2004) reported high parental involvement in the intervention (greater than 96% having conversations with their children and reported positive ratings on interest level, readability, and usefulness). In addition, comparisons between the children in the treatment group and the control group (n = 129; no handbook) at the end of the summer revealed significantly lower self-reported intentional sunbathing, significantly fewer sunburns, and significantly lower sunburn severity in the children whose parents received the handbook. In addition, differences were observed between the groups on attitudes toward appearance, tanning, sun block, sunscreen, risk, and normative perceptions.

However, just because the program changed these attitudinal constructs there is no assurance that the observed changes were sufficient to also observe change in sunbathing tendencies. Specific mediational analyses are required to assess change in sunbathing as a function of change in the mediators. Mediation analyses can be used to assess whether observed program effects are a result of changes in targeted individual level variables (e.g., attitudes and beliefs). The mediating variables we chose to examine are based on the theoretical model guiding the current and previous studies (see Fig. 1). In some cases these are similar to constructs examined in Turrisi et al. (2004) for the purposes of determining if the observed changes in the mediators did in fact have the desired effect of changing sunbathing tendencies. These will now be discussed in turn.

The parent-based intervention utilized core concepts from the Behavioral Alternative Model (see Turrisi et al. 1998) and research linking expectancies to behavioral tendencies (Hillhouse et al. 1997; Turrisi et al. 1998, 1999). According to our model, to effectively reduce skin cancer risk in the form of sunburns, one must decrease sunbathing behaviors and increase sun protection behaviors while also improving perceptions about engaging in alternative activities. Thus, the intervention targeted the attitude toward sunbathing for tanning purposes (e.g., Arthey and Clarke 1995; Branstrom et al. 2004; Broadstock et al. 1992; Cokkinides et al. 2001; Hillhouse et al. 1996; Shoveller et al. 2003; Turrisi et al. 1998, 1999; Wichstrom 1994), as well as attitudes toward alternatives to sunbathing (e.g., indoor activities and shopping). Second, the current intervention attempted to convey information about the deleterious effects of UV exposure and influence individuals' health orientation (engaging in UV protective behaviors). Third, several studies have reported stronger relationships between UV risk behaviors and appearance (e.g., photo-aging, premature wrinkling, etc.) than health-orientated beliefs (Cokkinides et al. 2001; Hillhouse and Turrisi 2002; Jones and Leary 1994; Lazovich et al. 2004; Mahler et al. 1997, 2003). Thus, the intervention focused on changing children's beliefs about the appearance enhancing effects of tanning as well as media and social efforts to influence self-esteem by appearing tan. Lastly, the intervention encouraged parents to talk with children about confronting peer pressures and other social normative components that might influence children's UV-related behavior.

Taken together, these cognitive constructs theoretically influence sunbathing tendencies, which in turn impact sunburn frequency. According to the theoretical model, we hypothesize that the observed reductions in sunburns are a direct result of reductions in sunbathing tendencies. Thus, sunbathing reductions mediate the relationship of the intervention program to sunburn outcome. In turn, the relationship between the intervention program and sunbathing tendencies is mediated through changes in attitudes about sunbathing, attitudes about alternative activities to sunbathing, increased awareness of the negative health and appearance consequences of UV-risky behavior, and changes in the child's social normative beliefs regarding such behavior.

Methods

Sample

Participants consisted of 469 children ages 9–12 (51% female, 49% male). Three hundred and forty parent-child dyads were assigned to the experimental group and received the intervention materials. The control group consisted of 129 children matched on gender, age, and school. Half of the participants were recruited from a mid-sized metropolitan area in the northwestern United States and half from a similar area in the southeast. These locations were selected in part because of proximity to the authors and also to acquire a reasonably heterogeneous sample with respect to United States geography. All participation occurred during the summer months (e.g., generally sunny, temperatures in the 80s and 90s, UV index > 7). The reported rates of sunbathing and sunburns are high enough in these areas to warrant examination (Hillhouse et al. 1997; Turrisi et al. 1998, 1999).

Recruitment

Children's names were randomly selected from elementary and middle school yearbooks of all rural, urban, and

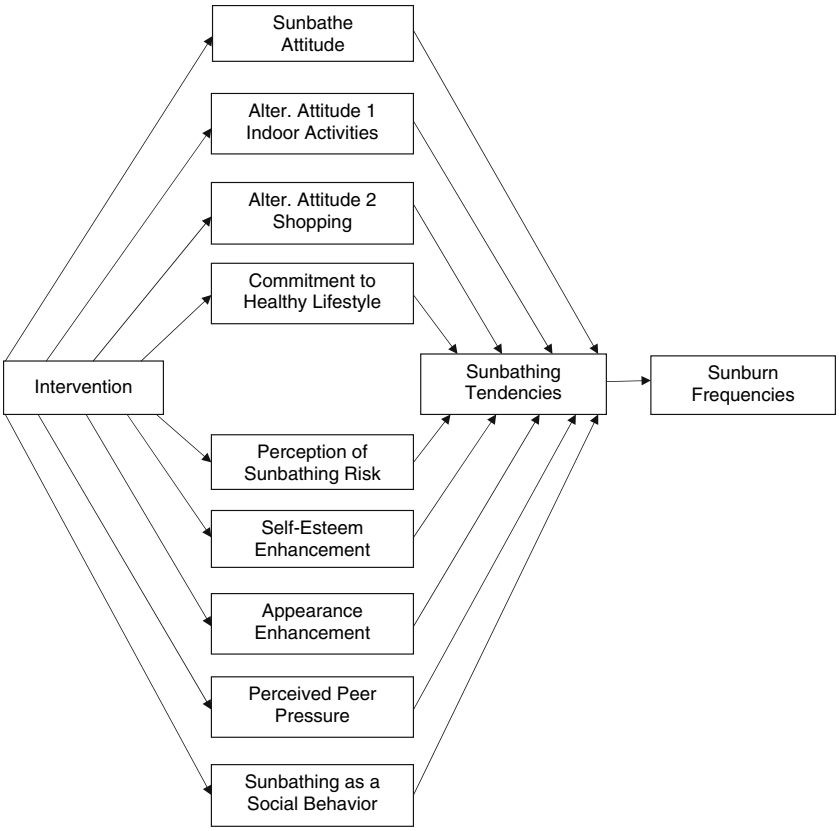

Fig. 1 Theoretical mediation model of the relationships between the intervention program, mediation constructs, sunbathing tendencies, and sunburn frequencies

suburban public and private schools in Boise, Idaho, and Johnson City, Tennessee. This approach has been utilized to develop sampling lists in previously funded research (Turrisi and Jaccard 1992; Turrisi et al. 2001, 2004). Children participants were offered $25 for pre-test participation and $25 for completing post-tests; parents were offered $40. We observed no significant differences when comparing treatment and control groups on demographic characteristics that could be relevant to study outcomes or the mediators (e.g., skin type). The sample characteristics were as follows: 49.3% male, 50.7% female; 95.25% White Non-Hispanic; 15% parents having high school or less, 13% having a post-baccalaureate degree; 55% parent reporting income about average with most families; 35% reporting income higher than most families. Also, no significant demographic or general attitudinal biases were present when we compared families who agreed to participate in the study (85% of parents and 99% of children agreed to participate) with those who were unwilling to participate.

