Amended Safety Assessment of Hydroquinone as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed hydroquinone to address the new 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 hydroquinone is safe at concentrations ≤1% in cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair. Hydroquinone is safe for use in nail adhesives and as a polymerization inhibitor in artificial nail coatings that are cured by LED (light emitting diode) light. Hydroquinone is unsafe for use in other leave-on cosmetic products.

INTRODUCTION

This is an amended safety assessment of hydroquinone. In 1986, the Panel published a safety assessment of hydroquinone and pyrocatechol with the conclusion that these 2 ingredients were "…safe for use in cosmetics at concentrations up to 1.0% in formulations designed for discontinuous, brief use followed by rinsing from the skin and hair."[1] In 1994, an amended safety assessment of hydroquinone was published with the conclusion "…safe at concentrations of 1.0% or less for aqueous cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair."[2] Hydroquinone should not be used in leave-on nondrug cosmetic products. In 2010, the Panel concluded that hydroquinone was "…safe at concentrations of ≤1% for cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair.[3] Hydroquinone is safe for use in nail adhesives in the practices of use and concentration described in this safety assessment. Hydroquinone should not be used in other leave-on cosmetic products." The summaries of these reports are provided below. Since these safety assessments, a new use in nail gels and adhesives that require curing with light has been identified, and therefore the safety of this use was evaluated. New data pertinent to this new use in nail products as well as new toxicity data that have become available since the last review of this ingredient are presented in this safety assessment.

This assessment was initiated in response to a request from industry to review both hydroquinone and *p*-hydroxyanisole, which are used interchangeably or in combination as polymerization inhibitors in nail gels.[4] *p*-Hydroxyanisole is the focus of a separate amended safety assessment addressing this additional use in nail products.[5]

SUMMARIES OF HYDROQUINONE SAFETY ASSESSMENTS

1986

[Note: References to data exclusively on pyrocatechol in this summary have been removed.]

Hydroquinone and pyrocatechol are two benzenediol isomers, 1,4-benzenediol and 1,2-benzenediol.[1] Both ingredients are used in cosmetics as couplers in oxidative hair dyes at concentrations of less than 1.0%. Hydroquinone, a known skin-depigmenting agent, is also used in cleansing preparations at concentrations between 1% and 5%.

Both Hydroquinone and pyrocatechol inhibit bacterial growth.

Both compounds are absorbed from the gastrointestinal tract. Small amounts of nonmetabolized hydroquinone are excreted in the urine of rabbits; however, most of the compound is excreted as hydroquinone ethereal monosulfate and as the monoglucuronide.

The results of acute oral studies in animals indicate that hydroquinone is practically nontoxic to moderately toxic; the data from subchronic feeding studies of hydroquinone indicated that it was not toxic at 1%, slightly toxic at 2%, and toxic at 5%.

No adverse local systemic effects were produced in rabbits when 2.0% hydroquinone was applied to intact and abraded skin (3.9 - 9.4 mL/kg). The results of subchronic and chronic dermal studies of hydroquinone in animals for time intervals up to 6 months indicated that the ingredient was a weak depigmenter at 1.0%. Other animal studies indicated that the time required for depigmentation was dependent upon both the concentration and the dispersion medium used. When 2.0% hydroquinone was tested in rabbits using a single-insult patch test, a [primary irritation index] *PII of 1.22 (scale 0 - 4) was reported. Guinea pigs were sensitized to hydroquinone when injected at concentrations above 2.0%. The severity of the sensitivity reaction induced by 10% hydroquinone was not increased when exposed to UVA light.*

In a rabbit eye irritation test, an undiluted product formulation containing 2.0% hydroquinone produced mild conjunctivitis in 3 of 6 animals evaluated at 24 h. The conjunctivitis had subsided on the second day.

