NEW DATA

Formaldehyde and Methylene Glycol

CIR EXPERT PANEL MEETING

MARCH 5-6, 2012

Formaldehyde and Methylene Glycol – New Data

Cosmetic Ingredient Review
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Memorandum

To: CIR Expert Panel and Liaisons
From: Ivan J. Boyer, Ph.D., D.A.B.T.
Senior Toxicologist, CIR
Subject: Formaldehyde/Methylene Glycol – Women's Voices for the Earth Letter on Nail Hardeners
Date February 10, 2012

At the September 2012 meeting, the CIR Panel concluded that formaldehyde and methylene glycol are safe for use in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should the formalin[1] concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. Additionally, formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardening products. However, formaldehyde and methylene glycol are unsafe in the present practices of use and concentration in hair smoothing products (a.k.a. hair straightening products).

On 12 December 2011, the Panel received an e-mail message from Ms. Alexandra Scranton, Director of Science and Research for Women's Voices for the Earth, which is a national organization that works to eliminate toxic chemicals that impact women's health. Ms. Scranton's e-mail (enclosed) expresses disappointment in the Panel's conclusion that formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardeners. She states that this decision "appears somewhat arbitrary and contradictory, given" the conclusion that cosmetics should not exceed 0.2% formalin when current practices include concentrations up to 2% or more "formaldehyde" in nail hardeners and adverse effects have been reported by consumers using nail hardeners containing 1% to 2.2% "formaldehyde." Ms. Scranton outlines three specific concerns with the Panel's conclusion, including:

- Inadequate explanation for the apparent inconsistency between the concentrations considered to be safe in cosmetics versus nail hardeners, and failure to address the hazards of skin contact during the use of nail hardeners
- Failure to establish a concentration limit for use in nail hardeners
- Inadequate explanation for the apparent dismissal of the 35 adverse-event self-reports compiled from online product review websites or posted on blogs and submitted to the Panel on 21 June 2011 by Ms. Scranton on behalf of Women Voices for the Earth and other consumer advocacy groups (enclosed).

In addition to Ms. Scranton's June and December 2011 submissions to the Panel, excerpts of the transcripts of the 27-28 June and 26-27 September 2011 Panel meeting and a draft response to Ms. Scranton's submissions are enclosed for your review and consideration. The Panel should review this material to ensure that Ms. Scranton's concerns have been adequately addressed or re-open the formaldehyde and methylene glycol safety assessment if warranted.

[1] Formalin is an aqueous solution wherein formaldehyde (gas) has been added to water to a saturation point, which is typically 37% formaldehyde (w/w). Because of the equilibrium between formaldehyde and methylene glycol in aqueous solution, formalin is composed of both formaldehyde and methylene glycol.

From: CIRINFO
Sent: Monday, December 12, 2011 9:30 AM
To: Alan Andersen
Subject: FW: Letter regarding formaldehyde decision in nail hardeners

To: F. Alan Andersen, PhD, Dr. James G. Marks, Dr. Donald V. Belsito, and members of the Cosmetic Ingredient Review:

As scientists, public health advocates and concerned citizens, we are writing to you to express our disappointment in the CIR's recent decision on formaldehyde and methylene glycol (hereafter simply referred to as "formaldehyde") with respect to nail hardeners. Formaldehyde is both a potent irritant and a carcinogen. The CIR has acknowledged this by establishing a "safe" level of just .074% formaldehyde for use in cosmetics. The CIR similarly made a strong statement by declaring the use of formaldehyde in hair smoothing products as "unsafe". Both of these decisions clearly have the health of the cosmetic's user in mind. The decision to declare as "safe in the present practices of use and concentration in nail hardening products" appears somewhat arbitrary and contradictory, given the established levels of 1-2% formaldehyde in nail hardeners.

We have a few specific concerns with the decision:

1) The formaldehyde report did not provide an adequate explanation for why exposure from the use of nail hardeners differed so significantly from the use of any other type of cosmetics. In the transcripts, it appears there was discussion regarding a "rapid reaction" of formaldehyde with the nail, however no evidence of this phenomenon was actually presented. While reference was made to cautions regarding limiting skin contact with nail hardeners, in practice, this is extremely difficult to do. Some skin contact from nail hardeners during application, even by trained practitioners, is almost inevitable. Certainly, for the untrained consumer, skin contact is in fact likely. In any case, the final recommendation of the CIR neglects to mention concerns regarding skin contact at all.

2) The language used regarding the safety of formaldehyde use in nail hardeners is vague and open-ended, stating that use is safe "in the present practices of use and concentration" – without clarifying any numerical limit. If manufacturers choose to increase the levels of formaldehyde in nail hardeners over time, would not those new levels still be described as "current levels of use"? This would effectively allow any level of formaldehyde in nail hardeners as safe according to the CIR. Furthermore, the reason for not establishing a numerical limit appears to have been based solely on the desires of the nail manufacturers, and their concerns that formaldehyde resin residues might put them over a limit of 2%.

3) The discussion from the CIR's June 2011 meeting clearly established a consensus that adverse events from exposure to nail hardeners containing formaldehyde can occur at current levels of formaldehyde use. Yet when data was provided to the CIR as to what the formaldehyde levels actually were, the concern for those same adverse events appears to have been inexplicably dismissed.

The data we provided to the CIR of online customer complaints with nail hardeners showed adverse events such as skin irritation, burning sensation in fingers and hands, severe finger pain, strong unpleasant odor, coughing, dried out and peeling nails and other symptoms. While a considerable number of these reports of symptoms were associated with the Quimica Alemana product, the submitted record also reported similar adverse reactions for Duri Cosmetics Rejuvacote, OPI Nail Envy, Nail Magic, Mavala Scientifique, and Witchcraft Nail Hardener, all of which contain formaldehyde as an ingredient in the 1-2.2% range. Thus the argument that perhaps it was not the formaldehyde, but another ingredient in Quimica Alemana that was causing reactions, was not only based on a lack of evidence, but was ignoring the evidence that other brands of nail hardeners also containing formaldehyde were in fact causing the very same impacts.

The mission of the CIR is to "thoroughly review and assess the safety of ingredients used in cosmetics in an open, unbiased, and expert manner". We were disappointed to see a decision on formaldehyde use in nail hardeners which appears to ignore obvious evidence of harm to consumers and which contradicts the CIR's own assessments on formaldehyde safety in order to satisfy the needs and desires of one business sector, specifically nail product manufacturers. We believe that some consumers, and likely salon workers, are being harmed by the presence of formaldehyde in nail hardeners. We are disappointed that the CIR is not providing information or even recommending warning language with respect to nail hardeners in light of these adverse events. We believe the decision to deem formaldehyde in nail hardeners "safe in the present practices of use and concentration" both contradicts the CIR's findings and undermines the credibility of the CIR with respect to their future decisions.

We would appreciate a written response to our concerns.

Thank you for your consideration,

Alexandra Scranton
Director of Science and Research, Women's Voices for the Earth
On Behalf of the National Healthy Nail Salon Alliance

cc:Linda Katz, Food and Drug Administration; linda.katz@fda.hhs.gov

Formaldehyde and Methylene Glycol: Draft Response to Women's Voices for the Earth's 12 December 2011 "Letter Regarding Formaldehyde Decision in Nail Hardeners"

Ms. Alexandra Scranton, Director of Science and Research for Women's Voices for the Earth, submitted an e-mail message to the CIR Panel on 12 December 2011 (enclosed) expressing disappointment in the Panel's conclusion that formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardeners. She states that this decision appears to be arbitrary, given her earlier submission to the Panel (21 June 2011, enclosed) which included a summary of adverse effects reported on the Internet by customers using nail hardeners containing formaldehyde/methylene glycol, and inconsistent, given the Panel's conclusion that cosmetics should not contain 0.2% formalin (which is equivalent to about 0.074% calculated as formaldehyde) while nail hardeners contain formaldehyde/methylene glycol up to 2.2%, expressed as "formaldehyde." Ms. Scranton outlines three specific concerns with the Panel's conclusion, which are summarized and addressed below.

Specific Comment 1 Summary: The Final Formaldehyde/Methylene Glycol safety assessment does not provide adequate explanation for the apparent discrepancy between the Panel's conclusion that formalin in cosmetics should not exceed 0.2% (w/w) formalin and that formaldehyde/methylene glycol in nail hardeners is safe as used in current practices of use and concentrations, which (1) have been demonstrated to be up to 2.2% reported as "formaldehyde," and (2) have been associated with reports of adverse effects attributed to skin contact during the use of such products. The Panel discussed the "rapid reaction of formaldehyde with the nail," which would reduce the chance of skin contact and skin reactions upon using such products, but no data was presented to document this phenomenon. The Panel's conclusion "neglects to mention concerns regarding skin contact at all."

