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

Status: Final Amended Report
Release Date: January 13, 2015
Panel Meeting Date: December 8-9, 2014

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed *p*-hydroxyanisole to address the uses in nail gels reported by industry, which require curing by light. The Panel reviewed the relevant animal and human data related to this ingredient, as well as data on the possible adverse effects of using nail products that require curing by light. The Panel concluded that *p*-hydroxyanisole is safe for use in nail adhesives and in artificial nail coatings, as a polymerization inhibitor, that are cured by LED light. *p*-Hydroxyanisole is unsafe for use in all other cosmetic products because of the potential for dermal depigmentation.

INTRODUCTION

This is an amended safety assessment of *p*-hydroxyanisole. Use in artificial nail coatings and adhesives that requires curing using a light source has been identified by industry as a new use and represents a change from the previous CIR safety assessment of this ingredient.[1] *p*-Hydroxyanisole and hydroquinone are used interchangeably or in combination as polymerization inhibitors in nail gels and adhesive products. Hydroquinone is the focus of a separate amended safety assessment addressing this new use.[2]

p-Hydroxyanisole (CAS No. 150-76-5) is a substituted phenol that is reported to function as an antioxidant, fragrance ingredient, and reducing agent in cosmetics.[3] *p*-Hydroxyanisole is a common name for 4-methoxyphenol.

In 1985, the Panel concluded that *p*-hydroxyanisole is unsafe for use in cosmetics due to dermal depigmentation.[4] The summary of that report is provided below. The use categories in the 1985 safety assessment 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 initial 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.*[4] *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.l% 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^{-2} *M or* 10^{-3} *M* p-*hydroxyanisole in disperse tissue culture. However, whole epidermis (human) exposed in vitro to* 10^{-1} *M for 1, 5, and 24 hours had extensive damage to melanocytes and keratinocytes. Concentrations as low as* 10^{-8} *and* 10^{-9} *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_{50} *of* p-*hydroxyanisole in rats was estimated as 1630 mg/kg. The oral* LD_{50} *in rats of 50%* p-*hydroxyanisole in corn oil was 740 mg/kg. The acute* LD_{50} *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.*

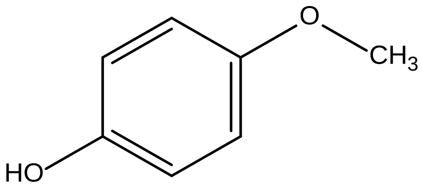
Undiluted p-*hydroxyanisole was a severe skin and ocular irritant in rabbits; a single exposure to the compound produced extensive skin edema and necrosis and cornea1 injury. Minimal irritation was observed in the eyes of rabbits* *exposed to a 0.1% aqueous solution of the antioxidant and on rabbit skin 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

p-Hydroxyanisole (CAS No. 150-76-5) is defined in the *International Cosmetic Ingredient Dictionary and Handbook* as the substituted phenolic compound that conforms to the formula in Figure 1.[3] This aromatic ether is a waxy solid prepared by the reaction of hydroquinone with dimethylether.[4] As noted in the original report, *p*-hydroxyanisole has acidic properties characteristic of phenols. It interacts by hydrogen bonding to other molecules of *p*-hydroxyanisole, 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 ultraviolet (UV) light by *p*-hydroxyanisole occurs at about 340 nm.



p-Hydroxyanisole

Figure 1. *p*-Hydroxyanisole

USE

Cosmetic Use in Nail Products

p-Hydroxyanisole is currently reported to function in cosmetics as an antioxidant, fragrance ingredient, and reducing agent.[5]

Data on ingredient use are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP).[6] In 2014, it was reported by the VCRP that *p*-hydroxyanisole is used in 3 basecoats and undercoats and 2 nail extenders. An industry survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for this ingredient.[7] No uses were reported for *p*-hydroxyanisole to the Council by industry.

An internet search for "*p*-hydroxyanisole" and "cosmetic ingredients" showed that there are more nail gel products available on the market than those reported to either the VCRP or the Council. While a full inventory of the results was not taken, multiple professional and home-kits were available for sale that included nail gels containing *p*-hydroxyanisole requiring UV curing. Because industry is not required to register products with the VCRP, the database represents a sampling of cosmetics that are available on the market.