When hydroquinone (0.003% - 0.3%) was included in the diet of two groups of 10 pregnant female rats, no differences were found between the test and control groups relative to gestation length, mean litter size, viability, and lactation index. In a second study 0.5 g [total dose] *of hydroquinone included in the diets of a group of 10 mated female rats produced no significant difference in resorptions when compared to control groups. Hydroquinone was evaluated in a teratology study in which daily dermal exposure of pregnant rats (20 animals/group) was up to 810 mg/kg; no remarkable difference was found between the control and test groups.*

The results of mutagenesis assays of hydroquinone have varied with the assay system used. In four Salmonella typhimurium *strains, both with and without activation, the mutagenesis assay was negative. One strain tested was positive, with activation using one medium, but not with a second medium. Hydroquinone did not increase antibiotic resistance in* Staphylococcus aureus. *Hydroquinone was mutagenic in the* Escherichia coli *DNA polymerase and* Saccharomyces

cerevisiae *mitotic recombination assays. Hydroquinone produced positive results both with and without activation in the HeLa DNA synthesis test but was not considered mutagenic in assays using Chinese hamster cells. Hydroquinone induced Sister Chromatid Exchanges (SCE) and delayed cell turnover time in human lymphocyte studies. Oral doses of hydroquinone did not inhibit testicular DNA synthesis in male mice and was nonmutagenic in the mouse sperm-head abnormality test. Hydroquinone is considered a mitotic poison.*

In multigeneration rat studies of topically applied hair dyes containing 0.2[%], *hydroquinone, no effect on reproduction was observed and embryotoxicity and teratogenesis were not produced. The F_{1A} animals were used for carcinogenic assay of the hair dyes. The results were negative. Hydroquinone, when applied topically, was neither a tumor promoter nor a cocarcinogen in Swiss mice. Harding-Passey melanoma transplants were decreased when hydroquinone was administered after implantation.*

Hydroquinone studies in humans at doses of 500 mg and 300 mg to males and females, respectively, for 5 months produced no signs of toxicity.

Positive sensitization reactions to hydroquinone were reported in 8.9% of 536 dermatologic patients challenged with a 5.0% solution. At higher concentrations (10% and 30%) dermatitis was produced in 2 of 5 black subjects. A cosmetic formulation containing 2% hydroquinone produced one or more mild irritation reactions in 69 of 90 subjects in the induction phase of a sensitization test. In this latter study, 22 subjects had a mild reaction when challenged by the same formulation and scored at 24 h. Only 3 of the 22 subjects had either mild or barely perceptible reactions at 48 h. The use of ointments containing 2, 3, and 5% hydroquinone in 94 white and 43 black men with normal skin produced at least minimal depigmentation in white but not black subjects. Two of 38 patients treated with an ointment containing 5.4% hydroquinone became sensitized. Other studies on dark-skinned subjects have confirmed these sensitization results.

Ocular lesions but no other systemic effects have been found in workers involved in the manufacture of hydroquinone. Recommended limits for occupational exposure of hydroquinone have been set 2 [mg/m^3].

1994

This addendum to the final report on hydroquinone was prepared in response to the release of a National Toxicology Program (NTP; 1989)[6] report of an oral carcinogenicity study.[2] In the original CIR report, it was concluded that hydroquinone was safe for cosmetic use at ~1% in formulations designed for discontinuous, brief use followed by rinsing from skin and hair. This conclusion applied primarily to the use of hydroquinone in hair dye formulations. The use of hydroquinone to lighten the skin was not addressed because such use is regarded by the Food and Drug Administration (FDA) as a drug use.

In 1993, hydroquinone was reported to be used in 206 formulations, 185 hair dyes, two lipsticks, one skin freshener, and 18 other skin care preparations.

Hydroquinone in an alcoholic vehicle was absorbed through the skin of the forehead of male subjects; absorption of hydroquinone from a solution that also contained Escalol 507 (a sunscreen) and Azone (a penetration enhancer) was 35 ± 17%, from a solution containing Azone was 66 ± 13%, from a solution containing Escalol 507 was 26 ± 14%, and from a solution containing only hydroquinone was 57 ± 11%. The average percutaneous absorption rate of hydroquinone using 48-h excretion data from dermal and i.v. absorption studies using dogs was estimated to be ~0.15 nmol/cm^2/min (1.1 kg/cm^2/h). Hydroquinone was rapidly absorbed and excreted by male and female Fischer rats following oral administration; overall recovery was ≥ 96% from females after 24 h and from males after 48 h. In a study using urinary excretion data, dermal absorption was estimated to be 10.5% for male rats using 72-h data and 11.5% for female rats using cumulative 48-h data.

