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# Amended Safety Assessment of *p*-Hydroxyanisole as Used in Cosmetics

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*All interested persons are provided 60 days from the above date to comment on this Tentative Amended Report and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. Lillian J. Gill.*

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

## INTRODUCTION

This is an amended safety assessment of *p*-hydroxyanisole. A new use in artificial nail coatings and adhesives that requires UV curing has been identified and new data are being considered to evaluate the safety of this use. Both *p*-hydroxyanisole and hydroquinone are used interchangeably or in combination as polymerization inhibitors in nail gels and adhesive products sold directly to consumers for home use. Hydroquinone is the focus of a separate amended safety assessment addressing this new use.

*p*-Hydroxyanisole (CAS No. 150-76-5) is defined as the substituted phenolic compound that conforms to the formula in Figure 1. It is currently reported to function as an antioxidant, fragrance ingredient, and reducing agent.<sup>1</sup> *p*-Hydroxyanisole is the common name for 4-methoxyphenol.

In 1985, the Panel concluded that *p*-hydroxyanisole is unsafe for use in cosmetics due to dermal depigmentation and irritation and sensitization potential.<sup>2</sup> The summary of this report is provided below. The unsafe conclusion was reaffirmed at the September, 2003 Panel meeting. The use categories in these safety assessments included dermal products but did not include nail products.

This report presents new data pertinent to the new use in nail products, as well as new toxicity data that have become available since the review of this ingredient.

### **Summary from 1985 *p*-Hydroxyanisole Safety Assessment**

*p*-Hydroxyanisole is a waxy solid prepared by the reaction of hydroquinone with dimethylether.<sup>2</sup> When used for cosmetic purposes, the compound typically has a purity of 99.5%. Impurities consist of hydroquinone dimethylether (about 0.1%) and an unidentified compound with a "high boiling point" (about 0.4%).

*p*-Hydroxyanisole has acidic properties characteristic of phenols. It binds by hydrogen bonding to itself, water molecules, and various proteins. The compound is readily oxidized and can undergo a variety of reactions, including alkylation, halogenation, and other substitutions on the aromatic nucleus. Peak absorbance of UV light by *p*-hydroxyanisole occurs at about 340 nm.

Noncosmetic uses of *p*-hydroxyanisole include applications as an antioxidant, as a polymerization inhibitor, as a chemical intermediate, and as a stabilizer. It is used in cosmetics as an antioxidant.

Data submitted to the FDA by cosmetic firms participating in the voluntary cosmetic registration program indicated that this antioxidant was used in 31 cosmetic products during 1981 at concentrations of >0.1% to 1.0% (8 products) and ≤ 0.1% (23 products). Cosmetic formulations containing this compound, such as eye makeup, sachets, makeup bases, and skin care preparations, are normally applied to or have the potential to come in contact with the skin and eyes.

Results of numerous studies indicated that *p*-hydroxyanisole is a skin-depigmenting agent. Unpublished data strongly suggested that this cosmetic ingredient was a depigmenter of the skin at concentrations approximating those used in cosmetic products. Skin depigmentation was observed in guinea pigs exposed 6 weeks to 0.25% of the antioxidant and in guinea pigs exposed 6 months to 0.5% and 1.0% *p*-hydroxyanisole. Exposure for 6 weeks to 0.1% produced depigmentation at the site of skin application in 1 of 6 guinea pigs. Associated with the skin-depigmenting action of this compound was a selective cytotoxic effect on the melanocyte. The melanocytotoxic effect was dependent upon both antioxidant concentration and duration of exposure. No cytotoxic effects on human melanocytes or morphological changes in human keratinocytes were observed following a 45-minute exposure to either 10<sup>-2</sup> M or 10<sup>-3</sup> M *p*-hydroxyanisole in disperse tissue culture. However, whole epidermis (human) exposed *in vitro* to 10<sup>-1</sup> M for 1, 5, and 24 hours had extensive damage to melanocytes and keratinocytes. Concentrations as low as 10<sup>-8</sup> and 10<sup>-9</sup> M were cytotoxic to guinea pig melanocytes *in vitro*. These latter concentrations are lower than *p*-hydroxyanisole concentrations typically used in cosmetics. *p*-Hydroxyanisole given orally to rats and mice caused induction and inhibition of various enzymes in the esophagus, nonglandular stomach, and microsomal fraction of the liver. *In vitro* studies with isolated rat liver suggested that the antioxidant interferes with ribonucleic acid synthesis, protein synthesis, and mitochondrial respiration. The compound inhibited growth or was microcidal in studies with bacteria and fungi. Chromosomal aberrations in plants and denaturation of DNA in bacteriophage were observed following *p*-hydroxyanisole exposure.

*p*-Hydroxyanisole was absorbed by guinea pig skin *in vitro*. Oral doses of the antioxidant were excreted by rabbits primarily as conjugates of glucuronic and sulfuric acids; small amounts were demethylated and excreted as hydroquinone.

The acute oral LD<sub>50</sub> of *p*-hydroxyanisole in rats was estimated as 1630 mg/kg. The oral LD<sub>50</sub> in rats of 50% *p*-hydroxyanisole in corn oil was 740 mg/kg. The acute LD<sub>50</sub> of the antioxidant when administered by intraperitoneal injection was 250 mg/kg and 430 mg/kg for mice, 730 mg/kg for rats, and 720 to 970 mg/kg for rabbits.