The *p*-hydroxyanisole content was reported to be 223.2 ppm (0.02232%) for soft nail gels for coloring, 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.[8]

p-Hydroxyanisole, alone or in combination with hydroquinone, serves as a stabilizer or inhibitor that stops the reaction in the liquid component of 2-component methacrylate artificial nail systems.[9] When used as a stabilizer/inhibitor the maximum concentration for 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 2 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.[9]

p-Hydroxyanisole is added to the monomer or oligomer (e.g., dimer, trimer, tetramer) preparations during manufacturing to prevent polymerization.[1] 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. Some *p*-hydroxyanisole is destroyed during polymerization (using light) and any residual inhibitor is enclosed in the hardened polymer. Nail polish gels, containing *p*-hydroxyanisole, alone or in combination with hydroquinone, are cured using nail lamps with either a UVA light source or a LED light source (in the visible light range).[10]

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.[11] 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.

The nail gels and adhesives are removed by the application of a solvent (provided on a presoaked pad) for 15 to 30 min.[12,13]

p-Hydroxyanisole is listed in European Cosmetic Regulations with the following precautions and restrictions: only for use in artificial nail systems, maximum concentration of 0.02% (200 ppm) after mixing, for professional use only, avoid skin contact, and read use directions carefully.[14]

Health Canada[15] has restrictions for the use of p-hydroxyanisole in cosmetics. This ingredient is permitted at concentrations equal to or less than 0.02% (after mixing), for professional use only, in artificial nail systems. Additionally, the inner label and the outer label of the cosmetic shall carry statements to the effect: "For professional use only", "Avoid skin contact", and "Read use directions carefully."

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Dermal/Percutaneous

The permeability coefficient, for skin and receptor fluid, of *p*-hydroxyanisole (35 mg/mL in water; 469 µL/cm^2) was 9.39 x10^{-3} cm/h; the flux at 10 min was 283.0 µg/cm^2/h and at 60 min was 223.0 µg/cm^2/h.[16] The experiment was performed in accordance with the Occupational 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 3 donors and 6 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%; a prescription drug) twice/day for 21 days.[17] The test material was administered to 400 cm^2 of the back. After the last treatment, the subjects received a single topical application of 2% *p*-hydroxyanisole/0.01% (^{3}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_{max} at 2 h for *p*-hydroxyanisole was 9.92 ± 7.48 ng/mL with AUC_{0-12} 33.43 ± 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 (12, 40 mg/kg; 132, 440 mg/m^2, respectively) and tretinoin.[18] The authors stated that this is in the range of the maximum possible human daily dose. The maximum human daily dose is defined as the amount of solution applied daily to 5% of the total body surface area. There were no differences among treatment groups in fetal malformation data. The summary of the study does not provide details on timing, length of study, or the concentration of the low-dose group. In a repeat of this study of this depigmentation cream containing only *p*-hydroxyanisole, the no observed effect level (NOEL) for teratogenicity was 4 mg/kg (0.22 mg/m^2).

In a study of the same depigmentation cream containing both *p*-hydroxyanisole and tretinoin, the cream was not teratogenic in Sprague-Dawley rats (n not provided) when given in topical doses equal to 80 mg/kg (480 mg/m^2) *p*-hydroxyanisole (or 11 times the maximum human daily dose).[18] No further information was provided about this study.

In another study using rats of a depigmentation cream containing *p*-hydroxyanisole (2%) and tretinoin (0.01%), the maternal, neonatal, and developmental no observed adverse effects levels (NOAEL) for *p*-hydroxyanisole were 40 mg/kg/d (0.240 mg/cm^2/d).[19] *p*-Hydroxyanisole (0, 0.6, 2.0, 6.0 mL/kg/d; 0, 0.072, 0.240, 0.720 mg/cm^2/d) was administered dermally to 10% of the body surface of pregnant Crl: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). The F_1 generation was not treated. Dams in the F_1 generation underwent laparotomy on gestation day 20 and the fetuses were evaluated. F_1 rats were necropsied.

