
Amended Safety Assessment of Hydroquinone as Used in Cosmetics

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The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, 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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MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: August 18, 2014

Subject: Hydroquinone As Used In in Cosmetics

In June 2014, the Panel issued a Tentative Amended Report of hydroquinone with the conclusion that it is safe at concentrations of $\leq 1\%$ 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 that are cured by UV light when photo-protective materials (e.g., gloves, sunscreen) in professional settings but unsafe for home use when used with UVA light. Hydroquinone should not be used in other leave-on cosmetic products.

Comments from industry were addressed.

No new data on this ingredient or UV nail lamps have been submitted by industry. However, a paper reporting severe pseudoleukonychia as a result of superficial nail plate desquamation from nail gel use was submitted by Industry. Since the ingredients in the gels were not provided, the Panel may decide that this is an unnecessary addition. Also, due to the increased focus on UV nail lamp bulbs, the summary of the Markova/Weinstock paper was expanded to provide more relevant information.

Since the discussion on hydroquinone and *p*-hydroxyanisole overlapped, especially with regards to UV exposure and application of nail gels, the transcripts of both ingredients from the June meeting are included in each Panel book.

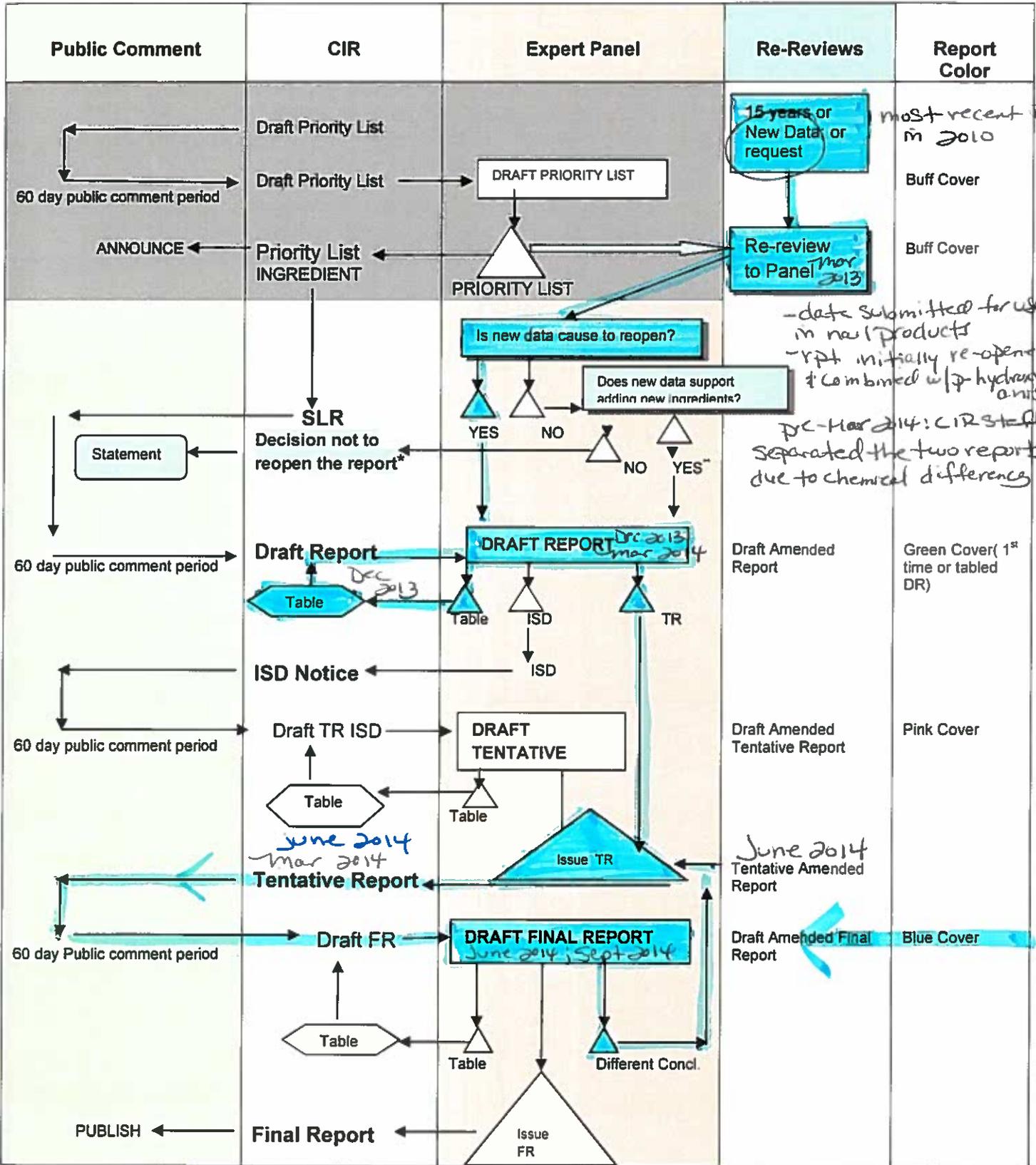
For the Panel's information, additional web searches were conducted for UV bulbs and UV nail lamps. Examples of the results of these searches are provided in the Search Strategy document. Representative links are provided so that the different models of consumer and professional UV nail lamps available to the public may be examined and the product descriptions and specifications may be read as well as what types of UV bulbs are available.

The Panel is to review the Abstract, Discussion, and Conclusion to ensure that they reflect the Panel's thinking. A Final Amended Report is to be issued.

Hydroquinone

Safety Assessment Flow Chart

Sept 2014



- data submitted for use in new products
 - rpt initially re-opened & combined w/ hydroxy-anisole
 PC-Mar 2014: CIR staff separated the two reports due to chemical difference

*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.



History of Hydroquinone and p-Hydroxyanisole

- 1985** – Safety assessment of p-Hydroxyanisole published with an unsafe for use as a cosmetic ingredient.” This conclusion was based primarily on depigmentation of black guinea pig skin in studies in which concentrations as low as 0.25% or less (0.1% in some animals) were applied to the skin daily for 1 or more months (which were close to use concentrations up to 0.1% to 1.0% at the time of the FDA survey in 1981).
- 1986** - A safety assessment of hydroquinone and pyrocatechol was published 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.
- 1994** - An amended safety assessment of hydroquinone alone was published with the conclusion that hydroquinone was 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 was not safe for use in leave-on, non-drug cosmetic products.
- 2010** – Safety assessment of hydroquinone published with a safe at concentrations $\leq 1\%$ in hair dyes” and “safe for use in nail adhesives in the practices of use and concentration described in this safety assessment,” although it “should not be used in other leave-on cosmetics.” The Panel noted that, while absorption through the skin could be appreciable in leave-on products, hydroquinone in nail adhesives “is oxidized during use and is no longer present in the preparation and minimal dermal exposure and absorption is expected to occur from this application.” The use concentration was reported to be 0.5% in nail adhesives at the time of the survey (2008). The Panel’s discussion does not explicitly include a warning to avoid skin contact or specify that nail adhesives containing this ingredient should be for professional use only. The cosmetic use section of the CIR safety assessment noted that the EU banned the use of this ingredient in hair dyes in 2008 and approved its use in professional-use-only artificial nail systems up to a maximum of 0.02% after mixing with methacrylate monomers (hydroquinone at 0.02% in methacrylate monomer preparations was undetectable in the finished product).
- March, 2013** - Data were submitted to the Panel with the request to reopen these two safety assessments with the purpose of changing the conclusion with regard to hydroquinone and p-hydroxyanisole’s use in nail products using UV for polymerization and drying.
- December, 2013** – The Panel tabled the report without a conclusion to have further information collected on UV nail lamps.
- March, 2014** – The CIR staff split the report for these two ingredients due to their chemical differences. The Panel is to examine each report separately and come to independent conclusions.

New data on UV lamps and photo effects have been added.

The Panel examined the newly presented data and come to a conclusion of safe at concentrations of $\leq 1\%$ 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.

- June, 2014** – At Industry’s request, the Panel re-examined the Dowdy Sayre paper. The Panel became more concerned about the safety of the home use of UV nail lamps.

The Panel changed the conclusion to: safe at concentrations of $\leq 1\%$ 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 that are

cured by UV light when photo-protective materials (e.g., gloves, sunscreen) for the *skin are used in professional settings; these products are unsafe for the new in-home use*. Hydroquinone is unsafe for use in other leave-on cosmetic products.

September, 2014 - The Panel examines the Draft Final Amended Report

Search Strategy – Hydroquinone & *p*-Hydroxyanisole

SciFinder – Searched by CAS No. Refined by date, publication type, and toxicity terms. 10 papers ordered.

ECHA – Data for hydroquinone.

Web Search – by CAS Nos. and ingredient names. Located FDA drug application documents; SCCNFP opinion; and NAILS Magazine.

UV Lamps

SciFinder – “UV nail lamp” – 4 hits.

Web Search – found www.hooked-on-nails.com and incorporated useful information.

