
Amended Safety Assessment of Hydroquinone as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: May 16, 2014
Panel Meeting Date: June 9-10, 2014

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.

MEMORANDUM

To: CIR Expert Panel and Liaisons

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

Date: April 16, 2014

Subject: Hydroquinone As Used In in Cosmetics

In March 2014, the Panel issued a Tentative Amended Report of hydroquinone with the conclusion 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 (e.g., gloves, sunscreen) for the skin are used. Hydroquinone should not be used in other leave-on cosmetic products. Comments from the public and industry were addressed.

No new data have been submitted by industry.

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 March meeting are included in each Panel book.

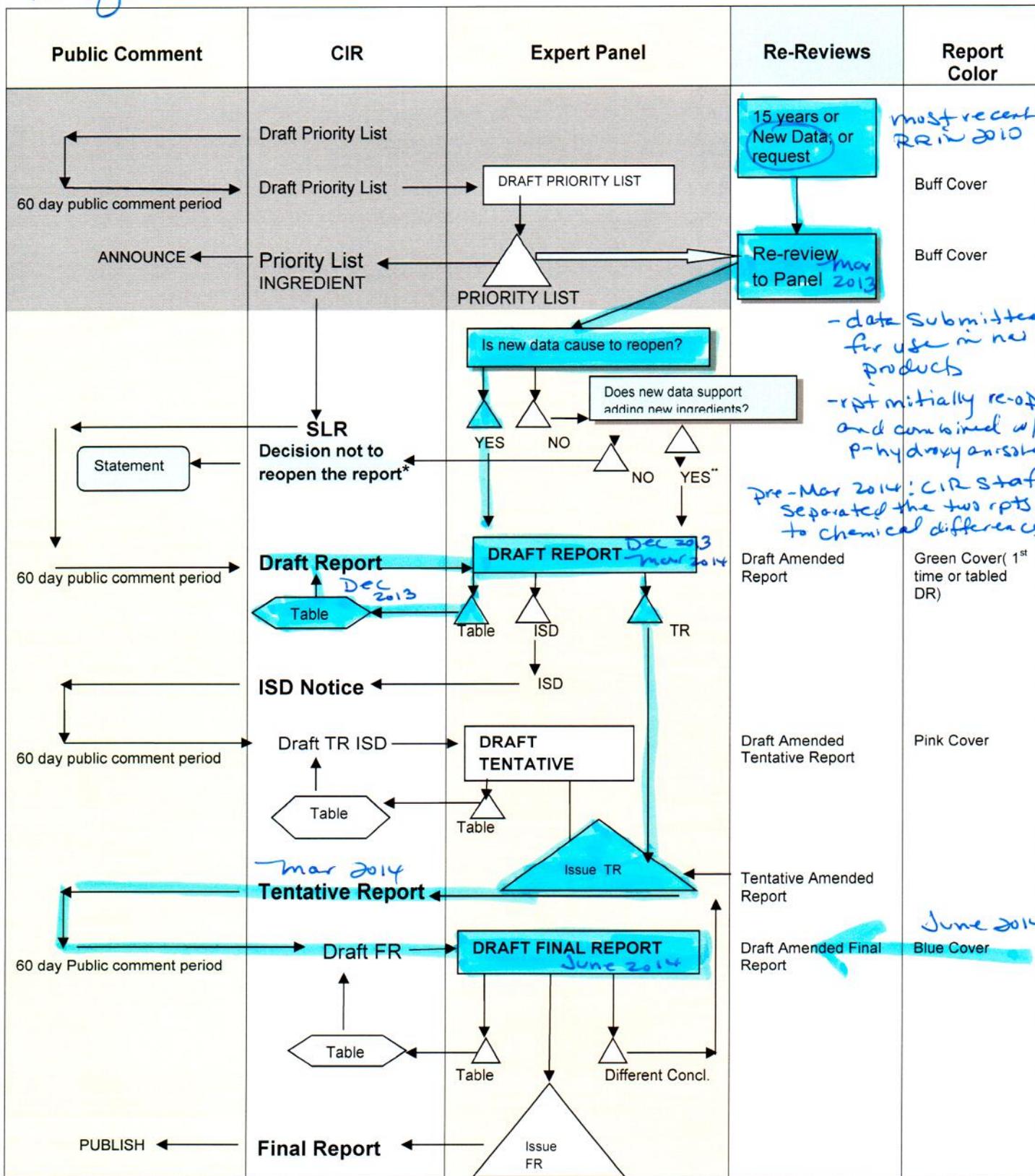
As requested, an additional web search was conducted for cosmetics containing this ingredient (see the Search Strategy). All results found were for skin lightening/brightening products (drugs) and not for cosmetics.

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.

SAFETY ASSESSMENT FLOW CHART

Hydrogumoni

June 2014



- data submitted for use in next products

- rpt initially re-opened and combined w/ p-hydroxy anisole

Pre-Mar 2014: CIR staff separated the two rpt's due to chemical differences

*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** – 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

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 were skin lighteners/brighteners

"hydroquinone cosmetics" – No hits. All possible hits were skin lighteners/brighteners

"hydroquinone cream" – No hits. All possible hits were skin lighteners/brighteners

Transcripts – Hydroquinone and *p*-Hydroxyanisole

Dr. Marks' Team

DR. MARKS: ...Okay. Next one is hydroquinone. This is going to be equally -- so, actually, hydroquinone and *p*-hydroxyanisole, which is chemically known, David, as --

MR. STEINBERG: MEHQ.

DR. MARKS: MEHQ.

MR. STEINBERG: Monomethyl ether hydroquinone.

DR. MARKS: These were split out for today's session, and so we can deal with them individually, but, at any rate, there's a relationship, because the concern that brought these up where they're used in nail products. And, prior with hydroquinone, which is the first one we're going to deal with, it was concluded safe in 2010, including nail adhesives. And, I'll mention -- even though it's going to be in the next report -- *p*-hydroxyanisole safe only for use in nail products.

In 1985, it was unsafe because of depigmentation. That's possible to have them together. At any rate, one, no need to re-open hydroquinone since the conclusion already states it's safe for nail products. So, I think that's where we could go with this one, is do you want to open it or not or leave it stand as previously and just do a re-review with a discussion of UV light exposure, and that's the biggest, I think, concern that was raised by those two patients reported with squamous cell carcinoma on their hands.

So, two case reports and then a number of papers subsequent to that doing a risk assessment and comments about how hazardous or non-hazardous the light exposure from this procedure used in the salons. And, I have a feeling that this session is going to be the same for both in terms of the light. So, that will be repeated. So, let's first decide, do we want to re-open or not the hydroquinone.

And, I also should mention there was an issue of depigmentation that is possible in the workers within these nail salons and the manicurists and that a Google search from the Women's Voices letter in Wave 3 found other uses in consumer products and then the question of nail penetration. So, there are a lot of issues involved.

Do we want to decide whether we want to re-open or -- Rachel, I ask for your input of this, because there's some real concerns from a consumer's point of view, and if there's somebody here from Women's Voices who wants to speak and certainly David and Doug. So, Rachel, maybe.

MS. WEINTRAUB: At a minimum, I think the letter raised very important issues that the panel has to consider.

DR. MARKS: Absolutely.

MS. WEINTRAUB: So, you know, I think we need to proceed and investigate the issues that it raises and address it in the discussion at a minimum.

DR. STEINBERG: Do you want to go through each point of the letter, or just talk in general about the letter? Because, there are several things about the letter which are just -- they're interesting, but they're really not relevant. For example, the comments that there were no reported uses under VCRP of the MEHQ. That's because it was always used for professional-use-only products and professional-use-only products are prohibited from registering under VCRP.

So, I'm not sure there would be no use, because that was the only use, until the gel nail polishes came about which were originally sold and continue to be sold for professional use only, but there are not home kits, as these are possible for you to do at home, where the other use, the nail extenders, are extremely difficult to use at home.

I actually last month had a fingernail done, this fingernail done, with an at-home kit, and the person who did it to me or applied it basically followed the instructions that are on the kit. There was a wooden stylus and that you are to be sure that none of the first coat goes on the skin or on the cuticle. If you do, it's not going to give you a satisfactory nail gel. And, with the stylus, which is like a very thin

wooden pencil, she made sure that there was no coat on the nail itself. She then had me place it in the light source.

The light source -- Doug can speak a little bit more about it, but the light source that I was exposed to had a range of about 380, 390 to 420. It was basically the visible light which is curing the nail gels, not the UV radiation. It's the visible light which does the curing. The problem is buying light bulbs that allow you to have just visible light. The exposure time was very short.

She then checked it and then she put the colored coat on. And, I asked her deliberately to put some on my skin, okay, and these gels are extremely hydrophobic. She put some on my skin. She took the wooden stylus and promptly rolled it into a little ball, took a tissue, and it went into the trash. That leaving it on the skin -- you don't leave it on, because a) you don't want nail polish on the skin when you're cured, and second, it is just so easy to remove that it was done. She then proceeded to put two nail polishes and then the top coat. So, there were four exposures.

I'm going to say the total procedure took maybe two minutes, and I had this beautiful red fingernail. I then asked the question how do you remove it, and that's when they showed me how to remove it, and, because of the VOC regulations in California where this was being done, they have to use acetone as the nail polish remover. So, they took what I would call a Band-Aid -- it's a little bit bigger than that -- they soaked in acetone and they wrapped it around the nail. It took around 10 minutes. They opened it. It didn't quite come off, so they gave it another 2 minutes. She took the wood stylus, put it right by the fingernail, and she just peeled it off like you peel off an onion skin, and it just came right off, and there was no residual part.

The nail gels last 2 to 3 weeks, so you're not doing this every day. The exposure is extremely limited, and, like I say, there are now at-home kits that are being sold. You can get them at most of the beauty shops and also on QVC, I believe they're on, and a couple of other places that they've become very popular. So, in general, one of the comments -- that there is a tremendous exposure to light -- the light that they're being exposed to is basically visible light, and we're being exposed right now to visible light. And, there are papers that we have submitted and documents showing that the light is just a very, very, very minor, very small amount of exposure and it is perfectly safe.

The question about the nail salon use, which was raised by the question at the nail salon, workers are exposed to much more of the light. Again, the light, as you saw on the examples that we had submitted with the original documents, were pictures of these machines. They lie flat and you put your finger underneath it and it's turned on. The only way in which the nail technicians are exposed to light is if they don't follow the directions, and that's something we can't force them to do.

So, we have found that the use of the MEHQ and the HQ, they are put in the monomers; the cosmetic companies who sell these products do not add them. In theory, these would be called processing aids, but since they are now being sold and can be sold to consumers, we felt that they should meet the CIR requirements and be approved as safe in their intended purpose. Like I say, they are destroyed in the polymerization process, so there's no residual MEHQ or HQ present.

DR. MARKS: Are there other comments? So, let's get first the hydroquinone. That's the first report we have here. Do we want to keep it separated, and if we do, not re-open or re-open? Because, it's already been approved for nail use, and if we do not re-open, then I think the discussion can reflect what David talked about. I think the article I cited -- there were some others -- the original one with the two squamous cells was McFarland and Alonzo, but Diffy did an extensive risk assessment and found it to be -- the conclusion was very low, and of course you may have some comments specifically about that one report. You have others. Visible light -- it's --

MR. SCHOON: Yes, sir.

DR. MARKS: So, I certainly have not seen clinically an epidemic of squamous cell carcinomas in individuals who have these UV-cured polymers applied to their nails.

MR. SCHOON: Well, I would agree with you, and I also would point out that since the original observations, no one has come forth and made similar claims or had similar problems. And,

besides the Diffy report, there was another report by Dr. Sayre and Dr. Dowdy who were two really well-known photobiologists who did a thorough study to the ANSI International Standard, the RP-27, which is really probably the best standard for measuring these kind of lights. And, they've demonstrated that exposure is very, very low as well, and they also agreed with the Diffy report that there's not much risk of exposure.

So, this has been -- I mean, the challenge was raised by the original dermatologists who asked the question, and there have been several studies who have addressed this and taken it very, very seriously, I can assure you. And, I think that all the information to date points to the fact that these lamps are not just accidentally safe.

They're designed to be safe in very output of UV, just enough UV, as David pointed out, really hovering near the visible range to cause polymerization, and exposure times are very, very short, getting shorter all the time, and it only occurs every 2 months. So, we're pretty confident in making the statement that we believe these lamps are safe as used, from our perspective.

MR. STEINBERG: One of the questions I was asked on this was what happens if my teenage granddaughter gets a gel kit, has her nails gelled red, and tomorrow she decides she wants to wear a blue dress and wants her nails gelled blue. And, she would ask me, you know, can I take it off and then do another, and I said, why use a 2-week gel if you're going to change the color every day. Just go back to good old-fashioned nail polish then. And, she looked and she says oh, Grandpa, you're so smart. (Laughter)

MR. SCHOON: Two weeks would be a minimum. Some people go 3 weeks, so 2 weeks is actually the minimum.

DR. MARKS: So, Ron, Ron, Tom, presumably tomorrow I'll be seconding a motion by Don Belsito, but we would move that we don't re-open the hydroquinone assessment. Essentially, this is a re-review, but in the discussion it would say that we're not concerned with the safety, and we support the conclusion of 2010.

MS. GILL: That the proposed new use falls under the previous conclusion.

DR. MARKS: Yes. Any other comments? So, Rachel.

DR. WEINTRAUB: I don't have the letter in front of me. I'm trying to find it, but I can't.

DR. MARKS: I have it here.

DR. WEINTRAUB: But, wasn't there another concern that this is in other --

SPEAKER: Non-nail (inaudible).

DR. WEINTRAUB: Yeah, and non-nail and nail uses.

DR. MARKS: To me, the issue there was are we now going to start saying the use concentration and uses -- do we do more than, you know, where's the limit of same? What do you do as your limit of search? So, doing a Google search, I don't know how reliable that is. Of course, voluntary reporting to the FDA may not be perhaps as reliable, but where do you end your search in that. So, I had less concern about the Google search. I thought it was interesting David addressed that, but I didn't know how we would handle it, other than saying, yeah, it may be in some other products, but we got it.

DR. HILL: The other issue that raised with me -- and David can comment on this -- is that clearly there are products where there is both HQ and MEHQ, so one will be present at 1 percent and one at 2 percent, according to an MSDS. This is MSDS for something called LeChat Powder Nail Gel System. It contains both hydroquinone, less than 1 percent, and 4-methoxyphenol, less than 2 percent. There were several others in here that have both, and I was wondering if they're using that to get around -- how do we limit on our current conclusion with hydroquinone? Is it 2 percent or is it --

DR. MARKS: No, I think it's less than 1 percent, but that's on page 4 if you go on the document.