Hydroquinone was found to have some immunologic effects; it especially had effects on bone marrow. In a functional-observation battery (FOB), hydroquinone was not found to cause central or peripheral nervous system lesions. Hydroquinone was nephrotoxic in male F344 rats. Hydroquinone also showed cytotoxic properties.

According to the terminology of Hodge and Sterner (1949)[7], hydroquinone is slightly toxic, with an oral LD_{50} of 743 and 627 mg/kg for male and female rats, respectively.

Administration of hydroquinone to rats in drinking water (2,500 - 10,000 ppm) for 8 weeks resulted in significant increases in liver and kidney weights. Hydroquinone administered orally to rats (63 - l000 mg/kg) and mice (3l - 500 mg/kg) for 14 days resulted in tremors and deaths in the high-dose groups. Dermal administration to rats (240-3840 mg/kg) and mice (300 - 4800 mg/kg) for 14 days caused neither death nor any significant adverse effects. For mice given i.p. injections of 10 mg/kg hydroquinone for 6 weeks, it was concluded that hydroquinone may cause hematologic injury.

Rats given 1000 - 4000 ppm hydroquinone in drinking water for 15 weeks had significantly increased liver and kidney weights. Oral administration of 25–400 mg/kg hydroquinone to rats and mice for 13 weeks resulted in mortality in the high-dose groups for both rats and mice. Other adverse signs, such as lethargy, tremors, and changes in relative liver to body weight ratios, were observed.

Dermal application of 25 or 150 mg/kg hydroquinone to rats produced slight to severe erythema.

In a Magnusson-Kligman guinea pig maximization test, hydroquinone was classified as an extreme sensitizer. Hydroquinone was positive for sensitization in an LLNA.

Oral administration of hydroquinone did not produce embryotoxic, fetotoxic, or teratogenic effects in rats, nor did it produce significant adverse reproductive effects in a two-generation study. Using rabbits, various teratogenic/reproductive treatment-related effects were observed at doses of 200-500 mg/kg. All dams dosed with 300 to 500 mg/kg hydroquinone died. Some maternal toxicity was observed at a number of dose concentrations.

Hydroquinone induced SCEs, chromosomal aberrations, and mitotic division aberrations increased the frequency of mitotic crossovers, caused c-mitotic effects, and induced chromosome loss. It was clastogenic for male mouse germ cells and for mouse bone marrow cells. Hydroquinone induced DNA strand breaks and inhibited DNA, nuclear DNA, and mtDNA synthesis in rabbit bone marrow mitochondria. It also inhibited mtDNA transcription synthesis and RNA synthesis. Hydroquinone caused the formation of hydrogen peroxide and 8-hydroxydeoxyguanosine (8-OHdG) in calf thymus DNA and produced DNA adducts in HL-60 and other cells. Forward mutation assays with and without metabolic activation were positive, as were numerous micronucleus assays. Results of the Ames test and a mouse spot test for somatic gene mutations were negative.

In an NTP study, hydroquinone was given to rats orally by gavage five times per week for up to 103 weeks at doses of 25 or 50 mg/kg. The higher dose induced a significant incidence of renal adenomas in males and both doses caused a significant increase in the incidence of mononuclear cell leukemia in females. Mice were dosed with 50 or 100 mg/kg hydroquinone following the same schedule as that used for the rats. The incidence of hepatocellular adenoma was significantly increased in female mice.

NTP concluded that Hydroquinone produced "some evidence of carcinogenic activity" for male and female F344/N rats and female B6C3F, mice but "no evidence of carcinogenic activity" for male B6C3F, mice in an oral carcinogenicity study.