The intervention was given to parents in the experimental group at the beginning of summer (the last 2 weeks in May). Parents were asked to comment on the materials and return them at the beginning of June as a validity check to ensure they read the materials. Child assessment occurred approximately 45 days later, to allow time for parents to read and implement the intervention (for more details on the procedures and validity checks see Turrisi et al. 2004). Participants in the control group did not receive the intervention materials but were given a post-test assessment during the same time interval.

Measures

Measurement Issues

The primary concern of measurement with children in this age group was socially desirable responding. Several steps were employed to reduce motivation for socially desirable responding. First, respondents were assured of the confidentiality of all of their responses. Second, the importance of honest answers was stressed. Third, the data collection was structured so that all answers were marked down on separate questionnaires so the children never had to reveal potentially socially undesirable behavior to an interviewer in a face-to-face situation. Fourth, children were asked to sign a statement saying that they would be providing truthful answers.

In addition, a measure was included assessing general social desirability tendencies (Good Impression Scale from the California Personality Inventory) and it was not found

to be significantly correlated to the self-reports of sunbathing tendencies or sunburn frequencies.

Sunburn Frequencies

Four items were used to assess sunburn frequencies which asked the participants to estimate the number of times in 30 days their skin had become red because of sun exposure. The remaining three items were identically phrased but the word ''skin'' was replaced with ''face'', ''neck'', and ''arms''. The items were averaged to create an overall index of sunburn frequencies (coefficient α = .92).

Sunbathing Tendencies

Sunbathing tendencies were assessed using four items drawn from the literature (e.g., Buller et al. 1996; Hillhouse et al. 1996; Robinson et al. 1997a, b; Turrisi et al. 1998). Two items were used to assess the frequency of sunbathing behavior (e.g. ''Within the past 2 months, how often did you lie out to sunbathe'' and ''In the last month, approximately how many times did you lie out in the sun to get a tan''). The same items were reworded and used to measure the frequency of lying in the sun to get some color in the skin. The items were averaged to create an index of sunbathing activities (coefficient α = .85).

Mediators

The items used to assess the mediators and coefficient alphas are presented in Table 1. These mediators include measures of attitudes toward sunbathing, attitudes toward alternatives to sunbathing (e.g., indoor activities and shopping), health beliefs about UV exposure (healthy lifestyle orientation and perceived risks of sunbathing), appearance related beliefs (the self-esteem and appearance enhancing effects of having a tan), and social normative beliefs (perceived peer pressure and sunbathing as a social behavior). For each item respondents were given five-point (1) strongly disagree to (5) strongly agree Likert-type scales.

Statistical Analysis

The joint significance test of α and β was used to assess mediation. MacKinnon and colleagues (2002) compared the joint significance test to several other mediation techniques and found that the joint significance test had the most power and the most conservative Type I error rates. Regression analyses are used to test the α and β paths in a model shown in Fig. 2 using AMOS 5.0 in SPSS. First the α path, the effect of the program on the hypothesized mediator, is assessed for statistical significance. Second the β path, the effect of the mediator on the outcome while controlling for treatment program effects in the equation, is assessed for significance. If both the α and β paths jointly show significance at the .05 level there is evidence for a significant mediating relationship (e.g., being in the control/treatment group affects the outcome variable through changes in the mediating variables) (MacKinnon 1994). The mediated effect is the product of the α and β b-values ($\alpha\beta$) and provides an estimate of the relative strength between the mediated effects. The τ' value is the residual direct effect which represents the amount of variation in the program outcome relationship not explained by the mediated effect.

When there is evidence for mediation, confidence intervals (95%) can be calculated to provide a range of estimates for the actual mediated effect value (Shrout and Bolger 2002). Given that the product of the α and β path regression coefficients provide an estimate for the actual mediated effect ($\alpha\beta$), if the confidence intervals around the mediated effect do not contain the value of zero then this is considered further evidence that the mediating effect is different than zero or statistically significant. We derived confidence intervals using a bootstrapping procedure in AMOS 5.0 in SPSS. This approach was utilized because the technique provides confidence interval estimates regardless of whether assumptions about normal distributions between groups on the outcome measures are met. We used the EM method as implemented in SPSS 13.0 Missing Value Analysis to impute missing data (Little and Rubin 1987). For all of the analyses treatment is coded as 1 and control is 0.

Results

The first focus of the analyses examined whether sunbathing tendencies significantly mediated the relationship between the intervention and sunburn frequencies. The results revealed the intervention significantly reduced sunbathing (α = –.478, $P < .001$), sunbathing tendencies were significantly related to sunburn frequencies (β = .519, $P < .001$), and the intervention significantly reduced sunburn frequencies through the mediated effect of reducing sunbathing tendencies ($\alpha\beta$ = –.248, CI_{L95} = –.586, CI_{U95} = –.089). These findings offer evidence that the change in sunbathing was in fact sufficient to observe changes in sunburns.

The second focus of the analyses examined whether the theoretical attitudes and cognitive constructs significantly mediated the relationship between the intervention and sunbathing tendencies. Results of the mediation analyses are reported in Table 2.