DR. HILL: I was trying to find the original conclusion.

DR. MARKS: Yeah, it's on page 4.

DR. HILL: All right. Well, I've got to --

DR. MARKS: On page 4, look under 2010, Safety assessment on hydroquinone, safe at concentrations of less than 1 percent in hair dyes and safe for use in nail adhesives. So, you'd have to go back and look at the concentrations --

DR. HILL: Okay. So, the nail adhesives, we'd have to actually know what was in the report in terms of concentrations.

DR. MARKS: And, I assume the concentration -- I assumed it hadn't changed in 2 years in nail adhesives.

DR. STEINBERG: As far as I know, the major producer of the nail adhesives in the United States -- this is Krazy Glue, just, in simple terms. This is cyanoacrylate, Krazy Glue, which are sold in these very small tubes, and they have basically found that they can use an antioxidant. They were originally using VHA which is a Prop 65 issue in California. I think they have switched over to BHT, and that gives them -- because they're selling such small quantities, and no one ever uses up a tube, because it just goes bad. As soon as it's exposed to air, it polymerizes and it's done its adhesive job.

The first comment that you made, Dr. Hill, had to do -- there are two specific different types of nail products. There's the two-part acrylate system, which is professional use only. There are some retail kits that were sold. I don't think they were very successful, because consumers just don't have the skills that are needed. You need a trained salon worker to actually get an artificial nail, and the way it is done, as we said back in 2000 and -- it's over 2003 whenever this issue came up -- they basically take what looks like a very small paint brush and they dip it into monomer.

The monomer's a mixture of several monomers, and, again, the monomers are inhibited by HQ or MEHQ, depending on the producer of the monomer, and the level is very interest, defined by the producers by how the product is basically sold. If they're selling a barge and they do ship monomers like this in barges to the plastic industry, they tend to have a different level, usually a smaller or lower level of inhibitor in the barge than if they're shipping it in drums, because the drums are going to have to last so much longer and will have different, you know, people pouring it. And, what we do in the industry, we basically buy them from distributors. No manufacturer of monomers will sell direct, because our use is so small, which is why you'll see these different levels.

Once you take the paint brush and put it into the liquid, it's then dipped into the powder. In the powder is benzoyl peroxide and polymerized material. What happens is the benzoyl peroxide reacts with the inhibitor and polymerization starts. You have a playtime of about 5 minutes to shape it into the nail before it gets too hard a plastic and you have to toss it, which is why consumers -- and then once it's in the correct form, and you have molds, you then glue it on. That's the professional use. We came about the nail gel use for polishes, what, 4 years ago?

MR. SCHOON: About 4 years.

DR. STEINBERG: About 4 years ago. And, this is a derivation of, again, plain chemistry in which they were basically moving away from solvent-based lacquers for automobiles. It all came from the automobile industry, and these products consist of a gel which consists of monomers and techmers which form a jellylike substance. It has the consistency of jelly, okay? They are very sheer thinning, so when you take the brush -- when the technician takes the brush and puts the brush in and pushes it on your fingernail, it sheer thins, so it smoothes and comes out as a coating.

Again, this was sold, professional-use only, okay. But, then, it was discovered that people could do this at home and home kits were -- nail salons basically were buying much bigger quantities. They put much small quantities in along with the lamp exposure media, and those give you the nail gel polishes. So, you have the acrylates which is an artificial nail enhancement -- you're actually building a nail -- and the gel which is a polish. So, there are two separate, different uses. And, again, like I said, we do not add the inhibitors. They just come with what we get, and, like I said, they do tend to vary, which is why there tends to be ranges. And, at no point have we ever seen before polymerization above -- what's it, 1,000 parts per million total?

MR. SCHOON: Yeah.

DR. STEINBERG: I think, that's about the maximum. Most of the time, we're way below that, but occasionally you'll get some material.

MR. SCHOON: Yeah, the cyanoacrylates tend to be the most reactive, so they will have up to 1,000 ppm, and, while you might see several in one formulation is because you may buy one monomer from someone and another monomer from another company, and this monomer has to be stabilized using MEHQ, and the other company will use hydroquinone. Because, really, what we're talking about is a safety issue. We don't want these polymerizing on the way to the consumer or on the way to the manufacturer. So, they're in there to inhibit polymerization. So, they'll use the most effective polymerization inhibitor at the most effective concentration.

DR. STEINBERG: Yeah. They really want to limit the concentration, because the more inhibitor, the harder it is to polymerize.

MR. SCHOON: Right. If you get too much in there, the product just won't work. When the nail technician goes to make the nail, it won't polymerize. So, when you do start the polymerization process, it overwhelms the quinones and destroys them, and that's how the polymerization proceeds.

DR. MARKS: So, again, tomorrow, presumably I'll second a motion that we do not re-open the hydroquinone report from 2010 and we deal with it as a re-review and specifically in that re-review talk about the UV light not being a hazard. Does that sound -- We'll talk more about depigmentation in the next chemical, because the concentration of hydroquinones and this -- I'm not worried about depigmentation. Yes.

DR. WEINTRAUB: Would we also address the home use issue? Because, it seems like there are products.

DR. STEINBERG: The home use are the gel polishes --

DR. WEINTRAUB: Yeah.

DR. STEINBERG: -- as opposed to the artificial nail-building type products.

DR. WEINTRAUB: Right, but they contain this ingredient.

DR. STEINBERG: Yes, they will contain this ingredient, too, inhibit polymerization to exposure to the light.

DR. MARKS: So, the concern about home use versus salon use with this ingredient -- what is that, Rachel, if we feel the main issue was ultraviolet light, and at least that's why this was brought back to us, is because of the concern that is this enough light to cause squamous cell carcinomas. So, to me, it is -- I think we can put it certainly under the use. We need to note that it's home use, but does anybody on the panel feel concern about home use of this versus salon?

MS. BECKER: I just want to point out that, in the salon, they are trained to use it, and I doubt very much that people at home are. Just a thought.

DR. STEINBERG: I think the answer to that question is -- for someone who has tried it, myself -- you're going to learn real quick that if you want to get a satisfactory nail polish gel, you're going to follow the directions, because otherwise, it just -- basically what happens is you'll get it to lift like this. If you have any of the gel on the cuticle instead of getting a flat polish, you will have it lifting off, and then you can just take tweezers and peel it right off. It would be very unsatisfactory. You have to follow directions. And, all the kits are sold with very complete directions. I think in our submission, back when Tara presented it last year, we had the directions for both of the two major manufacturers of these, which stipulate you have to follow the directions in home use.

MR. ANSELL: Yeah, but it really goes to performance. Is there a safety issue? I mean, the fact that they won't perform well at home doesn't seem to me to be concerned, unless we think there's an exposure issue, which --

MS. WEINTRAUB: Right. It could increase exposure if people are doing it at home as well.

DR. STEINBERG: Well, the home care uses for this particular type of product are not much different than applying nail polish, so most people understand how to apply nail polish. They're not

really trying to extend the nail or do any of the fancier things that you would have done in a nail salon. So, the retail gel polish kits that we're talking about are really nothing more than a UV-curing type of nail polish.

MR. SCHOON: Your other question which is very important is the overexposure -- the machine, the light source is a timer. You press the button and it gives you a shot for, I think it's what -- 10 seconds or whatever.

MR. STEINBERG: Depending on the cure.

MR. SCHOON: Depending on the cure. And, you get that one shot. It's not like you turn it on and have to count to 15 and then turn the switch off. These are timers that automatically go off.

DR. BERGFELD: The other question that was in the Voice of the Women was the butyl phthalates, and because the women who paint their nails have higher phthalate blood levels. So, I think when we respond to this, I don't think it's appropriate here, because they use it also as the control in looking at absorption through the nail. But, I think, you know, in response to the writer, we need to clarify and say something in that paragraph.

MR. SCHOON: Well, in response to your question from last time, we've also submitted information, talking about the nail as a very, very good barrier, prevents penetration. In fact, this is one of the challenges that medical professionals have with curing nail fungus. You can't get anything into the nail to cure it. So, we've provided several different papers that give that information. The nail plate really should be thought of, not as an impenetrable barrier, but you've got to do something extraordinary to get penetration through the nail plate. It's not going to happen casually.

DR. STEINBERG: I gave a new publication that we found, what, 2 days ago, which came from England and which was a rather complete review of attempts to penetrate the nail with different solvents. The only thing that was vaguely successful was a 50-50 water-alcohol solution which are just not used here. They just can't get anything through the nail. And, these people have been trying for years to get something to penetrate the nail for the treatment of fungal infections, and they've basically said the only thing that works is through ingestion. They just can't get anything through the nail.

DR. MARKS: That's why I essentially didn't address the phthalates, because we've already done that before.

DR. STEINBERG: The phthalate paper --

DR. MARKS: We've already done that, so.

DR. STEINBERG: -- was years ago, and it was just an example --

DR. BERGFELD: (inaudible) on this that we have to respond to, because it is their last question.

DR. MARKS: Well, I think the response to the letter comes from CIR.

DR. BERGFELD: Yeah. No, it's not us.

DR. HILL: The last sentence of her letter says, on that section, while there may be little absorption through the nail bed itself, clearly there is significant bodily exposure to dibutyl phthalate from the use of nail products containing this chemical, which seem to indicate that the CIR should be concerned, that are because there must be additional exposure routes as well.

MR. SCHOON: Well, to be clear, what we're talking about --

SPEAKER: No one uses dibutyl phthalate anymore.

DR. HILL: They were saying that if dibutyl phthalate can do it, then hydroquinone or MEHQ could do it. I think that's what they were saying is that we can see this chemical getting in, so, therefore, these might as well.

MR. ANSELL: The people wrote a letter. CIR is going to respond to the letter. We're focused on hydroquinone here. We're not going to re-open the whole phthalate discussion.

SPEAKER: I agree.

DR. HILL: I wasn't trying to either. My point was they were saying this is a surrogate, can detect the levels. We don't believe it's going through the nail bed, ergo people are breathing too much of

the stuff. I mean, that's the only -- or it's getting through the skin because people are sloppy. I don't know what they're saying. They're saying the levels are there. How are they getting there? Can this also happen with MEHQ?

DR. MARKS: Yeah, well, we're dealing with hydroquinone and I think we've come to the conclusion don't re-open in the re-review. It will be a re-review. We'll see a summary addressing the ultraviolet light concern and production of squamous cell carcinoma and also a bit of a discussion on home use each, too, compared to salon.

DR. HILL: The reason I babbled on about that is because the next ingredient is the p-hydroxyanisole.

DR. MARKS: Yeah. I want to move through this ingredient and go on to the next, and I don't want to discuss phthalates.

DR. HILL: We're not going to re-open phthalates on this topic either.

DR. MARKS: Yeah. Exactly. I agree. Okay. Let me --

SPEAKER: Sorry I brought it up. (Laughter)

DR. MARKS: No, no. That's okay. No. Everything is. Why is this doing this? So, now we are to p-hydroxyanisole. And, obviously in the way we handled this, we're going to dig over these two ingredients separately as they have been in the past, and so, the decision today, Tom and Rons, is do we re-open this to indicate that it is safe for nail products only? The HRIPT was okay. We can go over the UVL again, but we've already done that. The risk is small. To me, the greatest concern was depigmentation. That's why we had -- it originally had an unsafe conclusion back in 1985.

I have difficulty point blank just saying well don't worry about depigmentation, even though it's being used, and, again, in reference to the letter, a lot of the manicurists have skin of color now. I can say I haven't, again, seen reports in the literature of depigmentation occurring in nail salon operators and manicurists, but I don't have any data on that. So, David, do you want to say something. I can see, then I'll have the Panel members chime in. To me, the biggest concern is not squamous cell carcinoma but could depigmentation still be an issue with the use of the p-hydroxyanisole in these nail adhesives.

DR. STEINBERG: Okay. It's not the nail adhesives that -- we're concerned about the nail gels.

DR. MARKS: Yeah, nail gel.

DR. STEINBERG: The report back from the '80s -- the only use of p-hydroxyanisole, as cited in the report for cosmetics, was as a skin bleaching agent which we promptly said is depigmentation and is a drug. In fact, it is still sold as a prescription drug. I believe the concentration is like 4 percent and applied twice a day to bleach the skin. It is mentioned in the report back in the '80s that they are aware, that the Panel was aware, of the use of MEHQ as an inhibitor for monomers, and we were not selling monomers to the consumer. So, it was not a question back then.

Now, we have a use in which we're actually having to sell, and we are selling MEHQ at levels, which are very low, in the monomers which are part of the jelly which the consumers are applying to their nails. There is certainly nowhere near enough exposure to depigment the nail, and it doesn't even react with the pigments that are present in the gels. It's a very, very low level. So, we want to basically re-open that conclusion that it is unsafe but say that it is safe for the use as a monomer inhibitor in the use of artificial or nail gel preparations. That's the only use that we know of.

DR. MARKS: Rons? Tom?

DR. BERGFELD: Could you speak to the life of the inhibitory process? Is it a matter of miniseconds or -- And, some of these polymerizations are pretty quick and complete.

MR. SCHOON: Typically, you're not going to -- it depends on the type of formulation, truthfully. If you're looking at the liquid and powder formulations that David described earlier, in 2 to 3 minutes, probably by 5 minutes, I would say the majority of the chemical reaction has occurred and the majority of the quinones have been destroyed. With the UV gel systems, it can happen even quicker. There are systems that cure in 30 seconds. So, the UV gel formulations that we're specifically talking

about now, at-home use, like I said, cured very, very quickly, certainly within the first few minutes.

DR. STEINBERG: Yeah, I was exposed. I'm going to say maybe at the most 20 seconds at a time. I just stuck my finger in there and boom. It's gone.

DR. MARKS: So, in the animal studies in the '80s, I think, although we couldn't set a low limit, it looked like 0.1 percent of p-hydroxyanisole. And, what is the INCI name we should be using? You used the chemical name.

DR. STEINBERG: P-hydroxyanisole is the INCI name.

DR. MARKS: Okay.

DR. STEINBERG: I mean, we just (inaudible). We call it MEHQ because that's what the monomer people want.

DR. MARKS: So, in the black guinea pig studies, they had depigmentation occurring at 0.1 percent in some animals. What kind of concentration is occurring? Even though I know it's used up very quickly, there should be very little exposure. From what you said, David, it balls up on the skin. So, again, if I were a manicurist and applying this and maybe sloppy or my manual dexterity wasn't very good, and I got repeated applications on my hands, are we talking about concentrations in the gel which are markedly less than 0.1 percent?