Draft Response to Specific Comment 1: The Clinical Use, Adverse Event Reporting section of the safety assessment summarizes the compilation of customer/blog reports on the Internet of adverse effects during the use of nail hardeners as follows:

> *"A compilation of 33 customer self-reports from Internet sites and blogs of nail hardening products indicate adverse effects including skin irritation, burning sensation of nail beds and exposed skin, severe finger pain, scabbing under the nails, and drying, flaking, splitting, crumbling, or peeling of the nails. Two additional reports noted that the product contained formaldehyde and has a strong odor, without noting any other adverse effects. Three reports indicated that the product contained 4%-4.5% formaldehyde."*

Although the Conclusion of the safety assessment does not explicitly express the Panel's concerns about skin contact, other sections of the report clearly address this issue. For example, the abstract states the following:

> "*Formaldehyde and methylene glycol … are safe for use in nail hardeners in the present practices of use and concentration, which include instructions to avoid skin contact.*"

The Discussion section states:

> "*The Panel noted that the present practices of use of nail hardeners include instructions that cautioned users to limit application of the material to the top surface of the nail only, to allow it to dry fully, and to not get the material on the skin.*"

In addition, the Discussion section explains why formaldehyde/methylene glycol in nail hardeners is safe as used in the present practices of use and concentrations, as follows:

> "*The additional data confirmed the current use concentration of formaldehyde/methylene glycol in the 1 – 2% range in nail hardeners (one product tested had a value of 2.2%). Given the rapid reaction on the nail surface and the use of nail hardeners at room temperature, the Panel did not consider that formaldehyde/methylene glycol at 1 – 2% in nail hardeners would present a risk of sensory irritation to the eyes, nose, or throat of users.*"

Based on the professional judgment and expertise of the chemists and other members of the Panel, the assertion that formaldehyde/methylene glycol in nail hardeners reacts rapidly with the nail is reasonable. Unlike the formaldehyde and methylene glycol in the hair straighteners of concern, exposure of the eyes and respiratory tract to formaldehyde in the air during the use of nail hardeners appears to be too low to cause the same effects. For example, the Nail Manufacturers Council submitted credible exposure data supporting this conclusion. In addition, there are no adverse event reports of eye or respiratory tract irritation during the use of nail hardeners even in the reports compiled and submitted by Ms. Scranton. All of this information is summarized in CIR's safety assessment report to back-up the conclusion.

Specific Comment 2 Summary: The Final safety assessment concludes that "formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardening products," but does not establish concentration limits for these ingredients in nail hardeners. Thus, manufacturers can simply alter their "current practices" to increase the concentrations of these ingredients in nail hardeners without violating the Panel's recommendations. The Panel's conclusion "appears to have been based on… the nail manufacturers… concerns that formaldehyde resin residues might put them over a limit of 2%."

Draft Response to Specific Comment 2: Table 1 in the safety assessment shows maximum concentration of use of 2.2% reported as "formaldehyde." This value (2.2%) is the maximum concentration of the present practices of use and concentration in nail hardeners. The Panel defines, and expects it to be understood that, present practices of use and concentration of cosmetic ingredients are those detailed in its safety assessment reports. Any changes in practices yielding products in the future that exceed the limits of present practices would be considered by the Panel as violating the Panel's recommendations. The Panel acknowledged that the presence of formaldehyde resin residues in nail products may cause the concentration of formaldehyde/methylene glycol to appear to exceed 2.2%, using the common analytical chemistry methods of the day, and noted that these resins are much less likely to cause skin reactions than formaldehyde/methytlene glycol on skin contact. However, this observation has no bearing on the Panel's conclusion.

Specific Comment 3 Summary: The Final safety assessment provides no adequate explanation for apparently dismissing 35 adverse event self-reports (e.g., reports of skin irritation, severe finger pain, and dried out and peeling nails) compiled from online product review websites or posted on blogs and submitted to the Panel on 21 June 2011 by Ms. Scranton on behalf of Women Voices for the Earth and other consumer advocacy groups. The assessment also appears to ignore that the reported effects were attributed by the customers/bloggers to the application of 6 brands of nail hardeners containing 1% to 2% formalin, not to 1 or 2 brands.

Draft Response to Specific Comment 3: The Panel did not dismiss the customer and blogger reports of adverse effects compiled and submitted to the Panel by Ms. Scranton. As noted above, this information was summarized in the Clinical Use, Adverse Event Reporting section of the safety assessment. The Panel noted that the reported effects were attributed by the customers/bloggers mainly to the use of 3 brands of nail hardener, including Quimica Alemana (aka Quimica Alemana Esmalte Endurecodor de Una) (12 reports), Nail Magic (9 reports) and Mavala (5 reports), and that the customers/bloggers indicated that these products contained up to 4% to 4.5% "formaldehyde." One of the Panelists indicated that two of his patients presented with severe eyelid dermatitis after the application of Quimica Alemana Nail Hardener to their nails, which he attributed to the patients' touching their eyelids before the product completely dried on the nails. This product was found to contain 2.2% formaldehyde/methylene glycol

(reported as “formaldehyde”). However, neither of these patients tested positive in patch tests using 1% aqueous formalin, suggesting that the reactions were caused by a substance other than formaldehyde/methylene glycol (e.g., propyl gallate) in the product.

In any case, the Panel noted that skin reactions to formaldehyde/metyhylene glycol in nail hardeners are attributable to skin contact in susceptible persons. The Panel considered whether formaldehyde/methylene glycol in such products could penetrate the nails of people with flaky or cracked nails to cause a reaction under the nail. However, the argument that formaldehyde/methylene glycol in nail hardeners reacts rapidly with the nail was persuasive (as noted above), the relevant circumstances of the people reporting effects on the Internet (e.g., the health and integrity of their nails before using a nail hardener) after the application of formaldehyde/methylene glycol-containing products are not known, and the attribution of the reported reactions specifically to formaldehyde/methylene glycol in these products has not been demonstrated. Thus, the Panel stands by its conclusion.

Conclusion

In sum, CIR takes seriously its mission to review and assess the safety of ingredients used in cosmetics in an open, unbiased, thorough, and expert manner. With regard to the concerns of Women’s Voices for the Earth about formaldehyde/methylene glycol in nail hardeners, the CIR carefully evaluated all of the information presented, including the information that they provided on online customer complaints with nail hardeners, before issuing its decision. The Panel stands by its conclusion, and remains open to evaluating any additional science-based data that may change that conclusion in the future.

Excerpts of Minutes from the 27-28 June and 26-27 September CIR Panel Meetings

Minutes Excerpts of the 27-28 June 2011 CIR Panel Meeting

Introductory Panel Session 27 June 2011

DR. ANDERSEN: …We also had further input on Friday from the Nail Manufacturer's Council re: the submission by the Consumer Alliance Group, National Healthy Nail Salon Alliance making comment on that input. We've provided for the panel the published study, Kelly, et al., that the National Healthy Nail Salon Alliance had provided. They summarized the results of that study but if you wish to look at the actual study you now have it to look at. All of that relates to formaldehyde.

Dr. Belsito's Team Discussion 27 June 2011

DR. BELSITO: And the consumers is just, I mean, and we'll get -- I have some comments on the consumer reports. I mean, it's basically a whole list of things that have appeared on the web. But it's interesting that there are one or two products that pop out. And in fact, I've had experience with one of those in the past two weeks that would cause me to want to maybe hold off on the safety of use even in nail products until that product is analyzed.
…

From the Nail Manufacturing Council they dispute consumer groups' challenge of no significant history of adverse events associated with nail hardeners containing formaldehyde.

So, I mean, this is pretty straightforward and I guess it ties in the consumer reports where you've got all those e-mails. What I have to say is that in the past two weeks I've had the opportunity to see two women with severe eyelid dermatitis, both using the Quimica Esmalte Endurecedor product that had numerous consumer complaints. It's a Colombian product. It contains formaldehyde, para- tertiary toluene sulphonamide formaldehyde resin, so it has both formaldehyde and toluene sulphonamide resin. And these patients tested negative to 1 percent formaldehyde. The Europeans use 2 percent; we don't because of concerns with irritation. And so I have very strong positive patch test reactions to this Colombia product. And all of my other patch test reactions are negative.

And I really was confused, you know. You see two women and you can't explain it until I read the formaldehyde report. And I would like to know the percentage of formaldehyde in that specific product because if it's 5 percent or less than I don't think 5 percent in a nail product will necessarily be appropriate. And then there was a second product that I had no familiarity with but if you looked at all the consumer complaints, the greatest number were about the one I just had two experiences with and then there was another one that I never heard of. But the complaints were very focused on really two products. So it would be nice to know what the level of formaldehyde and other ingredients in those two products were.