Table 1 Items assessing mediator constructs and Cronbach's reliability coefficients

Sunbathing attitude	.747
• Overall, I feel bad about lying out in the sun to get a tan at this time in my life	
• At this point in my life I have a negative attitude toward lying out in the sun to get a tan	
Attitude toward alternative—indoor activities	n/a
• I feel good about an indoor activity such as: working out, swimming indoors, etc	
Attitude toward alternative—shopping	.858
• I don't enjoy shopping	
• I would rather stay home and relax than go to the mall	
• I think going shopping is boring	
• I think going to the mall is boring	
Commitment to a healthy lifestyle	n/a
• Because I am committed to a healthy lifestyle I don't sunbathe	
Perception of sunbathing risk	.607
• If I continue to go in the sun without taking precautions, I could eventually get skin cancer	
• If I got really sunburned one afternoon, I might end up getting skin cancer	
Self-esteem enhancing effects of a tan	.828
• A tan makes me feel more confident	
• I often feel better when I have a tan	
Appearance enhancing effects of a tan	.802
• A tan makes me look better	
• I think I look healthier with a tan	
Perceived peer pressure	.808
• It can't be that bad if everyone in my age group is lying out in the sun	
• Lying out in the sun to get a tan can't be that bad if all my friends do it	
Sunbathing as a social behavior	.682
• I feel good about lying in the sun to sunbathe on a hot day	
• I enjoy lying out in the sun with my friends	

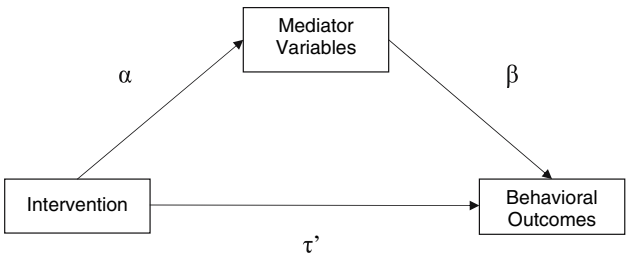

Fig. 2 Statistical mediation model

Program Effects

Significant program effects ($P < .001$) were found in the anticipated directions on all of the predicted sunbathing mediators except for the attitudes toward alternatives to sunbathing (column α). For example, individuals in the treatment condition had more negative attitudes toward sunbathing than individuals in the control condition. Similarly, individuals in the treatment condition were more committed to healthy lifestyles in relation to sunbathing, perceived greater risk of sunbathing, were less concerned about the self-esteem and appearance enhancing effects of a tan, and perceived less social/peer pressure to tan relative to controls.

Mediator Effects on Sunbathing Tendencies

Examination of the β paths in Table 2 revealed significant relationships in the anticipated directions with all of the hypothesized mediators when controlling for intervention program effects except for the perception of sunbathing risk. For example, attitudes toward sunbathing, self-esteem and appearance enhancing effects of a tan, and perceived social/peer pressure to tan were positively related to sunbathing. Similarly, attitudes toward alternative activities and commitment to healthy lifestyles were negatively related to sunbathing tendencies.

Mediated Effects

Significant mediated effects ($\alpha\beta$) were observed for the following constructs—attitudes toward sunbathing to get a tan, commitment to a healthy lifestyle, beliefs about the

Table 2 Program effects on mediators, mediator effects on sunbathing tendencies, indirect effects, and confidence intervals

Mediator	(α) Program effect on mediator	(β) Mediator effect on outcome	($\alpha\beta$) Indirect effect	Upper 95% CI of mediated effect	Lower 95% CI of mediated effect	*P*-value
Sunbathing attitude	–1.067** (.228)	.203** (.026)	–.211	–.121	–.351	.001
Attitude toward alternative—indoor activities	071 (.088)	–.194* (.072)	–.014	.013	–.085	ns
Attitude toward alternative—shopping	462 (.450)	–.069** (.014)	-.032	.030	–.100	ns
Commitment to a healthy lifestyle	665** (.130)	–.370** (.046)	–.246	–.140	–.371	.001
Perception of sunbathing risk	639** (.182)	–.065 (.035)	–.041	.000	–.101	ns
Self-esteem enhancing effects of a tan	–1.105** (.240)	.181** (.025)	–.200	–.112	–.325	.001
Appearance enhancing effects of a tan	–1.182**(.234)	.186**(.026)	–.220	–.129	–.339	.001
Perceived peer pressure	–.981** (.206)	.251** (.029)	–.246	–.137	–.402	.001
Sunbathing as a social behavior	–.640** (.178)	.401** (.031)	–.257	–.122	–.420	.001

* $P < .01$, ** $P < .001$ two-tailed

self-esteem enhancing effects of a tan, beliefs about the appearance enhancing effects of a tan, perceived peer pressure, and beliefs about sunbathing as a social behavior. Thus, the intervention had the desired result of changing theoretical mediators which in turn changed sunbathing as predicted.

The final analysis examined the effect of intervention program on sunburn frequencies via the mediational effects of the attitudinal, cognitive and sunbathing constructs found to be significant in previous analyses (see Fig. 3). The results revealed that the intervention significantly reduced sunburn frequencies through the mediated effect of reducing sunbathing tendencies, attitudinal and cognitive constructs ($\alpha\beta = -.261$, $CI_{L95} = -.610$, $CI_{U95} = -.091$). Thus, the intervention had the desired result of changing theoretical mediators which in turn changed sunburn frequencies as predicted.

Discussion

Recent studies have demonstrated that parents can be effective change agents in increasing positive sun-safe behaviors in children ages 9–12 (Turrisi et al. 2004, 2006). The present study extended this work by conducting mediation analyses to identify specific variables underlying the influence of the parents on their children. First, the analyses revealed that children in the treatment group reported less sunburns than those in the control group and this relationship was mediated by their sunbathing tendencies. The intervention seemed to greatly reduce immediate skin damage by reducing sunbathing activity. Given that recent studies have shown significant relationships between the frequency of sunburns and increased skin cancer risk (Harris et al. 2001; Titus-Ernstoff et al. 2005), there is evidence then that the present intervention can be an effective approach to reduce potential future skin cancer risk by altering sunbathing behavioral tendencies.

Second, the analyses also revealed children's sunbathing tendencies were changed as a result of specific successful parent communications that influenced their children's commitment to a healthy lifestyle, and their perceptions of the importance of tanning for the sake of appearance, self-esteem, socializing, and perceived peer pressure. Examination of the indirect effect size can provide important information about the relative importance of each mediator (MacKinnon 1994). The social and peer pressure mediators had the strongest effect sizes indicating that peer influences play a large role in the decision of children to sunbathe. Commitment to a healthy lifestyle was also a strong mediator in the current study, whereas the perception of sunbathing risk was not a significant mediator. Past work has suggested that health orientations play a smaller role relative to appearance orientations (Jones and Leary 1994) in motivating sunbathing tendencies and recent skin cancer prevention efforts have focused on appearance related beliefs (Hillhouse and Turrisi 2002). The present study suggests that the role of health beliefs may be more complicated and may be dependent on the specific focus of the health related beliefs (e.g., more general commitment to health versus specific sunbathing risk). Despite the importance of appearance as a motivator in young people, the data from the present study suggest that it might be beneficial to consider interventions focusing on health