MR. SCHOON: Typically, yes. Typically, we're looking, you know, under 1,000 ppm is generally what we're looking at. And, when skin contact does occur, which shouldn't happen very often, again, it's transient. It's removed right away. And, truthfully, in all my years in this industry, I've never once seen a case of depigmentation caused by skin contact.

DR. MARKS: That's sort of my sense, but it's anecdotal.

MR. ANSELL: Remember --

DR. MARKS: It's jelly.

MR. ANSELL: -- you're looking at the older studies. The concern was for as a cosmetic ingredient intentionally applied to the skin at these concentrations and not at 200 ppm as an inhibitor or in a product not intended for skin contact. So, it's a very, very different --

DR. MARKS: I know that. I just wanted to be reassured that the concentration is less than the way it's been, because I'm -- again, if I weren't asking this question, I would expect Rachel to be probing and saying, okay, if I'm a manicurist, I have skin of color, you know, what's my risk. It's very low now. Doug, you used ranges that were fairly large. You used 200 parts per million, I think, Jay. But, Doug, you said it could vary. Do you know what the top parts per million or concentration would be in a nail gel?

MR. STEINBERG: The highest that we've ever seen before polymerization is 1,000 parts per million, and that was just in one product. Most of the time it's in the area of about 200 parts per million. It just depends on when you get the monomer, who you're buying it from --

DR. MARKS: Yeah. That type of thing.

DR. HILL: That's a fair question, because one of the products -- grant you, the MSDS was from 1999 date, and the letter that she sent says 2 percent for methoxyphenol, which is a synonym for MEHQ.

MR. SCHOON: Well, often times on the (inaudible) sheet, they don't want to reveal too much information, so they'll give it ranges. So, if it said less than --

DR. HILL: It says less than .2 percent.

MR. SCHOON: Yeah.

DR. HILL: You're thinking it's a lot less than 2 percent.

SPEAKER: Or it wouldn't work.

MR. SCHOON: Correct.

SPEAKER: You'd never get polymerization.

MR. SCHOON: And, one other thing. The ones that have the highest amount of MEHQ, the cyanoacrylates, they cure instantly on contact with skin, so, and there is not going to be much chance

of diffusion out of that, which is another reason why they have to be kept off the skin, because they will polymerize.

MS. BECKER: There is a summary of the submitted data on that at the bottom of page 19. I'm sorry. It's the bottom of page 18. I got two pages -- up the middle -- there.

SPEAKER: Mine says 19.

DR. MARKS: Yeah, mine is -- or is that the one Use of Nail Products as the heading.

SPEAKER: Yes.

DR. MARKS: As reported to be just like you said, basically 200 parts per million or --

SPEAKER: In that general range.

DR. MARKS: -- 0.02 percent, which, again, is significantly less than depigmentation. And, then, that was the gels. Soft nail gel, soft gel, top coats -- okay. So, let's go back to -- I think that's been a robust discussion of the issue with depigmentation. So, re-open? And, with the new conclusion that it's safe for nail products only in the present use concentration.

DR. SLAGA: Correct.

DR. MARKS: Ron Shank, does that look good to you?

DR. SHANK: Yes, I would repeat the caution that it's not to be used on any other products.

DR. MARKS: Right. Okay. Re-open? Safe. Now, just to be clear, I used the general term nail products. Would you prefer it be specific to nail gels or as a polymerization inhibitor for nail gels, and that should be the only safe use? Because, I don't want to say nail products and then, you know, 2 years from now we find it's in some other nail product.

MS. BECKER: Because, we have cuticle softeners, which is a nail product but is --

SPEAKER: Right.

SPEAKER: Typically, we refer to them in general as artificial nail coatings.

DR. MARKS: Safe in. Okay.

MR. STEINBERG: The question is do we have the function as a monomer, as a polymerization inhibitor.

SPEAKER: As a polymerization inhibitor.

SPEAKER: Polymerization inhibitor.

MR. STEINBERG: So, that would be fine.

SPEAKER: Good point.

MS. BECKER: So, do we want to limit it by the function as well?

DR. MARKS: Artificial nail --

MR. STEINBERG: Coatings.

DR. MARKS: -- coatings, specifically --

SPEAKER: As a polymerization inhibitor.

DR. GILL: So, these -- just for my clarification -- you're saying this -- it's me, David.

(Laughter) The gels aren't used on anything other than artificial nails?

MR. SCHOON: No. No.

DR. GILL: I think they're used.

MR. SCHOON: No. They're used on regular nails, the gels.

DR. GILL: Right.

MR SCHOON: They're used to create artificial nail coatings.

DR. GILL: Okay.

MR. SCHOON: And, there are several different types of ways of doing that, so that's why we use that word, generic terminology, as a catchall.

DR. GILL: I've had them all probably. (Laughter)

DR. MARKS: So, Ron Shank, Ron Hill, and Tom, what I'm going to presumably -- oh, yeah, I will make the motion tomorrow. I'll move that we re-open the safety assessment. The new conclusion will be safe in artificial nail coatings as a polymerization inhibitor. It's unsafe for other uses

(inaudible). Okay. What do you want?

MR. ANSELL: The specific inclusion would state unsafe for other applications.

DR. HILL: That's what we said before.

DR. MARKS: Yeah, I think the key there is we don't --

MR. ANSELL: But, we don't have a --

DR. MARKS: So, yeah, how do you want to deal with our previous conclusion? Just say that it's only safe for this, and then in the discussion we could say that we -- I think it's how you wordsmith the conclusion, whether you want to be really strong and say we only approve it for this one use and say it's not safe for others or --

MR. ANSELL: I guess that's just what I envisioned was that the discussion would we -- we had as the discussion in the report. Now, is we had a specific request to use this as an inhibitor of polymerization and nail products. We re-opened and concluded that it's okay, but, I guess, if that's the only conclusion, re-stating it isn't going to be a problem.

DR. SHANK: Because, in the original report (inaudible) it was unsafe for use in cosmetics.

MR. ANSELL: Right. And, I had no problem with that. I guess I was just caught a little unaware. I was thinking it would be very narrow to a very specific application.

DR. MARKS: You didn't hear Ron Shanks say that earlier -- unsafe for everything else. (Laughter) I was just making sure that got in the conclusion. So, again, re-open, a tentative report with safe in artificial nail coatings, as a polymerization inhibitor, unsafe for other cosmetic uses, or however you want to word it, and that will --

DR. HILL: So, one quick -- Allow me to be lazy for a second. So, the MEHQ is destroyed before it goes under the UV lamp. It's what it's for.

MR. SCHOON: No, the UV radiation destroys it.

DR. HILL: The reason I asked that question is somebody puts this gel on and then they get a phone call, a very important phone call from their BFF, and that lasts for 35 minutes, is it sitting on there basically still as MEHQ during that period of time?

SPEAKER: (inaudible)

MR. STEINBERG: Yes, well, yes, but her fingernails will be extremely wet, you know, with a lot of jelly on them.

DR. HILL: Coated jelly.

DR. MARKS: It's actually an interesting hypothesis or scenario, but I don't think it's going to impact on the safety. Any other comments about this ingredient?

MS. GILL: And discussion on the UV?

DR. MARKS: Same as the prior. As hydroquinone, essentially it'll be identical. Okay.

Dr. Belsito's Team

DR. BELSITO: ...The next one is hydroquinone.

So we've got Wave 2, and we've got Wave 3 with hydroquinones, and ah-ah, so it's just *camellia*. So, you know, I don't think the issue here is the safety of hydroquinone as used in UV-cured nail gels, or with para-hydroxyanisole as used in UV-cured nail gels. I think the issue is whether we think a product that requires UV exposure as these do, should be out for general public use. And you know, I'm not convinced by Dr. Cyrus letter because there were a number of issues in that letter where he said that torso and hand skin is four times more resistant than back skin.

He's talking about minimal erythema doses, he's not talking about sunburn effects. He's not talking about toxic effects to sun exposure. He's talking about the ability to see erythema on the skin 6 to 24 hours after radiating with light. And so when you do minimal erythema dose testing, you do it on buttock skin, or skin that's presumptively been unexposed, or exposed but with clothing over it, since there is some UV. You don't do it on hand skin, you don't do it on back skin, you do it on unexposed buttocks skin. So, I don't buy that four times more resistant.

And, you know, I think that, you know, you look at Mary Weinstock's evaluation, but then there are contrary evaluations, and then we have an estimate that, yeah, it may be one more squamous cell carcinoma out of however many tens of thousands of people, but is that justifiable to allow that one person to develop squamous cell carcinoma for the purpose of having a manicure that lasts longer.

I mean, I'm just raising these ethical questions. On the other hand, it was suggested that there may be ways to get around that. That these be provided with a sunscreen. That these be provided with a very strong warning caution, use of these UV nail machines may induce skin cancers. Should they be provided with gloves to cover, you know -- opaque gloves that cover all of the skin of the hand except for the nail bed.

The issue is not the penetration of light through the nail bed, but I agree with Mark Lebwohl's light isn't going to get into the nail bed, it's the rest of the skin around the nail bed, and the fact that when you get squamous cell carcinoma of the digit, it has a much greater chance of metastasis than squamous cell carcinomas that occur on many other areas of the skin. The lip is the highest, but the finger, in terms of general skin is also fairly high. So, again, this is -- it's a very -- for me, it's a very curious thing, because I think the chemicals are safe. I just am a little bit concerned with the procedure in which these chemicals are going to be used. So I've said what I have to say.

DR. LIEBLER: So it sounds to me -- I mean, I agree with you, Don, from your first point is that there are really two separate issues here. There's the safety of the chemicals, and then there's the issue of, what is the hazard of two individuals associated with the entire procedure. I agree, I have no problem with the chemicals under the use conditions. And it seems to me that much of the literature on the hazards suggest that there is minimal hazard risk. But it cannot be completely eliminated. So I don't see --

DR. BELSITO: So, it's the minimal hazard, and the hazard, "Oh. You've got a skin rash the little top of steroids is going to get rid of." The hazard is, "You've a cancer, skin cancer."

DR. LIEBLER: Fair enough.

DR. BELSITO: And not a basal cell that's not likely to metastasize, you've got squamous cell, the (inaudible) cell.

DR. LIEBLER: Okay. Fair enough. But what do we do in this context?

DR. BELSITO: I don't know. I'm just telling you my concerns.

DR. LIEBLER: Yeah. So I guess mine is that the discussion should explain the significant potential risk, and that it is not entirely resolved.

DR. SNYDER: It does go to what we do. I mean, we talk about the safety and the use, and you can always put those two together. So we are not concerned about the safety of these chemicals, but we do have concerns about the use. Right?

DR. BELSITO: Well, we are not even concerned about the use of the chemical, we are concerned about the procedures under which the chemicals are used. I mean, that -- it sounds semantic, but it's not. I mean, if you were just asking me, can hydroquinone be used at this level, and in acrylic-based nail product, as an antioxidant to prevent polymerization before the product is applied to the nail? I would say, yes, it can.

If you're asking me, can UV-cured nail gels be released to the general population and be used safely? I would say, I have concerns. You know, one in a million allergic contact dermatitis doesn't bother me. You know, but one squamous cell carcinoma, you know, does.

DR. LIEBLER: So how do you deal with your concern? Do you say that this is not safe?

DR. BELSITO: No.

DR. LIEBLER: --

DR. BELSITO: What I'm saying is, I'm offering you opportunities. I think, you know, as with lactic acid, we say it's safe to use with sunscreen, where, you know, the FDA has recommended labeling the -- I don't know what the labeling is about photocarcinogenesis. You know, if you are going to allow this to go forward, then I think we need to set very stringent requirements that the product be provided

with a sunscreen for application, or with a glove, with a cuticle cut out for application.

DR. SNYDER: It's smelling an awful lot like Brazilian blowout. Where we are starting to trend into guidelines for use, and things, which we are not really -- right? Isn't it -- I mean, isn't this --

DR. BRESLAWEC: You've described the use -- that you have no problem with the use of the ingredient, as a polymerization --

DR. BELSITO: Inhibitor?

DR. BRESLAWEC: Yeah.

DR. BELSITO: All right.

DR. BRESLAWEC: The use is under conditions of use, which require UV cure. Correct?

DR. BELSITO: Right.

DR. BRESLAWEC: Okay. So I think the UV part, is part of the conditions of use.

DR. BELSITO: Okay.

DR. BRESLAWEC: And you can, and should be able to consider it, and the question is, how safe is safe. And that's where you need clinical judgment.

SPEAKER: It sounds like, unless you --

DR. BRESLAWEC: One in a million is a risk for carcinogenicity but I think FDA has accepted in a number of different circumstances, I cannot tell you --

SPEAKER: For cosmetic?

DR. BRESLAWEC: I think maybe for colorants in cosmetics, but I can't -- I don't trust my memory that much, but I think it is in the color area, color additive areas. We do have some experts in this area. I mean --

MR. SCHOON: Yeah. If I might add something. I think it's interesting to note that even with all the media scrutiny that we've had over the last couple of years, which, believe me has been intense. I'm sure you've seen it. No one else has come forward and made these similar claims. There's been no other doctors coming up and saying we are seeing the same thing happen here or there. So I think that's important to -- and also I think it's important to understand that these UV lamps have been used prior to the use of the development of the gel manicures.

They've actually been used widely in the industry to creating artificial nail coatings for longer than I've been in the industry. So I would venture to guess 30 years or more. And also, I think what Dr. Sayer's and other's papers are showing, is that these lamps aren't accidentally safe. They were actually designed to be safe. Special bulbs are used; special electronics are used to minimize the amount of exposure.

And what Dr. Sayer and others have done, especially Dr. Sayer, is use the international standard to test these and compare these to workplace exposures, and find that they are far below any other kind of workplace exposure standard there is, and as the original claim was made, nothing in comparison with (inaudible) beds. People's skin don't become red or tan from use of these lamps, largely because they are only used for very short periods of time, twice per month, sometimes only once -- every three weeks, rather than every two weeks, but never more often.

DR. STIENBERG: The other thing is that radiation that does the curing is basically and virtually invisible range. Most of the curing takes place around 400 and 420, which is in the visible range. If we could buy bulbs that were only from 400 to 420 economically, we would. The bulbs that are used are very low wattage, and they are usually, what, 380 to 420, so that was a narrow a cut as we can get, in terms of the (inaudible).

MR. SCHOON: Right. The newer lamps coming on the market now are 395 to 405 region. So really in the very safest part of the region like that, we can be as well, as on top of all the other things that I've noted.