Undiluted *p*-hydroxyanisole was a severe skin and ocular irritant in rabbits; a single exposure to the compound produced extensive skin edema and necrosis and corneal injury. Minimal irritation was observed in the eyes of rabbits exposed to a 0.1% aqueous solution of the antioxidant and on rabbit skin treated with 5% *p*-hydroxyanisole in sweet almond oil. Skin sensitization to *p*-hydroxyanisole (0.5 M and 1.0 M) was observed in guinea pigs in both the "maximization test" and the "Freund's complete adjuvant test." Cross skin sensitization of guinea pigs to hydroquinone (1 M) and *p*-hydroxyanisole (3 M) was also reported. No photosensitization was observed in guinea pigs exposed to both *p*-hydroxyanisole (0.1% and 1.0%) and UV irradiation. Application of a water-oil emulsion containing 1.0% *p*-hydroxyanisole to the skin of guinea pigs for 30 days produced hyperemia, edema, and desquamation. Skin irritation and depigmentation

were observed in guinea pigs and mice treated for 4 weeks with 20% *p*-hydroxyanisole in petroleum jelly and in guinea pigs treated 1 to 6 months with antioxidant concentrations of 0.25 M or 1.0 M in acetone, 0.5 M in dimethylsulfoxide, and 5.0 or 10.0 percent in hydrophilic ointment. Application of 20% *p*-hydroxyanisole in lanolin base to guinea pig skin for up to 6 months and to hamster cheekpouch 3 times a week for 45 days caused encroachment of basal cell pseudopodia into the dermis. In addition, the hamster cheekpouch had erythema, hyperkeratosis, epithelial hyperplasia, bullae, and muscular degeneration. Rats and rabbits fed diets containing 5% and 10% *p*-hydroxyanisole and dogs fed up to 12 g daily for 2 weeks had growth inhibition and changes in hematological parameters and organ weights; no other significant toxicological effects were noted.

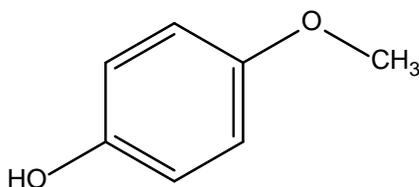
*p*-Hydroxyanisole was nonmutagenic in the Ames assay with and without metabolic activation. No local toxic changes or tumors were observed following application of 5% and 10% *p*-hydroxyanisole in acetone to the skin of mice and rabbits in a lifetime study. The antioxidant (13.1% in benzene) was inactive as a tumor promoter when applied for 20 weeks to the 7,12-dimethylbenz(a)anthracene (DMBA)-initiated skin of mice. Application of a bleach cream containing 5% *p*-hydroxyanisole and a water-oil emulsion containing 25 percent of the antioxidant to the skin of pregnant rats produced embryotoxicity but not teratogenicity.

In clinical studies, *p*-hydroxyanisole at a concentration of 2.0% in petrolatum and 2.0% in sweet almond oil was, at most, minimally irritating to the skin. A 5.0% concentration of the antioxidant in sweet almond oil was both nonirritating and nonsensitizing to humans. Several cases were reported in the literature of individuals who developed skin depigmentation following exposure to products containing *p*-hydroxyanisole or following occupational exposure to the antioxidant.

## **CHEMISTRY**

### **Definition and Structure**

*p*-Hydroxyanisole is a substituted phenol (Figure 1).



*p*-Hydroxyanisole

**Figure 1.** *p*-Hydroxyanisole

## **USE**

### **Cosmetic**

Data on ingredient use are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP).<sup>3</sup> The VCRP reports that *p*-hydroxyanisole is used in 3 basecoats and undercoats and 2 nail extenders. Industry is not required to register products with the VCRP. It is understood that the data in the database are a sampling of what cosmetics are available on the market and are not comprehensive.

A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for this ingredient.<sup>4</sup> No uses were reported for *p*-hydroxyanisole by the Council.

A web search for *p*-hydroxyanisole in cosmetic ingredients resulted in a list of nail gel products available on the market that may not have reported to the VCRP or the Council. These products offered for sale as professional and home kits included nail gels that contain *p*-hydroxyanisole and require UV curing.

*p*-Hydroxyanisole is listed in Annex III of the European Council Directive with the following restrictions: only for use in artificial nail system, max concentration of 200 ppm after mixing, for professional use only, avoid skin contact, and read use directions carefully.<sup>5</sup>

Health Canada<sup>6</sup> has the following restrictions for the use of *p*-Hydroxyanisole in cosmetics:

- Permitted at concentrations equal to or less than 0.02% (after mixing), for professional use only, in artificial nail systems
- The inner label and the outer label of the cosmetic shall carry statements to the effect: "For professional use only", "Avoid skin contact", "Read use directions carefully."

### ***Use In Nail Products***

The *p*-hydroxyanisole content of soft nail gels for coloring was reported to be 223.2 ppm (0.02232%), 142.6 ppm

(0.01426%) for soft gel top coats, 426.3 ppm (0.04263%) for hard gel no cleanse top sealer, and 147.2 ppm (0.01472%) for hard gel sculpting before curing.<sup>7</sup>

*p*-Hydroxyanisole alone or in combination with hydroquinone serves as the stabilizer or inhibitor that stops the reaction, in the liquid component of two component methacrylate artificial nail systems.<sup>5</sup> When used as a stabilizer/inhibitor in a two component artificial nail system, the maximum concentration for either hydroquinone or *p*-hydroxyanisole is 200 ppm (0.02%). After mixing 2 parts liquid to 1 part powder the final concentration is reduced to approximately 133 ppm (0.0133%).

When used as a nail adhesive, a brush is wetted in the liquid component which contains the stabilizer(s) and acrylate monomers. The wetted brush is then dipped into the powder which contains the initiator to produce an 'aspirin sized' bead. The liquid:powder ratio is approximately 2:1. The two components are mixed into a 'slurry bead', which is applied to the center of the nail plate and then shaped. The polymerization is complete in 5 - 15 min. Contact is to the keratin of the nail plate and not to the skin or cuticle.<sup>5</sup>

Hydroquinone is added to the monomer as oligomer (i.e., dimer, trimer, tetramer) preparations during manufacturing to prevent polymerization.<sup>8</sup> This preserves the integrity of the monomers or oligomers until they are used to produce polymers or other derivatives. For polymerization to occur, the inhibitors must either be destroyed or inactivated. Hydroquinone (and *p*-hydroxyanisole) is destroyed during polymerization (using light) and any residual inhibitor is enclosed in the hardened polymer. [Dr. David Steinberg, pers. comm.]