Shibata et al. (1991)[8] conducted a study in which rats and mice were fed diet containing 0.8% hydroquinone for 104 and 96 weeks, respectively, and concluded that "the study strongly suggested that since hydroquinone has apparent carcinogenic potential for rodents, there is a possibility that it may play a role in human cancer development." Hydroquinone did not induce a significant number of neoplasms in either the glandular or nonglandular stomach of hamsters fed 0.5% hydroquinone in the diet for 20 weeks or rats fed 0.8% hydroquinone in the diet for 51, 49, or 8 weeks.

When hydroquinone was fed to rats after pretreatment with methyl-N-amylnitrosamine (MNAN), hydroquinone was marginally effective in enhancing esophageal carcinogenesis and had marginal activity in the promotion of upper digestive tract carcinogenesis. Other studies did not prove hydroquinone to be a tumor promoter.

No reaction to hydroquinone was observed when patients positive to at least one hapten of the para group of the International Contact Dermatitis Research Group (ICDRG) standard series were tested using the Al test. Hydroquinone contact has caused dermatitis and hydroquinone exposure can result in ocular effects. Hydroquinone has caused hypomelanosis hyperpigmentation of the skin and depigmentation of black skin. Ingestion of 1 g hydroquinone by humans can produce severe toxicity; ingestion of 5-10 g can be fatal.

2010

Hydroquinone is reportedly used in hair dye preparations, skin care products, nail products, and as recently as 2007 in lipstick.[3] Information provided to the FDA through the Voluntary Cosmetic Registration Program (VCRP) indicates that the use of hydroquinone has decreased from 206 uses in 1993 to 151 uses in 2007 to 32 reported uses in 2009. Hydroquinone is a component of artificial nail products because it is added to all types of acrylic monomers to prevent the polymerization of these materials. Upon polymerization of the acrylic monomers, hydroquinone is oxidized and is no longer detectable in the final polymer using analytical techniques for identifying trace amounts in a solid matrix. Any residual hydroquinone is trapped in the polymer and is therefore unavailable and not likely to be absorbed.

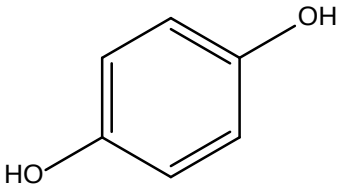
While an earlier in vitro study suggested that hydroquinone would be considered a ''slow permeant,'' a more recent in vivo study demonstrated that hydroquinone is in fact rapidly absorbed through the skin from an aqueous preparation. Hydroquinone is metabolized to the sulfate and glucuronide conjugates, with oxidation to 1,4-benzoquinone, resulting in a reactive metabolite that forms mono- or polyglutathione conjugates. The glutathione conjugates are believed to be responsible for the nephrotoxicity observed in rats. In addition to nephrotoxicity, hydroquinone has some immunotoxic effects and has been positive in many mammalian cell assays in vitro and in vivo including micronuclei formation, SCE, and chromosomal aberrations despite being mostly negative in in vitro bacterial mutagenicity assays. The induction of renal cell tubule tumors in male F344 rats has raised concern regarding the nephrocarcinogenicity of hydroquinone and has led to several mechanistic studies which suggest that the male F344 rat is more susceptible to the glutathione conjugates of hydroquinone due to the spontaneous occurrence of chronic progressive nephropathy (CPN) which nearly all rats develop as they age. There is no human disease that shares all of the features of rodent CPN, however, there are histopathological similarities between human chronic renal disease and CPN that do not allow the proposed mode of action (MOA) to be ruled out entirely on a qualitative basis. Quantitatively, the use of hydroquinone containing hair dyes or nail adhesives is unlikely to result in renal neoplasia through this MOA.

Hydroquinone has been reported to cause exogenous ochronosis in several ethnic populations following prolonged use (>6 months) of at least a 1% to 2% cream. These effects along with the NTP cancer study findings have led the FDA to reconsider the generally recognized as safe and effective (GRASE) label for hydroquinone in leave-on drug products. The most recent comprehensive review of available epidemiology studies concluded that there is insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers. A summary of the available hair dye epidemiology data is available at [http://www.cir-safety.org/cir-findings].