DR. BELSITO: Okay. But then -- so, what about this aphakic eye, would you ever get a lens implant wasn't a UV absorber, number one? And even in his letter, at the end of his letter he says, "Another concern is that the incorrect replacement light bulb may be inserted into the UV nail unit,

therefore, those admitting UVB or UVC." So how do you propose to sell units that would not allow that to happen?

MR. SCHOON: Well, I've talked to them about both of these issues, and the first one was related to a type of lens that used to be implanted and no longer is implanted, so they fear this was a really -- at very, very low risk. These guys are just very careful about everything they say. And although it is possible you could purchase a lens -- the incorrect bulb and insert it in there, manufacturers sell replacement bulbs and encourage people to purchase the replacement bulbs to put them back in their lamps, so that the cure --

DR. BELSITO: I understand, but consumers go out and Google UV bulb.

MR. SCHOON: Well hopefully they will --

DR. BELSITO: And they find a bulb on Amazon.Com that's one-fifth the price of what you're manufacturer wants to sell them, and they order it, and it's a UVC bulb, or it's a UVB bulb.

MR. SCHOON: What?

DR. BELSITO: Are you going to create a special bulb, a manufacturer will create a special socket like my iPhone, that I can't use Android socket to charge. You could do that, no?

MR. SCHOON: Well, I can't speak for manufacturers, and also --

DR. BELSITO: Well I mean, but wouldn't you have to, I mean, because otherwise if it's a simple screw-in incandescent light bulb, or a little plug like a fluorescent bulb that I the adaptor for any UV, consumers are going to go out and they are going to use the wrong UV sources.

MR. SCHOON: Well, to my knowledge it hasn't happened, and I think it will be difficult to do because these bulbs just aren't commercially available, a UVC bulb like that. You would have to call a bulb manufacturer and request it, and rather than request a UVA lamp, which is clearly marked on the bulb. So it's not inconceivable that it could never happen, I just think it's pretty low possibility.

DR. BELSITO: I have to disagree with you. Dealing with lots of patients who do lots of very silly things, I can see a patient going out and Googling, 6-inch UV bulb, and getting something delivered from China that's a UVC germicidal bulb, and not understanding the difference between what they just did, and potentially with the UVC blinding themselves, so you know --

SPEAKER: We do have to consider conditions of use, and then misuse. Deliberate misuse, and I can't imagine how you could ever consider something safe when it is deliberately being misused.

DR. BELSITO: Okay. I'm mean, I'm just pointing all these things out.

MR. SCHOON: And Dr. Belsito, can I make one more comment?

DR. BELSITO: Sure.

MR. SCHOON: There's not much risk of eye contact, actually. The international standard require them to measure at a certain distance which was about half as close as a client would ever get. And then the lamp faces the opposite direction from the operators, so the operator is never going to be actually looking at the UV light themselves. So there's little risk to the operator, and there's even lower risk -- to the consumers low, because of -- again, because of these other things I've said.

It just happens to be that where they had to do the measurement, made the intensity look like it was higher -- it was closer to the eye than whatever would actually occur. No one would ever look down inside the chamber.

DR. BELSITO: So the lamp itself, there's obviously a cover to the lamp of some sort.

MR. SCHOON: Correct.

SPEAKER: --

DR. BELSITO: That cover is not movable?

MR. SCHOON: Not movable, and there's a front baffle too, so your hand goes into there, and there's a baffle that actually covers the light. You cannot see the light directly.

DR. SNYDER: Can't see any of the light?

MR. SCHOON: Can't see the bulb directly, I should clarify.

DR. BRESLAWEC: Concerns would be that interaction with the lens as UV (inaudible)?

DR. BELSITO: That it burns the right one.

DR. BRESLAWEC: Those have been around for at least eight years.

DR. BELSITO: Using this letter or now, just to -- I'm just trying to do my due diligence here, you know.

DR. LIEBLER: Well, I just Googled UV light bulb shopping, on Google (inaudible), and there is quite a dazzling array of different socket types, and bulb configurations and lengths, shapes.

MR. SCHOON: And don't all the bulbs come with a stamp directly on it, the actual part number and type of bulb, and whenever anyone is going to purchase that, they would likely go by the number that was on the bulb, it's very visible and easy to see, and they would order based on that number.

DR. LIEBLER: I would agree, you would be presented with a situation where you would have to try and match it with the right part.

DR. SNYDER: It's not easy.

DR. LIEBLER: So I supposed we could go on and on about the possible hazards that could involve somebody who, you know, because their combination of not careful enough or not lucky enough would incur a serious, very serious adverse consequences to be using this products as it was designed to be used. Right? And you can't completely rule that out. So it comes back to, how can we respond to this given the way our Panel operates? We basically have the options of safe as used, insufficient --

DR. SNYDER: Well, we have any language we want, so I mean, I was just thinking out of the --

DR. LIEBLER: We have language, but we have language that we have to reach --

DR. SNYDER: The language could be; safe as intended for use, or something.

MR. SCHOON: And I want to make one other point very clear, just so you understand this, the newer types of lamps that are coming up, the LEDs, the bulbs are not replaceable.

SPEAKER: You have to buy the whole machine.

MR. SCHOON: You buy the whole new machine.

MR. STREMBERG: They last a long time.

MR. SCHOON: Probably lasts four or five years.

DR. BELSITO: And recommendations for gloves, for sunscreens for -- about warning about the possibility for inducing a cancer.

DR. LIEBLER: So, I'm inclined towards safe as used with all of those things in the discussion.

DR. BELSITO: Just one, maybe the two in one --

DR. SNYDER: --I was going to say an absence of data is not an indication of safety. I mean to say, where is the data that says that fewer sunscreen, and where is the data that says, wear gloves.

DR. BELSITO: I'm just going to be Ron Hill on this, but you guys don't have to follow my --

DR. LIEBLER: Ron Hill or Ron Shank?

DR. BELSITO: No. Not Rank Shank -- He wants his nails done, now that he's retired. I'm kidding.

DR. LIEBLER: Well, I haven't really heard where you are. If they have --

DR. BELSITO: I have -- you've heard where I'm at, I just have ethical concerns and, you know, in going to abstain.

DR. KLASSEN: One also has to realize that this one -- one in a million; it isn't really one in a million, or one in 50 million, you know, those are such extrapolations that --

DR. BELSITO: I understand.

DR. LIEBLER: Or 1 in 20,000. I don't know where the areas are in that model.

DR. BELSITO: Right.

DR. LIEBLER: It was presented to us.

DR. BELSITO: Okay. So you guys want to go, safe as used, and I presume this will transmit to the para-hydroxyanisole, report as well?

DR. LIEBLER: Right. I mean I'm prepared to do the --

DR. BELSITO: To discuss, an unknown risk of an increase in skin cancer recommendations that they be used with either photoprotective gloves or sunscreens. Is that what I'm hearing?

DR. LIEBLER: That's what you're hearing from me. I'm the only one who's saying that.

DR. BELSITO: Well, Paul, I think, has said --

DR. SNYDER: I run the risk in running guidelines, and it's something that we can -- I know it's not what we are supposed to do.

DR. BELSITO: We did for alpha hydroxy acids.

DR. SNYDER: We said anything --

DR. BELSITO: We said, yeah, to use sunscreens.

MS. EISENMANN: My understanding is that -- that CIR's -- that evaluates the safety, but the label and the regulatory requirements is not part of the -- the charge -- I mean, it seems to me that a discussion was -- there is a risk, a potential small risk, and to mitigate that risk the sort of things you can do, is a reasonable part of the discussion. But I'm not familiar with the CIR requirements on labeling.

DR. BELSITO: Let's look at -- we reviewed alpha hydroxy acids here, let's see what we said for that.

MR. SCHOON: These lamps typically do come with some pretty hefty warnings --

SPEAKER: I think you have to leave it at --

MR. SCHOON: -- because they have to either be CE or UL approved, or CSA approved, they get approval to ship them to other countries, and CSA will usually look at the lamp and tell you what kind of warning should go on to the lamp.

MS. EISENMANN: It may have been, and I don't know this, but the FDA acted to the model and CIR's determination and AHA, and close (inaudible)--

DR. BELSITO: We will soon see. So, our conclusion for alpha hydroxy acids was -- concluded glycolic -- safe for use in cosmetic products in concentrations less than maybe 10 percent of final concentrations, pH-graded, and then reached to 3.5 and formulated to avoid increase in sun sensitivity, or wind directions for use include the daily use of sun protection. That was our conclusion.

DR. LIEBLER: Oh. I can deal with that. When directions include the use of sun protection, or UV protection such as sunscreens, or use of gloves, or --

DR. BELSITO: We did do it.

SPEAKER: You did do it.

DR. LIEBLER: Then you could sell the glove with the machine. And everybody wins.

SPEAKER: --

DR. LIEBLER: Designer colors.

DR. BRESLAWEC: Hello Kitty.

DR. LIEBLER: Spiderman. Hello, Kitty. Spiderman would be, because you put it in --

DR. BRESLAWEC: How could the risk of some of the image. The quantitative risk from AHAs compared to the kind of risk you are dealing with here. And was that more than 1 million, less than 1 million? I don't know, I wasn't --

DR. BELSITO: No. You know, AHAs were sunburned cells but, you know, I mean basically, you know, if you look at what -- if you look at what cosmetics/salon AHAs do, they are basically getting rid of the stratum corneum which has a sun-protective factor of about 4. So, they are not really doing a lot. The question here is depending upon how you do the calculations, is exposure to high

intensity UVA light, and what is the relationship of UVA light and skin cancer, and that's an evolving issue.

You know, it was thought that it was UVB that was carcinogenic, do you know that the Australian experiment with sunscreen it has taught us that UVA is probably more responsible for melanoma than UVB? Because that was that whole scare in The National Enquirer that sunscreens promote UVA, or promote melanoma, because what happened was Australians started using sunscreen, then went out to Bondi Beach longer. They got more UVA in (inaudible) their instance of melanoma went up.

Now, there aren't really good models for melanoma so we don't know what drives that, other than we know there is a relationship with light, but there's a strong suggestion, since UVA has done melanogenic ray, that it may be more UVA. But anyway, so the people in Utah did this calculation that suggested the amount of exposure to UVA may be greater with these lights and what you would get with sun exposure and then some other guy did this risk calculation, that said that you, you know, in English women, that you may have a slight increase.

I'm just saying, you know. I mean, we seem to be struggling all the time to define whether para-phenylenediamine actually is a risk for skin cancer, so I don't know what cosmetic regulations are. You know, and I don't know how FDA considers a carcinogenic risk in terms of a cosmetic product. You know, I know how they consider carcinogenic risks in terms of, you know, pharmaceuticals, that that's an acceptable risk particularly, you know, depending upon the disease you are dealing with. I'm just pointing these things out.

MR. SCHOON: In the case of the sun -- AHAs, the sun screen was there to prevent sunburns from occurring. Sunburns don't occur with these lamps.

DR. BELSITO: I understand. The point of that, Doug, was that we have put in conclusions before, measures to prevent issues that we are concerned about, and Halyna said we had never done that before. It was in discussion but we did it for AHA. So, you know, if in the discussion we talk about an unknown but possible slight increase in the risk of squamous cell carcinoma, if we put in our conclusion; safe when used in association with either physical or chemical sun blockers such as gloves or sunscreens, that protect in the UVA range on the exposed skin, you know, I'm okay with that. Then let the consumer beware.

DR. STRENBURG: If you can't say the use of sunscreens, I would inject that it should be, labeled as the use as a broad spectrum sunscreen.

DR. BELSITO: That's what I just said, UVA.

MR. STRENBURG: No. The FDA is specific in saying, broad spectrum --

DR. BELSITO: No. I understand.

MR. STRENBURG: I know we mean UVA, but the FDA --

DR. BELSITO: We could even say titanium dioxide.

DR. LIEBLER: Sounds like a good idea.

SPEAKER: I'm right on that.

DR. BELSITO: Okay. So then I guess that covers the para-hydroxyanisole, except that I do have to comment to CIR that I'm very disappointed that we got a letter from a woman who works for Women Health, that Google para-hydroxyanisole, and finds it used in a number of cosmetic products that can be purchased online. And we are told that there are no consumer uses. I find that disturbing. Yes?

DR. STRENBURG: Just to comment that they are two issues on that letter which are relevant. The first is that the CIR just -- they're given the information from the VCRP, no professionally-used products are allowed to be registered under VCRP, and some of the things that she found, were professionally-use only products; which is why she can find them, but they are not on the VCRP.

The second thing is something that we all know is that not every company participates in VCRP, and that will be interesting to know based on what -- the product that she did find, what's very interesting to me was, there was a skin bleaching cream which used para-hydroxyanisole, which is not an

approved drug. It's not sold as skin bleaching but you can just look at the label, and you can infer this is for skin bleaching, and they are not registered in the VCRP at all.

DR. BELSITO: Okay, but my -- then I will continue my point, I think in the future we shouldn't rely simply on FDA and on -- I mean, according to her, it took her 10 minutes to get this information.

DR. BRESLAWEC: The industry has long supported mandatory registration, VCRP registration.

DR. BELSITO: I understand that. What I'm saying is, I know what you have supported, et cetera, et cetera. I am disturbed that we produce a document to say that there are no recorded uses of para-hydroxyanisole in consumer products, when some lady at Missoula, Montana, spends 10 minutes on the Internet and comes out with a list of products and provides it to the so-called experts. That makes me look like I'm not doing my homework.

MR. SCHOON: Well, many of these are actually nail products, and one of them has been discontinued, so really only two of them are outside of scope of what we are talking about today.

MS. EISENMANN: Two things, if I may? I know that in the past when VCRP has not reported any uses but CIR staff have suspected that in fact, those ingredients are being used, they have gone to Canada which does have a mandatory ingredient reporting system, and have received information from Canada that does confirm ingredient usage.

Second of all, it may very well be that these are illegal products, and you wouldn't really expect somebody who is manufacturing an illegal product to voluntarily submit information to VCRP, that's often the case when people say, "Oh, my, god, there's mercury in cosmetics." Well, mercury is a banned ingredient for cosmetics, and yet that occasionally will filter through that.

MS. BECKER: There's also, Carol, survey is only from member groups, and not every --

MS. EISENMANN: We have actually -- we've extended our survey to members of the small manufacturers.

SPEAKER: Not just everybody.

DR. BELSITO: I understand, but Mario Badescu is a very popular product in New York, and whether they are a member or not, the fact that their Vitamin E Night Cream contains para-hydroxyanisole, I think is disturbing, you know. And maybe it's a rogue product. My whole point is, that I think in the future, before we say that there are not products on the market for commercial use that contain an ingredient, could we please Google and see if you've come up with a product.