DR. BERGFELD: Yeah, but if you restrict the concentration --

DR. BELSITO: We don't know what the concentration was though.

DR. BERGFELD: I know. But if you restrict it by the document then you don't have to worry about the specific product.

DR. BELSITO: Yeah, but if those two products have 5 percent or less formaldehyde, then I don't think that's necessarily a safe level to be at though regardless of what we say in the document. I mean --

DR. EISENMANN: The use levels that I got in are less than 2 percent. I mean, I don't have any information other than that and that's the nail manufacturers', their original submission is also lower than 5 percent.

DR. BELSITO: Yeah. I mean, this product comes out of Colombia so, I mean, you know, I'm sure they are not part of the PCPC. It's manufactured in Bogotá but it's being sold all over New York City. It's the hottest thing for brittle nails. So.

DR. ANDERSEN: And Don, it was eyelid dermatitis?

DR. BELSITO: Eyelid. Both ladies. The typical nail polish type of thing. You know, I was shocked when they were negative to toluene sulphonamide resin but when I peeled off their nail polish that I put on as is they literally had vesicular and bolus eruptions.

DR. BOYER: Can I ask a question? Were they stylists or customers?

DR. BELSITO: They were both consumers. Now, the product is -- it's not sold as a salon product. It's sold as, you know, a commercial product. It's $2.98, extremely cheap. You can purchase it off the Internet.

DR. LIEBLER: Don, are we going to talk later about the input from Women's Voices for the Earth?

DR. BELSITO: That's --

DR. LIEBLER: Blog postings and so forth?

DR. BELSITO: That's all part of this. If you look at that listing --

DR. LIEBLER: Do you want to bring that up now?

DR. BELSITO: That Quimica product is probably the most frequently referenced product that's giving problems. So that's why, you know, before I would feel comfortable signing off on being able to go up to 5 percent formaldehyde in a product such as this, I guess how are you going to restrict it? At what point do you -- where do you restrict something that's sold through the Internet versus something that's used only in salons?

And I don't know. You know, I mean, it could just be a fluke that in two weeks, you know, I see two ladies who are using the same product and have problems or it could be real. I don't know. But I personally would feel more comfortable if someone would go out and pay $2.98 and purchase a bottle of this Quimica Esmalte Endurecedor off of the Internet and analyze the level of formaldehyde or methylene glycol or however they want to measure it and let me know what's in the product. Interestingly, it's not labeled as methylene glycol. It's labeled as formaldehyde toluene sulphonamide formaldehyde resin, camphor. There was something else, you know, butanol. I mean, there were a couple of other things but no methylene glycol on the label.

So anyway, that's my comment on the Nail Council and the consumer. If anyone else has other comments.

DR. LIEBLER: Well, since we're on the nail topic and we do have the other stuff that was in the Wave 2 from the Women's Voices for the Earth which was a series of blog postings, you know, these are, I guess, culled from review of websites that focus on nail products or personal care products. And there were a number of these that represented individual experiences having had essentially burning sensation and pain from applying these products to their fingernails. And these are nail hardening products and apparently the women who were using these who were complaining said that they were using nail hardening products because they had unstable or flaky or cracking nails and they were using this to try and address that problem.

And the question it raised in my mind is whether or not a product like this is more likely to cause a problem in somebody with either thin nails or flaky nails or nails that would not necessarily protect the nail bed from the compound as well as somebody with nails that don't need a product. In other words, does the condition of the nails actually select for people who might be more susceptible? And I don't think we have any data to allow us to evaluate the incidence of these adverse effects in women who have this particular characteristic of their fingernails.

So it actually raised in my mind the question of whether or not we should take another look at whether or not we have sufficient data to justify a safe as used at 5 percent or less. And I would suggest that we perhaps don't.

DR. BELSITO: Okay. Other comments on nail products?

DR. ANDERSEN: I think just as a follow up to the implication to what Dan just went through, going back to the original safety assessment of formaldehyde, the panel discussion and the minutes run up against just that same concern that there was an inability to justify higher than 0.2 percent of what was then called free formaldehyde for the nail products just because there weren't any data on which to base such an increase, even though I think the sense was that old FDA value of 5 percent as an action level was floating around even then but nobody was willing to go up to that level. And I think you've just said the same thing again circa 2011.

DR. BRONAUGH: Excuse me. I just wanted to add that we went back and tried to find any evidence that there really was a regulation of some kind that limited 5 percent for nail products and we couldn't find that. We are doing a survey now of nail products for formaldehyde. And Don Havery tells me that to date we've looked at seven products and three of them -- I believe he said three of them had no formaldehyde at all. And the other 4 were, you know, 1 or 2 percent formaldehyde. So it looks like companies may be actually using lower levels. That's what we seem to be finding now.

DR. BELSITO: So could you, if you're doing that, purchase this Quimica product?

DR. BRONAUGH: That occurred to me and I think we could do that. We could add it to the list.

DR. BELSITO: Okay. Because, again, look at the list of consumer complaints and that product was the number one product at least in the list that was provided.

Okay. So I guess the last point we've heard most of then would be formaldehyde/methylene glycol as a protein keratin smoothing device. And so again some personal experience, believe it or not. My oldest daughter had this done and I didn't know it and she was told that this was not a formaldehyde-containing material. So your hair stylists, I think, need to be aware of that. She had it done in a salon in New York and I asked her if she noticed any smell or had any sensory irritation and she did not. So maybe under certain conditions, she said basically her hair was sucked up straight up off of her head and she has quite long hair. So, you know, maybe under certain conditions it could be done safely but, I mean, I don't know. I think under a lot of conditions it cannot be done safely.

DR. BELSITO: So that so far our conclusions regarding formaldehyde/methylene glycol aren't changing. So for aerosolized products the data are insufficient. So then the question comes down to whether they are sufficient to allow nail products. And then the second issue in reviewing this is when you look at our data, when you read the old report, our conclusion of 0.2 percent was actually based, it seems to me, on sensitization and irritation data that was 0.2 percent formalin, not 0.2 percent formaldehyde equivalents. So that scales it down to 0.074 percent, not 0.2 percent.

… Okay. So insufficient for aerosolized, dropping the concentration down to 0.074 percent for leave-ons. And then the question becomes what are we doing with nails?

Are we allowing it up to 5 percent? Are we allowing it up to 2 percent where we're getting reports? Are we saying the data are insufficient pending -- I really -- personally I would really like to see what's going on with that Quimica product. It really bothers me.

MR. STEINBERG: Just one comment. The professional nail manufacturers who are the largest producers and the largest sellers of the nail hardeners, not one member has ever used anything like 5 percent formalin in their products. That number, and this is where no one seems to know where it came from that 5 percent number, it scares me because it sounds like what you have found in Colombia was they just looked at that number and probably put 5 percent in.

DR. BELSITO: I don't know what they put in but that product is causing a problem and, therefore, apparently, as again, you know, it could be, you know, you've got two cases and I might not see another 2 cases for 10 years. But I've had two cases in two weeks and interestingly, that product was on the list, you know, was the major product on the list of consumer complaints, the exact same product. I would like to know what it contained before I'd be

comfortable signing off on any number. I mean, that's just me. I'm one vote so, I mean, I can easily get overwhelmed by all the panel members.

DR. BERGFELD: But I don't think you have to know -- we've dealt with this before. We just put a concentration that we're comfortable with.

DR. BELSITO: But I'm not comfortable --

DR. BERGFELD: And if they don't – if they don't meet that, then that's their problem.

DR. LIEBLER: So where does the number come from though? That's the problem I have. I don't know if we have enough data to determine what an appropriate concentration should be in nail products if it's going to be different and in other cosmetic products. Right now we're 0.2 percent on other cosmetic products. One possibility is we just delete that second bullet conclusion but, you know, I don't know what the concentrations are in nail products and I don't know if there's a rationale for having anything higher. It sounds like there's no good reason for 5 percent. It just sort of happened.

MR. STEINBERG: That's correct. If you want -- if it's of value we can certainly come up with the numbers that the different manufacturers use in terms of commercial products. I don't believe there's anything that's above 2 percent as formalin.

DR. ANDERSEN: I think the data that Carol provided that were max 2 percent in nail products, Bob confirmed that with the testing so far that the FDA has done. So there is a pattern but it isn't two-tenths of a percent formalin. It's easily 10 times higher than that. And that, now I don't quite know how to marry with the safety data. I have the same consternation Don does of how to marry that number with the reported adverse reactions.