Under various conditions, including after curing under a UV lamp (291 nm), *p*-hydroxyanisole in a nail polish was not detected by high-performance liquid chromatography (Table 1). A nail polish gel had reduced amounts of *p*-hydroxyanisole after curing (Table 2). However, a nail polish medium for coloring had no detectable *p*-hydroxyanisole after curing. In a nail polish top coat, *p*-hydroxyanisole was reduced from 123.2 ppm to below 10 ppm after curing. The amount of *p*-hydroxyanisole in a soft gel nail base coat was reduced from 488.3 ppm (0.04883%) to 447.5, 409.3, and 352.1 ppm (0.04475%, 0.04093%, and 0.03521%) after 10, 20, and 30 sec, respectively, of curing under a UV lamp.<sup>7</sup>

In a guide to using UV gel enhancements, the manicurist is instructed to carefully prepare the nail bed by removing the cuticle from the area of the nail where the product is to be applied.<sup>9</sup> If the cuticles are not cleared, natural oils and moisture under the nail gel or the enhancement adhesive prevents the product from adhering to the nail and the product will peel off, creating an unsatisfactory result. [Dr. David Steinberg, pers. comm.]

The direct sale to consumers of nail products containing one or both of these stabilizers constitutes the new use considered in this safety assessment.<sup>8</sup>

The nail gels and adhesives are removed by the application of a solvent (that is provided on a presoaked pad) for 15 to 30 min.<sup>10,11</sup>

## **TOXICOKINETICS**

### **Absorption, Distribution, Metabolism, and Excretion**

#### ***Dermal/Percutaneous***

The permeability coefficient, for skin and receptor fluid, of radio-labeled *p*-hydroxyanisole (35 mg/mL in water; 469  $\mu\text{L}/\text{cm}^2$ ) was  $9.39 \times 10^{-3}$  cm/h; the flux at 10 min was 283.0  $\mu\text{g}/\text{cm}^2/\text{h}$  and at 60 min was 223.0  $\mu\text{g}/\text{cm}^2/\text{h}$ .<sup>12</sup> The experiment was performed in accordance with the Occupation Safety and Health Administration (OSHA) procedures. [Federal Register Vol. 69, No. 80] These procedures include the use of only abdominal cadaver skin that is either dermatomed or heat separated using a minimum of three donors and six replications. The dose applied to each skin replicate was "infinite", which provides an undepletable reservoir.

There was low systemic exposure to *p*-hydroxyanisole (2%) when administered to human subjects (n = 8) in a cream that also contained tretinoin (0.01%) twice/day for 21 days.<sup>13</sup> The test material was administered to 400  $\text{cm}^2$  of the back. After the last treatment, the subjects received a single topical application of 2% *p*-hydroxyanisole/0.01% (<sup>3</sup>H) tretinoin solution. After 12 h, the radiolabelled dose was removed and treatment with the non-radiolabelled 2% *p*-hydroxyanisole/0.01% tretinoin solution was continued for 7 days. Plasma was analyzed for *p*-hydroxyanisole by gas chromatography/mass spectrometry (GC/MS). The  $C_{\text{max}}$  for *p*-hydroxyanisole was  $9.92 \pm 7.48$  ng/mL with  $\text{AUC}_{0-12}$   $33.43 \pm 14.30$  ng h/mL.

## **REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

In a dermal teratology study in New Zealand White rabbits (n not provided), there were no effects observed that could be attributed to treatment in rabbits topically administered a depigmentation cream containing *p*-hydroxyanisole (40 mg/kg; 440  $\text{mg}/\text{m}^2$ ) and tretinoin.<sup>14</sup> In a second study of this depigmentation cream containing only *p*-hydroxyanisole, the no observed effect level (NOEL) for teratogenicity was 4 mg/kg (0.22  $\text{mg}/\text{m}^2$ ). The authors stated that this is approximately the maximum possible human daily dose, based on clinical application to 5% of total body surface area. There were no differences among treatment groups in fetal malformation data. The test material (12, 40 mg/kg; 132, 440  $\text{mg}/\text{m}^2$  *p*-hydroxyanisole, respectively) was administered dermally to the rabbits. The summary of the study does not provide details on timing, length of study, or the concentration of the low-dose group.

In a study of the same depigmentation cream, it was not teratogenic in Sprague-Dawley rats (n not provided) when given in topical doses equal to 80 mg/kg (480 mg/m<sup>2</sup>) *p*-hydroxyanisole (or 11 times the maximum human daily dose).<sup>14</sup> The maximum human dose is defined as the amount of solution applied daily to 5% of the total body surface area. No further information was provided about this study.

In another study of a depigmentation cream containing *p*-hydroxyanisole (2%), the maternal, neonatal, and developmental NOAELs for *p*-hydroxyanisole were 40 mg/kg/d (12 µL/cm<sup>2</sup>).<sup>15</sup> *p*-Hydroxyanisole (0, 0.6, 2.0, 6.0 mL/kg/d; 0.072, 0.240, 0.720 mg/cm<sup>2</sup>/d) was administered dermally to 10% of the body surface of pregnant CrI:CD (SD) Br rats (n = 25/sex) for 6 h/day 7 days/week (assumed through entire pregnancy). At post-natal day 4, the litters were culled to 8 pups. At age 8 – 13 days, pups were randomly selected for physical and functional development (n = 10/sex), and reproductive performance (n = 15/sex). Dams in the F1 generation underwent laparotomy on gestation day 20 and the fetuses were evaluated. F1 rats were necropsied.

There were no deaths in any group. Clinical signs in the F0 rats were very slight to severe erythema (first noted on study day 8), very slight to moderate edema, including fissuring (especially at the high dose), desquamation (first noted on study day 13), eschar, and focal eschar and exfoliation (first noted on study day 14) at the treatment sites. Vocalization was observed on application of the test material in mid- and high-dose groups. High dose animals exhibited decreased body weight on gestation day 20 and lactation day 1, in mean body weight gain during gestation, and in food consumption during gestation days 9 - 12. Increased food consumption in the first few days of lactation was observed in those animals before they were killed for humane reasons.

Six dams in the mid- and high-dose groups failed to deliver by post-mating day 25, as compared to two each in the control and low dose groups; all but one of the controls were found to be gravid. Four high dose females had total litter loss between lactation days 1 and 5. Gross necropsy revealed reddening, thickening and scabbing of skin at treated sites in the F0 dams.