Depigmentation in Manicurists

SCIFINDER -

March 20, 2014 7:23 PM

Explore references by research topic: depigmentation in manicurists initiated, resulting in 2 candidates

March 20, 2014 7:24 PM

Explore references by research topic: nail polish depigmentation initiated, resulting in 1 candidate

March 20, 2014 7:25 PM

Explore references by research topic: nail gel depigmentation initiated, resulting in 2 candidates

Explore complete

Candidates Selected

14 references were found containing all of the concepts "nail", "gel" and "depigmentation".

Explore results

Answer set 1 created with 14 answers from CAPLUS

March 20, 2014 7:31 PM

Explore references by research topic: manicure depigmentation initiated, resulting in 1 candidate

March 20, 2014 7:41 PM

Explore references by research topic: manicure hazard initiated, resulting in 1 candidate

Explore complete
Candidates Selected

4 references were found containing the concept "manicure hazard".

Explore results

Answer set 2 created with
3 answers from CAPLUS
1 answer from MEDLINE

GOOGLE

"hydroquinone" – No hits. All possible hits (other than nail gels) were skin lighteners/brighteners

"hydroquinone cosmetics" – No hits. All possible hits (other than nail gels) were skin lighteners/brighteners

"hydroquinone cream" – No hits. All possible hits (other than nail gels) were skin lighteners/brighteners

GOOGLE

"UV nail lamp" – UV nail lamps available on Amazon, Salon Supply Store, Walmart, Sally Beauty, eBay, etc.

EXAMPLES:

<http://www.amazon.com/Thermal-Spa-49135-Professional-Light/dp/B001RMP7M6>

<http://www.ebay.com/itm/310729068451>

[http://www.salonsupplystore.com/watt-nail-lamps-c-](http://www.salonsupplystore.com/watt-nail-lamps-c-2717_2718_2959_2771.html?CAPCID=24941836456&cadevice=c&gclid=CMu2tfPK3r8CFQQQ7AodigwAOg&CA_6C15C=330011670000004245)

[2717_2718_2959_2771.html?CAPCID=24941836456&cadevice=c&gclid=CMu2tfPK3r8CFQQQ7AodigwAOg&CA_6C15C=330011670000004245](http://www.salonsupplystore.com/watt-nail-lamps-c-2717_2718_2959_2771.html?CAPCID=24941836456&cadevice=c&gclid=CMu2tfPK3r8CFQQQ7AodigwAOg&CA_6C15C=330011670000004245)

<http://www.walmart.com/c/kp/uv-lamp-for-nails>

<http://www.ebay.com/sch/Nail-Dryers-UV-LED-Lamps-/67653/i.html>

http://www.premiernailsources.com/index.php?main_page=index&cPath=87

<http://sale-fire.com/Uv%20Nail%20Lamp?p=gcp&gclid=CKShprPS3r8CFSDp7Aod8nAAUw>

"Professional UV nail lamp" – UV nail lamps available from Amazon. More product line dedicated sources of lamps.

EXAMPLES:

<http://www.tmart.com/UV-Curing-Lamp-Nail-Dryer/?cc=usd&gclid=CNjstpvM3r8CFQMT7AodilgA1w>

<http://www.sallybeauty.com/uv-lamp/SBS-156500,default,pd.html>

http://www.nailiteinc.com/index.php?main_page=index&cPath=420

Of interest: Includes product descriptions of professional lamps that can be set for up to 15 or constant on.

“UV bulbs” – UV bulbs from Walmart, 1000bulbs,

Germicidal UV bulbs were available from 1000bulbs, Walmart, Home Depot, Top Bulb.

EXAMPLES:

<http://www.walmart.com/c/ep/uv-bulbs>

<https://www.1000bulbs.com/category/ultraviolet-germicidal/>

<http://www.homedepot.com/b/Electrical-Light-Bulbs-Specialty-Light-Bulbs-Germicidal-UV-Light-Bulbs/N-5yc1vZc5sv>

<http://www.atlantelightbulbs.com/germicidal.asp>

“UV nail lamp replacement bulbs”- Amazon and multiple product line dedicated sources.

EXAMPLES:

<http://www.amazon.com/Light-Replacement-Extra-Dryer-Machine/dp/B005IHEC40>

<http://www.sallybeauty.com/uv-bulb/SBS-128450,default,pd.html>

<https://www.nailsuperstore.com/nail-supply/uv-gel-nail-lights>

http://www.salonsupplystore.com/lamps-dryers-c-2717_2718.html

**Transcripts – Hydroquinone and *p*-Hydroxyanisole
June, 2014**

Dr. Belsito's Team

DR. BELSITO: ...So, now, I guess we really should do hydroquinone and peri-hydroxyanisole together, because the reports are very intertwined, and we did receive comments and we did receive Wave 2 data, right?

So, I had some real concerns. I know that the NOW Manufacturers Council sent us the Dowdy/Sayre paper to show how safe they showed this to be versus the one paper where there were two squamous cells reported in the literature, and you obviously know my view. I think two is two too many.

But what really bothered me as I read this -- now, we're talking about potentially releasing this to the public for home use, correct? I mean, this is where we're at. And, you know, in the Dowdy paper, he's talking about how you can easily insert a UVC bulb into this; you can insert a UVB bulb into this. And, I'm sorry, folks, but in a country where everything has to be at fifth-grade language for informed consent and where McDonald's has to label their coffee, do not place it in your lap while driving, I'm not really comfortable releasing a light machine on the market that someone could go and put a UVB bulb in, that someone's child could be sitting under the table while they're irradiating their fingernails.

I'm okay with salon use, you know? Yes, you have to put sunscreen on or protect the hand, but I'm not -- I think the machine, as it exists, as you buy it, is okay. But it's quite clear from this paper that there's nothing to prevent the individual from going out into the marketplace and buying a germicidal UVC bulb that can blind you or a UVB bulb and putting it into this machine.

So, I'm not comfortable -- I'm comfortable with the ingredients; I'm not comfortable with the whole totality of how this will be used in the home environment. So, that's where I am, and I will certainly present your view, but I will tell you that I will vote against this going out into the home market.

DR. LIEBLER: Would you be more comfortable with a conclusion that it's safe for use in a salon setting or in --

DR. BELSITO: I'm comfortable saying it's safe for use in salons under a professional setting. I'm not comfortable allowing these products to be marketed on the Internet where a consumer can buy them and then the bulb dies and goes out and Googles UVB bulb and finds out that the cheapest one is a -- you know, buy some UVB bulb or UVC bulb and it easily fits in and suddenly they're irradiating their hands with UVC. I'm just not comfortable with that. I mean, the potential for product misuse here is so high in the consumer marketplace, in my view, because I see people do stuff all the time that's just incredible, like gargle shampoo. So --

Yes, David.

MR. STEINBERG: Does it work?

(Laughter)

DR. BELSITO: Suppose it helps halitosis, I don't know, bacterial growth of the tongue.

MR. STEINBERG: Two things, Don. First (inaudible). It just doesn't cure it. You need divisible - it's 400 to 410.

SPEAKER: Could you start over from "two things," Don.

MR. STEINBERG: Oh, I'm sorry. Two things. The bulbs. If the consumer substitutes a UVC bulb, which I'm not even sure you can purchase, but let's say you can, or a UVB bulb -- same question -- they won't cure the gel. You need the 400 to 410 irradiation divisible light, which is what cures the gel. The bulbs that come with the kits, both home and professional, have very little -- 380. Mostly it is some 390. The vast majority is 400 to 410, 420.

The second thought -- and this came out this morning -- was the industry certainly is willing to put on the instructions to use only replacement bulbs from the manufacturer to secure adequate results or (inaudible).

DR. BELSITO: How many people read instructions?

MR. STEINBERG: For these, they do, because otherwise they won't use the machine properly and they won't get their nail polishes done. You know, this is -- if you don't follow the directions, it won't dry. It will still be sticky and tacky, and it won't be your two weeks of nail polish, which is what their desired approach is.

DR. BELSITO: I understand what you're saying, David. But, you know, I've seen what consumers do, from a dermalogic standpoint, and it's just amazing what people do. (Inaudible) what I do. I hardly ever read the directions for anything. I mean, I might for this read exactly how to cure my nails, but I'm not going to read the rest of 10 pages of an insert, and I don't know that your average consumer is going to know the difference between UVB and UVC.

Now, if you created a device where the only available bulbs that would plug into that device were UVA bulbs, I would feel differently. But right now, what Dowdy and Sayre are saying is you can put any UV bulb into there, and so I don't think, based upon my own view of consumers in the marketplace and the potential for harm, that these should be mass marketed. I don't think you have the level of protection there.

I mean, it's my own personal view. And nothing anyone says is going to change that. I've argued with myself, so I want to hear what my Panel members say, and I understand what you're saying.

DR. BERGFELD: How about Linda Katz. Maybe Linda could talk about this.

DR. BELSITO: Yes.

DR. BERGFELD: About the UV bulbs and the nail curing.

