Amended Safety Assessment of Hydroquinone as Used in Cosmetics

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comment on this Tentative Amended Report and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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

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

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INTRODUCTION

This is an amended safety assessment of hydroquinone. A new use in nail gels and adhesives that require UV curing has been identified and new data are being considered to evaluate the safety of this use. 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 sold separately to consumers for home use. *p*-Hydroxyanisole is the focus of a separate amended safety assessment addressing this new use.

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

In 1986, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a safety assessment of hydroquinone and pyrocatechol with the conclusion that these two 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."[2] 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."[3] Hydroquinone was not safe for use in leave-on, non-drug 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.[4] 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.

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 last review of this ingredient.

Summaries of Hydroquinone Safety Assessments

1986

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

Hydroquinone and pyrocatechol are two benzenediol isomers, 1,4-benzenediol and 1,2-benzenediol. 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 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)[5] report of an oral carcinogenicity study. 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)[6], 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 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)[7] 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. 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.

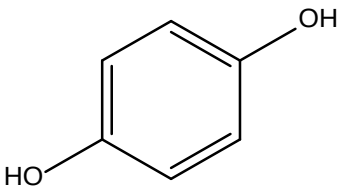
Hydroquinone has been reported to cause exogenous ochronosis in several ethnic populations following prolonged use (>6 months) of at least a 1% to 2% cream. These effects along with the NTP cancer study findings have led the FDA to reconsider the generally recognized as safe and effective (GRASE) label 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/findings.shtml.

CHEMISTRY

Definition and Structure

Hydroxyquinone is a substituted phenol (Figure 1).



Hydroquinone

Figure 1. Hydroquinone.

USE

Cosmetic

Data on ingredient use are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP).[8] The VCRP reports that hydroquinone is used in 1 nail extender, 7 hair dyes and colors, and 10 skin care preparations. There were no reported uses for other nail products. Industry is not required to register products with the VCRP. It is understood that the data in the database are a sampling of what cosmetics are available on the market and are not comprehensive. Similar results were reported by a survey by the Environmental Working Group.[9]

A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for these ingredients.[10] There were no reported uses for this ingredient.

A web search for hydroquinone and cosmetic ingredients showed that there are more nail gel products available on the market than what was 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 UV curing.

Hydroquinone is listed in Annex III of the European Council Directive with the following restrictions: only for use in artificial nail system, maximum concentration of 200 ppm after mixing, for professional use only, avoid skin contact, read use directions carefully.[11] 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.[12]

Health Canada[13] 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 two-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."

Use In Nail Products

Hydroquinone, alone or in combination with *p*-hydroxyanisole, is used as a stabilizer that inhibits the polymerization in the liquid component of two-component methacrylate artificial nail systems.[11] 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 two components are mixed into a ‘slurry bead’, which is applied to the

center of the nail plate and then shaped. The polymerization is complete in 5 - 15 min. Contact is to the keratin of the nail plate and not to the skin or cuticle.[11]

Hydroquinone is added to the monomer and oligomer (i.e., dimer, trimer, tetramer) preparations during manufacturing to prevent polymerization.[14] This preserves the integrity of the monomers or oligomers until they are used to produce polymers or other derivatives. For polymerization to occur, the inhibitors must either be destroyed or inactivated. Hydroquinone (and *p*-hydroxyanisole) is destroyed during polymerization (using light) and any residual inhibitor is enclosed in the hardened polymer.[Dr. David Steinberg, pers. comm.]

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.[15] 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.[Dr. David Steinberg, pers. comm.]

The direct sales to consumers of these products, which contain hydroquinone and/or *p*-hydroxyanisole are being offered for "at home" use. The direct sale to consumers of such products, which contain one or both of these stabilizers, constitutes the new use considered in this safety assessment.[14]

The nail gels and adhesives are removed by the application of a solvent (that is provided on a presoaked pad) for 15 to 30 min.[16,17]

Non-Cosmetic

The re-evaluation of hydroquinone's GRASE label in leave-on drug products by the FDA, noted in the 2010 summary above, has not been completed.[18]

TOXICOKINETICS

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.[19] Cell survival was determined using the MTT assay.