Clinical signs in the F1 rats were only observed at the maternally toxic high dose. There was increased pup mortality, decreased pup body weight, and an increased incidence of clinical signs. Clinical signs in the high dose pups included small size, hypoactivity, cool to the touch, and paleness in appearance.

There was reduced F1 pup survival and a higher rate of missing or cannibalized pups in high dose litters after postnatal day (PND) 1. There was an increased incidence of F1 pup clinical and necropsy findings. Balanopreputial separation and vaginal patency were unaffected by treatment. Auditory startle testing on or about PND 21 and 60 revealed no treatment-related effects. Motor activity (total and ambulatory) measurements were made on or about PND 60 and there was no effect of treatment on total or ambulatory counts. Testing in the water maze was initiated between PND 20-23 and between PND 57-62 and evaluated; no effect of treatment on swimming ability, learning and memory was demonstrated. Estrous cycling in F1 females and reproductive performance in F1 animals were unaffected by treatment. Gravid uterine weights and the fetuses were also unaffected.

In F1 pups found dead or euthanized, gross findings in the high dose group included absence of milk in the stomach, renal papilla not developed or not fully developed and/or distended ureters or urinary bladder. One external malformation (anury) was noted in one animal in one litter. At the low dose, one pup was found to have the renal papilla not fully developed. In F1 euthanized surplus pups, high dose animals were again noted with the absence of milk in the stomach, and one litter had pups in which the renal papilla was not developed or not fully developed and/or ureters or urinary bladder were distended. In the high dose group, there was one pup in one litter with a hemorrhagic ring around the iris. In F1 adults, no findings were seen that could be attributed to treatment.<sup>15</sup>

## **GENOTOXICITY**

### **In Vivo**

No genotoxic effects were observed when Sprague-Dawley rats (n and sex not specified) were dermally administered *p*-hydroxyanisole (4, 12, 40 mg/kg) in a depigmentation cream for 6 months.<sup>16</sup> No further details were provided.

## **CARCINOGENICITY**

*p*-Hydroxyanisole (0, 2% in feed) was carcinogenic to the forestomach of male and female F344 rats (n = 30/sex) when administered for 104 weeks.<sup>17</sup> Histopathological findings included atypical hyperplasias (male, 67%; female; 37%), papillomas (50%; 23%) and squamous-cell carcinomas (77%; 20%) in the forestomach. The body weights as well as the liver and kidney weights were reduced for both sexes in the treatment group.

*p*-Hydroxyanisole (0, 0.25%, 0.5%, 1.0%, 2.0% in feed) administered for 51 weeks to male F344 rats (n = 15) did not increase the incidence of either papillomas or squamous cell carcinomas caused by the prior administration of N-methyl-N'-nitro-N-nitrosoguanidine- (MNNG; 150 mg/kg) initiated rat forestomach carcinogenesis.<sup>18</sup> Increased epithelial damage and hyperplasia in a dose-dependent manner in the forestomach epithelium was observed. The control rats (administered *p*-hydroxyanisole but not MNNG) had reduced body weights in a dose-dependent manner and increased relative kidney and liver weights. All rats in the 2% *p*-hydroxyanisole, without MNNG pretreatment, had large forestomach ulcers without tumor formation.

## IRRITATION AND SENSITIZATION

### **Irritation**

#### ***Dermal – Non-Human***

When *p*-hydroxyanisole (0, 0.6, 2.0, 6.0 ml/kg/d) was administered dermally to Crl:CD (SD) Br rats (n = 25/sex) for 6 h/day 7 days/week (assumed through entire pregnancy), the dams and offspring were killed within the first week of lactation because of extreme irritation at the application site.<sup>15</sup>

When *p*-hydroxyanisole (5% in propylene glycol/ethanol, 50:50) was dermally administered to multiple sites of the backs of Yucatan miniature pigs (n = 2), *p*-hydroxyanisole was rated as mildly irritating.<sup>19</sup> The test substance was administered twice/day, 7 days/week for 90 days. Microscopic examination of biopsies of the test area showed reduction in pigment and number of melanocytes.

### **Sensitization**

#### ***Dermal – Human***

In multiple human repeated insult patch tests (HRIPT) of nail products, there were no signs of potential cuticle irritation or allergic contact sensitization (Table 3).<sup>20-31</sup> The test materials were administered to a fingernail of the subjects and removed by wiping with a proprietary remover solution after 10 minutes three times per week for nine applications. Two weeks later, the test material was administered to the same fingernail in the same manner. The amounts of hydroquinone and/or *p*-hydroxyanisole were not provided.

## UV NAIL LAMPS

UV lamps are used to cure nail gels, acrylic nails, and nail fill-ins, and to dry traditional nail polish and UV top sealers/topcoats.<sup>32</sup>

The UV nail lamps produce light mostly in the UVA-1 range with little UVA-2, and there is virtually no UVB or UVC radiation emitted.<sup>33</sup> UVA-1 is the least erythemic and photocarcinogenic range in the UV spectrum. The bulbs in UV nail lamps have internal filters to eliminate UVB and are reported to emit exclusively in the 265 – 370 nm range.<sup>34</sup>

Estimates of exposure duration per visit vary with the specified procedure and number of applied acrylic coats.

In 2010-2011, over 87% of professional nail salons reported using UV nail lamps.<sup>35</sup> Typical client usage is 1 – 4 times/month for 2 min or less per visit.<sup>34</sup>

Another researcher stated that typical salon exposures are 10 minutes or less per hand and with exposures occurring only twice per month.<sup>36</sup>

An instructional pamphlet for the application of nail polish directs, that in the course of applying a base coat, color coat, and top coat, the polish is to be cured for 30 sec for each coat using the proprietary UV light (for a total of 90 sec) or for 1min, 2 min, and 3 min, respectively for a total of 6 min using another UV light.<sup>37</sup>

Nail gels shrink with curing under UV lamps. Thus, it has been recommended that three or four separate thin coats of nail gel be applied and cured for 3 min each coat to achieve the desired results.<sup>32,38</sup>