DR. KATZ: Well, at this point in time, there's not much really I can say. We've been trying to look at the data that's in literature and look for first-event reports that come into the agency. But we agree with you that under the appropriate conditions -- it looks like right now we don't have data to support that it would be unsafe, meaning in professional circumstances -- a salon. We don't really have enough data to support home use. We wouldn't regulate necessarily the bulbs and the actual kit. That would go under devices rather than ours probably if the two need to be sold together, because it would cross jurisdictional lines. So, I'm not sure I could be of much more help, but I wouldn't disagree with you on a personal level. Not necessarily saying this is the FDA's policy, that it probably seems that it's more reasonable to use it in a salon setting than in a home setting. But, again, this is not necessarily FDA's opinion, because we really haven't formulated a definite opinion yet as to what to do about these products.

DR. WEINTRAUB: Don, I just want to mention that there's a whole body of literature about how warnings and instructions are the least helpful form of safety. Consumers very much don't read them,

don't know what's on warning labels. There's study after study with all types of different products, and there's something really focused on sort of a paradigm for safety, and obviously the strongest thing to do is to design out a potential hazard; and, really, the weakest form is to include a warning label or instructions that data shows are not likely followed.

DR. BELSITO: Well, I mean, obviously that's my feeling, but I need to -- I'm representing my team tomorrow when we discuss this, so.

DR. LIEBLER: So, I basically agree with your position, Don. I mean, we talked about this last time. Had a chance to think about it a bit more. I agree with your interpretation of the Dowdy paper, which I read yesterday, and, I mean, it's a unique situation where we're really not talking about the ingredient as much as the circumstances under which the ingredient needs to be used to produce its effect. And I think that I would only support a conclusion that specified the conditions under which it could be safely used, and the current conclusion doesn't.

DR. BELSITO: Paul?

DR. SNYDER: I mean, obviously we're going to not go with the conclusion that we've drafted already. So, you're proposing then to go insufficient?

DR. BELSITO: No, I'm saying that basically let me get out a Wave 2 in the Dowdy paper and go back to the actual document in conclusion.

So, you know, for the conclusion -- oh, God -- can anyone tell me what page it's on for hydroxy --

MS. BECKER: Forty-five.

DR. LIEBLER: Page 45.

DR. BELSITO: Forty-five, okay. We pretty much say that -- concluded that hydroquinone is safe, ya-da- ya-da-ya-da, "Hydroquinone is safe for use in nail adhesives and is a polymerization inhibitor in artificial nail coatings that are cured with UV light when photo protective materials and sunscreens for the skin are used in a professional setting" or something like that.

DR. LIEBLER: Because we discussed all the bulb stuff in the discussion and things so -- yes.

DR. BELSITO: Right. So, you know, that we restrict our conclusion of safe as used to a professional setting and then the discussions say that we do not feel that these could be safely use at home but their risk of unsafe use at home is unknown and we feel that at this point it should not be marketed for home use. And that goes in the discussion, and our conclusion that in a professional setting, hydroquinone is safe for use in nail adhesives and as a polymerization inhibitor and artificial nail coatings that are cured without gloves and sunscreens for the skin (inaudible) he used. So, it is a changing conclusion, because we're saying "professional setting" or "professional use."

And I'm comfortable with that. You know, people take risks all the time, and, you know, if they are having to put gloves on or sunscreen on, they know that there is some question, although the Dowdy paper again would argue that it's not an issue. But there are two case reports and some calculations that go the other way. But, fine, professional use, but not -- I mean, it's the same concern that I raised at the last meeting: The bulbs and whether they could easily substituted with UVB/UVC, and in this paper we got, that's what they say.

DR. SNYDER: How did we handle the Brazilian Blowout? It was (inaudible).

DR. BELSITO: We banned it.

DR. SNYDER: Banned it.

DR. BERGFELD: But we haven't assembled nail products so that it could only be used on the nail, and there had to be protection of the cuticle.

DR. BELSITO: Yes, but this -- again, it's --

DR. BERGFELD: I'm talking about --

DR. BELSITO: It's not about the chemical. It's about how the whole cosmetic package is put together. And in this case, the package has to include UV curing. And so I could care less about hydroquinone or peri-hydroxyanisole in a nail enamel if it didn't have to be UV cured. And I really -- if it came with a warning to put on gloves or sunscreen and the bulbs couldn't be substituted, I might be okay with home use. But I'm not okay. I mean, I just see all the stupid things consumers do with things, and I don't think these machines are safe out in public.

DR. SNYDER: Yes, I'm conflicted, because I think that the ingredients are safe "which use properly." It's that the -- it's the device that -- as Linda said, it has to be a kit when it includes the gel and the device. And so it's almost out of our purview from the standpoint that once you put the device in, it's a different issue -- the lamp. So, that's -- to me, it's a real risk certainly within our boundaries.

MR. STEINBERG: You only buy the device once. It isn't like it's a unit-dose device. You just buy the device, and then you get different shades of nail polish and gels and whatever you want, and the device lasts a tremendous amount of time until, as Don says, the bulbs burn out. And at some point the bulbs will burn out, and they'll have to be replaced.

DR. LIEBLER: So, Paul --

MR. STEINBERG: But it's not the type of bulb that you just go into Home Depot and find the bulb.

DR. BERGFELD: The socket is the same.

MR. STEINBERG: The socket is the same, but the bulb is not, yes.

DR. LIEBLER: So, I was right where you were, Paul, as of the last meeting. I was conflicted on this, because I wasn't sure if it's really our purview to regulate or to pronounce on a device as opposed to the ingredient. But when the use of the ingredient -- so, we always talk about under concentrations and conditions of use. The conditions of use have a potential hazardous exposure under the circumstances of somebody using the wrong bulb. And so under conditions of use, in my view, makes it something that we need to consider, and the conditions of use are potentially unsafe, and that's why I agree with the restriction to a professional situation.

DR. BERGFELD: I would just like to put an anecdote. I did talk to my beautician, a male who owns the shop, and I said, you know, this is a problem for you and you need to be cautious of your lights. He

said, well, I can't replace those lights. They're a thousand dollars apiece. So, he was substituting. I said, you'd better.

DR. SNYDER: Not safe under conditions of use. Are we going to say that?

DR. BELSITO: No.

DR. SNYDER: No? You were going to --

DR. BELSITO: Simply, in the discussion, point out that we don't feel that there's adequate data that shows safety for home use because of the ability to switch out bulbs from UVA to UVB or C, and then in the discussion say that hydroquinone is safe for use in a professional setting in NOW adhesives and as a polymerization inhibitor in artificial nail coatings so they're UV cured when photo protective materials -- that is, gloves and sunscreen -- for the skin are used. So, we simply limit the "UV cured" to professional settings.

So, I guess it would be, "Hydroquinone is safe to use in nail adhesives and in a professional setting as the polymerization inhibitor in artificial nail coatings that are cured." So, we're limiting the UV curing to salons.

DR. SNYDER: Okay.

DR. BELSITO: Which should make the salon-operative people very happy. If you want those gels, you have to go to a salon.

DR. KLAASEN: I've got a question for you, Don. If you couldn't put in a different bulb, would you be okay with it for home use?

DR. BELSITO: Yes. If they could guarantee me that they produced a socket that -- I mean, it's just like -- I mean, it's exactly like the Brazilian Blowout. You know, if you could create a device that would suck out all that formaldehyde, then, you know, we wouldn't have an issue with it. But in the studies that we saw, even in salons that knew that they were being monitored, there were unacceptable levels of formaldehyde. Right now, what we know is that in the devices as they currently exist you can change out the bulbs.

DR. KLAASEN: I guess the thing that makes me pause a little bit is what David said a few minutes ago, in that with these other bulbs it won't work, and would that kind of limit the use of these wrong bulbs?

DR. BELSITO: Yes, but let me give you scenario. So, you go out and you buy a UVB bulb, and you're a woman and you've just coated your nails and you're putting it underneath there, okay? And it's a UVB -- or, let's make it even worse, a UVC -- you can still buy germicidal lamps. And my nail gel isn't curing. Is the light not on? One exposure is all you need, Curt, to blind yourself.

DR. KLAASEN: Or just keep it under there longer.

MR. STEINBERG: (Inaudible) the wrong time. Now, you can't --

DR. BELSITO: I understand that, but I can see a consumer going -- my nail job isn't hardening, is the light on? -- and looking at the damned light. So, I'm just very concerned. And I personally -- I mean, I'll represent you people and say, "But I'm not voting for this wrong use."

MR. STEINBERG: Don, on a theory – and I have no knowledge whether this is possible – I don't think it's possible for us to change the sockets, because of the electronic issues. But how about if we can change the device so they can't remove the bulb? So, they have to buy a new device if that bulb goes out -- bulbs go out. They're multi-bulbs.

And I think it might be possible to make the home kits so that they cannot replace the bulb, that if the bulbs go they have to get a new kit. But I don't think we can change the sockets. I think that is probably an impossibility.

DR. BELSITO: Then I'd become less concerned. But right now, that's not the state of the art.

MS. BECKER: Can I ask a question?

DR. BELSITO: Sure.

MS. BECKER: David --

MR. STEINBERG: Yes.