CHEMISTRY

Definition and Structure

Hydroquinone (CAS No, 123-31-9) is defined in the *International Cosmetic Ingredient Dictionary and Handbook* as the aromatic organic compound that conforms to the formula in Figure 1.[9] It is currently reported to function in cosmetics as an antioxidant, fragrance ingredient, hair colorant, reducing agent, and skin bleaching agent. Hydroquinone is a common name for 1,4-dihydroxybenzene.



Hydroquinone

Figure 1. Hydroquinone.

Hydroquinone is a substituted phenol (Figure 1). This aromatic diol is a white to off-white crystalline material. As noted in the year 2010 report on this ingredient, hydroquinone is most commonly produced through hydroperoxidation of *p*-diisopropylbenzene, hydroxylation of phenol, or oxidation of aniline.[3]

USE

Cosmetic

Hydroquinone, alone or in combination with *p*-hydroxyanisole, is used as a stabilizer that inhibits the polymerization in the liquid component of 2-component methacrylate artificial nail systems.[10] The maximum concentration of hydroquinone alone, or in combination with *p*-hydroxyanisole, is reported to be 200 ppm (0.02%). After mixing 2 parts liquid to 1 part powder in preparation for use, the final concentration of hydroquinone, or hydroquinone and *p*-hydroxyanisole combined is 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.[10]

Hydroquinone is added to the monomer and oligomer (ie, dimer, trimer, tetramer) preparations during manufacturing to prevent polymerization.[4] 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 hydroquinone is destroyed during polymerization (using light) and any residual inhibitor is enclosed in the hardened polymer. Nail polish gels, containing hydroquinone, alone or in combination with *p*-hydroxyanisole, are cured using nail lamps with either an unltraviolet A (UVA) light source or a LED light source (in the visible light range).[11]

A nail polish gel had reduced amounts of hydroquinone after curing (Table 1).[12]

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.[13] If the cuticles are not cleared away from the nail bed, 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 direct sales to consumers of these products, which contain hydroquinone and/or *p*-hydroxyanisole, are being offered for "at home" use.[4] The direct sale to consumers of such products, which contain 1 or both of these stabilizers, constitutes the new use considered in this safety assessment.

The nail gels and adhesives are removed by the application of a solvent (that is provided on a presoaked pad) for 15-30 min.[14,15]

Data on ingredient use are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP).[16] The VCRP reports that hydroquinone is used in 1 nail extender, 7 hair dyes and colors, and 10 skin care preparations. There were no other reported uses for other nail products.

A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations of hydroquinone.[17] No uses were reported by industry to the Council for this ingredient.

An internet search for “hydroquinone” and “cosmetic ingredients” showed that there are more nail gel products available on the market than reported to either the VCRP or the Council. While a full inventory of the results were not taken, there were multiple professional and home kits available for sale that contained nail gels that contain hydroquinone and require light curing. Industry is not required to register products with the VCRP; the data in the database are a sampling of

what cosmetics are available on the market and are not comprehensive.

Hydroquinone is listed in Annex III of the European Council Directive with the following restrictions: only for use in artificial nail systems, maximum concentration of 0.02% (200 ppm) after mixing, for professional use only, avoid skin contact, read use directions carefully.[18] Hydroquinone is also listed under Annex II and may not be used in cosmetic products with the exception of the use listed in Annex III.[19]

Health Canada[20] has the following rules for the use of hydroquinone in cosmetics:

- Restricted to hair dye products, nail products, and cyanoacrylate-based adhesives
- Permitted at concentrations equal to or less than 0.3% as an oxidizing coloring agent for hair dyes. The inner and outer labels of hair dye products containing hydroquinone must carry a cautionary statement, in English and French, to the effect: "Contains hydroquinone."; "Do not use to dye eyelashes or eyebrows."; "Rinse eyes immediately if the product comes into contact with eyes."
- Permitted at concentrations equal to or less than 0.02% in 2-component (acrylic) artificial nail systems (after mixing for use). The inner and outer labels of nail products containing hydroquinone must carry a cautionary statement, in English and French, to the effect: "Avoid skin contact."; "Read directions carefully before using."
- Permitted at concentrations equal to or less than 0.1% in cyanoacrylate adhesive products. The inner and outer labels of cyanoacrylate adhesive products containing hydroquinone must carry a cautionary statement, in English and French, to the effect: "Avoid skin contact."; "Read directions carefully before using."