There were no deaths in any group. Clinical signs in the F_0 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 decreases in 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 2 each in the control and low dose groups; all but 1 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 F_0 dams.

Clinical signs in the F_1 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 F_1 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 F_1 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 F_1 females and reproductive performance in F_1 animals were unaffected by treatment. Gravid uterine weights and the fetuses were also unaffected.

In F_1 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 1 animal in 1 litter. At the low dose, 1 pup was found to have the renal papilla not fully developed. In F_1 euthanized surplus pups, high dose animals were again noted with the absence of milk in the stomach, and 1 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 1 pup in 1 litter with a hemorrhagic ring around the iris. In F_1 adults, no findings were seen that could be attributed to treatment.[19]

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 ethanol) in a depigmentation cream for 6 months.[20] No further details were provided.

CARCINOGENICITY

p-Hydroxyanisole (2% in feed) was carcinogenic to the forestomach of male and female F344 rats (n=30/sex) when administered for 104 weeks.[21] Histopathological findings included atypical hyperplasias (male, 67%; female, 37%), papillomas (male, 50%; female, 23%) and squamous-cell carcinomas (male, 77%; female, 20%) in the forestomach. The body weights as well as the liver and kidney weights were reduced for both sexes in the treatment group compared to controls.

p-Hydroxyanisole (0, 0.4% in feed) was carcinogenic to F344 rats (n=30-31) when administered for 104 weeks.[22] An increase of forestomach papillary or nodular hyperplasia incidence as compared to the control group was observed. There were no incidences of glandular stomach submucosal hyperplasia or adenoma observed. The final average body weight of the treatment group was lower than the controls. Relative liver and kidney weights were similar between the 2 groups.

In a second study, F344 rats were pretreated with *N*-diethylnitrosamine, *N*-methylnitrosourea, 1,2-dimethylhydrazine, or *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine for 2 to 4 weeks, and then fed a diet containing *p*-hydroxyanisole (0, 0.08%, and 0.4%) for 24 to 26 weeks.[22] There were increased incidences of forestomach papillary or nodular hyperplasia and papilloma in the high-dose group. There were no additive or synergistic effects seen in the groups receiving a combination of chemicals.

In a synergistic test where *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine- (MNNG; 150 mg/kg) was administered to male F344 rats (n=15) in a single dose followed by *p*-hydroxyanisole (0, 0.25%, 0.5%, 1.0%, 2.0% in feed) for 51 weeks, *p*-hydroxyanisole did not increase the incidence of either papillomas or squamous cell carcinomas caused by the prior administration of MNNG.[23] There was no increase in MNNG-initiated forestomach carcinogenesis caused by the *p*-hydroxyanisole. 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

Dermal administration of *p*-hydroxyanisole (0, 0.6, 2.0, 6.0 mL/kg/d) to Crl:CD (SD) Br rats (n=25/sex) for 6 h/d 7 days/week (assumed through entire pregnancy) resulted in extreme irritation at the application site.[19] The dams in the high-dose group were killed within the first week of lactation because of the resulting irritation.

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.[24] The test substance was administered twice daily, 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 1).[25-36] The test materials were administered to a fingernail of the subjects and removed by wiping with a proprietary remover solution after 10 minutes 3 times per week for 9 applications. The nail gels were not dried using a UV nail lamp. Two weeks later, the test material was administered to the same fingernail in the same manner. The amounts of *p*-hydroxyanisole were not provided. The inhibitor in these gels can be hydroquinone or *p*-hydroxyanisole or some combination of these ingredients.

NAIL LAMPS

There have been several studies on the potential effects of using UV and LED nail lamps to dry artificial nail coatings. This is an overview of these studies as well as other information pertaining to using these nail products.