MS. BECKER: If they put -- if there's a UV light broader spectrum but includes the 400 range, will that dry the nail even though there's a broader range in there?

MR. STEINBERG: You've got to have in the area of -- about 80 percent of the radiation has got to be 400 to 410 to cure. So, you can have -- you know, if you go down lower it's just not going to cure. Or if you're going to be higher, if you're going to be up in the 450, 480, 500, 600, it's not going to cure the reaction.

MS. BECKER: If I've got 380 to 420 --

MR. STEINBERG: Twenty -- is the commercial bulbs that are available that would give us the 400 to 420 that we needed to cure.

DR. BERGFELD: Where does the client buy these?

MR. STEINBERG: I'm sorry?

DR. BERGFELD: Where do they get the replacement bulbs? How do they get them?

MR. STEINBERG: I believe it hasn't come up yet, but the bulbs last amount of time, because you're only using it for around eight seconds each time. It takes less than two minutes to do your whole set of nails four times. You need four coatings -- you know, the base coat, the color coats, and the top coat. They last a very long time, and I don't believe, as far as I know, that people have been looking to replace the bulbs. They haven't burned out yet. They're not that type of -- it's not like the light bulbs that we're used to. These are very small bulbs.

DR. BERGFELD: But they do not include a coupon to get a new bulb if needed or anything like that?

MR. STEINBERG: No, nothing like that. But I think it's possible -- I'm just saying it theoretically because I don't know for sure -- that it might be possible to design the kit so that you cannot replace the bulb. You'd have to break it apart -- and then it would be useless -- to get the bulb out.

DR. BELSITO: Well, come back to us with that, and we'll re-review it. But my point is that as it currently exists I can't vote for it.

Dan, I got the sense you're with me.

DR. LIEBLER: I'm where you are. Paul?

DR. SNYDER: Yes.

DR. KLAASEN: Yes, I think I'm going in that direction.

DR. BELSITO: Okay, let's move on.

START NEXT INGREDIENT

MS. BECKER: Just so you --

DR. BELSITO: Yes.

MS. BECKER: It's on eBay.

DR. BELSITO: Yes, so the cheapest bulb was -- yes, now gel bulbs.

MS. BECKER: How much are they?

DR. BELSITO: About \$54.

DR. BERGFELD: Yes, that's four pounds that somehow (inaudible) the U.K. Thank you.

Dr. Marks' Team

DR. MARKS: Okay. So, next is hydroquinone. And this is an amended safety assessment. And as you recall, the biggest concern and reason we opened this was the issue of hydroquinone particularly in nail coatings that are cured with UV light and there was some issue with a possibility of calling squamous cell carcinoma with the exposure to UV light.

In March we issued a tentative amended report with hydroquinone as safe at concentrations of less than or equal 1 percent, discontinuous brief use, rinsing the skin and hair, safe for nail adhesives, and then photo protective material, such as sunscreen, be used -- should not be used for leave-on products, so we're at the point to issue a final amended -- I think we can do that. We've got another paper by Dowdy and Sayer and interesting, Lillian, I thought your discussion was great.

MS. BECKER: Thank Ivan. He did an amazing job, but that's the same paper you've had. I just gave it to you again in case you wanted to look at it.

DR. MARKS: Well, what I liked is, don't change the (inaudible) --

MS. BECKER: Don't change?

DR. MARKS: Don't change the bulbs, the UV source bulbs, and that was what I got as the main conclusion is you should use the bulbs that are supplied with the lamp and don't go to your local Ace Hardware store and buy something else and put it in there.

But at any rate, I think the conclusion stands as it is and I think we're ready to issue a final amended report, but Tom, Rons?

DR. SHANK: I would like to suggest in the last line of the conclusion where it says, "Hydroquinone should not be used", et cetera, I would change that to "would be unsafe for use" –

DR. MARKS: Okay.

DR. SHANK: Because that's the original conclusion that we have.

DR. MARKS: Okay. I think moving to issue a final, that's an editorial change. I don't think we have to go out for another -- what is the waiting period? Three months, Lillian? Does that sound -- I think the intent is the same.

DR. SHANK: Okay.

DR. MARKS: Is that okay with you, Ron Shank? Would you delay it another three months changing from "should not" to "unsafe"?

DR. SHANK: Since the original conclusion said very clearly, "unsafe" I think this is editorial and we can just change it to "Hydroquinone is unsafe for use in other leave-on cosmetic products" because that was the original conclusion. So, yes, it does -- or no, it does not need to go out again.

DR. MARKS: How do you feel about that, Lillian?

DR. GILL: That's fine.

DR. MARKS: Is anybody here from the consumer –

MR. STEINBERG: I'm not a consumer on this.

DR. GILL: You mean from Rachel's –

MR. STEINBERG: Rachel's group?

DR. MARKS: Yeah, Rachel's group. Is anybody in the room from Rachel's group? Would this be a misinterpreted -- I think not. Okay.

DR. HILL: I have a quick question about one point of language in the discussion. It's in the fourth paragraph of the discussion. It's really the last sentence of that fourth paragraph. It says -- and I think it's just because I'm not abundantly clear on the meaning as written.

So, it says, "While these studies do 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." Does that mean the lack of observed sensitization in usage so far by the public? Is that what it's trying to say?

MS. BECKER: That has to do with the studies where they just put the nail polish on the subjects and took it off and looked for sensitization over time. So, they're saying if you use it properly, you shouldn't get sensitized, is the point. If it needs rewording, I'd be glad to do that.

DR. HILL: I don't know how it would be reworded. I'm trying to figure out how it would be clear what the meaning is.

MS. BECKER: Well, they didn't apply any of the nail polish to the skin, they just applied it to the nails.

DR. HILL: Right, so -- right, and then the concentration wasn't known because it would be hard to know the concentration under these conditions, so, you know, the lack of data is not the same as an assurance of safety and I think that's what this is trying to cautiously say.

MR. STEINBERG: That's just before (inaudible). It's just a monomer that's applied and then removed. This is not after (inaudible) takes place.

DR. HILL: Okay. All right, so it's just -- but it's just to the nail.

MR. STEINBERG: Yes.

DR. GILL: But I kind of like that wording, the lack of observed sensitization, because I think the discussion said we didn't see any sensitization.

DR. HILL: That would solve the issue for me is just to put the word observed in there, but I don't know if that clouds it any worse.

MS. BECKER: You have it.

MS. LORETZ: The last sentence of the discussion where it says, "Requested the industry clarify" about ingredient usage in professional products being included in the VCRP, and the FDA website actually says that VCRP does not apply to cosmetic products for professional use only such as products used in beauty salons, spas, or skin care clinics. So, I think that sentence should probably be deleted.

MR. STEINBERG: That's why --

MS. LORETZ: Yeah.

MS. BECKER: Or that sentence added.

MS. LORETZ: Right, right. One or the other.

MR. STEINBERG: They were submitted. The FDA rejected them because they're professional -- when they were used in professional use only, so the only ones that are showing up now are those that are for consumer use.

DR. MARKS: So, you're going to make that change, Lillian? Okay.

DR. HILL: But then the question arose that -- I don't know if it was the last meeting or the previous meeting when this was discussed, is that reasonable policy?

DR. MARKS: Well, that's not our --

DR. HILL: I know it's not.

DR. MARKS: We're not going to waste time on that.

DR. HILL: I know. I'm a change the world guy if the world doesn't make good sense. I'm sorry about that. You know that about me already.

DR. MARKS: Okay. Any other comments about (inaudible). Okay. If no other comments, we'll -- yes, Dave.

MR. STEINBERG: We want to say on behalf of the Nail Manufacturer's Council that on our website will be very shortly a complete review of the results of when (inaudible) and Dowdy did their testing using the (inaudible) procedures, and their conclusion was that in the worst case scenario getting your nails done every two weeks, that the amount of radiation exposure -- most of it is visible, it's not UV, it's in the 400 to 410 (inaudible) is equivalent to staying out in the sun for eight minutes.

DR. HILL: Which is not even enough to make a good dose of vitamin D and B12.

DR. MARKS: So, okay. Any other comments? Again, in that paper in the conclusion I think they said stick with the original light bulbs. Don't change.

MR. STEINBERG: Use original -- yeah.

DR. MARKS: Yeah.

DR. HILL: I interpret this sentence to mean that the manufacturer should change the design of their lamps so that it would only take the right kind of bulb, which would be nice. It's not going to happen --

MR. STEINBERG: It's not.

DR. HILL: I told you, I'm a change the world guy. That would be the right solution.

MS. BECKER: Dr. Marks, would you like that sentence or some kind of related sentence added

about only use the original light bulbs.

DR. MARKS: I think that would be good, actually.

MS. BECKER: In the discussion.

DR. MARKS: Lillian, I think that would be good because that's an important point. When you read through the paper you're reassured about everything and then in the conclusion, they're very clear about saying all this is applicable to the original light bulbs that the manufacturers put in for this use, but if you put in another light bulb –

MR. STEINBERG: It might not work, for one thing.

DR. MARKS: But whatever.