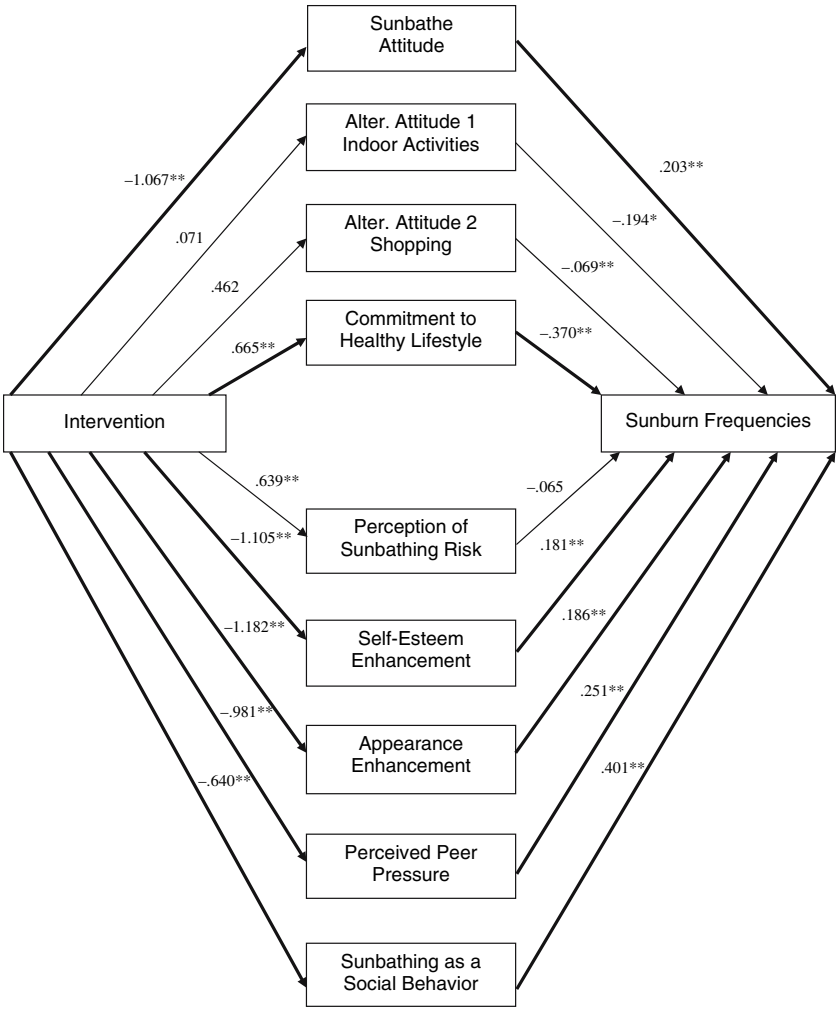

Fig. 3 Final mediation model. *Bold lines* indicate significant mediated effect. * $P < .01$, ** $P < .001$

orientations with this population. It is also possible that some children, because of personality, beliefs, and/or behavioral characteristics, may be more influenced by the appearance as opposed to the health oriented message or vice versa. Future research may be needed to identify how children interpret and internalize these different messages.

Third, the analyses revealed attitudes toward alternative activities (e.g., indoor activities) remained important influences on sunbathing tendencies (examination of the β paths). Although these findings were consistent with previous reports (Turrisi et al. 1998), our program's parent communication efforts were less successful in bringing about change on these constructs. It is not clear from our analyses whether it was due to the emphasis parents placed on alternatives relative to other mediational constructs (e.g., appearance, peer pressure) or whether these variables are more resistant to change efforts. Further research needs to identify how parent-based efforts might be used to encourage and support alternative behaviors.

There are a few limitations to the present study that are worthy of consideration. First, the present study only evaluated short-term effects of the parent-based intervention. Future research should be conducted to evaluate whether the promising results observed in the short-term will be long lasting. Other limitations include that we did not measure the skin type of the consenting parents and we only studied one child per family. For the former, we were concerned about response burden on individuals and tried to keep the measures as brief as possible. Future studies could focus on more family related risk characteristics. For the latter, we considered asking the parents to talk to all of their children, but decided to reduce the burden of the study on parents with multiple children. It is plausible to assume that parents were likely to have conversations with all of their children whether they were asked to have these conversations or not, however this remains an empirical question. Third, further efforts need to focus on examining ways to disseminate and evaluate the effectiveness of parent-based approaches in real-world environments. While dermatologists have tried to enlist parents in promoting the sun protection practices of their children, the effort has had variable results with children continuing to

experiencing sunburns (Robinson et al. 2000). Future research will explore ways that dermatologists can target families that will most benefit from the parent-based intervention. Moreover, parental interventions, like the one that was examined in the present research, can be added as a module to school and community based efforts in order to assess how additional messages from home impact UV risk tendencies. Few studies in the skin cancer prevention domain have explored the combined effects of different interventions that have shown to be efficacious in independent studies. Finally, the amount of communication between parents and children, or dosage effects, was not measured. Dosage effects are difficult to measure in the current context because it is likely that parents might have different styles of communicating the information in the handbook to children. Some parents might have effectively discussed the issue with one quality communication while other parents might have used several smaller discussions with their child. Despite the few limitations noted above, the overall emerging picture is a parent–child communication-based skin cancer intervention that shows tremendous promise. The present study supports the notion that parents can be viable change agents for child behaviors and adds to the growing literature that indicates that the quality of the family relationship is critical to the success of such interventions (Turrisi et al. 2006).

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ORIGINAL ARTICLE

Maternal/Female Caregiver Influences on Adolescent Indoor Tanning

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Purpose: **To identify aspects of maternal/female caregiver (MFC) influences on adolescents' indoor tanning, including modeling, cognitions (MFC knowledge and attitudes about indoor tanning), and gatekeeping/monitoring (MFC permissiveness and concern) of indoor tanning.**

Methods: **A telephone survey of adolescents aged 14–17 years and their female parent/caregiver in Minnesota and Massachusetts was conducted in 2000–2001 (n = 1284 matched pairs). Logistic regression was used to obtain odds ratios for relationships between measures of MFC influence and teens' indoor tanning practices, adjusting for demographic and sun sensitivity differences.**