DR. LIEBLER: So the table, let's see, I guess in the report it's Table 1, which is the use concentrations and uses. For nail, including hardeners, there are eight uses and it lists formaldehyde as 0.5 and methylene glycol as less than two. So that's what's currently used. And I don't --

DR. EISENMANN: That's nail hardeners. That's not --

DR. LIEBLER: Nail hardeners.

DR. EISENMANN: Right.

DR. LIEBLER: Well, it says nail, including hardeners for that line.

DR. EISENMANN: It's nail hardeners, period.

DR. LIEBLER: Oh, it says --

DR. EISENMANN: It's not any other nail products. Just --

DR. LIEBLER: Okay. So maybe the table could be edited to just say nail hardeners.

DR. EISENMANN: Right.

DR. LIEBLER: Because it suggests that there are other nail-related uses.

DR. EISENMANN: No.

DR. LIEBLER: And so I guess where we are is that we have usage up to 2 percent or less than 2 percent. Almost up to 2 percent. And we have no data on safety at 2 percent on the nail.

DR. BELSITO: The only that that we have really is the air analysis. I mean, that seemed to be the concern. And so the air analysis, at least from the salons for nails as opposed to for the straightening seemed to be okay. But, you know, my question now is even though it's only supposed to get on the nail, it's having the typical eyelid distribution of nail care products, at least from this product. So before I'm comfortable in signing off on any level other than the restriction, I would like to know what's in that product that's causing a lot of consumer complaints and that I just saw two of in two weeks.

MR. STEINBERG: Just one comment on that. I wasn't here at the previous meeting. I was teaching in Canada. But I believe Doug Schoon was here and I believe he said that when you apply the nail hardener to the nail, the reaction takes places extremely rapidly to form the film and the release of whatever are the volatiles as opposed to the formaldehyde or methylene glycol. The reaction of the formaldehyde to the keratin protein is very, very rapid.

DR. BELSITO: I just know that I got two to three plus positive reactions to Quimica Esmalte Endurecedor in the past two weeks associated with eyelid dermatitis. That's all I know. It makes me worried.

DR. KLAASSEN: I was wondering if the FDA has any information that they would like to share with us in regard to this situation?

DR. BRONAUGH: Nothing more than what, excuse me, nothing more than what I said a few minutes ago. I think we will have some more information as we continue this survey but in terms of adverse reactions, we don't have any more information.

DR. KLAASSEN: Has anything been done or planning to be done in regard to analytical chemistry on the product?

DR. BRONAUGH: That's what I'm talking about. We are doing that, yes.

DR. KLAASSEN: Okay, thank you.

DR. BELSITO: Okay. So --

DR. LIEBLER: One additional comment. Bob, would you recommend that we strike the mentioning of the policy statement that limits it to 5 percent?

DR. BRONAUGH: Yes, I do.

DR. BELSITO: Okay. So that needs to be removed from the document.

Okay. So I think, let me summarize where we are. Panel agrees that safe as used with a limit of less than or equal to 0.2 percent formalin, and a little bit in the discussion why we chose that. The data are insufficient for products that would be aerosolized or could be aerosolized under conditions of use, which would be the hair smoothing products. You've heard my opinion about the nail products. I think it's insufficient until we get some more information on the levels out there but I haven't heard your opinion of the other people on the panel.

DR. LIEBLER: I agree, insufficient.

DR. BELSITO: Paul?

DR. SNYDER: Yeah, I mean, I was fine with under conditions of use knowing that it was around 2 percent or less. But you provided new information that I agree that we need to explore that a little bit more and find out what the concentration is.

DR. KLAASSEN: I agree.

DR. BELSITO: Okay.

...

DR. BELSITO: Okay. Not to cut this any shorter. I know we've been spending a considerable amount of time. I think our team has already decided the data are insufficient for the hair products at this point. So to bring us back to where we were, so we're setting a new limit, less than or equal to 0.2 percent formalin. We're saying insufficient for hair care products. Where are as a team for nail care products? Insufficient?

DR. SNYDER: Insufficient.

DR. EISENMANN: I have one quick comment. On the 0.2 percent you're not limiting that to preservative use. Correct?

DR. BELSITO: No, 0.2 percent is formalin.

DR. EISENMANN: It slips in there occasionally that it's preservative use.

DR. BELSITO: Right. I mean, if a nail company wanted to come in at 0.2 percent formalin for a nail hardener, we'd be very happy with that. If they want to go above 0.2 percent we need a little more information. The information I would like, I mean, I would like to see that this Quimica product has 5, 6 percent formaldehyde and you're telling me it's used at less than 2 percent. I'd probably be happy, but I just don't know.

DR. BERGFELD: What's the status of this report then? It's in a Blue Book.

DR. BELSITO: It was in Blue, and I guess the status of the report changes in a sense that we've focused more on methylene glycol. We had mentioned in the initial report, though, I mean it's really very prescient that supposedly the FDA allowed it up to 5 percent in nail care products, and then we chose to ignore that in the conclusion. So I'm not a legal expert. So I guess does this go back out as another tentative final since we've made it the methylene glycol and now clearly state it's insufficient for nail care products or was this a final?

DR. BERGFELD: I'd like to make a comment on what we should do. You've changed in the conclusion, actually taken out one of the points, and that's the nail that's changed. So it really has to go out for a 60-day comment period if you've changed a conclusion. It's not editorial.

DR. LIEBLER: Yeah, that was going to be my question. Since we had changed it in the conclusion, what's that do to the status?

DR. BELSITO: Okay. Where is our original conclusion here again?

DR. BERGFELD: Panel Book page 76 --

DR. BELSITO: That's true. So it's going out as another tentative final for comment.

DR. LIEBLER: So what would be the tentative conclusion for bullet two on nail care products?

DR. BELSITO: Insufficient.

DR. ANDERSEN: Above.2 percent.

DR. BELSITO: "Insufficient for sensitization-irritation at concentrations of
use." And then we have to find out what the true concentrations of use are. I mean, there are two products that if you look through what we got from the women's group, there were two specific nail hardeners that were the most frequent, the Quimica product and another. If FDA's going to analyze products, I'd like to see those two products analyzed.

DR. LIEBLER: Okay, so insufficient for?

DR. BELSITO: Sensitization-irritation.

DR. LIEBLER: Irritation-sensitization at concentrations of use.

DR. BELSITO: Right.

DR. BERGFELD: How about vaporization or gas --

DR. BELSITO: We have that from the nail salons. I mean, that's what their argument was, I think. They were looking more like okay, protect the skin, and that still may be a viable argument. So I think we have the air levels in nail salons. Those were okay.

DR. LIEBLER: But this is a product -- these are products that you can just buy and go and use in your bathroom without any professional guidance and get sore nails or itchy eyelids, right?

DR. BELSITO: Yes.

DR. LIEBLER: So that's the problem. I mean, it's not controlled. It's not a professional-use-only product. Anybody can just go get it and use it and --

DR. BELSITO: Well, right now, I mean, we need to find out what these products are. I mean, the ethyl acrylate -- I mean, I don't know if you were on the Panel when we did that.

Presumably those products are only sold to salons. Now we can --

DR. BERGFELD: Nail hardeners everybody has (inaudible).

DR. BELSITO: Right.

DR. LIEBLER: Right. So this is different. In fact, the discussion refers to those acrylates as sort of a precedent for this and actually is not applicable because anybody can buy these products and use them in any circumstance.

DR. BELSITO: That's correct.

DR. BOYER: Also, if I could just make one point about the data that we got from the Nail Manufacturers Council. They did some air monitoring in these salons. The duration of the sampling, air sampling, ranged from about two hours to eight hours or so. Most of them were taken over a four-hour period. There were typically several customers serviced during the sampling period. And they didn't necessarily use nail hardeners during each of these procedures, although there's no doubt that at least in some of them, maybe many of them, they did use a nail hardener. So that's something to keep in mind. The air concentration data we have here was not specifically for the use of the nail hardening products.

DR. BELSITO: Okay, very good. Thank you for that. Okay, anything more about formaldehyde and methylene glycol?

DR. ANDERSEN: So we've got a revised --

DR. BELSITO: Tentative final.

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DR. MARKS: … And there's also a letter dated June 24th from the Nail Manufacturers Council.
…

DR. SHANK: I would like to add the phrase "formaldehyde, methylene glycol are safe in cosmetic products," and then add, "for which dermal penetration is probable," and then continue. That sets it aside from the second bullet

which talks about nail hardeners, and then that can be left alone. That was questioned, should nail hardeners be a part of this report and why do we separate it out? Why do we have two different concentrations?

So the answer, in my opinion, is we're concerned about dermal penetration, but not for nail hardeners, where dermal penetration, if the product is used appropriately, there is little to no dermal penetration.

DR. MARKS: So how do -- can you repeat that?