MS. BECKER: And also the newest paper that I've added to this version, they went and tested one that are actually in use in salons instead of buying new ones.

DR. MARKS: So, yeah, I think their editorial comments as is, we'll see how it goes tomorrow, but substituting on safe to me is just an editorial comment in the conclusion.

Okay. Are we up for one more? Sure we are.

DR. HILL: So, anecdotally, our daughter -- second daughter loves these nail gel things and she inquired with me, are they safe? I actually sent her language from the internal memo about protecting the skin and, yeah, she loves these things though. I'll tell you.

MR. STEINBERG: So do the consumers. She's not alone.

DR. HILL: It's always fun to have something play out -- how it plays out in the trenches with an actual consumer.

MR. STEINBERG: My 10-year-old granddaughter asked me about (inaudible).

DR. HILL: Well, she works with people in the film production industry, so I get a lot of these kinds of questions from her. A lot.

DR. MARKS: Okay. Now we have a p-hydroxyanisole. And we're at the point, I think, of issuing the final amended report safe in nail coatings with photo protection of the hands and unsafe for other cosmetics. Page 43. Any comments about that?

And, let's see, that would be -- in the discussion, the use of nail coating?

MR. STEINBERG: Why are we using it, I think that's my question, because it's used as a (inaudible) inhibitor.

DR. MARKS: Lillian, I thought you had that in there.

MR. STEINBERG: That was my question, because that's the specific purpose, none other.

DR. MARKS: Right.

MS. BECKER: Are you asking about in the discussion or in the paper? Because it is in the -- it is in the text of the paper.

MR. STEINBERG: Okay.

DR. MARKS: Okay. Any other comments?

DR. GILL: It's in your discussion as well.

MS. BECKER: Thank you.

DR. MARKS: Okay.

MS. LORETZ: Actually, I had a comment on -- I think it's more than one place, but on the introduction, the Panel concluded -- in 1985 the panel concluded that p-hydroxyanisole is unsafe for use due to dermal pigmentation and irritation and sensitization potential, but wasn't the conclusion really based just on the de-pigmentation because that was the most sensitive effect?

?: That was the only known cosmetic use back in 1985, so skin (inaudible), which was a drug and they said they're putting it into a cosmetic, they're using it for de-pigmentation, which is a drug and should not be allowed as a cosmetic.

DR. MARKS: What you're saying is, it's really the DP -- de-pigmentation that's concern, not sensitization.

MS. LORETZ: Right, right.

MS. BECKER: Right.

DR. MARKS: If that were the case, you would just leave out the others and just say the concern about de- pigmentation? Lillian, you can confirm that. That's what I -- also was my sense. It was mainly the de-pigmentation we couldn't determine -- do you think it was sensitization --

MR. STEINBERG: No, it's sold -- it continues to be sold as a prescription drug at, I think, 4 percent or 2 percent concentration for repeated use.

DR. MARKS: That's hydroxy -- that's not the p- hydroxyanisole.

MR. STEINBERG: Oh, yeah. Yeah, there's a prescription drug for skin bleaching that's prescription only and it's very high concentrations and repeat use, you know, twice or three times a day.

DR. MARKS: I know that with hydroxyquinone, that's all (inaudible), I didn't know hydroxyanisole

was also a prescription product.

MR. STEINBERG: Yeah, there is one.

DR. MARKS: Okay. You're educating me, David. Thank you. So, that's -- I'm not sure we need to hold it up for that. Lillian, I'll let you work that out.

MS. BECKER: Okay.

DR. MARKS: Okay. Any other comments? Final amended report safe in nail coatings with photo protection on hands, unsafe for other cosmetics. That's part of the conclusion just as we did with the hydroquinone. To me it's similar to hydroquinone because the real issue is the concern about the UV lights, so it should be the same as hydroquinone in terms of it is stated in hydroquinone as it is safe for use in nail adhesives and as a polymerization inhibitor in nail coatings that are cured by UV light when photo protection materials, for example, (inaudible) and sun screen, for the skin are used. So, it would be a similar thing because what we're really concerned about is the light. And what we're coming back --

MR. STEINBERG: It's miniscule.

DR. MARKS: I know, but that's what --

SPEAKER: Even though the UV exposure is --

DR. MARKS: Yeah, the other -- I agree.

SPEAKER: (Inaudible) clarify it a little bit, just the -- the requirement for protection of the hands is in the conclusion for the discussion for (inaudible) to consider (inaudible) saying it is required.

MS. BECKER: I don't know.

SPEAKER: I thought it was some -- there was some language changes between the beginning of March meeting to --

MS. LORETZ: Yeah, someone would know better than I would here at the table.

MS. BECKER: I'm not sure what the question is. Would you --

SPEAKER: So, the question is that in terms of the skin protection requirements, was it part of the conclusion or just part of the discussion for manufacturers to consider?

MS. BECKER: It is part of the conclusion.

DR. HILL: She's asking March, was it also part of the conclusion then?

MS. BECKER: Oh, in March?

DR. MARKS: Well, yes, because that's when we went over the issue of how we were going to deal with protection and, you know, the most conservative approach is to protect the hands and that was what was suggested in one of the articles we reviewed.

So, the Belsito team really wanted to have that as part of the conclusion and that's, I think –

DR. HILL: There was no conclusion in the document –

MS. BECKER: Yeah, the conclusion was made in March to add the protection –

DR. MARKS: Right.

MS. BECKER: -- and it was more than one paper that suggested having protection.

DR. MARKS: Yes. Okay. So, to me the conclusion would be similar for both -- not similar, the same, in terms of photo protection.

DR. HILL: Although, in reality, if we knew the consumer was using the right bulb and using one of these that had very low risk, we wouldn't need that.

DR. MARKS: Even more reason to have the photo protection because if the wrong bulb is in there, you're protecting this.

Okay.

MS. BECKER: Yes. You may change the world yet.

DR. MARKS: There you go. Any –

DR. HILL: May.

DR. MARKS: Does that clarify for you?

SPEAKER: Yes. I had a (inaudible).

DR. GILL: Well, it may have gone into the March meeting without that language in it.

DR. HILL: There was -- I just looked at the document. There was no conclusion. It was developed in the discussion of the March meeting.

DR. GILL: So, it came out of the March meeting with that conclusion in the final minutes.

SPEAKER: Okay.

DR. HILL: The nice thing about paperless, I can't find it.

DR. MARKS: Any other comments? It is -- we have –

DR. HILL: Don't go to polyoxyalkylenes before lunch.

DR. MARKS: Yeah. It's three of, I don't think we're going to deal with that in three minutes or five minutes. Is that what you're saying?

DR. HILL: I'm saying I would prefer not to try.

DR. MARKS: Yeah. Okay. So, we'll adjourn for lunch and we will meet back at five after the hour.

Day Two

DR. BERGFELD: ...So moving on to the third ingredient, Hydroquinone, Dr. Marks.

DR. MARKS: So this is an amended safety assessment of Hydroquinone. If you recall in the past, the reason this was reopened was the issue of possible UV light induced skin cancer. With that in mind, a tentative amended report was issued in March. After our March meeting, I moved that we issue a final amended report with a conclusion that Hydroquinone is safe at concentrations less than or equal to 1 percent 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 polymerization inhibitor in artificial nail coatings that are cured by a UV light when photo protection material, such as gloves or sunscreens for the skin are used. Hydroquinone, and we changed the wording in this, based on what had been before. Hydroquinone is unsafe in other leave on cosmetic products. That was the wording in the previous report, so I think it's an editorial change. Changing should not be used to unsafe.

DR. BERGFELD: Comment, motion?

DR. BELSITO: If you're asking for comments -- we're very concerned by the Dowdy-Sayre paper which reinforced the issue that I brought up at the last meeting, that the bulbs could easily be interchanged with UVC or UVB bulbs and we felt, and I'll ask Rachel to comment on the effectiveness of a consumer alerts and inserts et cetera, as to whether, in a country where consent forms for clinical studies need to be at a fifth grade level, that there was the potential that the wrong bulb could easily be inserted into the machine. So we didn't have safety -- we didn't have issues with the safety of Hydroquinone and this pertains to para-hydroxyanisole, and we thought that the current UV cured nail coatings could be safely used in a salon setting, however we felt that in the present practice of use that require this machine to be used, that could, potentially with the wrong bulb, cause blindness, that they were not safe for use in the home. And I'll ask Rachel to comment on what she knows about consumer alerts.

DR. WEINTRAUB: Sure, in terms of the efficacy of warnings and information in instruction manuals, there's a lot of research that indicates that consumers don't read that information. They're not aware of warning labels, even on products, even on products that they ride for example, and really, in the safety hierarchy, the weakest thing that can be accomplished is to include a warning, or instructional information, whereas the safest thing to do is to design out a potential hazard.

DR. BELSITO: So we felt with the conclusion that to, specifically for the nails, that Hydroquinone is safe for use in nail adhesives and in a professional setting, as a polymerization inhibitor in artificial nail

coatings that are cured by UV light, when photo protected materials, and we'd agree that Hydroquinone is unsafe in other leave on products. So we're restricting the UV curing to a professional setting.