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.[37]

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.[38] 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.[39] The UV bulbs were also reported to emit in the 390-420 nm range.[1]

Estimates of exposure to UV light duration per visit to a professional nail salon 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.[40] Typical client usage is 1-4 times/month for 2 min or less per visit.[39] Another researcher stated that typical salon exposures are 10 minutes or less per hand and with exposures occurring only twice per month.[41]

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.[42]

Typically, 3 or 4 separate thin coats of nail gel are applied and cured for 3 min each coat to achieve the desired results.[37]

In a study of 2 UV nail lamps (for salon use; each from a different nail product company) cumulative exposure measured as minimal erythema doses (MED) were low.[43] However, measured in J/m^2, cumulative exposures were equivalent, in less than 10 min, to the recommended limit of 30 J/m^2 for 8 hours of outdoor work and recreation by the International Commission on Non-Ionizing Radiation Protection. 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 per 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 0.06-0.09 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^2/y from 15 and 22.5 J/m^2 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^2/nm) than the sun (UV Index=6) in the 355-385 nm range. The authors recommended the use of full spectrum sun block to the hands 30 minutes before exposure.[43]

In an evaluation of 6 UV nail lamps, the authors concluded that total exposure following programmed times and steps, analogous to nail polish application, accumulates to only a small fraction of the Recommended Practice (RP)-27 permissible daily occupational exposure of UV.[44] The UV nail lamps, submitted by the Nail Manufacturers Council on Safety (NMC), were representative of major US manufacturers; it was not clear if these were lamps for salon, home use, or a combination. They were 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 3 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 2 base types with tubes oriented either perpendicular or parallel to the fingers of a hand undergoing a procedure. The tubes in the 3- and 4-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 2-lamp unit were in a planar configuration above the fingertips. The other 3 devices were light-emitting diode (LED)-based with arrays of 6 or 32 LEDs or, in the case of a single finger unit, 1 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 4 of their LEDs oriented in 2 lateral pairs positioned on either side. The entrance aperture of the spectroradiometer was positioned to receive the full intensity expected at each of the 3 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 (low risk for 1 LED lamp tested) or 2 (moderate risk for the other 5 lamps) based on S(λ)-weighted (ie, relative spectral effectiveness-weighted, where S(λ) ranged from 0.2-1.7 µW/cm²) effective UV irradiances that yielded permissible daily exposure durations ranging from 29.8-276.25 min. 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 µW/cm² and unweighted near UV (320-400 nm) range was 0.001-0.483 mW/cm². The retinal photochemical blue light hazard and retinal thermal and cornea/lens IR were also exempt. One device using fluorescent bulbs 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.

The authors noted that improper UVB medical phototherapy, broad band full spectrum-type, narrow-band 311 nm phosphor, and 9 W short wavelength UVC germicidal bulbs easily fit into the UV nail lamps. They expressed concern about potential ocular hazard, even at arm's length, from the UVC bulbs. It was also noted that these bulbs were easily obtainable and inexpensive.[44]

In a survey of 17 commercial UV nail lamps in use at 16 different salons, the amount of irradiance was not consistent among these devices and the irradiance was different for the possible hand placements.[45] UVA irradiance ranged from 0.6-15.7 with an average of 10.6 mW/cm^2. UVA energy ranged from 0-8 with an average of 5.1 J/cm^2. It was calculated that it would take an average of 11.8 exposures (visits applying gel nails at a nail salon) to attain the threshold of the amount of irradiance to cause DNA damage (600 KJ/m^2; 60 J/cm^2). Higher wattage sources correlated with higher UVA irradiance emitted in the lamps. The survey was conducted using a UVA/UVB light meter (280-400 nm) in 5 different positions within each lamp to mimic possible hand positions.

When compared to the UV output of tanning bed lamps, UV nail lamps are vastly less hazardous.[41] The results indicate that a person could in their workplace, once every day, put their hand under a UV nail lamp for 25 min 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 3 different UV nail lamps used 10 min/week was estimated to be over 250 years.[46] The UV nail lamps tested were reported to have wave-lengths of 365-370 nm. Three common UV nail lamps were tested, but it was not clear if they were professional or home use units. The first contained 4 9-W UV fluorescent bulbs (36 W total). The second contained a 9-W UV fluorescent bulb (9 W total). The third contained 6 1-W light-emitting diode UV lights (6 W total). The UV nail lamps primarily emitted UVA with no detectable UVB or UVC (lower detection limit of 0.1-0.2 mWm^2). There was a difference in the spectral emission between the UV nail lamps containing fluorescent lamps (1 and 2) and the light-emitting diode lamp (3). The first 2 lamps had peak emission at wavelengths 368 and 370 nm, respectively, whereas the diode lamp had a peak emission at a wavelength of 405 nm.