Hydroquinone (500, 750 µM) was cytotoxic, in a concentration-dependent manner, to F344 rat hepatocytes when incubated for 2 h.[20]

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.[21]

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.[22] The test substance was administered daily to one or both ears of the rabbits or to the shaved abdomen; 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 propylene glycol/ethanol, 50:50) or *p*-hydroxyanisole (5% in 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.[23] Microscopic examination of biopsies from the test area showed decreased pigment and melanocytes.

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.[24] 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.[21] 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. 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 four different laboratories, hydroquinone (0, 0.10%, 0.25%, 0.50%, 1.00%, 2.50% in acetone:olive oil 4:1; > 99.5% pure) was predicted to be a dose-dependent sensitizer.[25] The EC_3 values were 0.07%, 0.03%, 0.08%, and 0.07% for the four laboratories.

When hydroquinone (5% in 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.[23] The test substance was administered twice/day, 7 days/week for 90 days. Microscopic examination of biopsies of the test area showed reduction in pigment and number of melanocytes.

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 1).[26-37] The test materials were administered to a fingernail of the subjects and removed by wiping with a proprietary remover solution after 10 minutes three times per week for nine applications. Two weeks later, the test material was administered to the same fingernail in the same manner. The amounts of hydroquinone or *p*-hydroxyanisole were not provided.

UV NAIL LAMPS

UV lamps are used to cure nail gels, acrylic nails, and nail fill-ins, and to dry traditional nail polish and UV top sealers/topcoats.[38]

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.[39] UVA-1 is the least erythemic and photocarcinogenic range in the UV spectrum. The bulbs in UV nail lamps have internal filters to eliminate UVB and are reported to emit exclusively in the 265 – 370 nm range.[40]

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

In 2010-2011, over 87% of professional nail salons reported using UV nail lamps.[41] Typical client usage is 1 – 4 times/month for 2 min or less per visit.[40]

Another researcher stated that typical salon exposures are 10 minutes or less per hand and with exposures occurring only twice per month.[42]

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.[43]

Nail gels shrink with curing under UV lamps. Thus, it has been recommended that three or four separate thin coats of nail gel be applied and cured for 3 min each coat to achieve the desired results.[38,44]

In a study of two UV nail lamps (each from a different nail product company) cumulative exposure measured as minimal erythema doses (MED) were low. However, measured in J/m^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.[45] Dosimeters that measure DNA damage caused by UV irradiation of viable spores were used to make these measurements. Manufacturer's instructions for curing acrylic nails using UV light were followed. It was assumed that the nails would be refinished every 3 weeks, or 17 times/year; the dosimeters were exposed for the equivalent of the cumulative dose that would be expected over 1 year of using such lamps. The UV lights yielded 0.6 MED/h for phototype II skin. The curing time recommended by the manufacturers yielded from 0.06 to 0.09 MED per treatment and yearly cumulative exposures estimated between 1.1 and 1.5 MEDs. Total exposures were estimated to be 285 and 386 $J/m^2/y$ 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 ($\mu W/cm^2/nm$) than the sun (UV Index = 6) in the 355to 385 nm range. The authors recommended the use of full spectrum sun block to the hands 30 minutes before exposure.[45]

In an evaluation of six UV nail lamps, the authors concluded that total exposure following programmed times and steps, analogous to nail polish application, accumulate to only a small fraction of the recommended practice (RP)-27 permissible daily occupational exposure of UV.[46] The UV nail lamps used were representative of major US manufacturers and evaluated for radiant hazards as defined in the American National Standards Institute/Illuminating Engineering Society of North America Recommended Practice - 27 (ANSI/IESNA RP-27), the Recommended Practice for Photobiological

Safety. Lamps were evaluated at three positions: 1 cm above the inner surface, which approximated exposure to the hand; 20 cm directly in front of the box opening; and 20 cm outside the box and 45° above the hand opening.