DR. BERGFELD: Mark's team?

DR. MARKS: I certainly that's, I think our team would support that. I guess the question is, does that change the conclusion enough that it needs to be sent out for public view again? So we would support that. I guess, Don, in your comments, I don't recall issues with blindness, if I heard you correctly. It was always induction of squamous cell carcinoma.

DR. BELSITO: Well I was concerned about that, but if you can easily and in the paper that was submitted by industry, there's an entire paragraph that the bulbs can be interchanged with UVB and UVC bulbs. And you know as well as I, and we were told that if you try and cure the nail enamel with that, it's not going to work. So I can see a scenario where a woman has put her hands, or whoever is doing this, under the bulb for 8 seconds, nothing's happening, they pick it up and look, is the bulb working, and they've known stared into UVB or UVC. I think that that's a real issue. Or they have it on a table, and a little kid is underneath the table, looking up at the bulb. I think there's a potential that blindness could occur, because we know that is a risk of looking at a UVB or UVC bulb. And so I don't think that it's safe under the current conditions of use, which required these UV curing, where the bulbs can be switched out with the wrong bulbs.

DR. MARKS: No that's fine. I just wanted to hear your rationale for the blindness, since that was a new effect that we hadn't discussed before.

DR. BERGFELD: Any other discussion? Any other points of interest?

DR. MARKS: So I will withdraw my motion, so that we can incorporate the changes that the Belsito team has recommended.

DR. BERGFELD: Okay.

DR. MARKS: The restriction as I understand it, basically, it's restriction of the use of these to salons.

DR. BELSITO: UV cured.

DR. MARKS: Yes.

DR. BELSITO: The nail adhesives, that's fine. Home setting is fine. But the UV cured nail coatings would be restricted to salon use.

DR. BERGFELD: So we'll have a second. Are you seconding it Doug?

DR. BELSITO: I made the motion.

DR. BERGFELD: Well we had –

DR. MARKS: Second.

DR. BERGFELD: Second.

DR. BELSITO: Okay.

DR. BERGFELD: All right. So we move forward with –

DR. MARKS: And I would like to move on.

DR. BERGFELD: Withdraw placed again, and second, and thank you. Any other discussion?

DR. SHANK: Is there any other way to handle this without putting it in the discussion?

DR. MARKS: Airing the conclusion you mean?

DR. SHANK: In the conclusion.

DR. BELSITO: No, I think if you're going to restrict it to salon use, it has to be in the conclusion.

DR. SHANK: Well, is it necessary to restrict it to salon use? If we can solve the issue about interchanging bulbs.

DR. BELSITO: Yeah but they -- if industry can come back to us and show us that there's a way to prevent the bulbs from being changed, but as it's currently, all of the units that are currently out there, according to the Sayre paper, the bulbs can be changed. And you can use a different wavelength of bulb. So I mean if industry wants to come back and say that they're only going to manufacture these machines with a bulb that can't be changed out or a socket that can only be used for a UVA bulb, I think that's a different issue. But we had this discussion with methylene glycol and keratin. You know if industry can come back and show us a way that they can properly vent this, we wouldn't have an issue with it. But we don't have that way yet. It's not out there, and until it is, I think that under the conditions of use that require the use of this machine, a home use is to me, not safe.

DR. BERGFELD: Lillian, anything? No? Any other discussion? Seeing none, I'll call the question, and the modification that's been made on use for the cured by, coatings cured by UV light when photo protected when gloves et cetera are used? That is the correction?

DR. BELSITO: Right.

DR. BERGFELD: Change in the motion. All right, I'll call the question. All those in favor, indicate by raising your hand. Unanimous. Then, moving on to the next ingredient.

DR. HILL: And we are changing that language to unsafe for use –

DR. BERGFELD: Yes we are.

DR. HILL: As opposed to (inaudible)

DR. BERGFELD: That was agreed upon, yes. Thank you. Hydroxyanisole, Dr. Belsito.

DR. BELSITO: Same issue.

DR. BERGFELD: Motion?

DR. BELSITO: That the use of Hydroxyanisole in UV cured nail enamels be restricted to professional use.

DR. BERGFELD: Kim, Marks?

DR. BELSITO: And unsafe for other.

DR. MARKS: Yeah, it's a little different conclusion because it's unsafe for other cosmetics, so there's no safe use other than for the UV cured nail coatings, so I would second that motion.

DR. BERGFELD: Any other discussion regarding this ingredient? Seeing none, I call the question. All those in favor, indicate by raising your hands. Unanimous, thank you. Then moving on to the next ingredient, Barium Sulfate, Dr. Marks.

DR. MARKS: So previously that will go out as a final amended then.

DR. BERGFELD: Yes.

DR. BELSITO: Wait a minute. We've changed the conclusion; will that still go out as a final amended?

DR. BERGFELD: It will need to come back.

DR. BELSITO: Right.

DR. BERGFELD: It will go out for review again.

DR. BELSITO: Right.

DR. BERGFELD: But it will be amended to the document.

DR. BELSITO: Right.

Amended Safety Assessment of Hydroquinone as Used in Cosmetics

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The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, 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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ABSTRACT

Hydroquinone was reviewed to address the new uses in nail gels reported by industry, which require UV curing. 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 UV curing. The Panel concluded that hydroquinone is safe at concentrations of $\leq 1\%$ 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 that are cured by UV light when photo-protective materials for the skin are used in professional settings; these products are unsafe for in-home use requiring a UVA light source. Hydroquinone is unsafe in other leave-on cosmetic products.

INTRODUCTION

This is an amended safety assessment of hydroquinone. 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."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 was not safe for use in leave-on, non-drug cosmetic products. In 2010, the Panel concluded that hydroquinone was "...safe at concentrations of $\leq 1\%$ 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. More recently, a new use in nail gels and adhesives that require UV curing 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 new use.⁵

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/m³].

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. 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 $35 \pm 17\%$, from a solution containing Azone was $66 \pm 13\%$, from a solution containing Escalol 507 was $26 \pm 14\%$, and from a solution containing only hydroquinone was $57 \pm 11\%$. 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/cm²/min (1.1 kg/cm²/h). Hydroquinone was rapidly absorbed and excreted by male and female Fischer rats following oral administration; overall recovery was $\geq 96\%$ 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 LD₅₀ 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 - 1000 mg/kg) and mice (31 - 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 B6C3F₁ mice but "no evidence of carcinogenic activity" for male B6C3F₁ 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-amyl nitrosamine (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

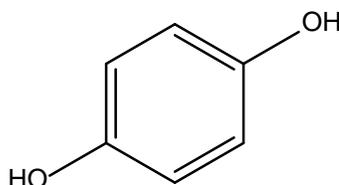
hair dye epidemiology data is available at <http://www.cir-safety.org/cir-findings>].

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 as an antioxidant, fragrance ingredient, hair colorant, reducing agent, and skin bleaching agent. Hydroquinone is a common name for 1,4-dihydroxybenzene.

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



Hydroquinone

Figure 1. Hydroquinone.

USE

Cosmetic

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.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 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.¹⁰

Hydroquinone is added to the monomer and oligomer (i.e., 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.

A nail polish gel had reduced amounts of hydroquinone after curing (Table 1).¹¹

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.¹² 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. 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.⁴

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.^{13,14}

An internet 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 Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) or the Personal Care Products Council (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.

Data on ingredient use are provided to the FDA 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. 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.

A survey was conducted by the Council of the maximum use concentrations for these ingredients.¹⁷ There were no reported uses for this ingredient.

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.¹⁰ 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.¹⁵

Health Canada¹⁸ 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."

Non-Cosmetic

The re-evaluation of hydroquinone's Generally Recognized as Safe and Effective (GRASE) label in leave-on drug products by the FDA, noted in the 2010 summary above, has not been completed.¹⁹

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.²⁰ The test substance was administered daily to one or both ears (volume not specified) of the rabbits or to the shaved abdomen (2 g/cm²); 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.²¹ 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.²² 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.²³

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.²⁴

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.²⁵ 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 Pol η -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 Pol η resulted in more enhanced apoptosis and more pronounced S phase arrest following hydroquinone treatment. The authors concluded that Pol η plays an important role in the response of L-02 cells to hydroquinone-induced DNA damage.

Hydroquinone (45-900 μ M; 50 μ L) was not clastogenic in cultured human lymphocytes with or without metabolic activation.²⁴ 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 μ M) 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; 25 μ L; > 99.5% pure) was predicted to be a dose-dependent sensitizer.²⁶ The EC₃ values were 0.07%, 0.03%, 0.08%, and 0.07% for the four laboratories.