A concern exists that it is possible to insert an incorrect replacement lamp/bulb into the UV nail lamp (eg, emitting UVB or UVC), which could be harmful to the skin if used.[41] The replacement bulb should be the exact same original manufacturer's UV lamp bulb that was supplied with the UV nail unit when it was purchased. There was also concern that special care should be taken in cases where potential users are taking medications that increase UV sensitivity. People who have been advised against venturing into natural sunlight without proper protection should also be cautious about using UV nail lamps.

Newer nail lamps, introduced in 2012, are manufactured with LED instead of fluorescent bulbs.[10] These bulbs are manufactured so that they emit a narrow range of light, 380-420 nm, encompassing the optimum wavelength for curing nail gels, 405 nm. These bulbs are soldered into place and cannot be easily replaced. Replacement from normal wear and tear should not be necessary since LEDs last for 50k h of use.[47] LED nail lamps are reported to cure nail gels in 30 sec, faster than the 2 min that it takes fluorescent nail lamps.[48]

Risk Analysis

In a risk analysis, it was concluded that 72,709 women would have to use UV nail lamps to cure their nail gels at 8 min/application, every 3 weeks, for 20 years to increase the chance that 1 more individual might develop squamous cell carcinoma on the back of the hand, compared to individuals who were never exposed to UV nail lamps (Table 3).[49] The model UV nail lamp used in this analysis had an unweighted UV irradiance of 115 W m^2 with an erythemally weighted output of 1.58 SED/h. It was not clear if this was for professional or home use. 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.

FINGERNAILS

UVB light did not penetrate the finger nails of a cadaver (n=10).[50] Only an average of 1.65% of UVA light penetrated the nails in this study.

Five women aged 28-59 years (average, 36.4 years) presented with severe pseudoleukonychia as a result of superficial nail plate desquamation and severe onychoschizia lamellina.[51,52] All subjects reported using gel polish and having difficulty in its removal. To remove the gel, their nails were soaked in acetone for 10-15 min and, in some cases, the polish had to be manually peeled off. All subjects noted that their nails became noticeably thinner after the manicure. All 5 manicures were done professionally in a salon but it is not known if the gel was removed at a salon or by the subject. The brand of nail gel or ingredients of the nail gel were not provided.

To evaluate the impact of gel polish on nail thickness, 1 of the authors measured the thickness of a thumb nail before and after receiving a professional UV light cured nail gel manicure at a salon and removing the gel at home with acetone. Measurements were taken using ultrasound and reflectance confocal microscopy (RCM).

Both ultrasound and RCM showed thinning of the nail plate after the removal of the gel manicure. The ultrasound measured an average thickness of 0.063 cm before the manicure and 0.050 cm after removal. The RCM measured a thickness of 588.90 µm (0.059 cm) and 298.57 µm (0.030 cm), respectively. In all subjects, the clinical appearance of the nails improved with time. For the author, pseudoleukonychia resolved in approximately 3 weeks; onychoschizia and subjective brittleness were still present 5 weeks after removal.[51,52]

Case Reports

Non-melanoma skin cancers were observed on the dorsum of the hands of 2 women who reported exposure to UV nail lamps.[53] 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, 2 further squamous cell cancers on the dorsum of both hands were treated. She had had exposure to UV nail lights 8 times within a year several years before the first appearance of the skin cancer.[53]

SUMMARY

The Panel concluded in 1985 that *p*-hydroxyanisole was unsafe as a cosmetic ingredient.