DR. SHANK: The first bullet says, "Formaldehyde, methylene glycol are safe in cosmetic products."

DR. MARKS: Yes.

DR. SHANK: And I add, "for which dermal penetration is probable." And then everything is left alone except the last number is 0.07 percent. And the reason I did that was just it separates dermal penetration -- products where dermal penetration is likely to occur versus the nail hardeners where dermal penetration is not likely to occur. And that's why we have two different concentration limits.

DR. BOYER: And I wonder if you might not refer to the term "dermal contact" because we're not going to get a whole lot of dermal penetration --

DR. SHANK: All right.

DR. BOYER: -- because of its reactivity and so forth. I mean, it has to penetrate far enough so that you get -- you can sensitize the individual and so forth. It's not going to be absorbed into the bloodstream.

DR. SHANK: That's fine, dermal contact. For which dermal contact, etc.

DR. MARKS: So formaldehyde and methylene glycol are safe for --

DR. SHANK: Are safe in cosmetic products.

DR. MARKS: Are safe -- so you wouldn't be -- you would delete this "for use as a preservative in cosmetics." You would just say "are safe in cosmetics." How would you word that?

…

DR. SHANK: Okay. Sorry. I didn't make that clear at all. So it says -- the first bullet says, "Formaldehyde, methylene glycol are safe in cosmetic products."

DR. MARKS: Mm-hmm.

DR. SHANK: And I would like to add, "for which dermal contact is probable when formulated to ensure use," et cetera, as it's here.

DR. MARKS: Dermal contact --

DR. SHANK: Is probable. So that may have to be separated by commas.

DR. ANDERSEN: This introduces that concept of dermal contact distinguished from the next bullet.

DR. SHANK: Correct. That's the purpose of it.

DR. MARKS: … So now in the second portion.

DR. SHANK: I had no changes for that.

DR. MARKS: This is the nail concentrations up to percent if provided with nail shields. Yes. I think that -- again, Rachel isn't here, but that should address the consumer complaints of the burning. It won't do anything about the concern of respiratory, but that was addressed in the nail --

DR. SHANK: We have data for that.

DR. MARKS: Right. And that's safe.

DR. SHANK: Respiratory data.

DR. MARKS: So --

DR. ANDERSEN: Before we get off of that, though, and since Rachel isn't here, the submission that we received from the Alliance of Concerned Women, --

DR. MARKS: Yeah.

DR. ANDERSEN: I'm having trouble with what the group titles were -- did present anecdotal data --

DR. MARKS: Yes.

DR. ANDERSEN: -- that the assertion that there are no adverse effects from the use of nail hardeners is not true. Then the Nail Manufacturers Council in their most recent submission rebuts that as hearsay evidence that we shouldn't pay that much attention to. The gauntlet is down and the two sides are hitting each other with it.

We have, as Ron pointed out, air measurements that suggest that the sensory irritation phenomenon just doesn't occur with nail hardeners, and that's what you're relying on essentially.

DR. SHANK: Right. Now the FDA, I don't quite understand the terminology, has a policy that the nail hardeners can contain up to 5 percent formaldehyde equivalents.

DR. ANDERSEN: It's essentially an action level --

DR. SHANK: Okay.

DR. ANDERSEN: -- that tells inspectors that if you saw something higher than that, whoa; lower than that relax, don't worry about it.

DR. SHANK: It seems they have not received very many complaints from that.

DR. HILL: FDA?

DR. SHANK: FDA, right, which is where consumers -- well, I don't know.

DR. MARKS: I think the name of the organization is Women's Voices for the Earth, and then this was the National Asian Pacific American Women's Forum, California Healthy Nail Salon Collaborative.

DR. ANDERSEN: That's why I was having trouble with what the organization --

DR. MARKS: And then the memo is addressed to Alan, myself, Don, and members of the CIR and also a copy to Linda Katz. And, yes, there are a number of anecdotal reports.

I probably would say -- I wouldn't necessarily say just because the FDA may not have heard any complaints that they don't exist. It might be just easier to go online and say, bam, a response in this (inaudible). I don't know. I don't know why this would generate more responses, say, than the FDA.

Yes?

MR. STEINBERG: Just one comment. I'm David Steinberg. The three major producers of nail hardeners for professional use, their statistics over the past, I think we're running now 14 or 15 years. I believe in that time we've gotten one adverse reaction, and that was not from the nail but from the cuticle.

DR. MARKS: Mm-hmm. Okay. Thank you. That's helpful.

Okay. So bullet number two you would leave as is --

DR. SHANK: I would. Yeah.

DR. MARKS: -- in the conclusion? Okay. And then number three is -- that's fine, Ron, Tom? And you're very specific in terms of provide with nail shields, restrict application to the nail tip and not the nail bed or fold. Probably only there, Alan, the only way we get it to the nail bed is if you avulse the nail plate. So probably you could leave that --

DR. ANDERSEN: I picked that language out of what FDA said --

DR. MARKS: Right.

DR. ANDERSEN: -- they expect to be in the label, and I presume that if FDA has instructions for what should be in the labeling in their compliance policy guide, the industry is probably already paying attention to that.

DR. MARKS: Yeah.

DR. ANDERSEN: So the question would be, do nail hardeners come with shields always? Is that -- David, do you know?

MR. STEINBERG: Very rarely. When they first started putting shields in with it, no one used them. Basically the nail hardeners are packaged in bottles. It looks like nail polish with a small brush, and they just apply it to the nail. And using -- there are two separate philosophies. One is nail shields and the other is putting petrolatum or grease around the cuticle so that you don't get it in -- consumers just won't use it. The beauty parlors just won't use it.

DR. MARKS: I think to me when I looked at that, I thought of the way we phrased it for the methacrylate or acrylate nail extenders. And there the wording was that the operator should use care not to get it on the skin.

MR. STEINBERG: Period.

DR. MARKS: And I might use that same thing if this is unrealistic in the real world about using shields because actually I'm more concerned about sensitivity from the acrylates, and I've seen that and not formaldehyde sensitivity from nail hardeners.

DR. ANDERSEN: That I think would be a good suggestion.

DR. MARKS: So we'll use the same wording as with the acrylates. Okay.

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DR. BELSITO …We're also made aware of the fact that the formaldehyde/methylene glycol mixture is used in nail care products and curiously that was mentioned in the original report as the FDA approved it up to 5 percent, but if I'm recalling yesterday's discussion correctly the FDA has really not approved it up to 5 percent, so there's no sort of gratis there with a 5 percent concentration.

We then looked at the formaldehyde/methylene glycol safety in nail care products up to 5 percent. We were provided with data regarding air concentrations in nail salons that seem to be within the range of various federal

agencies restrictions for formaldehyde exposure. We're also told that most products on the market, at least that FDA has analyzed up to date, have been less than 2 percent. However, in the past two weeks I've had two individual patients reacting to a nail product called Quimica, particularly strongly to what's called esmalta endurecedor, which is Spanish for nail polish hardener. And formaldehyde is on the label as is toluene sulfonamide resin mislabeled, N-butanol, and several other ingredients. And I would like to know before I sign off on the safety of this as nail hardeners, because as opposed to ethyl acrylate, where that would be a salon only product, these products are sold over the Internet, they're sold in stores, and you may tell patients to apply a wrap or a shield, but they may not necessarily do that. So, I think the mechanism for controlling these products is not quite as stringent as the mechanism for controlling ethyl acrylate in a nail sculpting process.
…

So, overall, while we feel that formaldehyde is safe in cosmetic products, less than 0.074 percent right now, we feel the data is insufficient both for nail care products and either insufficient or unsafe for hair straightening products -- we would like to hear from the other team. I think there are situations under which it probably could be used safely in hair product, but the requirements for ventilation would be very stringent and very difficult to control.

So, we're leaning between insufficient and unsafe for hair care products.

DR. BERGFELD: Is that a motion or a discussion?

DR. BELSITO: Well, it's not quite a motion because I'd like to hear what they feel about --

DR. BERGFELD: Thank you.

DR. BELSITO: It's a motion for 0.074 and for nail insufficient. I'd like to know what they feel about hair, unsafe or insufficient. I think we could go either way.

DR. MARKS: We certainly concur for which dermal contact is probably that the 0.07 percent limit is a good limit to establish.

It's interesting, we, in terms of the nail products, we really also agree in talking with industry individuals that the use of shields and that are probably not done. I guess I would ask, what data are needed -- so, we weren't prepared to say it was insufficient data, we just wanted to use the nail acrylic wording for that portion of this tentative conclusion. So, I guess we need to elucidate what's the insufficient data and that'd be interesting to hear from you.