In a study of two UV nail lamps (each from a different nail product company) cumulative exposure measured as minimal erythema doses (MED) were low. However, measured in J/m<sup>2</sup>, cumulative exposures were equivalent, in less than 10 min, to the recommended limit of 30 J/m<sup>2</sup> for 8 hours of outdoor work and recreation by the International Commission on Non-Ionizing Radiation Protection.<sup>39</sup> Dosimeters that measure DNA damage caused by UV irradiation of viable spores were used to make these measurements. Manufacturer's instructions for curing acrylic nails using UV light were followed. It was assumed that the nails would be refinished every 3 weeks or 17 times/year; the dosimeters were exposed for the equivalent of the cumulative dose that would be expected over 1 year of using such lamps. The UV lights yielded 0.6 MED/h for phototype II skin. The curing time recommended by the manufacturers yielded from 0.06 to 0.09 MED per treatment and yearly cumulative exposures estimated between 1.1 and 1.5 MEDs. Total exposures were estimated to be 285 and 386 J/m<sup>2</sup>/y from 15 and 22.5 J/m<sup>2</sup> per nail session, respectively (Table 2).

In the same study, a spectrometer calibrated to measure absolute UV irradiance was used to compare solar radiation with radiation emitted from the lamps. The spectra indicated that the lamps emitted 4.2 times more energy (μW/cm<sup>2</sup>/nm) than the sun (UV Index = 6) in the 355 to 385 nm range. The authors recommended the use of full spectrum sun block to the hands 30 minutes before exposure.<sup>39</sup>

In an evaluation of six UV nail lamps, the authors concluded that total exposure following programmed times and steps, analogous to nail polish application, accumulate to only a small fraction of the recommended practice (RP)-27 permissible daily occupational exposure of UV.<sup>40</sup> The UV nail lamps used were representative of major US manufacturers and evaluated for radiant hazards as defined in the American National Standards Institute/Illuminating Engineering Society of North America Recommended Practice - 27 (ANSI/IESNA RP-27), the Recommended Practice for Photobiological Safety. Lamps were evaluated at three positions: 1 cm above the inner surface, which approximated exposure to the hand; 20 cm directly in front of the box opening; and 20 cm outside the box and 45° above the hand opening.

Three of the devices were fluorescent UV nail lamp systems with 2, 3 or 4 small 9 W lamps. Lamps were of two base types with tubes oriented either perpendicular (in the case of the two-lamp device) or parallel to the fingers of a hand undergoing a procedure. The tubes in the three- and four-lamp units were arrayed in an arc-like configuration to irradiate

from above and from the sides of the hand while the perpendicular-oriented tubes of the two-lamp unit were in a planar configuration above the fingertips. The other three devices were light-emitting diode (LED)-based with arrays of 6 or 32 LEDs or, in the case of a single finger unit, one LED. These LED arrays were mounted in planar configurations oriented generally perpendicular to the fingers in approximately equidistant arcs above the fingertips. The 32 LED devices had four of its LEDs oriented in two lateral pairs positioned on either side. The entrance aperture of the spectroradiometer was positioned to receive the full intensity expected at each of the three different measurement positions chosen to approximate expected intensities to which a user's skin or eyes might be exposed.

Hazard to skin at intended-use distance enabled classification of these devices into Risk Group 1 or 2 (Low to Moderate) with the  $S(\lambda)$  (i.e., distance between the source and the object) weighted Actinic UV range of 1.2–1.7  $\mu\text{W}/\text{cm}^2$  and 29.8 - 276.25 min permissible daily exposure. At 20 cm on center and at 45° from center, UV risk to skin and eyes were within the Exempt classification. Actinic UV ranged 0.001–0.078  $\mu\text{W}/\text{cm}^2$  and unweighted near UV (320 - 400 nm) range was 0.001–0.483  $\text{mW}/\text{cm}^2$ . The retinal photochemical blue light hazard and retinal thermal and cornea/lens IR were also Exempt. One device was found to be an aphakic eye hazard slightly rising into Risk Group 1 (low hazard). There were no other photobiological risks to normal individuals. The potential risks estimated in this study are likely to be substantial overestimates of any actual risks in realistic non-occupational use scenarios because such exposures to these lamps would unlikely be a daily occurrence.<sup>40</sup>

When compared to the UV output of tan bed lamps, UV nail are vastly less hazardous.<sup>36</sup> The results indicate that a person could in their workplace, once every day, put their hand under a UV nail lamp for 25 minutes and remain within the permissible daily occupational exposure limits for workers, according to the applicable international ANSI/IESNA RP-27.1-05 standard.

The carcinogenic-effective irradiance from three different UV nail lamps used 10 min/week was estimated to be over 250 years.<sup>41</sup>

A concern exists that the incorrect replacement lamp/bulb may be inserted into the UV nail lamp (e.g. those emitting UV-B or UV-C) could be harmful to the skin if used.<sup>36</sup> UV lamps/bulb should be replaced with the exactly the same original manufacturer's UV lamp/bulb that was supplied with the UV nail unit when it was purchased.

### **Risk Analysis**

In a risk analysis, it was concluded that 72 709 women using UV nail lamps to cure their nail gels 8 min/application, every 3 weeks, for 20 years would increase the chance that one more woman might develop squamous cell carcinoma on the back of the hand compared to women who were never exposed to UV nail lamps (Table 3).<sup>42</sup> The model UV nail lamp used in this analysis had an unweighted UV irradiance of 115  $\text{W m}^2$  with an erythemally weighted output of 1.58 SED/h. The authors stated that the estimated risk of squamous cell carcinoma could be reduced to virtually zero by wearing fingerless gloves when the hands are being exposed to UV radiation from such lamps.

### **Light Penetration of Nails**

UVB light did not penetrate the finger nails of a cadaver ( $n = 10$ ).<sup>43</sup> Only an average of 1.65% of UVA light penetrated the nails in this study.

### **Case Reports**

Nonmelanoma skin cancers were observed on the dorsum of the hands of two women who reported exposure to UV nail lamps.<sup>32</sup> The first woman was 55 years old, in good health, and was not taking immunosuppressive medication. She had an indoor occupation and participated in little outdoor recreation. Her family had no history of skin cancer. She had been exposed to a UV nail light twice monthly for 15 years. She presented with an erythematous plaque on the dorsomedial aspect of her right index finger. Biopsy revealed a squamous cell carcinoma.