Non-Cosmetic

The re-evaluation of hydroquinone's Generally Recognized as Safe and Effective (GRASE) label for leave-on drug products by the FDA, noted in the 2010 summary above, has not been completed.[21,22]

TOXICOLOGICAL STUDIES

Repeated Dose Toxicity

Dermal – Non-Human

Hydroquinone (2% in a topical cream) caused liver and kidney damage when administered to rabbits (n=6) for 6 weeks.[23] The test substance was administered daily to 1 or both ears (volume not specified) of the rabbits or to the shaved abdomen (2 g/cm^2); the rabbits were killed and necropsied. Findings in the liver included hydropic degeneration, bile duct hyperplasia, and glycogen depletion. Hydropic degeneration, hyaline casts, congestion, perivascular edema, and fibrosis were observed in the kidneys. For both the kidneys and livers, the effects were greater in the groups in which the test substance was administered to the ears. Dermal effects included hyperkeratosis, lymphocytic and eosinophilic infiltration, and congestion of dermal blood vessels.

Dermal depigmentation was observed when hydroquinone (5% in 25 µL propylene glycol/ethanol, 50:50) was dermally administered to multiple sites of the backs of Yucatan miniature pigs (n=2) twice/day, 7 days/week for 90 days.[24] Microscopic examination of biopsies from the test area showed decreased pigment and melanocytes.

Cytotoxicity

Hydroquinone (0, 10, 20, 30, 40 µM) was not cytotoxic to human L-02 liver cells but was cytotoxic to the same cell line with silenced DNA polymerase eta (Polη) after 24 h of incubation.[25] Cell survival was determined using the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay.

Hydroquinone (500, 750 µM) was cytotoxic, in a concentration-dependent manner, to F344 rat hepatocytes when incubated for 2 h.[26]

Hydroquinone was cytotoxic to human lymphocytes at 270 µM, but not at 180 µM, when incubated for 3, 24, or 48 h with metabolic activation and 3 h without metabolic activation.[27]

GENOTOXICITY

In Vitro

Hydroquinone (0, 10, 20, 30, 40 µM) did not induce DNA damage to human L-02 liver cells but was genotoxic to the same cell line with silenced DNA Polη after 24 h of incubation.[28] DNA damage was determined by means of the Comet assay, apoptosis and cell cycle distribution were determined using flow cytometry, the mRNA expression levels of Polη were determined by real-time PCR, the protein expression levels of Polη and γ-H2AX were determined by Western blot, and γ-H2AX foci were visualized by confocal laser scanning fluorescence microscopy after cells were exposed to hydroquinone. The down-regulation of Polη led to a decrease in cell proliferation and an enhanced susceptibility to hydroquinone-induced cytotoxicity. Polη-deficient cells were 2-fold more sensitive to hydroquinone when compared with nonspecific siRNA control cells. Also, treated Polη-silenced L-02 cells displayed increased levels of DNA double-strand breaks as measured by olive tail moment, and an elevated DNA damage response, as indicated by the induction of γ-H2AX. In addition, knockdown of Polη resulted in more enhanced apoptosis and more pronounced S phase arrest following hydroquinone treatment. The authors concluded that Polη plays an important role in the response of L-02 cells to hydroquinone-induced DNA damage.

Hydroquinone (45-900 µM; 50 µL) was not clastogenic in cultured human lymphocytes with or without metabolic activation.[27] The lymphocytes were treated in accordance with the Organization for Economic Co-Operation and

Development (OECD), European Economic Community (EEC), and the Environmental Protection Agency (EPA) guidelines for mutagenicity testing. In an additional experiment, the lymphocytes were incubated with hydroquinone (18-73 μM) for 17 h prior to the addition of hydrogen peroxide (12 mM). Pre-incubation with hydroquinone reduced the number of chromosomal aberrations compared to negative controls.