Results: **Separately, each of the five MFC influence variables was significantly associated with adolescents' indoor tanning practices. In a multivariate model, significant independent contributors were parents' behavior, parents' concern about their children's indoor tanning practices, and MFC permissiveness of teen indoor tanning. Using a combined summed scale of the 5 influence factors, there was a monotonically increasing likelihood of tanning with each incremental scale increase: (in comparison to none, 1 factor aOR = 4.1, 95% CI: 1.3, 12.8; any 2 factors aOR = 8.3, 95% CI: 2.8, 24.6; any 3 factors aOR = 14.3, 95% CI = 4.9, 41.8; any 4 factors aOR = 30.5, 95% CI: 10.3, 90.3; all 5 factors aOR = 66.0, 95% CI: 20.0, 217.6).**

Conclusions: **Mothers/female caregivers may be a powerful influence on their teenagers' indoor tanning use, and are an important target for future health promotion efforts to discourage youth indoor tanning.** © ***Society for Adolescent Medicine, 2004***

KEY WORDS:
Skin cancer prevention
Adolescents
Health promotion
Ultraviolet rays/adverse effects
Skin neoplasms/prevention and control
Parents

Skin cancer is the fastest growing cancer in the United States, affecting approximately 1 million Americans every year [1]. Approximately one in five Americans will be diagnosed with skin cancer in their lifetime [2]. Exposure to ultraviolet radiation, particularly during childhood and adolescence, is believed to be a risk factor for both melanoma and nonmelanoma skin cancer (i.e., basal and squamous cell carcinoma) [3–11]. Ultraviolet radiation exposure can be emitted by the sun as well as indoor tanning facilities. Despite recommendations from national groups to avoid all sources of ultraviolet radiation [12–15], and the U.S. Department of Health and Human Services listing exposure to sunlamps and sunbeds as known human carcinogens [16], the indoor tanning industry has continued to expand. Although the epidemiological evidence linking tanning bed usage to skin cancer is currently inconclusive [17], it has been suggested that the popularity of

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indoor tanning facilities may be a contributing factor to the increasing prevalence of skin cancer [18]. Estimates suggest that a typical user of indoor tanning facilities (20 times per year) could increase their exposure to ultraviolet radiation A by 30% to 300% [19].

Indoor tanning is a health risk for youth in particular, because it appears to be most prevalent among younger people [17]. Three separate recent studies have revealed similarly high prevalence rates of teen indoor tanning, particularly among certain sub-groups [20–22]. In a nationally representative sample of 6903 non-Hispanic white adolescents aged 13 to 19 years, lifetime prevalence of indoor tanning (defined as using a tanning booth 3 or more times) was estimated at 7% for boys and 29.1% for girls [20]. Indoor tanning use increased monotonically with age (among girls aged 13–14 years: 11.2%; 15 years: 24.3%; 16 years: 29.2%; 17–18 years: 47.0%). Prevalence rates were higher in the Midwest and South compared with the Northeast and West (among girls, rates were 31.9% in the Midwest, 33.8% in the South, 18.5% in the Northeast, and 11.8% in the West). Other predictors of indoor tanning included substance use and dieting behavior. Indoor tanning was less prevalent among adolescents with greater cognitive ability, and whose mothers were college-educated.

In a cohort sample of more than 10,000 U.S. children and adolescents aged 12–18 years, prevalence of tanning bed use within the past year was estimated at 10%. Tanning bed use occurred primarily among girls and was higher for older girls [21]. Other predictors of indoor tanning included: having an olive or dark complexion; the belief that it was worth getting a little burned to get a tan; less regular use of sunscreen; and the belief that all, most, or some of their friends tanned.

In a study conducted by the American Cancer Society, the prevalence and correlates of indoor tanning by 1192 youth aged 11–18 years and their parents or caregivers was reported [22]. Among youth, results were similar to the previously reported study: overall indoor prevalence in the past year was 10%. Use occurred primarily among girls and was higher for older youth: prevalence rates were 3.9%, 12.4%, and 25.7% for adolescents, aged 13–14 years, 15–17 years and 17–18 years, respectively. Other predictors included having a darker complexion, nonregular use of sunscreen, and having a high appeal for a tanned look. There was also a strong influence of parents/caregivers on youth indoor tanning: prevalence of indoor tanning during the previous year was 30% for youth whose parents/caregivers had also used indoor tanning lamps in the previous year. This study was the first to examine the association between teen and parent/caregiver indoor tanning, and highlights the need for a greater understanding of how parents might influence their children's indoor tanning practices.

As the primary socialization agent, parents are important targets for children's behavior change [23–25]. In addition to their own direct experience, children may learn what behaviors are appropriate by observing how their parents behave, and whether or not this behavior is rewarded [26]. For example, Farkas et al reported that having a parent who quit smoking doubled the rate of cessation among their adolescent offspring [27]. However, modeling is only one mechanism through which parents may influence their children's health beliefs and behaviors. Parents' attitudes toward a health behavior are also predictive of children's adoption of that behavior [28,29]. Parents also serve important normative functions [30]: as agents of social support and gatekeepers [31,32]. The extent to which parents actively monitor and express disapproval of an unhealthy behavior has been associated with reductions in adolescent smoking [33–35], drinking [30,36], and illicit substance use [37–39].

Although it is typically believed that peers are a stronger influence on adolescents then parents, there is a growing body of evidence that parents also play an important role in shaping their children's health beliefs and behavior. Existing research has shown that the indoor tanning behavior of the primary caregiver is predictive of youth indoor tanning [22]. Our research extends this work by examining the underlying sources of maternal/female caregiver influence. An understanding of these influences on youth indoor tanning is the first step toward identifying strategies for a parent- or family-based intervention to reduce youth indoor tanning. We focused on mothers and female caregivers because women are much more likely to be the primary caregiver (presumably exerting more influence), and because the prevalence of indoor tanning is much higher in females compared with males [22,40].

Based on the literature addressing parental influences, we hypothesized that in addition to (1) modeling, female caregivers would influence their children's indoor tanning through cognitions including (2) MFC knowledge and (3) attitudes about tanning. Mothers/female caregivers may also serve a gatekeeping/monitoring function, including (4) expressing concern if their child were to tan indoors and (5)

giving their children permission to use an indoor tanning facility.

Methods

Study Population and Survey Methods

In January 2000, we initiated the Minnesota and Massachusetts Indoor Tanning Study (MMITS) to collect information about individual, environmental, and business practices related to indoor tanning. Surveys were conducted among adolescents aged 14–17 years and a female caregiver (described below), with representatives from public health agencies and with managers of indoor tanning businesses. The Institutional Review Boards at the two universities sponsoring the research approved all aspects of the study. The results reported here use data from the adolescent and female caregiver surveys.