The second woman was 48 years old, in good health, and not taking immunosuppressive medication. She had an indoor occupation with moderate outdoor recreational exposure to UV. She had no personal or family history of skin cancer except for a previous squamous cell cancer that had been removed from the dorsum the left finger 3 years earlier. She presented with a scaly papule on the dorsum of her right hand. Biopsy revealed a squamous cell cancer. Over the next 4 years, two further squamous cell cancers on the dorsum of both hands were treated. She had had exposure to UV nail lights eight times within a year several years before the first appearance of the skin cancer.<sup>32</sup>

### **SUMMARY**

This is an amended safety assessment of *p*-hydroxyanisole that addresses a new use, curing nail polishes with UV light. The Panel concluded in 1985 that *p*-hydroxyanisole was unsafe as a cosmetic ingredient.

Under various conditions, including after curing under a UV lamp (291 nm), *p*-hydroxyanisole in a nail polish was not detected by HPLC. A nail polish gel had reduced amounts of *p*-hydroxyanisole after curing and a nail polish medium for coloring had no detectable *p*-hydroxyanisole. In a nail polish top coat, the *p*-hydroxyanisole concentration was reduced from 123.2 ppm to below 10 ppm after curing. The amount of *p*-hydroxyanisole in a soft gel nail base coat was reduced from 488.3 ppm to 447.5, 409.3, and 352.1 ppm after 10, 20, and 30 sec of curing under a UV lamp.

The VCRP and a Council survey reported no uses for *p*-hydroxyanisole.

*p*-Hydroxyanisole was reported to be used in the liquid component of two-component artificial nail systems at a maximum concentration of 200 ppm, which reportedly decreases to approximately 133 ppm after the product hardens. Polymerization was reported to take 5 – 15 min in a nail adhesive product. *p*-Hydroxyanisole is used interchangeably and in combination with hydroquinone to control polymerization in nail gels and adhesives.

The permeability coefficient of radio-labeled *p*-hydroxyanisole was  $9.39 \times 10^{-3}$  cm/h; the flux at 10 min 283.0  $\mu\text{g}/\text{cm}^2/\text{h}$  and 223.0  $\mu\text{g}/\text{cm}^2/\text{h}$  at 60 min. There was low systemic exposure to 2% *p*-hydroxyanisole when administered in a cream to human subjects.

Dermal administration of a cream containing *p*-hydroxyanisole at 40 mg/kg caused no teratological effects in rabbits. The maternal, neonatal, and developmental NOAELs for *p*-hydroxyanisole were 40 mg/kg/d (12  $\mu\text{L}/\text{cm}^2$ ). The same depigmentation cream was not teratogenic in rats when given in topical doses equal to 80 mg/kg (480  $\text{mg}/\text{m}^2$ ) *p*-hydroxyanisole.

In a two-generation study of a depigmentation cream containing 2% *p*-hydroxyanisole, the maternal, neonatal, and developmental NOAELs for *p*-hydroxyanisole were 40 mg/kg/d (12  $\mu\text{L}/\text{cm}^2$ ) in rats. Clinical signs in the F0 rats were very slight to severe erythema, very slight to moderate edema, including fissuring, desquamation, eschar, focal eschar and exfoliation at the treatment sites. Vocalization was observed on application of the test material in the 2.0 and 6.0 mL groups. There was reduced F1 pup survival and a higher rate of missing or cannibalized pups in litters after PND 1 in the 6.0 mL group. F1 pups in the high-dose group had reduced body weights and an increased incidence of F1 pup clinical and necropsy findings.

No genotoxic effects were observed when rats were dermally administered *p*-hydroxyanisole up to 40 mg/kg in a depigmentation cream for 6 months.

*p*-Hydroxyanisole at 2% in feed was carcinogenic to the forestomach of rats when administered for 104 weeks.

When *p*-hydroxyanisole at 0.6, 2.0, and 6.0 ml/kg/d was administered dermally to rats for 6 h/day 7 days/week (assumed through entire pregnancy), the dams and offspring were killed in the first week of lactation because of extreme irritation at the application sites. *p*-Hydroxyanisole was rated as mildly irritating at 5% in miniature pigs.

In multiple HRIPTs of nail products, there were no signs of cuticle irritation or allergic contact sensitization when products containing hydroquinone and/or *p*-hydroxyanisole were administered to the fingernails.

UV lamps are used to cure nail gels, to cure acrylic nails and nail fill-ins, as well as to dry traditional nail polish and UV top sealers/topcoats.

In a study of UV exposure from different UV nail lamps using two different measurement methods, the cumulative minimal erythema doses (MED) were low. However, in less than 10 minutes, the exposure measured in  $\text{J}/\text{m}^2$  was equivalent to the day-long recommended limit for outdoor work and recreation.

In tests of multiple types of UV nail lamps used as intended, the estimated UV exposure was below levels associated with potential carcinogenicity.

A risk analysis of the use of UV nail lamps concluded that tens of thousands women would have to use UV nail lamps to dry their nail gels 8 min/manicure, every 3 weeks, for 20 years to increase the chance that one more woman would develop squamous cell carcinoma on the back of the hand, compared to women who were not exposed to UV nail lamps.

UVB light did not penetrate finger nails; very little UVA light penetrated fingernails.

There were two case reports of nonmelanoma skin cancers on the dorsum of the hands of two women who used UV nail lamps were reported.

It was recommended that gloves or full spectrum sun block be used when UV nail lamps are to be used.

## **DISCUSSION**

*p*-Hydroxyanisole was found to be unsafe as a cosmetic ingredient due to skin depigmentation at 0.25% as well as the potential to cause irritation and sensitization. These conclusions did not address the current use in nail applications.

The Panel noted that there is no dermal exposure to *p*-hydroxyanisole when artificial nail coatings are properly used. Users are advised to promptly remove any accidental application to the surrounding skin for best visual results and adherence as well as to minimize exposure. The Panel concluded that when following these instructions, there is no risk of more than a momentary exposure that should not result in skin depigmentation. However, the Panel stressed that contact with the skin is to be prevented and that professionals be properly trained in the application of these products. The Panel also noted that *p*-hydroxyanisole is either consumed during the curing process or is trapped within the polymerized matrix, so post application exposure is not an issue.