Can you go to the EWG website for that and put that product in and search it, because maybe -- you know, maybe these NGOs are not as bad as they seem to be.

SPEAKER: I agree with --

DR. BELSITO: I personally feel like if I have issued that statement, that I have not done my due diligence, and that worries me. It worries me when I'm looking at data, and I think I have all of the information, and a woman tells me in 15 minutes -- I'm sorry, I underestimated, I said 10; a 15-minute Google search she was able to come up with this.

DR. BRESLAWEC: Dr. Belsito, I want to point out that in the CIR report, very specifically says that based on VCRP, no report has been --

DR. BELSITO: I understand. So my point is, let's not base it on VCRP anymore, let's do a 15-minute Google search.

SPEAKER: In addition?

DR. BELSITO: In addition.

DR. SNYDER: So does this become part of our dataset now?

DR. BELSITO: I think it should.

DR. BRESLAWEC: I would strongly disagree, because I think what we've done is we've based our -- whether an ingredient is used on a legitimate, although not 100 percent, database. When you start Googling information, you're not going to get any kind of information that's particularly useful. If

you find things, you'll find a couple of ingredients here, a couple of products here, but what's -- what kind of useful information does that -- that's anecdotal information.

DR. BELSITO: Okay. But then I'm -- I don't feel that I can go out and say it's safe as used, knowing that it's used in Mario Badescu's Vitamin E Night Cream. Okay?

MS. EISENMANN: But in the document it doesn't -- it's safe as used --

DR. BELSITO: You know, I mean, I think you can interpret that in very many different ways. You know, if it's in fact used in the Mario Badescu Eye Cream, I think you should go to a store, look, verify that the ingredient is labeled there, and put in your discussion that the Panel is aware that there other manufacturers using this ingredient for other uses, we have specifically not looked at those other uses. Because otherwise, someone picks up a Mario Badescu product, sees para-hydroxyanisole, or one of its other names, and say, "Oh, the CIR said it's safe as used. Mario Badescu is using it." You know, just because we were not smart enough to know that they were using it, you know.

MS. EISENMANN: This conclusion should be, safe as used as a nail product --

SPEAKER: Used in a nail product, it's --

MS. EISENMANN: -- it's not a general as used. I don't think that's what they are looking for. I think it's just said, as used in nail products --

DR. BELSITO: Fine. I just -- this is very upsetting to me, because it calls into question whether I can rely on information that I am being provided.

MS. EISENMANN: I understand that.

DR. BELSITO: Okay?

MS. EISENMANN: Mm-hmm.

DR. BELSITO: It's more upsetting to me than Cosmetics Europe telling us they won't share the data with me. It gives me pause as to whether I should continue on a Panel and put my name out on the documents. If I can't be certain that the information that I'm given is complete information.

DR. SNYDER: I mean, she has a nice paragraph in here, she understands the shortfall of VCRP, and then talks about, "This seems to be between recording no uses and the truth, that the ingredients (inaudible) products is (inaudible). I think that's what you're getting to.

DR. BELSITO: Yeah.

DR. BRESLAWEC: Respectfully, I guess, I would again point out that with the documents and what the CIR reports do state is, "Uses as reported to the CIR," we were quite aware that they are not 100 percent accurate. I mean we all are -- I think that's the best we can do. I'm not sure I want to speak --

MS. BECKER: Are you asking for an extra sentence in that, saying that you know VCRP is not all encompassing?

DR. BELSITO: You know, I think we need to craft -- you know, I just think we can spend 15 minutes on Google, or go to EWG website and put in an ingredient and see if they have any listings for it. But, you know, I --

DR. BRESLAWEC: Is this letter a part of the file?

MS. BECKER: It was Wave 3. Yeah.

DR. BRESLAWEC: So we should refer to it, and look it up.

DR. BELSITO: Well, that's what I just said. I said we should include parts of this letter and say that we are aware that there are cosmetics products out there that are using para-hydroxyanisole, and that this is not an approved use. I'm comfortable saying that.

SPEAKER: No problem at all.

DR. BELSITO: But in the future, I'm going to be very uncomfortable when you tell me the product is not being used, if you haven't done a Google -- 15-minute Google search to where this will (inaudible).

MS. BECKER: And just so you know, I did look at the EWG and their results are fairly consistent with what VCRP has.

DR. BELSITO: Okay. We can speak to her and find out how she got this in 15 minutes.

DR. LIEBLER: So as a general rule if we were to find uses through sources other than VCRP, whether it's EWG or a Google search, or somebody's letter comes in the mail, do we simply refer to that on the discussion, the Panel has been, (inaudible), sort of make ourselves a boilerplate basically? The Panel has become aware of non-VCRP reported uses of this ingredient, and --

DR. BRESLAWEC: We've had that situation before, because --

MS. EISENMANN: There was a (inaudible) --

DR. BELSITO: -- get absorption analysis, that doesn't bother me, yeah. And I think at least another ingredient where, again, based on the Canadian database there were reports.

MS. BECKER: Well, that was from the EWG that I got for that.

DR. BELSITO: Well, and the only other thing in this -- the para-hydroxyanisole report, and I would agree with her, is that, you know, I'm really not concerned about para-hydroxyanisole getting through the nail plate, but I don't think dibutyl phthalate is the right comparative. So I would get rid of that, and say that there was no penetration data, but we are not concerned. Rather than saying we used dibutyl phthalate as a surrogate.

MR. SCHOON: We did submit a few other papers a little late we may not have seen and requested Dr.

(Inaudible) actually made the request, but someone requested that we provide information to show that the amount of -- that the nail is a very good barrier, very difficult to penetrate. And he submitted several papers to that effect; because it is a well-known barrier, not impenetrable, but very, very difficult to penetrate, for most substances.

DR. BELSITO: You're talking about the data on antifungals?

MR. SCHOON: Yes.

DR. BELSITO: In DMSO.

MR. SCHOON: And also, too, a paper on --

DR. BELSITO: We did any anti --

MR. SCHOON: -- Natural Known Barrier Characteristics on Permeation Cancelling. That we just actually got a hold of about a week ago.

DR. BELSITO: But you know, I mean -- Again, antifungal and para-hydroxyanisole are not comparatives, so you know, the nail plate is pretty impenetrable, and I'm not concerned about penetration for para-hydroxyanisole through it, but you're not going to convince me of that by showing me data of an antifungal, which is a much bigger animal, doesn't get across either.

But I think we look foolish saying the dibutyl phthalate can be used as a surrogate for para-hydroxyanisole. They are structurally not related at all. So, I would say, no penetration, we have no data; unless you can give me, no penetration of para-hydroxyanisole which you don't have. I mean, I'm sorry, but antifungals are not a surrogate for it, nor is dibutyl phthalate.

Okay. That's about it. So my guys are going say, safe in the discussion, and we'll talk about an unknown, but perhaps increased stress for squamous cell carcinoma, and say, safe as used -- and put in a little blurb about it being used to -- we have information that it's used in some other cosmetic products, but we are not reviewing those uses, we are reviewing uses only in UV-cured nail gels. And safe as used when it -- however we phrased the sun protection for lactic acids --

DR. BRESLAWEC: You can reemphasize that this -- para-hydroxyanisole unsafe for --

DR. BELSITO: And unsafe for -- unsafe for other cosmetic uses.

DR. BRESLAWEC: Right.

DR. BELSITO: Yeah. Sure. No problem.

DR. LIEBLER: So, I have written some language that we could incorporate in the discussion, I'm going to read it to you, and just get your reaction to it.

DR. BELSITO: Yeah.

DR. LIEBLER: And see. Use of home shifts, as potential for increased exposure

compared to application in salon setting, due to possible error in application by an experienced consumer's panel, recognize this issue, but noted that the exposure levels, were much lower for the compound in the context of the use of these nail products, thus the risk of skin-deep pigmentation of (inaudible) due to systemic exposures would just be minimal.

What I mainly wanted to capture was the idea that even though there could be less appropriate usage of these products in the context of home non-trained, non- professionally trained users, the risk of these other effects is still not determinative, unless (inaudible) for the Panel.

DR. BELSITO: Are you specifically going to mention, you mentioned deep pigmentation, are you specifically going to mention skin cancer?

DR. LIEBLER: No. I hadn't.

DR. BELSITO: Could you?

DR. LIEBLER: Sure.

MS. EISENMANN: It seems, what you're talking about is the chemical for skin cancer is related to the UV exposure but (inaudible)?

DR. BELSITO: In another sentence.

SPEAKER: One thing I'd like to suggest --

DR. LIEBLER: Well, I wouldn't --

SPEAKER: I'm sorry, Dan.

DR. LIEBLER: I wouldn't mention skin cancer unless I was saying that this Panel thought that the risk of skin cancer -- I wouldn't mention skin cancer unless I was tying it to the need for additional preventive measures in our discussion.

DR. BELSITO: But we are.

DR. LIEBLER: Right.

DR. BELSITO: I thought we had said that our conclusion was --

DR. LIEBLER: Right. In the conclusion, I'm talking about the discussion.

DR. BELSITO: But then we have to have some rationale in the discussion while we are putting that restriction in the conclusion. No?

DR. LIEBLER: Yeah.

DR. BELSITO: And the CPA for light sources, Doug, you said there was labeling on them?

MR. SCHOON: Right. The lamps are required to get like UL approval, or CSA approval back to some of the candidates must have this. So, manufacturers typically will either give UL or CSA approval, and these organizations are certifying organizations that will look at the lamp, they look at exposures, they look at data, and then they'll determine, first-off, is it safe, and then they will also give you warnings that you need to put onto your packaging.

DR. BELSITO: And do you know exactly what those typically say?

MR. SCHOON: I believe we've -- as a matter of fact, I don't believe we've seen it at that. Typically they warn people against looking inside the lamp or not -- be careful or --

MR. STREMBERG: It's not a flashlight.

MR. SCHOON: Yeah. Be careful. Don't pull by the cord, things of this nature. How to use the lamp safely to avoid a wide range of potential problems. Of course exposure would be one of them. They don't want people who would expose themselves either. Fortunately they said that their lamps are really designed to minimize that, because you're not typically going to be looking at the bulbs.

DR. BRESLAWEC: Is there an automatic turnoff for the timers?

MR. STREMBERG: There are timers. Yeah there are timers.

MR. SCHOON: And one other thing I'd like to suggest is that, before you consider that depigmentation as a risk, is to reevaluate that, because my view is that, well concentrations of a (inaudible) below the -- probably the threshold for causing depigmentation.

DR. BELSITO: Well, then I guess we -- if we are not going to put that in then we have to have the discussion, at least to make everything clear about -- I should refer to this only by name, Ms.

Grankin's concern about the aestheticians who are applying these, and the risk of depigmentation to them is that something we worry about, occupational, is that OSHA's problem, or is it CIR's problem?

DR. BRESLAWEC: Is there something that comes in to stay in contact with the aestheticians?

DR. BELSITO: I would imagine it shouldn't, but she raised it, so.

DR. STIENBERG: Then it's the brush -- it's basically a nail polish, but the brush that they use, and anytime it comes in contact with the skin, you just ball it up, and they are all gels, I would guess. They have a consistency of gelling, and when you get it onto the skin, since they are so hydrophobic, they just fall immediately, and just like -- either the dispatches that come with the kits, or you just pull it right off. It goes right into the trash can.

MR. SCHOON: And usually these are colored people, and the way of the skin contact, they wouldn't see on their skin, or get caught in their skin. It wipes off very easily. And the product doesn't work quite as well, if you do get skin contact, because you'll pour oils down on the nail plate, and then the product won't adhere that well.

SPEAKER: --

MR. SCHOON: So instructions usually affect always, instruct the ways they contact.

MR. STRENBORG: I had my nail done about six weeks ago, just to see what it was like using one of these kits.

DR. KLASSEN: You don't need to use that as an excuse.

SPEAKER: We do it every two weeks.

MR. STRENBORG: Just fingers, bright red. A lot of fun, but I asked the technicians to deliberately put the polish on my skin, and she now took the brush, and actually brushed my skin, as opposed to this -- and she probably took the (inaudible) it just balled right up. She would put it in the trash or something.

DR. BELSITO: Okay. So, Dan, you're going to go take a bio break. I assume Dan has captured his comments for the discussion. I would just like another sentence out of him to the discussion about concerns of an unknown but potential, small increase in the risk of skin cancers from the exposure to the light. Which will then account for our conclusion that they can end also in cosmetic use, undocumented reports of it being used in products other than nail gels. And you can reference the Google sites here, and then a discussion that the panel is aware that there may be products other than nail gels, cosmetic products other than nail gels using this.

We are not looking at the safety of those products, and at this point we feel they are unsafe because of the very depigmentation, since we don't know the concentration of the para-hydroxyanisole, et cetera.

DR. BRESLAWEC: And para-hydroxyanisole is unsafe, right?

SPEAKER: Yeah.

DR. BELSITO: Yes. So depigmentation.

MR. STRENBORG: It is a prescription drug, throughout the USA.

DR. BRESLAWEC: Right, right. Well, I know hydroquinone, so if we have --

MR. STRENBORG: -- is not what she's saying NEHQs, no.

DR. BRESLAWEC: -- an IT representative here, perhaps, point --

DR. BELSITO: I think we just need to, again, show that we've done due diligence, and searched all potential sources of information and not rely on a source that we know is unreliable, and that's the VCRP. That's just my point, you know, we are putting ourselves forward as a Body that's trying to protect consumer safety of cosmetics, and not to be using every available tool that we have, and then to say, "Oh, well, we relied on the VCRP, but we know the VCRP is tremendously inaccurate, and so the only other backup we do is we go out and poll industry.

DR. SNYDER: I think inaccurate is a little strong, I would say maybe it's not inclusive, all-inclusive.

DR. BELSITO: Well, you know, if it's not then maybe it should just be a policy that we check with Health Canada, or whoever I the Canadian registry for these products where it's mandatory.

SPEAKER: Mandatory, yes.

DR. BELSITO: You know, that our search terms include going out to industry, going out to FDA and going out to Health Canada if they are willing to show their data. Yes?

MS. BECKER: Okay. I just want to clarify conclusions because we start melding the two reports. Hydroxyquinol, repeating the old --

DR. BELSITO: Conclusion.

MS. BECKER: -- conclusion and adding safe on nail with use of gloves, sunscreen, et cetera, and then the para-hydroxyanisole are going from unsafe to safe in nail products but not safe for anything else.

DR. BELSITO: Right.

MS. BECKER: And I just want to point out that we need to clarify the nail products, because the nail products does include cuticle softeners, and that is direct contact with the skin.

DR. BELSITO: Nail -- UV-cured nail gels are the products we are talking about. Correct?