Three of the devices were fluorescent UV nail lamp systems with 2, 3 or 4 small 9 W lamps. Lamps were of two base types with tubes oriented either perpendicular (in the case of the two-lamp device) or parallel to the fingers of a hand undergoing a procedure. The tubes in the three- and four-lamp units were arrayed in an arc-like configuration to irradiate from above and from the sides of the hand while the perpendicular-oriented tubes of the two-lamp unit were in a planar configuration above the fingertips. The other three devices were light-emitting diode (LED)-based with arrays of 6 or 32 LEDs or, in the case of a single finger unit, one LED. These LED arrays were mounted in planar configurations oriented generally perpendicular to the fingers in approximately equidistant arcs above the fingertips. The 32 LED devices had four of its LEDs oriented in two lateral pairs positioned on either side. The entrance aperture of the spectroradiometer was positioned to receive the full intensity expected at each of the three different measurement positions chosen to approximate expected intensities to which a user's skin or eyes might be exposed.

Hazard to skin at intended-use distance enabled classification of these devices into Risk Group 1 or 2 (Low to Moderate) with the S(λ) (i.e., distance between the source and the object) weighted Actinic UV range of 1.2–1.7 μW/cm² and 29.8 - 276.25 min permissible daily exposure. At 20 cm on center and at 45° from center, UV risk to skin and eyes were within the Exempt classification. Actinic UV ranged 0.001–0.078 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 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.[46]

When compared to the UV output of tan bed lamps, UV nail are vastly less hazardous.[42] The results indicate that a person could in their workplace, once every day, put their hand under a UV nail lamp for 25 minutes and remain within the permissible daily occupational exposure limits for workers, according to the applicable international ANSI/IESNA RP-27.1-05 standard.

The carcinogenic-effective irradiance from three different UV nail lamps used 10 min/week was estimated to be over 250 years.[47]

A concern exists that the incorrect replacement lamp/bulb may to be inserted into the UV nail lamp (e.g. those emitting UV-B or UV-C) could be harmful to the skin if used.[42] UV lamps/bulb should be replaced with the exactly the same original manufacturer's UV lamp/bulb that was supplied with the UV nail unit when it was purchased.

Risk Analysis

In a risk analysis, it was concluded that 72 709 more women using UV nail lamps to cure their nail gels 8 min/application, every 3 weeks, for 20 years would increase the chance that one more woman might develop squamous cell carcinoma on the back of the hand compared to women who were never exposed to UV nail lamps (Table 3).[48] The model UV nail lamp used in this analysis had an unweighted UV irradiance of 115 W m2 with an erythemally weighted output of 1.58 SED/h. The authors stated that the estimated risk of squamous cell carcinoma could be reduced to virtually zero by wearing fingerless gloves when the hands are being exposed to UV radiation from such lamps.

Light Penetration of Nails

UVB light did not penetrate the finger nails of a cadaver (n = 10).[49] An average of 1.65% of UVA light penetrated the nails in this study. A Dermalite UV light machine was used.

Case Reports

Nonmelanoma skin cancers were observed on the dorsum of the hands of two women who reported exposure to UV nail lamps.[38] The first woman was 55 years old, in good health, and was not taking immunosuppressive medication. She had an indoor occupation and participated in little outdoor recreation. Her family had no history of skin cancer. She had been exposed to a UV nail light twice monthly for 15 years. She presented with an erythematous plaque on the dorsomedial aspect of her right index finger. Biopsy revealed a squamous cell carcinoma.