This amended safety assessment of *p*-hydroxyanisole addresses a new use in nail gels and adhesives that requires curing by light. These nail gels and adhesives are marketed as direct sales to consumers and are offered for “at home” use; this constituted the new use. *p*-Hydroxyanisole is used interchangeably and in combination with hydroquinone to control polymerization in nail gels and nail adhesives. *p*-Hydroxyanisole was reported to be used in the liquid component of 2-component artificial nail systems at a maximum concentration of 200 ppm, which decreases to approximately 133 ppm after mixing with the solid component just before application. Polymerization was reported to take 5-15 min in a nail adhesive product.

The VCRP reported that *p*-hydroxyanisole is used in 5 nail products. An industry survey conducted by the Council reported no uses for *p*-hydroxyanisole.

In an in vitro assay, the permeability coefficient for the skin of *p*-hydroxyanisole was 9.39 x 10^{-3} cm/h; the flux at 10 min 283.0 µg/cm^2/h and 223.0 µg/cm^2/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 4 or 40 mg/kg caused no teratological effects in rabbits. The maternal, neonatal, and developmental NOELs for *p*-hydroxyanisole were 40 mg/kg/d (12 µL/cm^2). The same depigmentation cream was not teratogenic in rats when given in topical doses equal to 80 mg/kg (480 mg/m^2) *p*-hydroxyanisole.

In a 2-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 µL/cm^2) in rats. Clinical signs in the F_0 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 F_1 pup survival and a higher rate of missing or cannibalized pups in litters after PND 1 in the 6.0 mL group. F_1 pups in the high-dose group had reduced body weights and an increased incidence of F_1 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 0.4% and 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 gravid rats for 6 h/day 7 days/week (assumed through entire pregnancy), the dams in the high-dose group 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 or *p*-hydroxyanisole or a mixture of both were administered to the fingernails (the exact inhibitor[s] used were not provided).

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 professional UV nail lamps using 2 different measurement methods, the cumulative MED were low. However, in less than 10 minutes, the exposure measured in J/m^2 was equivalent to the day-long recommended limit for outdoor work and recreation.

In tests of multiple types of professional UV nail lamps used as intended, the estimated UV exposure was below levels associated with potential carcinogenicity. The carcinogenic-effective irradiance from 3 common UV nail lamps used 10 min/week was estimated to be over 250 years.

UV bulbs were reported to emit in the 390-420 nm range. In 1 study, the UV nail lamps tested were reported to emit wave-lengths of 365-370 nm. Another study reported 355to 385 nm.

A risk analysis of the use of UV nail lamps concluded that tens of thousands of 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 1 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 2 case reports of squamous cell carcinomas on the dorsum of the hands of 2 women who used UV nail lamps.

It was recommended by multiple researchers that fingerless gloves or full-spectrum sun block be used when UV nail lamps are to be used. It was also recommended that special care should be taken in cases where potential users are taking medications that increase UV sensitivity. People who have been advised against venturing into natural sunlight without proper protection should also be cautious about using UV nail lamps.

A concern exists that it is possible to insert an incorrect replacement lamp/bulb into the UV nail lamp (eg those emitting UVB or UVC).

Newer professional and home-use nail lamps are manufactured with LEDs instead of fluorescent bulbs. These bulbs are manufactured so that they emit a narrow range of light, 380-420 nm, encompassing the optimum wavelength for curing nail gels, 405 nm. These bulbs cannot be easily replaced and are reported to last for 50k h of use. LED nail lamps are reported to cure nail gels in 30 sec, faster than the 2 min that it takes fluorescent nail lamps. LED lights are not associated with skin cancer.

DISCUSSION

In a safety assessment published in 1985, *p*-Hydroxyanisole was found to be unsafe as a cosmetic ingredient due to skin depigmentation at concentrations of 0.25% or greater. That conclusion did not contemplate use in artificial nail coatings that are cured under light.

The Panel noted that there is no dermal exposure to *p*-hydroxyanisole when artificial nail coatings are properly used and that the amount of *p*-hydroxyanisole in the nail gels are well below the concentrations that cause depigmentation. 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 must 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 exposures will not occur.