MR. SCHOON: Well, if we are talking about all kinds of artificial nail coatings, it's probably better to use the term artificial nail coatings.

DR. BELSITO: Okay. So, artificial nail coatings. So the conclusion for hydroquinone will be quite long including, safe as used in artificial nail coatings when it is accompanied by directions for use of sun protection, gloves or a broad spectrum of sunscreens.

MR. STRENBURG: It's not hard to acknowledge that the para-hydroxyanisole --

DR. BELSITO: It's both, because they both use the same machine, right?

MR. STRENBURG: Yeah.

DR. BELSITO: Again, the concern here is not the product it's the -- how the product is used. It's a long -- that, nice -- And the discussion in both will include the same boiler plate paragraph about concerns for an unknown but potential increase in the skin cancers, and therefore the recommendations of the sun protection for the nail gels, and then the para-hydroxyanisole is a separate issue of the bleaching, and therefore no other personal care products that were aware that, there appeared to be other personal care products out there using this, that are not artificial nail --

MR. SCHOON: Coatings.

DR. BELSITO: -- coatings. Okay. Anything more? Okay.

Day Two

DR. BERGFELD: Okay. Moving on to an oldie, hydroquinone.

Dr. Belsito?

DR. BELSITO: Yeah. This is about the fourth time I think we have reopened this for a new use. So the, I think, conclusion will be all of the very lengthy conclusion about the various types of uses that we had before. My team felt that the chemical itself was safe as used. Most of our debate was around the light sources that were used to harden it. So we felt that it was safe for use in nail gels when it was accompanied with recommendations for application of photo protective materials to the skin that would also be exposed, and those could either be broad spectrum sunscreens or gloves as were suggested, but that it had to carry in the discussion, and obviously, in our discussion, and it would be up to FDA how they would want to regulate the marketing, but there was at least some concern of the potential for a slight increase in the risk of squamous cell carcinoma in individuals who were placing their hands under this machine.

So, safe as used in nail coatings --

DR. SNYDER: Artificial.

DR. BELSITO: -- artificial nail coatings when the skin of the hand was protected either by

sunscreens or light, impermeable gloves.

DR. BERGFELD: Dr. Marks?

DR. MARKS: We took a slightly different tact. We agree with your approach, but we felt that the conclusion that was published in 2010 essentially stated that. So we felt we did not want to reopen this ingredient. And in the re-review discussion we clarify the issues about squamous cell carcinoma. What we heard was the light was visible light, and when you actually look at the risk, it's extremely small, if it really exists. We also in the re-review discussion, we also addressed the issue of home use of these nail products. So we felt that we didn't have to reopen.

DR. BERGFELD: Any comment? Dr. Belsito's team?

DR. BELSITO: We did look at it in the context of nail gels. We didn't look at it in the context of UV cured nail gels, necessarily. But, you know, I don't know what the procedures are for that and, you know, if we can open it and point out in the discussion that we're now aware that as part of their use there's UV curing and, you know, enter into it the various sides of the argument about whether there is an increased risk of squamous cell carcinoma or not. We also, you know, we heard the same presentation that it was primarily infrared light and not UV light, but there are papers that presumably use the machines that are being used and found high intensity UVA1 light that exceeded some exposure limits. So, I just -- I have some concerns. You know, when an endpoint is a one in a million allergic reaction that can be treated with a little steroid, that's one thing. When the endpoint is a potential end, we don't know. You know, it depends upon how you calculate it -- a one in a million squamous cell carcinoma of a digit, which as you know, Jim, after the limb or one that occurs in a burn is one that has a higher potential for metastases, then I'm not sure that I'm ethically comfortable allowing a product like that to go on the market, you know, as a dermatologist without very stringent warnings. And so it would have to be incorporated. There would have to be a lot more data incorporated into this re-review, not reopened, than normally would occur because there is new data that gives us some pause. You know, we didn't have this argument about photocarcinogenicity and the instruments that were used.

DR. MARKS: So would you restate your new conclusion then?

DR. BELSITO: The new conclusion is that -- and again, this is -- I'm stating the conclusion that my panel agreed to -- was that these were safe as used in UV cured artificial nail coatings when accompanied by however the AHA report is, that use of photo protection, either as sunscreens or as impermeable gloves to the skin of the hands that would be exposed to the UV light.

DR. BERGFELD: Halyna?

DR. BRESLAWEC: Yes. Doug Schoon is here representing the nail manufacturers, and if possible, we'd like a comment.

MR. SCHOON: Hi, thank you. I'm not sure it's proper to -- or fair to say these are high intensity UV. It's actually a low intensity light source, and I'm not aware of any regulatory limits or safe limits that are exceeded. In fact, I think the point of the data we presented was to show that regulatory limits are not exceeded or even closely approached. So obviously, there is some concern here, and we would love an opportunity to address this concern. If there's additional data that we can submit, we'd be more than happy to do that because we do believe these lamps, and have put quite a bit of effort into showing these lamps are safe, and we'd like an opportunity to continue to do that.

DR. BERGFELD: Thank you. Any comment, Don?

DR. BELSITO: Just trying to find the paper from UTIME. I forget who the first author is.

DR. HILL: Try Curtis Painter and John Childs. That one.

DR. BERGFELD: Jim, in the meantime?

DR. MARKS: Well, I think certainly we can reopen, or it's already open. I think the conclusion can change. I don't know if it can be shortened a bit to point out the concern. Obviously, the remainder of the conclusion from 2010, safe at concentrations less than 1 percent in hair dyes. It would be more specific to change the conclusion because it says safe for use in nail adhesives. We don't really address these nail coatings or polish in that conclusion. So in reality we probably should reopen just to

mention that. And that it should not be used on leave-on products.

DR. BELSITO: Okay.

DR. MARKS: I can -- our team, I think, can second, reopen it, or that new conclusion, Don and team, and then I think how wordy do you want to make the conclusion? It's fairly long what you said. I think the issue is really protection and the warning label.

DR. BERGFELD: Lillian is going to respond.

DR. GILL: Yeah. I just wanted to remind the Panel that we voted -- you voted to reopen this a couple of meetings ago, so it is already open. I think the discussion in Jim's group is whether or not to consider this a rereview or not. But it's already reopened.

DR. MARKS: Right.

DR. BELSITO: Okay. So I would just like to quote from the Curtis, et al. paper where they looked at, apparently, two of the ultraviolet nail measurements -- an OP product and a creative nail design product, and they say that although the cumulative MEDs are low, in less than 10 minutes a person's hands received an energy dose equivalent to the day-long recommended limit for outdoor workers. UVA radiation produces less cell cycle arrest than UVB; however, it produces DNA damage via oxidative stress and free radical formation, suggesting that UVA may be more mutagenic than UVB. Therefore, the amount and accumulation of DNA damage following short, high-intensity UVA exposures are unclear.

So in all due respect, Doug, I think there is at least one academic group out there that would disagree with your appraisal of the UVA exposure from those lamps, which again, causes me concern. There's some controversy. And I think when there's controversy, one never quite knows where the truth lies, and therefore, I think if we are going to go ahead and allow these products to go on market, then I think we need to make sure that the consumer who wants to use these is adequately aware that the risk of photocarcinogenicity is not known. But clearly, one way of protecting that is to apply a broad spectrum sunscreen to the skin of the hand or use some type of photoprotective glove. I don't have an issue with the nail bed. I mean, you didn't have to convince me and show me Mark Webwald's paper that UV light is not going to penetrate the nail unit. That's not the issue. It's the rest of the skin that gets exposed to the light that for me is the issue. So, I've said enough.

DR. BERGFELD: Are you wanting to respond, Doug?

MR. SCHOON: Certainly. Again, I would ask if there's additional data, we can -- because there's obviously a controversy. There's no denying that, but if there's additional data we can present for your consideration, we're more than happy to do that because we have vested interest, obviously in settling this controversy, and if the CIR can help us achieve that goal we'll definitely do the work.

DR. BELSITO: Doug, I don't think there's additional data. I mean, I think that, you know, there's still going to be this paper out there. There are still going to be other papers out there. The controversy is still going to be fueled. I think that from all -- I mean, we don't have a problem with your use of hydroquinone or p-Hydroxyanisole. The issue is with the other things that have to accompany the cosmetic use of this product. And I don't think however much data you bring, it's not -- unless you can speak to these authors who have come out and warned about risks, that they were wrong and have them retract these papers, that controversy is going to continue to exist. And I don't see why it's such a problem between what the CDA is going to make you put on the bulb itself to do the same thing that we did with the alphahydroxy acids and say, you know, should be used in association with a sunscreen. Here we're saying you should use photoprotection on the skin that would be in these lamps. If people choose to ignore that, it's just like cigarette smoke cautioning "may be hazardous to your health." If people still want to smoke cigarettes, it's a free country as long as they're not polluting my lungs. But I think for me it's very important that they have that regulation that a consumer using these be aware of it.

MR. SCHOON: Well, I appreciate that. And now that I have more information about what your actual concerns are, what we're really asking for is an opportunity to address that because we may be indeed able to come up with information that would make you think again about this. So that opportunity would be very appreciated.

DR. BELSITO: Okay.

DR. BERGFELD: So how -- do you want to table this till the next meeting to have this information?

DR. BELSITO: You know, I would say we can go ahead. You know, if the nail manufacturers can bring us the information, we can always change it.

DR. BERGFELD: Okay.

DR. MARKS: Yeah. This would go out as a tentative amended at this point.

DR. BELSITO: Right.

DR. MARKS: So there's opportunity. So I would second the motion.

DR. BERGFELD: Okay.

DR. MARKS: It would go as a tentative amended. And if I understood what you said, Don, really, in the conclusion there would be the UV photo protection portion of the conclusion, and then in the discussion we have a robust discussion on the UV light hazard of the -- potential UV light hazard.

DR. BELSITO: A discussion, you know, just to review the controversy in the literature over this.

DR. MARKS: Right.

DR. BELSITO: And, you know, you have very good people on both sides. You know, you have Marty Weinstock, who is a wonderful epidemiologist at Brown coming out and saying, you know, these don't pose a risk, but you also have other very good individuals who are concerned. So I think we need to address this in the discussion and then say, you know, basically, if there's a risk, it's very low. It's very hard for us to quantify it, but what does it take to slap a little sunscreen on your hands, you know, once or twice a month when you're going to be using these machines?

DR. BERGFELD: Any other comments?

DR. MARKS: Rachel, did you want to comment about home use? Because I think that needs to be in the discussion, too. And we talked about that yesterday.

MS. WEINTRAUB: Okay. Well, I just want to say that I very much support the direction that this is going. I think this was a great substantive conversation that the Panel has had.

In terms of home use, I think it's important, given some of the things that we discussed in the Marks meeting, that home use brings other types of issues. People are not trained. Information is not as well known. And a discussion about what it means for home use is different than what is in salons. So it's just important to include that as a separate category and discuss potential risks given limited knowledge, limited training.

DR. BELSITO: And that's my whole point. That these are -- we're talking about having sales to the consumer.

DR. BERGFELD: Thank you. Any other discussion? I'm going to call for the vote then. Those who approve as amended tentative final raise your hands. Thank you.

DR. BELSITO: When application is accompanied by directions for use of sun protection.

DR. BERGFELD: Yes. That was the addition.

DR. BELSITO: Okay.

DR. BERGFELD: Yes. I think that was understood by the voters.

Thank you. Unanimous.

(Motion passed)

DR. BERGFELD: Then moving on to the other related ingredient, the p-Hydroxyanisole.

Dr. Marks?

DR. MARKS: So this is similar and very much related to the discussion we just had. And as you recall, p-Hydroxyanisole in the past has been declared unsafe for cosmetic use. We would move to reopen this report with a tentative conclusion safe in artificial nail coatings as a polymerization inhibitor,

unsafe for other cosmetic uses. And certainly that conclusion can be embellished as you have stated previously as far as UV protection in there in the directions, Don.

DR. BERGFELD: Don?

DR. BELSITO: Yes. Again, when application is accompanied by directions for use with sun protection gloves or broad spectrum sunscreens. I would agree with that.

DR. BERGFELD: Any other discussion? Yes, Don?

DR. BELSITO: Yeah. I was just disturbed by the fact that in one of our waves we got a letter from Alexandra Scranton that point out in a 15-minute Google search she was able to find products on the market that contained p-Hydroxyanisole. And the explanation I got was, well, these weren't reported to the VCRP and that's what we search.

So I would like to make a motion that when we're looking to see what products are out on the market, that we not rely on VCRP, which we know is unreliable because it's voluntary; that we go to Health Canada as well and ask them if they're aware of any reported uses; and that we spend at least 15 minutes on Google or another search engine to see if, in fact, we can find products. Because the Mario Badescu Vitamin E Night Cream, now, I didn't go to a store to see if it actually contains p-Hydroxyanisole. You know, not everything that you find on the web is correct, but if, in fact, it does, it makes us look, as a Panel, to be very uninformed when we're relying only on, you know, use in the marketplace based upon a system that we all admit is flawed because it's voluntary and only affects companies that are members of the CIR. So that's my only discussion point that I wanted captured for the minutes.

DR. BERGFELD: That's a recommendation rather than a motion, isn't it?

DR. BELSITO: Yeah. It's not a motion. It's just a recommendation that we search not only VCRP but Health Canada where it's a little less voluntary, and that we just do a very -- I mean, I don't want you spending hours Googling but see what happens with a quick Google search because this lady said that it took her 15 minutes to find a variety of products.

DR. BERGFELD: Ron Hill?

DR. HILL: I would second. I mean, I feel exactly the same way. And also, the issue came up yesterday, and I'm not sure I'm clear on understanding.

So if a product is only sold for registered salon use, it doesn't show up in VCRP because they're not supposed to report to VCRP; is that correct?

DR. BERGFELD: Yes.

DR. HILL: But do we capture data from that -- whatever source they're using to register for salon use when we're reviewing ingredients?

DR. BERGFELD: I don't know. Lillian?

DR. GILL: That's an FDA question.

DR. BERGFELD: Oh, FDA question. I didn't see.

DR. MILSTEIN: Regarding the salon products, there is nothing to prevent a manufacturer of salon products from voluntarily submitting those products for listing as well with the FDA's VCRP. But it's not mandatory.

DR. BRESLAWEC: They get rejected. According to our manufacturers, if you submit a VCRP for salon products, the system rejects those applications.

DR. HILL: And for me that's a huge issue.