DR. BELSITO: FDA has said they will track down this Quimica product and analyze it, or industry, I heard from the NMC that they will look at it. I would like to know what the concentration of formaldehyde is in that product. If it's significantly above 2 percent and we're being told most of the industry uses less than 2 percent, then I would be comfortable.

DR. MARKS: Okay, I see.

DR. BELSITO: You know, with patch testing it may simply be a fluke --

DR. MARKS: Right.

DR. BELSITO: -- but two patients in two weeks, the consumer complaints that came in with the late arrival data, half of them were on the Quimica products, which is very curious.

DR. MARKS: Highly interesting.

DR. BELSITO: And, again, I think we should use the same terminology.

DR. MARKS: You mean formaldehyde equivalence?

DR. BELSITO: Yes.

DR. MARKS: Yeah. And then as far as -- so, I'm perfectly satisfied to have an insufficient on that and clarify what the level in nail products should be, whether it should be 5 percent or something lower than that. I certainly think that's a good way to move.
…

DR. BELSITO: … I think we need to be careful about aerosolized because, again, I think probably at less than 2 percent the data that we saw from nail salons will be okay as a nail hardener. Again, I would like to see the information for this product that has caused me problems over the past couple weeks, but -- so, I don't think we can do the aerosolized route because then we're going to get into issues with nail products that I think can be safely used.

DR. BERGFELD: So, you have a motion, you have three different motions, as I see it. The first you've set some --

DR. BELSITO: Safe for dermal contact at 0.074 percent.

DR. BERGFELD: And the nail?

DR. BELSITO: Insufficient at this point for further information from the FDA and industry in terms of the survey of what percent is actually used in nail hardeners.

DR. BELSITO: … We can't say it's not safe for aerosolized products because it's aerosolized in nail care products but the information we got from the nail salons were those levels were all below acceptable levels.

My only issue with nails happens to be that in the past two weeks I've seen two ladies who were sensitized to this Quimica nail polish. They patch tested negative to 1 percent formaldehyde in water and toluene sulfonamide resin. However, the Europeans feel that you miss some formaldehyde sensitive patients unless you test at 2 percent, which I didn't do. She had a 3+ reaction to the nail hardener, she was negative to tosylamide/formaldehyde resin, and she was negative to formaldehyde, so I really don't know what the cause of it is.

There was also n-Butanol and Ed Jackson had some comments as to what that may have meant regarding concentrations of formaldehyde far exceeding 2 or even 5 percent. So, I think we can rule on the safety of it in hardeners where it will be aerosolized, so I'm not saying it can't be used where it can't be aerosolized, but it can't be used where it's aerosolized in levels that exceed EPA and other limits. And what we've seen in the data that's been presented to us is when it's used -- when a hair-straightening product is used as directed in a salon, those levels are exceeded and, therefore, it is unsafe as currently used.

Minutes Excerpts of the 26-27 September 2011 CIR Panel Meeting

Introductory Panel Session 26 September 2011

120th COSMETIC INGREDIENT REVIEW EXPERT PANEL MEETING MAIN SESSION Monday, September 26, 2011

DR. ANDERSEN: So we have a lot of information additionally on the table. We had previously received input from the Nail Manufacturers Council that appeared to suggest formaldehyde/methylene glycol in nail hardeners was on the order of two percent. The one piece of data that I had seen on FDA testing, Don's products, since I can't pronounce it, it was 2.2 percent. So there was a level of consistency in those findings…

Dr. Marks' Team Discussion 26 September 2011

DR. MARKS: … So let's get to formaldehyde and methylene glycol. My first reaction when I looked at the memorandum was -- at least I couldn't remember when we had one or two ingredients where we said they were "safe," "insufficient," and "unsafe" all in the same report. So that was pretty interesting. So let's go through that.

At the June meeting we issued a revised tentative amended safety assessment for formaldehyde and methylene glycol. And, as you'll recall, we reopened formaldehyde to include methylene glycol. That they're safe in cosmetics applied to skin when formulated to ensure use at minimum effective concentration, but should be -- in no case should be greater than 0.074 percent formaldehyde equivalents. We'll get into that terminology in a minute. That "insufficient" for nail-hardening products.

I think we've received information, and now we could change that to "safe," and just eliminate the nail-hardening products. But I'll ask the team's input.

And that it's unsafe for hair-smoothing products. And, of course, that was probably the precipitating incident to reopen this, because of the Brazilian Blowout epidemic of adverse effects.

So, conclusions? And then we had a lot of discussion and input from various sources, in terms of the issue of formaldehyde equivalents. So where do want to -- do we want to take the second part, the "insufficient?" Is that now "safe" for nail hardening? Ron, Tom, Ron Hill?

DR. SLAGA: I think that part can be deleted.

DR. MARKS: Okay.

DR. HILL: Okay, I'm not clear what you're seeing.

DR. BERGFELD: I thought so, too. "Nail-hardener" defined.

DR. MARKS: Yes, that was brought up, remember? As I recollect, Don -- yes, this is the memorandum, right inside there. Don had concern about nail-hardeners. He had seen a couple individuals with contact dermatitis. And then we've subsequently gotten information that that was a higher concentration. So I think we can say the nail hardeners are safe. Okay. So we can eliminate the second

portion of the conclusion…

DR. SHANK: … I think eliminating, too, the nail-hardening statement, that can be eliminated entirely.

DR. MARKS: Right… In the final product, we would delete part two, with reference to the nail products…

DR. BERGFELD: Could I ask where you're putting nail? Because --

DR. MARKS: We delete the nail, because it's --

DR. BERGFELD: But --

DR. MARKS: -- tied to the skin. Do we have to specifically say "nail?"

DR. BERGFELD: Well, "skin and nails" -- we could put it.

DR. MARKS: Mm-hmm.

DR. BERGFELD: I would say you should do that. It's a major issue.

DR. EISENMANN: Well, the purported use concentrations were as applied to the hair, so I don't know --

DR. BERGFELD: So you're talking about hair rather than skin?

DR. EISENMANN: Well, I wonder why there was dermal in the first place.

DR. MARKS: I don't quite follow, Carol. Do you like that? So I think, in part one of the conclusion, on 73, do you want to just delete the skin? "Safe for use in cosmetics when formulated to ensure -- " --

DR. BERGFELD: That's good.

DR. EISENMANN: Yes.

DR. MARKS: - "-- minimal effective concentration-- " --?

DR. BERGFELD: I like that.

DR. MARKS: "Safe for use in hair-smoothing products --" --the use we refer to. So we don't pick out skin or nail. Does that sound appropriate? Ron, Tom? So in that first portion we would say are "safe for use in cosmetics, when formulated --" --and remove "applied to the skin. That would take care of the nails…

DR. ANDERSON: …I don't understand the elimination of the second bullet. I don't get it. Formaldehyde/methylene glycol is used in nail-hardeners. Is that safe or not? I can't tell, if you delete that. Why wouldn't you say, "Safe in nail-hardeners, in the present practices of use?"

DR. SHANK: You're right. Because the 0.07 percent in the final product would eliminate the nail-hardeners from the conclusion.

DR. ANDERSON: And I don't think --

DR. SHANK: So it has to be back in. You're right.

DR. ANDERSON: Yes, I think so.

DR. HILL: I was going to ask about that, but I assumed somebody else would notice it.

DR. ANDERSON: Yep.

DR. MARKS: So, Alan, we'd go back -- I wouldn't eliminate that, then, "cosmetics applied to the skin, and nail-hardeners? "Would we include it?

DR. ANDERSON: Well, no. I think the first -- I actually agree with Carol's pushing to delete that "applied to the skin" phrase, because it creates more trouble than it may be worth.

So, "are safe for use in cosmetics" in that first bullet is a just fine thing. And I'm not sure that you can have too much information content in that. I'm not sure I like the idea of mentioning formalin, because it's not listed as an ingredient. But the discussion can explain all of that. So, again, more information is probably better than less information in that first bullet -- with the exception of let's get rid of "applied to the skin." Then the second part focuses on nail-hardeners, and is very targeted. Nail-hardener, safe in the present practices of use. Again, assuming that you came to the conclusion that you believe that 2 percent is the kind of upper limit and that's what you're going to see in nail-hardener products, and that doesn't bother you. And then, number three, your conclusion was equally clear…

DR. MARKS: … essentially it says that it's safe in cosmetics when formulated to ensure that a minimal effective concentration, but in no case formaldehyde equivalents exceed 0.074 percent, formalin, 0.2 percent -- the formaldehyde, which you were specific, formaldehyde, not formaldehyde equivalents, 0.74 percent, and methylene glycol, 0.118 percent. And then the second bullet is that the nail-hardeners are safe, in the present use and concentration.

DR. BERGFELD: Now, no one will have a problem with the first one, because it's "use in cosmetics." Does that include hair care? We left the general statement.