When hydroquinone (5% in 25 μ L 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.²¹ 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 2).²⁷⁻³⁸ 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. 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 and 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.³⁹

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.⁴⁰ 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.⁴¹ The UV bulbs were also reported to emit in the 390-420 nm range.⁴

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.⁴² Typical client usage is 1–4 times/month for 2 min or less per visit.⁴¹

Another researcher stated that typical salon exposures are 10 minutes or less per hand and with exposures occurring only twice per month.⁴³

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 1 min, 2 min, and 3 min, respectively for a total of 6 min using another UV light.⁴⁴

Typically, 3 or 4 separate thin coats of nail gel be applied and cured for 3 min each coat to achieve the desired results.³⁹

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.⁴⁵ However, measured in J/m², cumulative exposures were equivalent, in less than 10 min, to the recommended limit of 30 J/m² 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/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/m²/y from 15 and 22.5 J/m² 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 (μ W/cm²/nm) than the sun (UV Index = 6) in the 355 to 385 nm range. The authors recommended the use of full spectrum sun block to the hands 30 minutes before exposure.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, submitted by the Nail Manufacturers Council on Safety (NMC), 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 (low risk for 1 lamp tested) or 2 (moderate risk for the other 5 lamps) based on $S(\lambda)$ -weighted (i.e., relative spectral effectiveness-weighted, where $S(\lambda)$ ranged from 0.2–1.7 $\mu\text{W}/\text{cm}^2$) 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 $\mu\text{W}/\text{cm}^2$ 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.

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.⁴⁶

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.⁴⁷ UVA irradiance ranges from 0.6 to 15.7 with an average of 10.6 mW/cm². UVA energy ranges from 0 to 8 with an average of 5.1 J/cm². 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/m²; 60 J/cm²). Higher wattage sources correlated with higher UVA irradiance emitted in the lamps. The survey was conducted using a UVA/UVB light meter (280 to 400 nm) in 5 different positions within each lamp to mimic possible hand positions.

When compared to the UV output of tan bed lamps, UV nail are vastly less hazardous.⁴³ 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.⁴⁸ 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 9-W UV fluorescent bulbs (36W total). The second contained one 9-W UV fluorescent bulb (9W). The third contained six 1-W light-emitting diode UV lights (6W). The UV nail lamps primarily emitted UVA with no detectable UVB or UVC (lower detection limit of 0.1–0.2mWm²). 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 two 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 UV-B or UV-C), which could be harmful to the skin if used.⁴³ 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.

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 one 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).⁴⁹ 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.

FINGER NAILS

UVB light did not penetrate the finger nails of a cadaver (n = 10).⁵⁰ 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.^{51,52} All subjects reported using gel polish and having difficulty in its removal. To remove the gel, their nails were soaked in acetone for 10-15 min and, in some cases, the polish had to be manually peeled off. All subjects noted that their nails became noticeably thinner after the manicure. All 5 manicures were done professionally in a salon, but it is not known if the gel was removed at a salon or by the subject. The brand of nail gel or ingredients of the nail gel were not provided.

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

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

CASE REPORTS

Non-melanoma skin cancers were observed on the dorsum of the hands of two women who reported exposure to UV nail lamps.³⁹ 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.³⁹

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 was not safe for use 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 require UV curing. Because these products are marketed as direct sales, they are being 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 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.

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 the survey 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 EC₃ 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. UV bulbs were also reported to emit in the 390-420 nm range. In one study, the UV nail lamps tested were reported to emit wave-lengths of 365-370 nm. Another study reported wave-length emissions of 355 to 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 two different measurement methods, the cumulative MED were low. However, in less than 10 minutes, the exposure measured in J/m² 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 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.

There were two case reports of squamous cell carcinomas on the dorsum of the hands of two women who used UV nail lamps reported.

It was recommended 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 UV-B or UV-C).

DISCUSSION

Hydroquinone caused depigmentation to the skin at concentrations greater than 1%. The Panel found hydroquinone to be safe at that concentration or less in rinse-off products and nail adhesives in 2010. That conclusion did not contemplate the new use in artificial nail coatings that are cured under UV 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 amount 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 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 Panel noted that the concentration of hydroquinone was not indicated in the sensitization studies conducted by applying the nail gel to the fingernails. While these studies do not demonstrate the dermal sensitization potential of these products when administered to the skin, the lack of observed sensitization when administered to the nail 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 carcinogenicity 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.

Nail lamps, as currently designed, are manufactured using universal light bulb sockets. The UVA bulbs used in nail lamps emanate 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 UVC bulb, incur eye damage from that light. Additionally, the Panel was concerned that these lamps might be used at the eye level of small children. Also, there was concern that home users may be exposed to additional UV light exposures to the hands if they increase the exposure duration when the nail gel does not set properly because the wrong bulb is used.

The Panel noted that there is substantial research demonstrating the general public's inattention to product warning labels and operating instructions, and discussed the possibility that an improper replacement bulb could be inserted into the UV lamp. The Panel stated that industry should manufacture lamps in which the bulbs cannot be replaced; so that the lamps will be disposed when the bulbs no longer function, or develop unique sockets for the lamps to ensure that only use the appropriate narrow-band UVA-only bulbs are used.

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 either products for skin lightening or brightening products (drugs) and not for 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 $\leq 1\%$ for cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair; safe for use in nail adhesives and as a polymerization inhibitor in artificial nail coatings that are cured by UV light when photo-protective materials (eg, gloves, sunscreen) for the skin are used in professional settings. Hydroquinone is unsafe for in-home nail products that require curing by UVA light; and 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.⁵³

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 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	n	Reference
UV gel top coat nail polish	51	³²
UV gel top coat nail polish	51	³¹
Builder gel	51	³⁰
Clear overlay gel	51	²⁹
Soak-off sealer	51	²⁸
Soak-off gel lacquer	51	²⁷
Gel system-thick gel sealer	50	³³
Base gel	51	³⁴
No-cleanser overlay gel	51	³⁵
Soft white sculpting gel	51	³⁶
Pink builder gel	51	³⁷
Luminous white overlay gel	51	³⁸

Table 3. 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 4. The number of individuals who would need to be exposed to ultraviolet A (UVA) nail lamps^a for one individual to develop squamous cell carcinoma who would not have done so otherwise.⁴⁹

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

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

REFERENCES

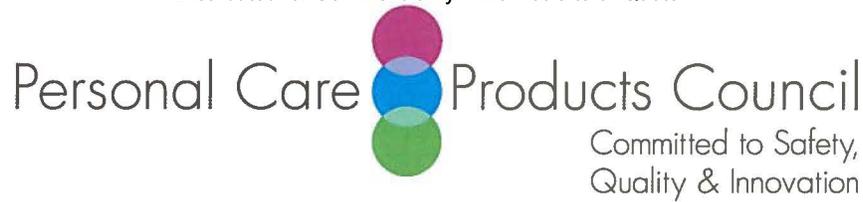
1. Elder RL. Final report on the safety assessment of hydroquinone and pyrochatechol. *Journal of the American College of Toxicology*. 1986;5(3):123-165.
2. Anderson FA. Addendum to the final report on the safety assessment of hydroquinone. *Journal of the American College of Toxicology*. 1994;13(3):167-230.
3. Anderson FA, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks, Jr JG, Shank RC, Slaga TJ, and Snyder PW. Final amended safety assessment of hydroquinone as used in cosmetics. *International Journal of Toxicology*. 2010;29(Suppl 4):274S-287S.
4. David Steinberg. Memo. 2-4-2013. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
5. Becker, LC, Bergfeld, WF, Belsito, DV, Hill, RA, Klaassen, CD, Liebler, DC, Marks Jr, JG, Shank, RC, Slaga, TJ, and Snyder, PW. Amended safety assessment of *p*-hydroxyanisole as used in cosmetics; Draft Final Amended Report. Washington, DC, Cosmetic Ingredient Review. 2014. pp. 1-11.
6. National Toxicology Program (NTP). NTP technical report on the toxicology and carcinogenesis studies of hydroquinone (CAS No. 123-31-9) in F344/N rats and B6C3F₁ mice (gavage studies). Research Triangle Park, NC, U.S. Department of Health and Human Services; Public Health Service; National Institutes of Health. 1989. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr366.pdf. Report No. NIH Publication No. 89-2821.
7. Hodge HC and Sterner JH. Tabulation of toxicity classes. *American Industrial Hygiene Association Quarterly*. 1949;10(4):93-96.
8. Shibaba M-A, Hirose M, Tanaka H, Asakawa E, Shirai T, and Ito N. Induction of renal cell tumors in rats and mice, and enhancement of hepatocellular tumor development in mice after long-term hydroquinone treatment. *Japanese Journal of Cancer Research*. 1991;82(11):1211-1219.
9. Nikitakis, J and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 15 ed. Washington, DC: Personal Care Products Council, 2014.
10. Scientific Committee on Consumer Products and Non-Food Products Intended for Consumers (SCCNFP). Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) concerning the use of benzoyl peroxide (BPO), hydroquinone (HQ), hydroquinone methylether (MeHQ) in artificial nail systems. 2002. http://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out167_en.pdf. Report No. SCCNFP/0486/01, final. pp. 1-15.
11. Anonymous. 2012. Monomethyl Ether Hydroxy Quinone (MEHQ) Detectability in Soft Gel Base Coat at Various Curing Time. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
12. Creative Nail Design Inc (CND). Brisa™ Swirl UV Gel Enhancements Sculpted on a Tip [pamphlet]. Vista, CA: Creative Nail Design; 2013.
13. Creative Nail Design Inc (CND). Brisa™ Lite Removable Sculpting Gel Enhancements Removal [pamphlet]. Vista, CA: Creative Nail Design; 2013.
14. Creative Nail Design Inc (CND). Brisa™ Lite Removable Smoothing Gel Enhancements Removal [pamphlet]. Vista, CA: Creative Nail Design; 2013.
15. European Commission. II (Non-legislative acts); Regulations; Commission regulations (EU) No. 344/2013 of 4 April 2013; amending Annexes II, III, V, VI to Regulation (EC) No 1223/2009 of the European Parliament and the Council on cosmetic products. *Official Journal of the European Union*. 2013;114:1-59.
16. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients; *FDA Database*. Washington, DC, FDA. 2014.
17. Personal Care Products Council. 11-20-2013. Concentration of use by FDA Product Category: Hydroquinone and *p*-Hydroxyanisole. Unpublished data submitted by Personal Care Products Council. 1 pages.
18. Health Canada. Health Canada: Cosmetic Ingredient Hotlist - March 2011. <http://www.hc-sc.gc.ca/cps-spc/cosmet-person/indust/hot-list-critique/hotlist-liste-eng.php#H>.
19. Food and Drug Administration (FDA), Department of Health and Human Services (HHS). Nomination profile: Hydroquinone [CAS 123-31-9]. Supporting information for the toxicological evaluation by the National Toxicology Program. 2009. http://ntp.niehs.nih.gov/NTP/Noms/Support_Docs/Hydroquinone_may2009.pdf#search=hydroquinone%20GRASE. pp. 1-49.
20. Jarrar BM, Alenezi MM, Al-Hiri A, and Jarrar Y. Hepatic and renal histological alterations induced by topical hydroquinone administration. *American Journal of Pharmacology and and Toxicology*. 2012;7(1):19-26.
21. Nair X and Tramposch KM. The Yucatan miniature swine as a *n in vivo* model for screening skin depigmentation. *Journal of Dermatological Science*. 1991;2(6):428-433.