DR. MARKS: Don, we also, our team, discussed that, and some of the questions I would have is most of our conclusions go with the present practice and use of concentration, and we base that off of we refer to the VCRP table as to what the uses are in the concentration. Once we start getting -- and I don't know what Healthcounter would show or drugstore.com. If you have different morey say perhaps uses but then you don't have the concentrations, you know, then does the table have an asterisk on it and at the bottom say we found on Google and such and such, and such and such, these other uses? I think it's important if the writers and the staff search this and find this data, then how do we capture it and then what do we do with it once we have it?

DR. BERGFELD: Don?

DR. BELSITO: Well, you know, in this case it really doesn't matter because we're saying it's unsafe for any other use, which then means that we feel that these products that are out on the marketplace with p-Hydroxyanisole are unsafe and it's not up to us to regulate them. I think it just -- it begs the question as to whether the Panel is doing its due diligence when we say that we are not aware of any reported uses other than in artificial nail coatings when, in fact, there are other reported uses out there.

So I'm not talking about how it affects our safety conclusions, et cetera, et cetera. You know, when there are uses out there and we say safe as used and we've defined concentrations, if there's a use we haven't captured that's above that concentration as it appears in several other reports or even in this report where there are uses and we said it shouldn't be used, we're not the regulatory body to go after those companies; someone else is. But again, it goes to our credibility and our due diligence if we're saying we're relying only on VCRP which we know is flawed to tell us what's out in the consumer marketplace and we're putting in a document that we're not aware that there are any other uses other than these nail gels when, in fact, there are other uses out there. They shouldn't be there. It doesn't change our conclusion. What it does is it makes it look like we're not doing our job.

DR. BERGFELD: Halyna?

DR. BRESLAWEC: I sympathize very much with Dr. Belsito's concerns because it's a concern that I know that CIR has had in the past and certainly with the industry we're concerned about it, too. But in this particular example, the reported use for us to be able to treat that I think, or for the Panel to be able to treat it as anything but anecdotal. You would have to go chase down the product, look at the label, and see if it, in fact, had that ingredient in it. If it did, it's clearly an ingredient or a product that's being used against CIR directives. And so the way the data are presented, the way the use information is presented very clearly states that it is based on the most standardized, although imperfect system available, which is the VCRP. From the manufacturer's perspective, we have not only included information from our own members but also from the Small Manufacturers Association in our use surveys and have encouraged them to use VCRP as well. Not perfect. I mean, I'd be the first to admit it. But it is a standardized system. It's something that you can rely on as an indicator of use. Not a guaranteed indicator. Is it the tip of the iceberg? I don't know. Is it 90 percent? I don't know either. But it is a standardized, generally recognized system. When you start Googling for information, it takes you down a lot of different routes, and I think for the Panel to be able to use that information will require a lot of follow-up that perhaps the CIR staff -- and I know our staff does not have the resources to do -- it's more of a regulatory function and that's not CIR's role.

DR. BERGFELD: Lillian?

DR. GILL: I think, Don, some of your concern may be the statement in the report that says we're not aware. I think we've tried to stay close to saying as reported in the VCRP because we do have to rely on that data. So I think we can be careful in the statements we make about nothing else available or we can make the statement that anecdotal information suggests their uses out there.

DR. BERGFELD: Halyna?

DR. BRESLAWEC: Yeah. I think part of our discussion, or part of the Panel's discussion yesterday was we are aware. There's a letter that's been submitted officially to CIR that points out that there is an ingredient. And I think that should be discussed in the discussion and, you know, discuss that VCRP is not perfect and we have been informed or the panel has been informed that that needs to be addressed. There's no question in my mind that it should.

DR. BERGFELD: Halyna, may I ask a question? And that is the salon use and the concentrations in the salon, when we call for an industry report, does that get included or is that not?

DR. BRESLAWEC: I'm going to direct that question to the expert.

Again, VCRP will not accept that.

DR. BERGFELD: I understand that.

DR. EISENMANN: I assume some companies are providing salon information. I mean, I don't ask for them to distinguish between home-use products and salon-use or other uses. Of the companies are providing, I presume some of them have some salon products and that they're reporting to me.

DR. BERGFELD: Would it be too much to ask that they break that down for us?

DR. BRESLAWEC: I guess my question would be what would be the purpose of that? What function would that serve?

DR. BERGFELD: Well, it seems to be a hole in the data as what the actual concentrations are used by the public, even though to be directed by the salon. The public is being exposed to that concentration.

DR. BRESLAWEC: You know what? I'm sorry. Let me go back because in terms of hair dye and that kind of information, you know we are getting information for salon use; correct? I would assume so.

DR. EISENMANN: I don't know. I mean, hair dye, I don't know if they're salon products or not.

DR. BRESLAWEC: Perhaps we can look into that and come back to the Panel with a clearer understanding of what exactly covers or not before we suggest any changes.

DR. BERGFELD: I'm sorry, David has his hand up. You can come to a mike, David.

DR. STEINBERG: For the nail industry, the exact same products are sold to the consumers that are sold in the salons that form the use of -- I mean, HQ and HQ are exactly the same. We're not adding them. They come with them on there. So the formulations are basically the same. We don't differentiate when we submit, and the manufacturers of the professional products do submit to the PCPC when they requested that information. So we do do it even though they're just the same.

DR. MARKS: Don, I hear your concern and my remark is what do we do with the information and how do we record it if you do the searches? And I don't mind trying it for a couple ingredients as a trial and see what happens. Perhaps with a staff writer. But if we get data, we can't ignore it. Somehow it has to appear and be recognized. We may use VCRP as the standard we make our decisions on, but then if we Google, use Health Canada, Drugstore.com or whatever, then we should acknowledge at least we're doing that data search which now is occurring when we look for ingredients. I don't have a problem with doing it. I have a problem with how do we capture that data in the report and then if we get something that raises concern, obviously we've got to address that. So that was my --

DR. BELSITO: I think we can continue to use tables based upon VCRP and in a sentence say that, you know, a check of the Health Canada database verified/did not verify anecdotal reports that there are products out there that do contain this ingredient, levels are not known. And when we get to our discussion say we are not considering the products that we don't have concentration ranges and that are safe as used as based upon the concentration ranges that are stated in table whatever. In the case of p-Hydroxyanisole, I think we should recognize the letter that we received from the woman and acknowledge that there may or may not be products out there that are meant as leave-on products that contain p-Hydroxyanisole, and the Panel wants to reiterate that it has found that p-Hydroxyanisole is unsafe for those types of leave-on products.

DR. MARKS: So I think since it's this ingredient, the p-Hydroxyanisole specifically the letter was referring to, what I would suggest is Lillian Becker do just what you suggested, Don. We have a -- we're reopening it. We're issuing a tentative report. So the next time we see this we can see a Google search. We can see Health Canada, whatever you think is appropriate, and then let's see what we find and then react to it before we do this same process for every ingredient. But we can use this as the prototype and see what happens.

DR. BERGFELD: Halyna?

DR. BRESLAWEC: I don't disagree with that approach if that's what the Panel wants to do. I want to point out that it will make absolutely no difference in the conclusion because the Panel has

already determined that use outside of the nail area is not safe.

DR. BELSITO: Right. And I just want to make sure that, you know, we -- it be quite clear that we acknowledge this letter from Ms. Scranton and we are aware that there are anecdotal reports that this ingredient, p-Hydroxyanisole may be being used in leave-on products and that would be an unsafe use according to the Panel. That's it. It doesn't change our conclusion. I just -- I am very concerned that it appear to the public, to all interested bodies, that the CIR Expert Panel is using all means that you can in 2014 to capture information about what's out in the marketplace and not solely rely on a system that everyone in this room agrees is flawed because it's voluntary; that there are other systems that we can try to use. That's my whole point.

DR. BERGFELD: I think that the minutes are going to reflect this discussion of the concern of what's out there and what's being used and at what concentrations, and I think that the staff will then be alerted that there may be other searches that are needed, but I'd like to move on.

DR. BELSITO: Yes.

DR. BERGFELD: I think that we have a motion that's been seconded, and we are going out with a tentative final. And Dr. Marks, will you restate the final conclusion?

DR. MARKS: So this is actually a tentative amended and the conclusion will be safe in artificial nail coatings as a polymerization inhibitor when application accompanied by UV light protection.

And I don't know if you want instructions in there or not but that can be worked out essentially, and it's unsafe for other cosmetic uses.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion? Seeing none, please indicate by raising your hand your approval. Thank you. Unanimous.

(Motion passed)

Amended Safety Assessment of Hydroquinone as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: May 16, 2014
Panel Meeting Date: June 9-10, 2014

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.

ABSTRACT

Hydroquinone was reviewed because new uses in nail gels and adhesives that require UV curing were identified. 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. Hydroquinone should not be used 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 sold.⁴ *p*-Hydroxyanisole is the focus of a separate amended safety assessment addressing this new use.⁵

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 1.⁶ It is currently reported to function as an antioxidant, fragrance ingredient, hair colorant, reducing agent, and skin bleaching agent. Hydroquinone is the common name for 1,4-dihydroxybenzene.

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)⁷ report of an oral carcinogenicity study. In the original CIR report, it was concluded that hydroquinone was safe for cosmetic use at ~1% in formulations designed for discontinuous, brief use followed by rinsing from skin and hair. This conclusion applied primarily to the use of hydroquinone in hair dye formulations. The use of hydroquinone to lighten the skin was not addressed because such use is regarded by the Food and Drug Administration (FDA) as a drug use.

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

Hydroquinone in an alcoholic vehicle was absorbed through the skin of the forehead of male subjects; absorption of hydroquinone from a solution that also contained Escalol 507 (a sunscreen) and Azone (a penetration enhancer) was 35 ± 17%, from a solution containing Azone was 66 ± 13%, from a solution containing Escalol 507 was 26 ± 14%, and from a solution containing only hydroquinone was 57 ± 11%. The average percutaneous absorption rate of hydroquinone using 48-h excretion data from dermal and i.v. absorption studies using dogs was estimated to be ~0.15 nmol/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 ≥ 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)⁸, 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)⁹ 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.

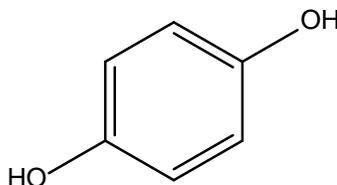
Hydroquinone has been reported to cause exogenous ochronosis in several ethnic populations following prolonged

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 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. Hydroquinone (and *p*-hydroxyanisole) is destroyed during polymerization (using light) and any residual inhibitor is enclosed in the hardened polymer.[Dr. David Steinberg, pers. comm.]

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

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

A web search for hydroquinone and cosmetic ingredients showed that there are more nail gel products available on the market than what was reported to either the VCRP or the Council. While a full inventory of the results were not taken, there were multiple professional and home kits available for sale that contained nail gels that contain hydroquinone and require UV curing.

Use in Other Cosmetic Products

Data on ingredient use are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP).¹⁵ The VCRP reports that hydroquinone is used in 1 nail extender, 7 hair dyes and colors, and 10 skin care preparations. There were no reported uses for other nail products. Industry is not required to register products with the VCRP. It is understood that the data in the database are a sampling of what cosmetics are available on the market and are not comprehensive. Similar results were reported in the Environmental Working Group database.¹⁶

A survey was conducted by the Personal Care Products Council (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.¹⁸

Health Canada¹⁹ 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.²⁰

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.²¹ The test substance was administered daily to one or both ears of the rabbits or to the shaved abdomen; the rabbits were killed and necropsied. Findings in the liver included hydropic degeneration, bile duct hyperplasia, and glycogen depletion. Hydropic degeneration, hyaline casts, congestion, perivascular edema, and fibrosis were observed in the kidneys. For both the kidneys and livers, the effects were greater in the groups in which the test substance was administered to the ears. Dermal effects included hyperkeratosis, lymphocytic and eosinophilic infiltration, and congestion of dermal blood vessels.

Dermal depigmentation was observed when hydroquinone (5% in propylene glycol/ethanol, 50:50) or *p*-hydroxyanisole (5% in propylene glycol/ethanol, 50:50) was dermally administered to multiple sites of the backs of Yucatan miniature pigs (n = 2) twice/day, 7 days/week for 90 days.²² Microscopic examination of biopsies from the test area showed decreased pigment and melanocytes.

Cytotoxicity

Hydroquinone (0, 10, 20, 30, 40 μ M) was not cytotoxic to human L-02 liver cells but was cytotoxic to the same cell line with silenced DNA polymerase eta (Pol η) after 24 h of incubation.²³ Cell survival was determined using the MTT assay.

Hydroquinone (500, 750 μ M) was cytotoxic, in a concentration-dependent manner, to F344 rat hepatocytes when incubated for 2 h.²⁴

Hydroquinone was cytotoxic to human lymphocytes at 270 μ M, but not at 180 μ M, when incubated for 3, 24, or 48 h with metabolic activation and 3 h without metabolic activation.²⁵

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 Pol η after 24 h of incubation.²⁶ 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 Pol η were determined by real-time PCR, the protein expression levels of Pol η 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 Pol η led to a decrease in cell proliferation and an enhanced susceptibility to hydroquinone-induced cytotoxicity. Pol η -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 μM ; 50 μL) was not clastogenic in cultured human lymphocytes with or without metabolic activation.²⁵ The lymphocytes were treated in accordance with the Organization for Economic Co-Operation and Development (OECD), European Economic Community (EEC), and the Environmental Protection Agency (EPA) guidelines for mutagenicity testing. The lymphocytes were incubated with hydroquinone (18 – 73 μM) for 17 h prior to the addition of hydrogen peroxide (12 mM). Pre-incubation with hydroquinone reduced the number of chromosomal aberrations compared to negative controls.

IRRITATION AND SENSITIZATION

Dermal – Non-Human

In a local lymph node assay (LLNA; n = 5) repeated in four different laboratories, hydroquinone (0, 0.10%, 0.25%, 0.50%, 1.00%, 2.50% in acetone:olive oil 4:1; > 99.5% pure) was predicted to be a dose-dependent sensitizer.²⁷ The EC₃ values were 0.07%, 0.03%, 0.08%, and 0.07% for the four laboratories.

When hydroquinone (5% in propylene glycol/ethanol, 50:50) was dermally administered to multiple sites of the backs of Yucatan miniature pigs (n = 2), the test sites exhibited severe erythema, scaling and crusting.²² 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 3).²⁸⁻³⁹ The test materials were administered to a fingernail of the subjects and removed by wiping with a proprietary remover solution after 10 minutes three times per week for nine applications. Two weeks later, the test material was administered to the same fingernail in the same manner. The amounts of hydroquinone or *p*-hydroxyanisole were not provided.