DR. MARKS: Well, that's what I tried to --

DR. SHANK: Yes, you did.

DR. ANDERSON: That's not terribly function in hair products, but --

DR. GOLDSTEIN: It is functional in hair products at 0.2 percent as a preservative.

DR. ANDERSON: Oh, okay. Point well taken.

DR. GOLDSTEIN: We don't use it, but it has been used, historically, up to -- usually that is the maximum level we've ever used to preserve a shampoo or conditioner.

DR. ANDERSON: Good point. But, yeah, I think that the first conclusion is somehow fundamental. And if you want to go higher than that -- okay, let's talk. Nail hardeners. Okay -- safe in the present practices of use. Hair-smoothers? Well, we have different views of what that should be, but it's a separate question, and deserves a separate answer.

DR. BERGFELD: We've never had a conclusion that had one, two, three. Somehow I'm agreeing with everything that's been said, but we've never had one that looked like this. One, two, three. Is there some other way of organizing this?

DR. MARKS: Yes, you could put "with the exception of nail hardeners, which are safe in the present use and concentration," and "with the exception of hair-smoothing products --" -- da, da, da, da.

DR. ANDERSON: No reason it couldn't be put into a sentence that includes all three. At this meeting, we're talking about amending --

DR. MARKS: This would be a re-revision. This is a re-revised tentative amendment.

DR. ANDERSON: The current conclusion for glutaral is a three-piece conclusion -- safe up to half a percent for leave-on, insufficient data for rinse-offs, and should not be used in aerosols. So we have often had three-part conclusions.

DR. BERGFELD: No, we haven't had --

DR. ANDERSON: But we've never had one, two three.

DR. BERGFELD: One, period, two, period, three, period.

DR. ANDERSON: Well, it seems somehow important to focus this one.

DR. BERGFELD: I don't mind the periods, but somehow to put this into a decent sentence --

DR. ANDERSON: But it can be put into a sentence.

DR. MARKS: I think that's -- if we go by our precedents set before, it will be all in one sentence. Or two -- with the exceptions, not as sort of numbered points or bolded points. Any other comments?

So tomorrow this is going to be presented by the Belsito team. I'm sure there are going to be some differences. (Laughter.) I'll elucidate our differences…

Dr. Belsito's Team Discussion 26 September 2011

DR. BELSITO: Well, next is one I'm sure we've all been just excited to approach: Formaldehyde/methylene glycol. So, we had come to a revised, tentative safety assessment back in June, three-part conclusion: Safe when used at the minimum effective concentration, but not to exceed 0.074 percent formaldehyde equivalents; insufficient data for nail hardeners. We needed use concentration, and we've gotten that. It appears that it's at about 2 percent.

The specific product that I was concerned about came in at 2.2 percent. An issue was raised that it may have contained high levels of propyl gallate, which may have caused the reactions. I cannot still tell you what caused the reactions. My patients are doing well avoiding the product and have elected not to come back for testing.

Again, I'm not a chemist, so I'll rely on my colleagues to comment on whether they feel the 2 percent concentration limit in a nail hardener should be sufficient to limit the aerosolized exposure to below the limits we're setting.

And we had come in as unsafe for use in hair- smoothing products, which involves application of high temperatures…

…We previously had an insufficient nail care products pending information on the assessment of levels there. Are you still insufficient there or is that a level of 2 percent -- 2.2 percent in a nail product that is not heated? Is that okay? Will that -- recall that I believe our last meeting we had information from air monitoring samples in nail salons that seemed to be all below limits that have been set by various agencies.

DR. LIEBLER: I mean, I think that last time the discussion on the nails was in large part influenced by your report of your experience with your two patients, which raised obviously an interesting question. But beyond that we don't -- I don't think we have any data to suggest that 2 percent is a problem.

DR. BELSITO: So you're saying that the use up to percent in a nail care product would be -- it's not intended to be heated, would be --

DR. LIEBLER: I have a much less problem with that than I do with the hair products and the heating and blow-drying and so forth. But I would like to hear what the others think.

DR. BELSITO: Curt?

DR. KLAASSEN: I agree. I mean, first of all, just the amount that's used in this situation is much less. And I don't have any trouble with the data that we have and with the fingernails.

DR. BELSITO: Paul?

DR. SNYDER: Yeah, on page 61 of the book where they cite that FDA recent data, I mean, we do cite it, particularly 2.2 percent in a nail hardening product was cited after a compilation of customers suffered an adverse affect, including skin irritation, burning sensation of the exposed skin, and pain. So it's not without -- so I don't know that we can ignore those reports.

So while we did ask for concentration of use data and went out for insufficient for concentration of use, but the data they gave us is maybe suggesting otherwise. It's on page 61 at the top of the page.

DR. BELSITO: One minute, David. Yeah, the interesting thing, though, is again, if you look at the bulk of those reports it was with the same product that I had issues with. So, I don't know if that's a product specific. And as David would have suggested in his letter, that it may have been due to ingredients other than formaldehyde, I mean, have not been resolved. But David, go ahead.

MR. STEINBERG: David Steinberg. When I did the survey of all of the people that I knew and we could find and it was quite extensive and trying to establish what the maximum levels of -- I'm going to use the term "formalin" because that is what I got the answers from. For example, one company in Europe replied to me, they put 5 percent formaldehyde in their nail hardeners, which I find to be impossible. And in checking, they put 5 percent of formalin in their product, which then calculates again down to that approximate 2 percent level.

The only concern I would have on that 2 percent level is the best way to describe the nail hardeners are a form of nail polish, clear nail polish, in which added formalin is put in to harden the nails, which reacts with the keratin.

One of the common constituencies of nail polish as opposed to nail -- and nail hardeners are urea formaldehyde resins. And depending on the methodology in which you test for formalin or formaldehyde, you can obtain slightly higher levels because of the destructive nature of the test. So although the industry says they really can live with the 2 percent formalin, those types of levels, I think we'd like to have just a little bit more because of the analytical methodologies that are available. So I think 2.5 would make more sense.

Like I said, we have not found anyone who adds more than 2 percent. But you can analyze to slightly higher, based on the fact that you have the urea formaldehyde polymer present.

DR. SNYDER: We have typically strayed away from putting -- I mean, why not 2.6, 2.7? Usually we have some scientific basis to put an upper limit. And just to arbitrarily say because --

MR. STEINBERG: I mean, historically the limit has always been 5 percent, which no one uses. Although I'm not sure how that 5 percent number ever came into being. The other comment is, most of the time you're using safe as used or safe as current practices, which is just as acceptable. You know, everyone is using those types of things. If there's a need for a maximum level, then we think that 2 percent -- 2.0 might be too demanding in terms of the analytical methodology that's available.

DR. BELSITO: Well, we say on page 18 when we're discussing the nail hardeners -- 18,Panel Book 72 -- available data suggests current use of formaldehyde/methylene glycol at only 1 to 2 percent nail hardeners, and then given the rapid reaction, yadda, yadda, yadda. So, would that allay the concern of the manufacturers that we're not asking them to assay their product for total formaldehyde that would then pick up the urea formaldehyde resins?

DR. ANSELL: Typically, we support that. I mean, the 2 percent in the discussion gets to the heart of what we're talking about. When you tie it to an analytical method, then we end up going off --

DR. BELSITO: Well, we haven't tied it to an analytical method, at least not in this specific discussion. We don't mention that it's used with other formaldehyde resins and the polish that act as plasticizers.

DR. ANSELL: But we think the discussion would be a perfect place to have that.

DR. BELSITO: Okay. And then continuing on that page in the next paragraph, of course, the whole bottom part of that paragraph would have to be changed because we did get the FDA reports on their content of the formaldehyde in that Quimica nail hardener as well that came in at, I think, 2 percent. Right?

MR. STEINBERG: That was what we found when we separated that out, too.

DR. BELSITO: Right. But FDA also analyzed it and found the same. So that paragraph needs to be updated. Okay, so, so far --

DR. ANDERSEN: Before you go off of the nail hardeners, the information received from the blogosphere, while not scientifically rigorous, does appear to indicate that some folks are reacting to nail hardeners. I've been making the presumption that part of that is because they're getting it on their skin. And if they didn't, there would be far fewer of those reports.

Does it make any sense to include -- you know, we abandoned the idea of nail shields because nobody ever used them. But is there any reason we couldn't ask manufacturers to put instructions, don't get this on your skin?

MR. STEINBERG: We already do.

DR. ANDERSEN: Good. So --

DR. LIEBLER: So one of the questions I raised -- I think I raised it last time, but the discussion went in other directions -- is the question of individuals who have riddled or cracked or flaky nails may have less of a barrier to the formaldehyde. In other words, more of the ingredient might penetrate into the nail bed because many of these blog posts were very specific about pain under the nails or pain in the fingernail bed as opposed to in the skin around the nail.