IRRITATION AND SENSITIZATION

Dermal – Non-Human

In a local lymph node assay (LLNA; n = 5) repeated in 4 different laboratories, hydroquinone (0, 0.10%, 0.25%, 0.50%, 1.00%, 2.50% in acetone:olive oil 4:1; 25μL; > 99.5% pure) was predicted to be a dose-dependent sensitizer.[29] The EC_3 values were 0.07%, 0.03%, 0.08%, and 0.07% for the 4 laboratories.

When hydroquinone (5% in 25μL propylene glycol/ethanol, 50:50) was dermally administered to multiple sites of the backs of Yucatan miniature pigs (n = 2), the test sites exhibited severe erythema, scaling and crusting.[24] Microscopic examination of biopsies of the test area showed reduction in pigment and number of melanocytes. The test substance was administered twice/day, 7 days/week for 90 days.

Dermal – Human

In multiple human repeated insult patch tests (HRIPT) of nail gel products, there were no signs of potential cuticle irritation or allergic contact sensitization (Table 2).[30-41] 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 hydroquinone 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.[42]

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.[43] 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.[44] The UV bulbs were also reported to emit in the 390-420 nm range.[4]

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.[45] Typical client usage is 1–4 times/month for 2 min or less per visit.[44] Another researcher stated that typical salon exposures are 10 minutes or less per hand and with exposures occurring only twice per month.[46]

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.[47]

Typically, 3 or 4 separate thin coats of nail gel are applied and cured for 3 min each coat to achieve the desired results.[42]

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.[48] 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 3).

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 ($\mu W/cm^2/nm$) 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.[48]

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.[49] 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.[49]

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.[50] 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.[46] 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.[51] 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.[46] 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.[11] 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.[52] LED nail lamps are reported to cure nail gels in 30 sec, faster than the 2 min that it takes fluorescent nail lamps.[53]

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 4).[54] The model UV nail lamp used in this analysis had 2 9-W fluorescent bulbs producing an unweighted UV irradiance of 115 W m^2

with an erythemically 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 0 by wearing fingerless gloves when the hands are being exposed to UV radiation from such lamps.

FINGER NAILS

UVB light did not penetrate the finger nails of a cadaver (n=10).[55] An average of 1.65% of UVA light penetrated the nails in this study. A Dermalite UV light was used.

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.[56,57] 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; 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.[56,57]

CASE REPORTS

Non-melanoma skin cancers were observed on the dorsum of the hands of 2 women who reported exposure to UV nail lamps.[42] 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.[42]

SUMMARY

In 1986, the Panel published a safety assessment of hydroquinone and pyrochatechol with the conclusion that these 2 ingredients were "…safe for use in cosmetics at concentrations up to 1.0% in formulations designed for discontinuous, brief use followed by rinsing, from the skin and hair." In 1994, an amended safety assessment of hydroquinone was published with the conclusion "…safe at concentrations of 1.0% or less for aqueous cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair. Hydroquinone should not be used in leave-on, non-drug cosmetic products." The CIR Expert Panel concluded in 2010 that hydroquinone is safe for use in nail adhesives and in rinse-off products up to 1.0% but is not safe for use in other leave-on cosmetic products.

This amended safety assessment of hydroquinone addresses a new use in nail gels and adhesives that requires curing by light. These nail gels and adhesives are marketed as direct sales and are offered for "at home" use. The direct sales to consumers of such products constitute the new use.

Hydroquinone is used interchangeably and in combination with *p*-hydroxyanisole to control polymerization in nail gels and nail adhesives. Hydroquinone 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 reports that hydroquinone is used in 1 nail extenders, 7 hair dyes and colors, and 10 skin care preparations. There were no reported uses for this ingredient in an industry survey conducted by the Council.

Six weeks of dermal administration of hydroquinone at 2% in a topical cream caused liver and kidney damage in rabbits.