UV NAIL LAMPS

UV lamps are used to cure nail gels, acrylic nails, and nail fill-ins, and to dry traditional nail polish and UV top sealers/topcoats.⁴⁰

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.⁴¹ UVA-1 is the least erythemic and photocarcinogenic range in the UV spectrum. The bulbs in UV nail lamps have internal filters to eliminate UVB and are reported to emit exclusively in the 265 – 370 nm range.⁴²

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.⁴³ Typical client usage is 1 – 4 times/month for 2 min or less per visit.⁴²

Another researcher stated that typical salon exposures are 10 minutes or less per hand and with exposures occurring only twice per month.⁴⁴

An instructional pamphlet for the application of nail polish directs, that in the course of applying a base coat, color coat, and top coat, the polish is to be cured for 30 sec for each coat using the proprietary UV light (for a total of 90 sec) or for 1min, 2 min, and 3 min, respectively for a total of 6 min using another UV light.⁴⁵

Nail gels shrink with curing under UV lamps. Thus, it has been recommended that three or four separate thin coats of nail gel be applied and cured for 3 min each coat to achieve the desired results.^{40,46}

In a study of two UV nail lamps (each from a different nail product company) cumulative exposure measured as minimal erythema doses (MED) were low. However, measured in J/m^2 , cumulative exposures were equivalent, in less than 10 min, to the recommended limit of $30 \text{ J}/\text{m}^2$ for 8 hours of outdoor work and recreation by the International Commission on Non-Ionizing Radiation Protection.⁴⁷ 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 4).

In the same study, a spectrometer calibrated to measure absolute UV irradiance was used to compare solar radiation with radiation emitted from the lamps. The spectra indicated that the lamps emitted 4.2 times more energy ($\mu\text{W}/\text{cm}^2/\text{nm}$) 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.⁴⁷

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.⁴⁸ The UV nail lamps used were representative of major US manufacturers and evaluated for radiant hazards as defined in the American National Standards Institute/Illuminating Engineering Society of North America Recommended Practice - 27 (ANSI/IESNA RP-27), the Recommended Practice for Photobiological Safety. Lamps were evaluated at three positions: 1 cm above the inner surface, which approximated exposure to the hand; 20 cm directly in front of the box opening; and 20 cm outside the box and 45° above the hand opening.

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

Hazard to skin at intended-use distance enabled classification of these devices into Risk Group 1 or 2 (Low to Moderate) with the $S(\lambda)$ (i.e., distance between the source and the object) weighted Actinic UV range of 1.2–1.7 $\mu\text{W}/\text{cm}^2$ and 29.8 - 276.25 min permissible daily exposure. At 20 cm on center and at 45° from center, UV risk to skin and eyes were within the Exempt classification. Actinic UV ranged 0.001–0.078 $\mu\text{W}/\text{cm}^2$ and unweighted near UV (320 - 400 nm) range was 0.001–0.483 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.⁴⁸

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.⁴⁹ UVA irradiance ranges from .06 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. A survey was conducted of commercial UV nail lamps that were in use at commercial salons. The lamps were examined 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.⁴⁴ 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.⁵⁰

A concern exists that the incorrect replacement lamp/bulb may be inserted into the UV nail lamp (e.g. those emitting UV-B or UV-C) could be harmful to the skin if used.⁴⁴ UV lamps/bulb should be replaced with the exactly the same original manufacturer's UV lamp/bulb that was supplied with the UV nail unit when it was purchased.

Risk Analysis

In a risk analysis, it was concluded that 72 709 more women using UV nail lamps to cure their nail gels 8 min/application, every 3 weeks, for 20 years would increase the chance that one more woman might develop squamous cell carcinoma on the back of the hand compared to women who were never exposed to UV nail lamps (Table 5).⁵¹ The model UV nail lamp used in this analysis had an unweighted UV irradiance of 115 W m² with an erythemally weighted output of 1.58 SED/h. The authors stated that the estimated risk of squamous cell carcinoma could be reduced to virtually zero by wearing fingerless gloves when the hands are being exposed to UV radiation from such lamps.

Light Penetration of Nails

UVB light did not penetrate the finger nails of a cadaver ($n = 10$).⁵² An average of 1.65% of UVA light penetrated the nails in this study. A Dermalite UV light machine was used.

Case Reports

Nonmelanoma skin cancers were observed on the dorsum of the hands of two women who reported exposure to UV nail lamps.⁴⁰ 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.⁴⁰

SUMMARY

This is an amended safety assessment of hydroquinone prepared to address a new use in nail gels and adhesives that require UV curing. This Summary does not address information in previous reports. The CIR Expert Panel concluded in 2010 that hydroquinone is safe for use in nail adhesives and in rinse-off products up to 1.0% but is not safe for use in other leave-on cosmetic products.

Hydroquinone was reported to be used in the liquid component of two-component artificial nail systems at a maximum concentration of 200 ppm, which decreases to approximately 133 ppm after mixing with the solid component just before application. Polymerization was reported to take 5 – 15 min in a nail adhesive product. Hydroxyquinone is used interchangeably and in combination with *p*-hydroxyanisole to control polymerization in nail gels and nail adhesives.

Because these products, which contain hydroquinone and/or *p*-hydroxyanisole, are marketed as direct sales, they 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.

The VCRP reports that hydroquinone is used in 1 nail extenders, 7 hair dyes and colors, and 10 skin care preparations.

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 multilaboratory LLNA. The EC_{30} values were 0.07%, 0.03%, 0.08%, and 0.07% for the four laboratories.

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

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

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

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

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

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

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

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

DISCUSSION

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

The Panel noted that there is little to no dermal exposure to hydroquinone when artificial nail coatings are used according to label instructions. Any accidental application to the surrounding skin should be promptly removed for best visual results and adherence as well as to minimize exposure. Therefore, the risk of skin depigmentation would be minimal during momentary exposure. However, the Panel stressed that contact with the skin is to be prevented and that professionals be properly trained in the application of these products. The Panel also noted that hydroquinone is either consumed during the curing or trapped within the polymerized matrix.

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

The Panel noted that the concentration of hydroquinone and/or *p*-hydroxyanisole was not indicated in the sensitization studies conducted by applying the nail gel to the fingernails. 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.

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

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

The Panel noted correspondence that provided information that the number of uses of this ingredient is greater than that reported by the VCRP. A number of these products containing hydroquinone appear to be products that may not be considered as safe by the Panel, or were in products for which medical claims were made, thus under the purview of the FDA. The Panel stated that it is important that companies report their ingredient usage to this program, as well as respond to the concentration of use surveys conducted by the Council, to facilitate the development of safety assessments based on accurate and comprehensive ingredient use information. Additionally, they requested that industry clarify whether or to what degree ingredient usage in professional products is included in the VCRP.

AMENDED CONCLUSION

The CIR Expert Panel concluded that hydroquinone is safe at concentrations of $\leq 1\%$ 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. Hydroquinone should not be used in other leave-on cosmetic products.

TABLES

Table 1. Detection of hydroquinone in nail polish with and without curing under a UV lamp (291 nm) under various conditions (limit of detection = 5 ppm; Initial concentration of 100 ppm).¹¹

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

Table 2. Detection of 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 3. 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.

Product	n	Result	Reference
UV gel top coat nail polish	51	No signs of potential cuticle irritation or allergic contact sensitization	³³
UV gel top coat nail polish	51	No signs of potential cuticle irritation or allergic contact sensitization	³²
Builder gel	51	No signs of potential cuticle irritation or allergic contact sensitization	³¹
Clear overlay gel	51	No signs of potential cuticle irritation or allergic contact sensitization	³⁰
Soak-off sealer	51	No signs of potential cuticle irritation or allergic contact sensitization	²⁹
Soak-off gel lacquer	51	No signs of potential cuticle irritation or allergic contact sensitization	²⁸
Gel system-thick gel sealer	50	No signs of potential cuticle irritation or allergic contact sensitization	³⁴
Base gel	51	No signs of potential cuticle irritation or allergic contact sensitization	³⁵
No-cleanser overlay gel	51	No signs of potential cuticle irritation or allergic contact sensitization	³⁶
Soft white sculpting gel	51	No signs of potential cuticle irritation or allergic contact sensitization	³⁷
Pink builder gel	51	No signs of potential cuticle irritation or allergic contact sensitization	³⁸
Luminous white overlay gel	51	No signs of potential cuticle irritation or allergic contact sensitization	³⁹

Table 4. Ultraviolet nail lamp measurements.⁴⁷

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 5. The number of women who would need to be exposed to ultraviolet A (UVA) nail lamps^a for one woman to develop squamous cell carcinoma who would not have done so otherwise.⁵¹

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

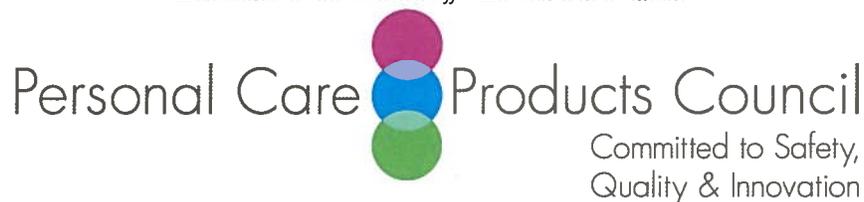
References

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. Nikitakis, J and Breslawec HP. *International Cosmetic Ingredient Dictionary and Handbook*. 15 ed. Washington, DC: Personal Care Products Council, 2014.
7. 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.
8. Hodge HC and Sterner JH. Tabulation of toxicity classes. *American Industrial Hygiene Association Quarterly*. 1949;10(4):93-96.
9. 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.
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. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients; *FDA Database*. Washington, DC, FDA. 2014.
16. Environmental Working Group (EWG). EWG's Skin Deep® Cosmetic Database: Products containing hydroquinone. <http://www.ewg.org/skindeep/browse.php?containing=703041&showproducts=1¬old=1>. Washington, DC.
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. 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.
19. 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>.
20. 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.

21. 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 Toxicology*. 2012;7(1):19-26.
22. 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.
23. 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 madated testing. *Regulatory Toxicology and Parmacology*. 2008;51(2):181-194.
24. Nakagawa Y and Moldéus P. Cytotoxic effects of phenyl-hydroquinone and some hydroquinones on isolated rat hepatocytes. *Biochemical Pharmacology*. 1992;44(6):1059-1065.
25. Roza L, de Vogel N, and van Delft JHM. Lack of clastogenic effects in cultured human lymphoctyes treated with hydroquinone. *Food and Chemical Toxicology*. 2003;41(10):1299-1305.
26. 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 hydoquinone. *Toxicology Letters*. 2012;214(2):209-217.
27. 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 sensitizaiton 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. 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.
40. MacFarlane DF and Alonso CA. Occurrence of nonmelanoma skin cancers onthe hands after UV nail light exposure. *Archives of Dermatology*. 2009;145(4):447-449.
41. Rapid Precision Testing Laboratories. CND UV Lamp. 9-28-2011. Submitted by Steinberg & Associates on behalf of the Nail Manufacturers Council.
42. 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.

43. Anonymous. 2011 - 2012 Industry statistics [pamphlet]. 2013.
44. Sayre RM. 2014. Letter regarding UV lights. Unpublished data submitted by Robter M. Sayre.
45. OPI Inc. Soak-off gel lacquer Application Instructions [pamphlet]. Hollywood, CA: OPI Inc; 2011.
46. Anonymous. Hooked on nails; UV gel application. www.hooked-on-nails.com.
47. 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.
48. Dowdy JC and Sayre RM. Photobiological safety evaluation of UV nail lamps. *Photochemistry and Photobiology*. 2013;89(4):1-7.
49. 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).
50. 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.
51. 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.
52. 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.
53. Anonymous. 2012. Methyl 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.

Shipp LR, Warner CA, Rueggeberg FA, Davis LS. Further Investigation Into the Risk of Skin Cancer Associated With the Use of UV Nail Lamps. *JAMA Dermatol*. Published online April 30, 2014. doi:10.1001/jamadermatol.2013.8740.



Memorandum

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

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 24, 2014

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

Key Issues

Generally, tentative CIR reports include an Abstract. This report does not include an Abstract.

p.4 - The re-review of Hydroquinone occurred because of the new use reported by industry.

Therefore, the Cosmetic Use section should start with the information provided by David Steinberg and the Nail Manufacturers Council. They indicated that Hydroquinone is used as a stabilizer to inhibit polymerization at a maximum concentration of 200 ppm.

p.4 - The EWG data base should not be mentioned in CIR reports, and it should not be called a survey.

Additional Comments

p.1 - In the Introduction, it is not clear what is meant by "in nail gels sold separately to consumers for home use".

p.4 - The reference (11) associated with the first sentence under Use In Nail Products is not correct; it should be 14.

p.5 - The studies concerning Cytotoxicity should not be in the Toxicokinetics section. If a Toxicokinetics section is going to be included in the report, it should include relevant studies published since the last review such as:

Poet TS, Carlton BD, Deyo JA, et al. 2010. Hydroquinone PBPK model refinement and application to dermal exposure. *Food Chem Toxicol.* 48(11): 3085-92.

Abstract

A physiologically based pharmacokinetic (PBPK) model for hydroquinone (HQ) was refined to include an expanded description of HQ-glucuronide metabolites

and a description of dermal exposures to support route-to-route and cross-species extrapolation. Total urinary excretion of metabolites from in vivo rat dermal exposures was used to estimate a percutaneous permeability coefficient ($K(p)$; 3.6×10^{-5} cm/h). The human in vivo $K(p)$ was estimated to be 1.62×10^{-4} cm/h, based on in vitro skin permeability data in rats and humans and rat in vivo values. The projected total multi-substituted glutathione (which was used as an internal dose surrogate for the toxic glutathione metabolites) was modeled following an exposure scenario based on submersion of both hands in a 5% aqueous solution of HQ (similar to black and white photographic developing solution) for 2 h, a worst-case exposure scenario. Total multi-substituted glutathione following this human dermal exposure scenario was several orders of magnitude lower than the internal total glutathione conjugates in rats following an oral exposure to the rat NOEL of 20 mg/kg. Thus, under more realistic human dermal exposure conditions, it is unlikely that toxic glutathione conjugates (primarily the di- and, to a lesser degree, the tri-glutathione conjugate) will reach significant levels in target tissues.

- p.8 - The use information from the Nail Manufacturers' Council should be added to the Summary.
- p.8 - As there is more than one type of "nonmelanoma skin cancer", please be more specific and state the actual type of cancer observed (squamous cell carcinomas).
- p.8 - Please correct the following sentence found in the Discussion. "The Panel noted that the concentration of hydroquinone and/or p-hydroxyanisole was not indicated in the sensitization studies conducted by applying the nail gel to the fingernails did not provide."