We identified adolescents, aged 14–17 years, from a targeted age list purchased from Survey Sampling, Inc., for the Boston and Minneapolis/St. Paul metropolitan statistical areas. Through linkages among telephone directory listed households, school registration lists, magazine subscription lists, voter registration lists, and driver's license information, households with a higher probability of having an adolescent member can be identified compared with simple random selection. From this list, households were drawn at random and called to determine if an eligible adolescent resided at that number. If the answer was "yes," we then asked to speak to the female guardian (mother, stepmother, or other), from whom we obtained both permission to interview the adolescent and consent to a brief interview about her own indoor tanning use. If more than one adolescent in the specified age range lived in the household, we enumerated all eligible adolescents and randomly selected one. Because past research indicated that indoor tanning was much more common among females than males [17], we over-sampled girls relative to boys by a 1.6 to 1 ratio to increase the likelihood that our sample would contain enough adolescents with tanning experience. The female caregiver was interviewed first; upon completion of the adult interview, the interviewer asked the adult to speak with the randomly selected teenager. If it was not a convenient time to speak to the selected teenager, a callback time was scheduled.

Surveys were conducted in 2000 and 2001. Of the 2699 households contacted in the Boston area, 33.0% were found to have an age-eligible adolescent in the household; in the Minneapolis-St. Paul area, 44.7% of 1650 households had an age-eligible adolescent (37.4% overall). Among eligible households, interviews with both a mother/guardian and a child were completed in 637 (71.5%) households in Boston and 647 (87.8%) in Minneapolis-St. Paul. In total, 1284 households completed both interviews (78.8% response overall). Only 246 households contacted refused to be interviewed (5.7%).

Measures

We developed new survey instruments for mothers/female caregivers and adolescents, drawing on focus groups with teens who had tanned indoors and existing surveys or published reports related to sun knowledge, attitudes, and behavior among adolescents and adults. In addition to measures related to sun protection, tanning, and skin cancer, we also inquired about demographic characteristics such as gender, age, and maternal/female caregiver (MFC) education.

Primary outcome. Our primary outcome, taken from the teen survey, is the proportion of adolescents having tanned indoors in the past year.

MFC influence measures. MODELING. (1) Modeling (MFC interview): mothers/female caregivers were asked how recently they had frequented an indoor tanning facility. For tanning behavior, mothers/female caregivers who had tanned indoors in the past year were compared with all other mothers/female caregivers who had not tanned recently (including those who had never tanned).

COGNITIONS. (2) Tanning knowledge (MFC interview): Knowledge about the consequences of tanning included 5 items: (a) people who tan have already damaged their skin; (b) indoor tanning is safer than natural sunlight (reverse coded); (c) indoor tanning could cause skin cancer; (d) as long as you don't get a burn from indoor tanning, you're safe from skin cancer (reverse coded); and (e) getting an indoor tan first gives people good protection from burning in the sun. Because these 5 questions assess knowledge about the consequences of tanning, it was not expected that respondents' answers to these items would be internally consistent, and thus reliability coefficients were not computed. These five items were summed for a knowledge score ranging from 0 to 5. This scale was recoded into a dichotomous measure based on a median split. (3) Attitudes

(MFC interview): Attitude toward tanning included 2 items: (a) having a tan makes people look healthier; and (b) people with a tan look more attractive. These 2 items formed a reliable scale (alpha = .76). This scale was recoded into a dichotomous measure based on a median split.

GATEKEEPING/MONITORING. (4) Concern about teen tanning (MFC interview): Mothers/female caregivers were asked if they would be concerned for the health of their teenager if they tanned indoors occasionally. (5) Permissiveness regarding teenager's tanning (teen interview): teenagers were asked if their parents would allow them to tan.

Although measures 4 and 5 were believed to represent the same general construct of "gatekeeping" or "monitoring," these items were analyzed separately because they did not form a reliable scale.

We developed a "risk factor" scale by summing the 5 MFC influence variables. The scale ranged from 0–5. A zero value on this scale meant that female caregivers did not display any of the risk factors (i.e., they did not tan indoors in the past year, were more knowledgeable about the consequences of tanning, had less positive attitudes toward tans, would be concerned if their teenager tanned indoors, and would not allow their teenager to tan), whereas a value of "5" would indicate that all risk factors were present.

Demographic and teen sun sensitivity characteristics. We treated city of survey, teen gender, teen age (14, 15, 16, and 17 years), MFC education (high school or below, some college, college degree, and advanced degree) and MFC age (less than 35, 35–44, 45–54, and 55 years or older) as categorical measures and potential confounders of the relationship between MFC influence and adolescent tanning. Teen sun sensitivity was treated as an interval-level confounder. Our measure of sun sensitivity was based on a previously validated measure [41], which included questions about the color of untanned skin, propensity to burn, and hair color. The sun sensitivity index ranged from 1 to 12, with higher scores indicated greater sun sensitivity.

Statistical analysis

All hypothesis testing made use of logistic regression to obtain odds ratios and 95% confidence limits for the associations of interest, controlling for demographic and sun sensitivity variables. We compared adolescents who had tanned indoors in the past year with those who had not for each MFC influence measure described above. We conducted two additional tests to determine the joint effects of MFC influences on indoor tanning: (a) we included all MFC influence variables in one multivariate logistic regression model to determine the relative contribution of each variable; and (b) we tested the "risk factor" scale to determine if the likelihood of teen tanning increased monotonically with the number of MFC influence factors present. Tests for interactions among our outcome variables and all other demographic and sun sensitivity variables were conducting using logistic regression.

Results

Characteristics of the Sample

The sample contained approximately even numbers of teenagers aged 14–17 years, with indoor tanning usage increasing monotonically with age. The vast majority (94%) of the mothers/caregivers were between the ages of 35 and 54 years. Although the prevalence of indoor tanning was much higher in the Twin Cities than the Boston area (41.0% vs. 22.3%), preliminary analyses indicated no important differences between cities in the associations of interest (i.e., there were no significant interactions between city and any of the MFC influence measures on adolescent indoor tanning) (Table 1). Similarly, we also tested for interactions among our outcome variables and all other demographic and teen sun sensitivity variables, and found that our results did not differ dramatically for boys compared with girls, between younger or older adolescents, those with more or less sensitivity to the sun, younger or older parents, or more or less educated parents. Therefore, all analyses are presented for the combined sample and adjusted for demographic and teen sun sensitivity characteristics.