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 concentrations of *p*-hydroxyanisole were not measured or were not divulged for the series of sensitization studies conducted by applying the nail gel to the fingernails and not to the skin. Although these studies do not demonstrate the dermal sensitization potential of these products as in the usual HRIPT, the lack of observed sensitization when administered to the nail does apparently 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 fluorescent UV light source. The Panel acknowledged that there is controversy about the potential carcinogenicity of UVA light under the conditions of use, indicating that a slightly elevated risk of developing squamous cell carcinoma may exist. The Panel noted that the potential risk of photocarcinogenicity warrants the precaution to use a broad-spectrum sunscreen or photo-protective covering, such as light-impermeable gloves, during the gel-curing process. These lights should only be used in a professional setting and are not safe for home use.

Nail lamps used to cure nail gels, as previously designed, were manufactured using universal light bulb sockets. The UVA bulbs used in nail lamps emit UVA light (390-420 nm), but can be easily replaced with UVB and UVC bulbs. The Panel had several concerns based on the possibility of the incorrect bulb being used upon replacement. First, the Panel discussed the damage that could occur to the eyes; it is possible that, in a home-use setting, an individual could look into the lamp and, if the bulb was replaced with a UVB or UVC bulb, incur eye damage from that light. Additionally, the Panel was concerned that these lamps might be used at the eye level of small children. Also, there was concern that home users may be exposed to additional UV light exposures to the hands if they increase the exposure duration when the nail gel does not set properly because the wrong bulb is used.

The Panel noted that there is substantial research demonstrating the general public's inattention to product warning labels and operating instructions, and discussed the possibility that an improper replacement fluorescent bulb could be inserted into the UV lamp. The Panel noted that curing lamps that use UV light are widely available to consumers. The Panel felt that use of UV lamps in non-professional settings was unsafe and should be discouraged.

Recently, however, safer LED lamps have also become widely available and have largely replaced standard UV lamps in nail gel kits sold to consumers. The bulbs in the LED nail lamps emit a narrow band of light (380-420 nm, encompassing the optimum wavelength for curing nail gels, 405 nm; very little in the UVA range), are very long-lasting (expected to last for 50k h of use), and cannot be replaced by the consumer. The Panel concluded that these lamps will not cause squamous cell carcinoma and are safe to use for curing artificial nail coatings.

The Panel emphasized that it is important for companies to report their ingredient usage to the VCRP program, as well as to respond to the concentration of use surveys conducted by the Council, to facilitate the development of safety assessments that are based on accurate and representative ingredient use information. The Panel noted that the VCRP collects data only on products sold to the general public, not on professional-use-only products.

AMENDED CONCLUSION

The CIR Expert Panel concluded that *p*-hydroxyanisole is safe for use in nail adhesives and in artificial nail coatings, as a polymerization inhibitor, that are cured by LED light; and unsafe for use in all other cosmetics due to dermal depigmentation potential. This conclusion supersedes the earlier conclusion issued by the Expert Panel in 1985, which stated that it was unsafe for use in all cosmetic products.

TABLES

Table 1. HRIPTs (n=50 or 51) of nail products containing *p*-hydroxyanisole and/or hydroquinone administered to the fingernails (not the skin) by trained technicians. The amount of *p*-hydroxyanisole in the products was not provided. All tests resulted in no signs of potential cuticle irritation or allergic contact sensitization.

Product	**Reference**
UV gel top coat nail polish	[30]
UV gel top coat nail polish	[29]
Builder gel	[28]
Clear overlay gel	[27]
Soak-off sealer	[26]
Soak-off gel lacquer	[25]
Gel system-thick gel sealer	[31]
Base gel	[32]
No-cleanse overlay gel	[33]
Soft white sculpting gel	[34]
Pink builder gel	[35]
Luminous white overlay gel	[36]

Table 2. Ultraviolet nail lamp measurements.[43]

Lamp	**Exposure time (min)**	**Total MED/yr**	**Total J/m^2**	**MED/h**	**Total MED/manicure**	**Total J/m^2/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 3. The number of individuals who would need to be exposed to ultraviolet A (UVA) nail lamps[a] for 1 individual to develop squamous cell carcinoma who would not have done so otherwise.[49]

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	-

[a] Assumes a typical level of exposure of 8 min per hand, once every 3 weeks with no sun block agents..

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