Hydroquinone was not cytotoxic to human liver cells up to 40 μM but was cytotoxic to rat hepatocytes at 500 and 750 μM. It was cytotoxic to human lymphocytes at 270 μM but not at 180 μM.

Hydroquinone up to 40 μM did not induce DNA damage in human liver cells but was genotoxic in the same cell line with silenced DNA polymerase eta (Pol-η). Hydroquinone up to 900 μM was not clastogenic in cultured human lymphocytes with or without metabolic activation.

Hydroquinone at 5% caused severe erythema, scaling and crusting in miniature pigs.

Hydroquinone at 0.10% to 2.50% was predicted to be a sensitizer in a multi-laboratory LLNA. The EC_3 values were 0.07%, 0.03%, 0.08%, and 0.07% for the 4 laboratories.

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, and to dry traditional nail polish and UV top sealers/topcoats. UV bulbs were also 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 wave-length emissions of 355-385 nm. UVB light did not penetrate finger nails; very little UVA light penetrated fingernails.

In a study of UV exposure from different professional UV nail lamps using 2 different measurement methods, the cumulative MEDs 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. 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.

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

Hydroquinone caused depigmentation to the skin at concentrations greater than 1%. The Panel found hydroquinone was safe at that concentration or less for discontinuous, brief use in rinse-off products and was safe for use in nail adhesives in 2010. This prior conclusion did not consider the new use in artificial nail gel coatings that are cured under light.

The Panel noted that there is little-to-no dermal exposure to hydroquinone when artificial nail coatings are used according to label instructions, and that the amounts of hydroquinone in the nail gels are well below the concentrations that cause depigmentation. Any accidental application to the surrounding skin should be promptly removed for best visual results and adherence, as well as to minimize dermal exposure. Therefore, the risk of skin depigmentation would be minimal during momentary exposure. The Panel stressed, however, 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 hydroquinone is either consumed during the curing or trapped within the polymerized matrix.

Since these products are now available to the consumer as “home kits,” the Panel considered the greater likelihood of accidental skin and nail bed exposure with application by consumers compared to experienced salon personnel. The Panel emphasized that directions should be carefully followed by both professionals and home users of nail gels.

The concentration of hydroquinone was not indicated in 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 demonstrate how unlikely it appears to be 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 might

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 documenting the general public's inattention to product warning labels and operating instructions, and discussed the possibility that an improper fluorescent replacement 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 become widely available and have largely replaced 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 noted correspondence indicating that the number of uses of this ingredient is greater than the number reported by the VCRP. All of the products listed as cosmetics in the correspondence appear to be skin bleaching drug products and consequently, are considered to be drugs and not cosmetics. Thus, those products in the correspondence are not under the purview of CIR, but of FDA. 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 hydroquinone is safe at concentrations of ≤ 1% for cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair. Hydroquinone is safe for use in nail adhesives and in artificial nail coatings, as a polymerization inhibitor, that are cured by LED light. Hydroquinone is unsafe for use in other leave-on cosmetic products. This conclusion supersedes the earlier conclusion issued by the Expert Panel in 2010.

TABLES

Table 1. Detection of hydroquinone in nail polish after various curing times.[58]

Description	Hydroquinone 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 2. HRIPTs (n=50 or 51) of nail products containing hydroquinone and/or *p*-hydroxyanisole administered to the fingernails (not the skin) by trained technicians. The amount of hydroquinone and/or *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	[35]
UV gel top coat nail polish	[34]
Builder gel	[33]
Clear overlay gel	[32]
Soak-off sealer	[31]
Soak-off gel lacquer	[30]
Gel system-thick gel sealer	[36]
Base gel	[37]
No-cleanse overlay gel	[38]
Soft white sculpting gel	[39]
Pink builder gel	[40]
Luminous white overlay gel	[41]

Table 3. Ultraviolet nail lamp measurements.[48]

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 4. The number of individuals who would need to be exposed to ultraviolet A (UVA) nail lamps[a] (2 9-W fluorescent bulbs producing an unweighted UV irradiance of 115 W m^2) for 1 individual to develop squamous cell carcinoma who would not have done so otherwise.[54]

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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