MFC Influence

Our results support all aspects of MFC influence on indoor tanning (Table 2). MFC modeling was strongly associated with youth indoor tanning: teenagers whose mothers or female caregivers had tanned indoors in the past year were much more likely to have been recent indoor tanners themselves, compared with teenagers whose mothers or female caregivers were not recent indoor tanners (aOR = 4.6, 95% CI: 3.0, 6.8). Cognitive aspects of MFC influence were also significant, although less influ-

Table 1. Prevalence of Teen Indoor Tanning Stratified by City, Teen Age, Gender, and Sun Sensitivity, As Well As Mother/Female Caregiver Age and Education

	n	% or Mean (SD)	% or Mean Teens Tanned Past Year (SD)
City			
Minneapolis	647	50.4	32.9
Boston	637	49.6	18.1
Age–teen (years)			
14	261	20.3	7.7
15	346	27.0	17.6
16	333	26.0	31.5
17	343	26.7	41.4
Gender–teen			
Male	493	38.4	7.7
Female	791	61.6	36.7
Sun sensitivity–teen (1–12)[a]	1284	4.8 (1.7)	4.8 (1.6)
Age-mother/female caregiver			
< 35	41	3.2	26.8
35–44	543	42.3	28.0
45–54	659	51.3	24.0
> 55	41	3.2	17.1
Education—mother/female, caregiver			
High school or below	265	20.7	33.2
Some college	155	32.5	28.8
College degree	104	25.3	26.9
Advanced degree	44	21.5	12.0

[a] Higher scores reflect greater sun sensitivity.

ential. MFC knowledge about the consequences of tanning as well as attitudes toward having a tan were comparably influential. Teenagers with less knowledgeable mothers or female caregivers were more likely to have tanned indoors in the past year than teenagers with more knowledgeable mothers or female caregivers (aOR = 1.8, 95% CI: 1.6, 2.0), whereas teenagers of mothers/female caregivers with positive attitudes toward having a tan were somewhat more likely to have used indoor tanning facilities than teenagers whose mothers/female caregivers did not have strong pro-tanning attitudes (aOR = 1.9, 95% CI: 1.4, 2.6). Finally, there were large associations between teenage indoor tanning practices and the two measures of MFC gatekeeping or monitoring functions. Teenagers whose mothers/female caregivers would not be greatly concerned if their teenager used indoor tanning facilities were more likely to have tanned indoors than teenagers whose mothers/female caregivers expressed great concern about their teenager tanning (aOR = 2.7, 95% CI: 2.0, 3.8). The strongest predictor of teen indoor tanning was MFC approval. Teenagers who reported that their mothers/female caregivers would allow them to tan indoors were far more likely to have visited a tanning salon than teenagers whose mothers/female caregivers would not allow them to tan indoors (aOR = 11.7, 95% CI: 7.5, 18.3).

Table 2. Estimates of Maternal/female Caregiver (MFC) Influences on Teen Indoor Tanning, Separately and Combined

	n (%)	% Teens Tanned Past Year	Adjusted OR (CI) Teens Tanned Past Year[a]	Multivariate Model Adjusted OR (CI) Teens Tanned Past Year[a,b]
Modeling (MFC survey)				
MFC did NOT tan past year	1086 (84.6)	20.2		
MFC tanned past year	198 (15.4)	55.1	4.6 (3.0, 6.8)***	3.2 (2.0, 5.0)***
Cognitive				
MFC Knowledge about tanning consequences (MFC survey)				
High	603 (49.3)	17.6		
Low	619 (50.7)	32.1	1.8 (1.6, 2.0)***	1.0 (.7, 1.4)
MFC Attitude toward having a tan (MFC survey)				
Less positive	533 (41.7)	22.3		
More positive	744 (58.3)	25.7	1.9 (1.4, 2.6)***	1.2 (.81, 1.7)
Gatekeeping/monitoring				
MFC concern if child tanned indoors occasionally				
A lot	633 (49.5)	14.7		
Not a lot	647 (50.5)	36.3	2.7 (2.0, 3.8)***	1.7 (1.2, 2.5)**
Teens' agreement with statement, "My parent would allow me to tan indoors." (Teen survey)				
Disagree	524 (40.9)	5.3		
Agree	757 (59.1)	39.6	11.7 (7.5, 18.3)***	9.1 (5.7, 14.7)***

*$p < .05$;** $p < .01$;*** $p < .001$.
[a] Adjusted for city, teen age, gender, and sun sensitivity, as well as mother/female caregiver age and education.
[b] All MFC variables included in one model.

Table 3. MFC Influence Risk Factor Scale

MFC Influence Scale[a]	n (%)	% Teen Tanned Past Year	Adjusted OR (CI) Teen Tanned Past Year[b]
0	127 (10.5)	3.1	–
1	250 (20.6)	9.2	4.1 (1.3, 12.8)*
2	283 (23.3)	20.1	8.3 (2.8, 24.6)***
3	272 (22.4)	27.9	14.3 (4.9, 41.8)***
4	200 (16.5)	46.0	30.5 (10.3, 90.3)***
5	81 (6.7)	65.4	66.0 (20.0, 217.6)***

* $p < .05$; ** $p < .01$; *** $p < .001$.

[a] Combined measure of MFC influence presented as risk, where 5 = all risk factors present: MFC tanned indoors, is not knowledgeable of the consequences of indoor tanning, has more positive attitudes about tanning, is permissive of youth tanning, and would not be concerned if teen tanned indoors.

[b] Adjusted for city, child gender, child age, child sun sensitivity, parent age, and parent education.

To determine the relative importance of different aspects of influence, all MFC influence measures were entered into one multivariate logistic regression equation, controlling for demographic and teen sun sensitivity characteristics (Table 2). Despite the fact that all aspects of MFC influence were significantly associated with teenagers' recent indoor tanning behavior when considered separately, certain factors emerged as more influential when considered simultaneously. Cognitive aspects of MFC influence (knowledge, attitudes) were no longer significant. However, the influence of MFC modeling and gatekeeping/monitoring (concern, permissiveness) remained. MFC permissiveness of tanning was the most important influence in the multivariate model: teenagers with permissive mothers/female caregivers (who would allow their children to tan) were much more likely to have tanned indoors than teenagers with less permissive mothers/female caregivers (aOR = 9.1, 95% CI: 5.7, 14.7). MFC concern was also an important element of the gatekeeping/monitoring influence: teenagers whose mothers/female caregivers were not greatly concerned about their teenagers' indoor tanning use were more likely to visit tanning facilities than teenagers whose mothers/female caregivers were greatly concerned about their teenagers' indoor tanning (aOR = 1.7, 95% CI: 1.2, 2.5). Finally, teenagers appear to be learning indoor tanning behaviors by observing their mothers'/female caregivers' behavior: teenagers whose mothers/female caregivers had recently tanned indoors were more likely to be indoor tanners themselves (aOR = 3.2, 95% CI: 2.0, 5.0) (Table 3).