*p*-Hydroxyanisole is an ingredient in nail products, marketed as “home kits”, that are now available to the consumer. The Panel considered the greater likelihood of accidental skin and nail bed exposure when nail products are applied by consumers compared to experienced salon personnel and emphasized that directions be followed carefully by consumers so that contact with the cuticle or skin is avoided.

The Panel noted that the sensitization studies that applied nail gel to the fingernails, did not provide the concentration of hydroquinone and/or *p*-hydroxyanisole. While the study does not demonstrate the dermal sensitization

potential of these products when administered to the skin, the lack of positive results does demonstrate how unlikely it is for sensitization to develop when these products are used properly.

The Panel reviewed estimates of risks of developing squamous cell carcinoma in individuals who are placing their hands under a UVA light source. The Panel acknowledged that there is controversy about the potential mutagenicity of UVA light under the conditions of use, indicating that a slightly elevated risk of developing squamous cell carcinoma is possible. The Panel noted that the possible risk of photo-carcinogenicity warrants the precaution to use a broad-spectrum sunscreen or photo-protective covering, such as light-impermeable gloves, during the gel-curing process.

UV nail lamps, as designed, are manufactured using universal light bulb sockets. Since it is possible to replace the original light bulb with a UV bulb not specified for use with the machine, the Panel discussed the concern about using unqualified replacement bulbs. The Panel encourages industry to identify ways to prevent this issue, for example by creating lamps/machines that have a dedicated socket type so that an inappropriate bulb cannot be used.

The Panel noted correspondence providing information that the number of uses of this ingredient is greater than that reported by the VCRP. The Panel stated that it is important that companies report their ingredient usage to this program, as well as responding to the concentration of use surveys conducted by the Council, to facilitate the development of safety assessments based on accurate and comprehensive ingredient use information. Additionally, they requested that industry clarify whether or to what degree ingredient usage in professional products is included in the VCRP.

#### **AMENDED CONCLUSION**

The CIR Expert Panel concluded that *p*-hydroxyanisole is safe for use in artificial nail coatings in the present practices of use and concentration described in this safety assessment. *p*-Hydroxyanisole is unsafe for use in all other cosmetics due to dermal depigmentation and irritation and sensitization potential.

## TABLES AND FIGURES

**Table 1.** Detection of *p*-hydroxyanisole in nail polish with and without curing under a UV lamp (291 nm) under various conditions (limit of detection = 5 ppm).<sup>7</sup>

Condition	<i>p</i> -Hydroxyanisole detected (ppm)
Uncured polish gel suspended in water for 5 minutes	Not detected
30 sec cured polish-on gel medium and soaked for 5 min in water	Not detected
30 sec cured polish-on gel medium and soaked 5 min in water with 1% soap	Not detected

**Table 2.** Detection of *p*-hydroxyanisole in nail polish after various curing times.

Description	<i>p</i> -Hydroxyanisole in uncured polish (ppm)	After curing Time (ppm)		
		10 sec	20 sec	30 sec
Polish-on soft gel	184.8	170.7	156.1	134.3
Polish-on soft gel medium for coloring	115.8	Not detected	Not detected	Not detected
Polish-on soft gel top coat	123.2	8.5	7.1	5.9

**Table 3.** HRIPTs of nail products containing hydroquinone and/or *p*-hydroxyanisole administered to the fingernails. The amount of hydroquinone and/or *p*-hydroxyanisole in the products was not provided.

Product	n	Result	Reference
UV gel top coat nail polish	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>25</sup>
UV gel top coat nail polish	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>24</sup>
Builder gel	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>23</sup>
Clear overlay gel	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>22</sup>
Soak-off sealer	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>21</sup>
Soak-off gel lacquer	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>20</sup>
Gel system-thick gel sealer	50	No signs of potential cuticle irritation or allergic contact sensitization	<sup>26</sup>
Base gel	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>27</sup>
No-cleanser overlay gel	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>28</sup>
Soft white sculpting gel	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>29</sup>
Pink builder gel	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>30</sup>
Luminous white overlay gel	51	No signs of potential cuticle irritation or allergic contact sensitization	<sup>31</sup>

**Table 4.** Ultraviolet nail lamp measurements.<sup>39</sup>

Lamp	Exposure time (min)	Total MED/yr	Total J/m <sup>2</sup>	MED/h	Total MED/manicure	Total J/m <sup>2</sup> /manicure
OPI lamp	150	1.5	386	0.62	0.09	22.5
CND lamp	108	1.1	285	0.63	0.06	15.0

**Table 5.** The number of women who would need to be exposed to ultraviolet A (UVA) nail lamps<sup>a</sup> for one woman to develop squamous cell carcinoma who would not have done so otherwise.<sup>42</sup>

Age when UVA nail lamp use begins	Number of years of use			
	5	10	20	40
20	218 604	125 629	72 709	44 254
30	271 521	155 688	89 435	52 952
40	332 747	189 670	107 287	60 863
50	395 768	223 255	123 290	-

<sup>a</sup> Assumes a typical level of exposure of 8 min per hand, once every 3 weeks with no sun block agents..