The second woman was 48 years old, in good health, and not taking immunosuppressive medication. She had an indoor occupation with moderate outdoor recreational exposure to UV. She had no personal or family history of skin cancer except for a previous squamous cell cancer that had been removed from the dorsum the left finger 3 years earlier. She presented with a scaly papule on the dorsum of her right hand. Biopsy revealed a squamous cell cancer. Over the next 4 years, two further squamous cell cancers on the dorsum of both hands were treated. She had had exposure to UV nail lights eight times within a year several years before the first appearance of the skin cancer.[38]

SUMMARY

This is an amended safety assessment of hydroquinone prepared to address a new use in nail gels and adhesives that require UV curing. This Summary does not address information in previous reports. The CIR Expert Panel concluded in

2010 that hydroquinone is safe for use in nail adhesives but should not be used in other leave-on cosmetic products.

The VCRP reports that hydroquinone is used in 7 nail extenders and 11 skin care preparations.

Hydroquinone was reported to be used in the liquid component of two-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. Hydroxyquinone is used interchangeably and in combination with *p*-hydroxyanisole to control polymerization in nail gels and nail adhesives.

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.

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

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 multilaboratory LLNA. The EC_3 values were 0.07%, 0.03%, 0.08%, and 0.07% for the four laboratories.

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

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

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

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

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

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

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

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

DISCUSSION

Hydroquinone causes depigmentation to the skin starting at 1% and was found to be safe at that concentration or less in rinse-off products and nail adhesives in 2010. This conclusion did not contemplate use in artificial nail coatings that are cured under UV light.

The Panel noted that there is no dermal exposure to hydroquinone when artificial nail coatings are used according to label instructions. Any accidental application to the surrounding skin should be promptly removed for best visual results and adherence as well as to minimize exposure. Therefore, the risk of skin depigmentation would be minimal during momentary exposure. However, the Panel stressed that contact with the skin is to be prevented and that professionals be properly trained in the application of these products. The Panel also noted that 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 Panel noted that the concentration of hydroquinone and/or *p*-hydroxyanisole was not indicated in the sensitization studies conducted by applying the nail gel to the fingernails did not provide. While the study does not demonstrate the dermal sensitization potential of these products when administered to the skin, the lack of sensitization does demonstrate how unlikely it is for sensitization to develop when these products are used properly.

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

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

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

AMENDED CONCLUSION

The CIR Expert Panel concluded that 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 as a polymerization inhibitor in artificial nail coatings when photo-protective materials for the skin are used. Hydroquinone should not be used in other leave-on cosmetic products.

TABLES

Table 1. HRIPTs of nail products containing hydroquinone and/or *p*-hydroxyanisole administered to the fingernails by trained technicians, not to the skin. The amount of hydroquinone and/or *p*-hydroxyanisole in the products was not provided.

Product	n	Result	Reference
UV gel top coat nail polish	51	No signs of potential cuticle irritation or allergic contact sensitization	[31]
UV gel top coat nail polish	51	No signs of potential cuticle irritation or allergic contact sensitization	[30]
Builder gel	51	No signs of potential cuticle irritation or allergic contact sensitization	[29]
Clear overlay gel	51	No signs of potential cuticle irritation or allergic contact sensitization	[28]
Soak-off sealer	51	No signs of potential cuticle irritation or allergic contact sensitization	[27]
Soak-off gel lacquer	51	No signs of potential cuticle irritation or allergic contact sensitization	[26]
Gel system-thick gel sealer	50	No signs of potential cuticle irritation or allergic contact sensitization	[32]
Base gel	51	No signs of potential cuticle irritation or allergic contact sensitization	[33]
No-cleanse overlay gel	51	No signs of potential cuticle irritation or allergic contact sensitization	[34]
Soft white sculpting gel	51	No signs of potential cuticle irritation or allergic contact sensitization	[35]
Pink builder gel	51	No signs of potential cuticle irritation or allergic contact sensitization	[36]
Luminous white overlay gel	51	No signs of potential cuticle irritation or allergic contact sensitization	[37]

Table 2. Ultraviolet nail lamp measurements.[45]

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 women who would need to be exposed to ultraviolet A (UVA) nail lamps[a] for one woman to develop squamous cell carcinoma who would not have done so otherwise.[48]

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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