There was a monotonically increasing likelihood of teenagers using indoor tanning facilities with each level of MFC approval of indoor tanning, measured by the risk factor scale. In contrast to teenagers whose mothers/female caregivers demonstrated no support for their teenagers' indoor tanning (i.e., defined as not tanning themselves, knowledgeable about the consequences of indoor tanning, not having strong positive attitudes toward having a tan, being greatly concerned if their teenager tanned indoors, and not allowing their teenager to tan), teenagers whose mothers/female caregivers had just one of these factors were slightly more likely to tan themselves (aOR = 4.1, 95% CI: 1.3, 12.8), whereas teenagers whose mothers/female caregivers completely condoned the behavior (who had all 5 risk factors) were much more likely to have used an indoor tanning facility (aOR = 66.0, 95% CI: 20.0, 217.6).

Another item on our MFC survey, not discussed elsewhere in this report, was a measure of whether or not mothers/female caregivers could recall if their teenager had ever frequented a tanning business. In a comparison of teenagers' responses regarding their ever having tanned indoors with mothers'/female caregivers' recall of whether or not their children had ever frequented a tanning business, we found that only 18% of teenagers had used an indoor tanning facility without their mothers'/female caregivers' knowledge (or recall). Conversely, only 1% of mothers/female caregivers incorrectly recalled that their teenagers had used a tanning salon (Kappa = .84, $p < .001$).

Discussion

The study results demonstrate that mothers/female caregivers may be an important influence on their adolescents' preventive health behaviors, and suggest the promise of parent- or family-targeted interventions to reduce teenage indoor tanning. Mothers/female caregivers appear to have a considerable and multifaceted influence on their adolescents' indoor tanning practices. This control extends beyond a simple observational learning hypothesis, whereby children observe and model their parents' behavior. In addition to mothers'/female caregivers' own tanning behavior, the extent to which mothers/female caregivers monitor and feel concerned about their teenagers' indoor tanning practices are particularly important. To a lesser extent, MFC cognitions (i.e., their knowledge and attitudes) appeared to affect their teenagers' tanning practices, although only when considered separately from other influence

variables. One explanation for why MFC cognitions were less influential than modeling and gatekeeping/monitoring variables, consistent with numerous cognitive theories of behavior change [42], is that cognitions are precursors to actions. If mothers'/female caregivers' knowledge and attitudes about indoor tanning precede their own actions (including their own tanning behavior as well as monitoring or gatekeeping of their teenagers' tanning), then these cognitions are more distal to their teenagers' behavior (i.e., the effects of MFC cognitions were attenuated in the multivariate model because cognitions are precursors to all other MFC influences). To support this explanation, we tested separate models that included cognitions with each of the other MFC influence variables, and found similar attenuation effects.

A parent-based intervention to reduce adolescent indoor tanning, in contrast to other adolescent health risk behaviors such as drinking or smoking, may be particularly successful because teenagers cannot easily conceal their use of indoor tanning facilities owing to the physical appearance of a tan. Data from our study supports this claim. Mothers'/female caregivers' recall of their teenagers' indoor tanning practices were consistent with teenagers' self- reporting of their behavior.

Limitations

Because our study design was cross-sectional rather than longitudinal, we cannot confidently conclude that mothers/female caregivers may serve as a protective factor against adolescent indoor tanning. Although we cannot definitively establish causal order, the fact that our primary outcome was taken from the teen survey and most of the influence measures from the MFC survey suggests that the observed associations are not artifacts of recall bias.

Additionally, we are cautious about generalizing our results beyond the population studied. The sampling strategies we employed were not meant to draw a nationally representative sample; we oversampled girls compared with boys, and gathered data only from youth and their female caregivers in two U.S. metropolitan areas, Boston and Minneapolis-St. Paul. In contrast to two recent national surveys [21,22], the prevalence of teen indoor tanning in our study was higher. However, we are confident that this difference is owing to regional variations in indoor tanning prevalence based on our sampling strategy rather than any unknown biases in our sample: our estimates of tanning prevalence in Boston and Minneapolis are comparable to the prevalence rates of teenagers in the Midwest and Northeast reported by a third study [20].

We also have some evidence to suggest that the associations between teens' indoor tanning and MFC influences would not be dramatically different in a more representative sample (i.e., a sample containing fewer indoor tanners). Our tests for interactions between certain teen demographic variables and MFC influence variables on teens' indoor tanning explored whether the relationships between MFC influence and teen indoor tanning were the same for different sub-groups of teenagers who were more or less likely to tan indoors. For example, we evaluated the magnitude and/or statistical significance of interactions between each of the MFC influence variables with gender (boys are less frequent tanners) and region (Massachusetts teens were less frequent tanners than Minnesota teens), and found a potential source of bias for only one MFC influence variable: the relationship between teen indoor tanning and MFC permissiveness of indoor tanning was significantly larger in girls compared with boys, with a similar but nonsignificant difference between Minnesota and Massachusetts. Given that the prevalence of indoor tanning was higher in girls and in Minnesota, we hypothesize that these relationships are stronger because more of these teens have actually asked their mothers/female caregivers for permission to tan, and hence are more likely to know the "correct" answer. Although the magnitude of the relationship between teen indoor tanning and MFC permissiveness may be over-estimated due to the high prevalence of indoor tanning in our sample, MFC permissiveness was still a significant predictor among boys and in Massachusetts, suggesting the importance of MFC permissiveness across different populations.

Finally, we sampled only mothers and female caregivers, and assume that they are the primary source of caregiver influence. This assumption is supported by the congruency of responses between teenagers and mothers/female caregivers regarding teenagers' indoor tanning practices, indicating that mothers/female caregivers are very aware of their teenagers' tanning practices. The consistency of responses also alleviates concerns that teenagers who may have been interviewed in the presence of their mothers/female caregivers felt pressured to provide more "socially desirable" responses, thereby underreporting their indoor tanning use.

Conclusions

Mothers/female caregivers may be a powerful deterrent on their teenagers' indoor tanning use, and represent an important target for future health promotion efforts to discourage adolescent indoor tanning. In addition to modeling appropriate behaviors (i.e., by not frequenting indoor tanning salons themselves), caregivers should express concern and communicate rules prohibiting indoor tanning to their children. It is important to develop strategies that will foster MFC disapproval and active monitoring of their teenagers' indoor tanning practices, as well as discourage mothers/female caregivers themselves from using indoor tanning facilities.

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