## REFERENCES

1. Gottschalck TE and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 14 ed. Washington, DC: Personal Care Products Council, 2012.
2. Elder RL. Final report on the safety assessment of p-hydroxyanisole. *Journal of the American College of Toxicology*. 1985;4(5):31-63.
3. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database*. 2013. Washington, DC: FDA.
4. Personal Care Products Council. 11-20-2013. Concentration of use by FDA Product Category: Hydroquinone and p-Hydroxyanisole. 1 pages.
5. Scientific Committee on Consumer Products and Non-Food Products Intended for Consumers (SCCNFP). Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) concerning the use of benzoyl peroxide (BPO), hydroquinone (HQ), hydroquinone methylether (MeHQ) in artificial nail systems. 2002. [http://ec.europa.eu/health/archive/ph\\_risk/committees/sccp/documents/out167\\_en.pdf](http://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out167_en.pdf). Report No. SCCNFP/0486/01, final. pp. 1-15.
6. Health Canada. Health Canada: Cosmetic Ingredient Hotlist - March 2011. <http://www.hc-sc.gc.ca/cps-spc/cosmet-person/indust/hot-list-critique/hotlist-liste-eng.php#H>.
7. Anonymous. 2012. Monomethyl Ether Hydroxy Quinone (MEHQ) Detectability in Soft Gel Base Coat at Various Curing Time.
8. David Steinberg. Memo. 2-4-2013.
9. Creative Nail Design Inc (CND). Brisa™ Swirl UV Gel Enhancements Sculpted on a Tip [pamphlet]. Vista, CA: Creative Nail Design; 2013.
10. Creative Nail Design Inc (CND). Brisa™ Lite Removable Sculpting Gel Enhancements Removal [pamphlet]. Vista, CA: Creative Nail Design; 2013.
11. Creative Nail Design Inc (CND). Brisa™ Lite Removable Smoothing Gel Enhancements Removal [pamphlet]. Vista, CA: Creative Nail Design; 2013.
12. Fasano WJ and McDougal JN. In vitro absorption rate testing of certain chemicals of interest to the Occupational Safety and Health Administration: Summary and evaluation of USEPA's mandated testing. *Regulatory Toxicology and Pharmacology*. 2008;51(2):181-194.
13. Everett DW, Franz TJ, Chando TJ, Gale PJ, Lehman PA, Schwarzel EH, Parab PV, D'Arienzo CJ, and Dripalani KJ. Percutaneous absorption of [3H]tretinoin and systemic exposure to mequinol after dermal application of 2% mequinol/0.01% [3H]tretinoin (Solage) solution in healthy volunteers. *Biopharmaceutics & Drug Disposition*. 1999;20(6):301-308.
14. Barrier Therapeutics, Inc. Solage (mequinol and tretinoin) solution [pamphlet]. 2007.
15. FDA Center for Drug Evaluation and Research Application Number 20-922. Endpoint details: Reproductive toxicity. [http://ofmpub.epa.gov/opthpv/Public\\_Search.PublicTabs?SECTION=1&epcount=1&v\\_rs\\_list=34018](http://ofmpub.epa.gov/opthpv/Public_Search.PublicTabs?SECTION=1&epcount=1&v_rs_list=34018).
16. FDA Center for Drug Evaluation and Research Application Number 20-922. Endpoint Details; Genetic toxicity in vivo. [http://ofmpub.epa.gov/opthpv/Public\\_Search.PublicTabs?SECTION=1&epcount=1&v\\_rs\\_list=33976](http://ofmpub.epa.gov/opthpv/Public_Search.PublicTabs?SECTION=1&epcount=1&v_rs_list=33976).
17. Asakawa E, Hirose M, Hagiwara A, Takahashi S, and Nobuyuki I. Carcinogenicity of 4-methoxyphenol and 4-methylcatechol in F344 rats. *International Journal of Cancer*. 1994;56(1):146-152.
18. Wada S, Hirose M, Takahashi S, Okazaki S, and Ito N. Para-methoxyphenol strongly stimulates cell proliferation in the rat forestomach but is not a promoter of rat forestomach carcinogenesis. *Carcinogenesis*. 1990;11(10):1891-1894.
19. Nair X and Tramposch KM. The Yucatan miniature swine as a n in vivo model for screening skin depigmentation. *Journal of Dermatological Science*. 1991;2(6):428-433.
20. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Soak-Off Gel Lacquer.
21. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Soak-Off Sealer.
22. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Clear Overlay Gel.
23. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Clear Builder Gel.
24. Biometrix Inc. 2010. Human Insult Repeat Patch Evaluation of the Nail Product Gel Color.
25. Biometrix Inc. 2010. Human Insult Repeat Patch Evaluation of the Nail Product UV Gel-EO Top Coat.

26. Biometrix Inc. 2010. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Gel System-Thick Gel Sealer.
27. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Base Gel.
28. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium No-Cleanse Overlay Gel.
29. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Soft White Sculpting Gel.
30. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Pink Builder Gel.
31. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Luminous White Overlay Gel.
32. MacFarlane DF and Alonso CA. Occurrence of nonmelanoma skin cancers on the hands after UV nail light exposure. *Archives of Dermatology*. 2009;145(4):447-449.
33. Rapid Precision Testing Laboratories. CND UV Lamp. 9-28-2011.
34. Schoon D, Bryson P, and McConnell J. Do UV nail lamps emit unsafe levels of ultraviolet light? 2010. <http://www.schoonscientific.com/downloads/UV-Nail-Lamp-Facts.pdf>. pp. 1-5.
35. Anonymous. 2011 - 2012 Industry statistics [pamphlet]. 2013.
36. Sayre RM. 2014. Letter regarding UV lights.
37. OPI Inc. Soak-off gel lacquer Application Instructions [pamphlet]. Hollywood, CA: OPI Inc; 2011.
38. Anonymous. Hooked on nails; UV gel application. [www.hooked-on-nails.com](http://www.hooked-on-nails.com).
39. Curtis, J, Tanner P, Judd C, Childs B, Hull C, and Leachman S. Acrylic nail curing UV lamps: High-intensity exposure warrants further research of skin cancer risk. *Journal of the American Academy of Dermatology*. 2013;69(6):1069-1070.
40. Dowdy JC and Sayre RM. Photobiological safety evaluation of UV nail lamps. *Photochemistry and Photobiology*. 2013;89(4):1-7.
41. Markova, A. and Weinstock, M. A. Risk of skin cancer associated with the use of UV nail lamp. *J.Invest Dermatol*. 2013;133(4):1097-1099.
42. Diffey BL. The risk of squamous cell carcinoma in women from exposure to UVA lamps used in cosmetic nail treatment. *British Journal of Dermatology*. 2012;167(5):1175-1178.
43. Stern DK, Creasey AA, Quijije J, and Lebwohl MG. UV-A and UV-B penetration of normal human cadaveric fingernail plate. *Archives of Dermatology*. 2011;147(4):439-441.