Distributed for Comment Only -- Do Not Cite or Quote

22. Fasano WJ and McDougal JN. In vitro absorption rate testing of certain chemicals of interest to the Occupational Safety and Health Administration: Summary and evaluation of USEPA's mandated testing. *Regulatory Toxicology and Pharmacology*. 2008;51(2):181-194.
23. Nakagawa Y and Moldéus P. Cytotoxic effects of phenyl-hydroquinone and some hydroquinones on isolated rat hepatocytes. *Biochemical Pharmacology*. 1992;44(6):1059-1065.
24. Roza L, de Vogel N, and van Delft JHM. Lack of clastogenic effects in cultured human lymphocytes treated with hydroquinone. *Food and Chemical Toxicology*. 2003;41(10):1299-1305.
25. Hu G, Huang H, Yang L, Zhong C, Xia B, Yang Y, Liu J, Wu: Liu Q, and Zhuang Z. Down-regulation of Polç expression leads to increased DNA damage, apoptosis, and enhanced S phase arrest in L-02 cells exposed to hydroquinone. *Toxicology Letters*. 2012;214(2):209-217.
26. Kimber I, Hilton J, Dearman RJ, Gerberick GF, Ryan CA, Basketter DA, Lea L, House RV, Ladics GS, Loveless SE, and Hastings KL. Assessment of the skin sensitization potential of topical medicaments using the local lymph node assay: An interlaboratory evaluation. *Journal of Toxicology and Environmental Health, Part A*. 1998;53(7):563-579.
27. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Soak-Off Gel Lacquer. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
28. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Soak-Off Sealer. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
29. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Clear Overlay Gel. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
30. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Clear Builder Gel. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
31. Biometrix Inc. 2010. Human Insult Repeat Patch Evaluation of the Nail Product Gel Color. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
32. Biometrix Inc. 2010. Human Insult Repeat Patch Evaluation of the Nail Product UV Gel-EO Top Coat. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
33. Biometrix Inc. 2010. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Gel System-Thick Gel Sealer. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
34. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Base Gel. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
35. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium No-Cleanse Overlay Gel. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
36. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Soft White Sculpting Gel. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
37. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Pink Builder Gel. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
38. Biometrix Inc. 2008. Human Insult Repeat Patch Evaluation of the Nail Product Axxium Luminous White Overlay Gel. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
39. MacFarlane DF and Alonso CA. Occurrence of nonmelanoma skin cancers on the hands after UV nail light exposure. *Archives of Dermatology*. 2009;145(4):447-449.
40. Rapid Precision Testing Laboratories. CND UV Lamp. 9-28-2011. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
41. Schoon D, Bryson P, and McConnell J. Do UV nail lamps emit unsafe levels of ultraviolet light? 2010. <http://www.schoonscientific.com/downloads/UV-Nail-Lamp-Facts.pdf>. pp. 1-5.
42. Anonymous. 2011 - 2012 Industry statistics [pamphlet]. 2013.
43. Sayre RM. 2014. Letter regarding UV lights. Unpublished data submitted by Robter M. Sayre.
44. OPI Inc. Soak-off gel lacquer Application Instructions [pamphlet]. Hollywood, CA: OPI Inc; 2011.

Distributed for Comment Only -- Do Not Cite or Quote

45. Curtis, J, Tanner P, Judd C, Childs B, Hull C, and Leachman S. Acrylic nail curing UV lamps: High-intensity exposure warrants further research of skin cancer risk. *Journal of the American Academy of Dermatology*. 2013;69(6):1069-1070.
46. Dowdy JC and Sayre RM. Photobiological safety evaluation of UV nail lamps. *Photochemistry and Photobiology*. 2013;89(4):961-967.
47. Shipp, LR, Warner, CA, Rueggeberg, FA, and Davis, LS. Further investigation into the risk of skin cancer associated with the use of UV nail lamps. *Journal of the American Medical Association Dermatology*. 2014;April(Epub ahead of print).
48. Markova, A. and Weinstock, M. A. Risk of skin cancer associated with the use of UV nail lamp. *J.Invest Dermatol*. 2013;133(4):1097-1099.
49. Diffey BL. The risk of squamous cell carcinoma in women from exposure to UVA lamps used in cosmetic nail treatment. *British Journal of Dermatology*. 2012;167(5):1175-1178.
50. Stern DK, Creasey AA, Quijije J, and Lebwohl MG. UV-A and UV-B penetration of normal human cadaveric fingernail plate. *Archives of Dermatology*. 2011;147(4):439-441.
51. Chen, AF, Chimento, SM, Hu, S, Sanchez, M, Zaiac, M, and Tosti, A. Nail damage from gel polish manicure. *Journal of Cosmetic Dermatology*. 2012;11(1):27-29.
52. Chen, AF. afederico@gmail.com. Question on Chen, et al 2011. 7-17-2014. Date Accessed 7-17-2014
53. Anonymous. 2012. Monomethyl Ether Hydroxy Quinone (MEHQ) Detectability in Polish-on Gel at Various Curing Time. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council. 8 pages.



Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D. 
Industry Liaison to the CIR Expert Panel

DATE: July 16, 2014

SUBJECT: Comments on the Tentative Report: Amended Safety Assessment of Hydroquinone as Used in Cosmetics

Key Issues

Although it is helpful for the CIR Expert Panel to express their concerns about the safety of lamps used to cure nail gels in the Discussion of the CIR report, the conclusion should not state that nail gel products are only safe in professional settings based primarily on a concern about the potential for incorrect bulb replacement. This report is about Hydroquinone. The Conclusion should state that the CIR Expert Panel found that Hydroquinone is safe as a polymerization inhibitor in artificial nail coatings that are cured by light.

Abstract - At the last CIR meeting David Steinberg stated that the wavelength required to cure the nail gel products being sold for home use was in the range of 400-420. This is visible light. Therefore, it is not appropriate to state that the home-use kits "require UV curing".

p.9, Discussion - At the December 2013 meeting, David Steinberg said that the lamps used to cure the nail gel products emit light in the range of 380 to 420 nm not 320-400 nm as stated in the Discussion.

Reference 45 - Although the website hooked-on-nails.com may provide some useful information, the website does not indicate who is responsible for the information. Anonymous websites should not be used as references in CIR reports.

Additional Comments

p.4-5 - It is not clear why there are subsections in the Cosmetic Use section as information about use in nail products is mention in both the subsection titled "Use in nail products" and the subsection titled "Use in Other Cosmetic Products".

p.5 - So that a dose of Hydroquinone could be calculated, please state the volume of material administered to rabbits (reference 20) and miniature pigs (reference 21).

p.6 - What was the dosing volume used in the LLNA (reference 26)?

p.6, p.8 - In the section on nail lamps and the Summary, it should be noted that the studies were on lamps used at salons.

p.8 - The Summary should also note that some study authors had concerns about replacing bulbs in lamps with incorrect bulbs.

p.9 - As product formulations change, and because both the VCRP and Council surveys are voluntary, the information will never be "comprehensive". Please change "comprehensive" to "representative".