And I find myself thinking that this is actually like the discussion we had, you know, a couple years ago about the PEGs and people with damaged skin, people with burns where they have ointments where their skin obviously is unable to prevent the penetration of the compounds as well as normal people.

So people with no nail problems aren't using nail hardeners, duh. But people with nail problems are using nail hardeners and they may have less resistance to penetration of a compound.

So I don't know how to translate that to a recommendation, or at least something in the discussion. But I almost think that we should consider pointing to this in the discussion that this actually could be an issue with some individuals who have, you know, compromised barrier due to whatever causes their nails to be brittle or flaky.

DR. ANDERSEN: I think -- I've been presuming all along that even for a brittle nail or a thin nail that there's an overabundance of protein to react with formaldehyde. So the concept of significant penetration through the nail just has not really been part of my thinking. How can that happen given that it's so reactive?

DR. LIEBLER: Are there cracks?

MR. STEINBERG: It's a surface reaction.

DR. LIEBLER: Yeah, I know. I mean, I get that part. You know, I understand. But what if, you know, what if you have cracks, or flaky nails mean flakes, which mean cracks? I'm just wondering if that's a relevant consideration. And I'd have to ask a dermatologist because I don't know.

DR. BELSITO: You know, you can go anywhere from, you know, diseases like in planopilaris of the nails where you essentially lose the nails. And I'm assuming you could have a consumer thinking if they spread it onto the little remaining nail tip that maybe they'll re-grow a strong nail. You know, I think you'd need to know the circumstances of the individuals who lodged the complaints --

DR. LIEBLER: Right --

DR. BELSITO: -- regarding these. And patients, there was very limited problems around the periungual area of the hands. They were either dermatitis, which is the classic nail polish-type of reaction, so it wasn't a matter of it penetrating through the nail and creating issues there.

The other complaints that -- on the blog, I don't know. But, I mean, I would agree with Alan's point. The major issue, assuming you don't have a consumer trying to apply it to a nonexistent nail in the hopes that they'll grow the nail, will, you know -- would be accidental contamination of the skin and assuring that the product is hardened before they start touching other areas of the body.

DR. LIEBLER: Okay. So, I'll drop that. I mean, I just wondered if other people felt that was an issue worth considering. Doesn't sound like it, so.

MS. BECKER: I do know people who use nail hardeners, guitar players. They put it under the end of the nail. I don't know if that matters or not, but.

DR. BELSITO: And should not be applied under the nail --

MR. STEINBERG: By guitar players.

DR. LIEBLER: You shouldn't trust finger-pickers, only trust flat fingers.

(Laughter)

MS. BECKER: They're bass players.

DR. BELSITO: Are they playing for us tonight?

DR. LIEBLER: No instrument on board, sorry.

MS. BECKER: That can be fixed. But you do have the pick. …

DR. BELSITO: Okay. So, are we happy with part 1 of our tripartite conclusion?

DR. SNYDER: Not totally, because we need to update the concentration of use table. Because on page 74, the next page, it -- concentration of use is 2010 in which we say nail hardeners 0.5 and less than 2, but we now know that it's -- so we need to make sure that that's updated.

DR. ANDERSEN: Yes, we do need to put the new data into that table. Thank you.

DR. BELSITO: Well, but nail hardeners is part 2. We haven't gotten to part 2 yet.

DR. ANDERSEN: Oh, sorry.

DR. BELSITO: Part 1 we're happy with.

DR. ANDERSEN: Okay.

DR. BELSITO: Part 2 previously was insufficient. So are we comfortable saying the available data are now sufficient for use of formaldehyde and methylene glycol in nail products?

DR. LIEBLER: Right.

DR. SNYDER: Yes.

DR. BELSITO: Yes. Curt?

DR. KLAASSEN: Yes.

DR. BELSITO: Okay. So how are we phrasing this, part 2? "Formaldehyde and methylene glycol are safe as used in nail hardening products," period and amen?

DR. ANDERSEN: For use of nail hardening products in the present concentration -- practices and use of concentration.

DR. BELSITO: Okay. So formaldehyde and methylene glycol are safe for use in nail hardeners under --

DR. ANDERSEN: Current use and concentration. In the present practices of use and concentration.

MS. WEINTRAUB: You're not going to mention 2 percent here?

DR. BELSITO: No, because of the 2 percent will be listed as the use range. But the issue became what industry was saying, Rachel, is that they use these urea formaldehyde resins as plasticizers. And there's -- if you were to analyze the product itself you'd end up with higher levels of formaldehyde than 2 percent. But these urea formaldehyde resins really aren't releasing a lot of airborne formaldehyde to begin with.

DR. LIEBLER: Depending on how you do the assay, you could get a jacked-up level of formaldehyde coming from the resin, even though the resin isn't a significant source of formaldehyde like methylene glycol would be in the tissue in regular use.

MS. WEINTRAUB: That is key to changing the table, as was mentioned.

DR. ANDERSEN: Just to give them -- right.

MS. WEINTRAUB: Right --

DR. ANSELL: It is mentioned, but it's mentioned in the table --

MS. WEINTRAUB: Right, that's correct, so it's (inaudible).

DR. BELSITO: So for use in concentration.

DR. ANSELL: Yeah.

MS. WEINTRAUB: Right.

DR. BELSITO: Okay. So, we're all comfortable with that. Formaldehyde/methylene glycol are safe for use in nail hardeners in the present practice of use and concentration.

DR. ANDERSEN: And present practices of use in that phraseology contemplates what David says in terms of labeling that says, don't get it onto your skin, et cetera.

DR. BELSITO: Okay.

DR. ANDERSEN: I don't think -- from the tenor of the discussion, you don't feel a need to include that in the conclusion, but it would be --

DR. BELSITO: It has to be hammered --

DR. ANDERSEN: -- part of the discussion.

DR. BELSITO: -- in the discussion.

DR. SNYDER: Well, we have a whole section of the discussion on formaldehyde/methylene glycol used as nail hardeners --

DR. BELSITO: Right.

DR. SNYDER: -- so it could be added in there.

DR. BELSITO: Right, yes.

DR. ANDERSEN: So, but your expectation is that users should be instructed to not get it in their skin should be clearer. I know how to write that.

DR. BELSITO: We don't need a footnote for that, though?

DR. ANDERSEN: Touché. SPEAKER: Two stars…

Don, I'm going to hazard a view that while we made a lot of changes to this conclusion, they're all changes that were contemplated based on data we asked for, et cetera, et cetera. And this could and should be considered editorial.

DR. BELSITO: Okay, we'll see what happens. I mean, I would agree. I think that the last meeting we're all comfortable with 2 percent with a nail hardener. We're all comfortable with unsafe in the -- as a hair straightener. The issue was with the consumer blog complaints that seemed to really center around one company's product. And it doesn't really, at least the way I'm interpreting it, it doesn't really seem to be formaldehyde in that product because that company's product doesn't exceed the formaldehyde level of other company's products of which there have not been multiple consumer complaints. It may well be -- and my patients, as I pointed out, tested negative to formaldehyde, albeit 1 percent formaldehyde, not 2. But they were still patch test negative, so.

DR. SNYDER: Maybe it's just editorial for clarification?

DR. BELSITO: Yeah, what I'm suggesting is I think we're done with formaldehyde…

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DR. BERGFELD: … move to the first large ingredient and that's formaldehyde and methylene glycol, Dr. Belsito presenting.

DR. BELSITO: When we looked at this last we had come to some tentative safety assessments in June. It's safe when used at minimal effective concentration but not to exceed 0.074 percent formaldehyde equivalents, that there was insufficient data for nail hardeners.

In particular we wanted to know the concentration of formaldehyde in one specific product about which there a number of consumer complaints. And that it was unsafe for use in hair-smoothing products, the use of which involves application of high temperatures.

We've gotten if you count the oral presentation yesterday five waves of information on formaldehyde as well as comments from the Personal Care Products Council. And following digestion of all that information, my team decided the following, that formaldehyde and methylene glycol is safe for use in cosmetics when formulated to ensure use at the minimal effective concentration but in no case should formalin at the recommendation of the PCPC with an asterisk indicating that formalin is 30 percent formaldehyde and water as supplied to the industry, so in no case should formalin exceed 0.2 percent (weight, weight) (total formaldehyde and methylene glycol.

Number two, that formaldehyde and methylene glycol are safe for use in nail hardeners and the present practices of use and concentration with instructions to protect the skin either in the discussion or in the conclusion. Then thirdly, in the present practices and concentration of use, formaldehyde and methylene glycol are unsafe for use in hair-smoothing products.

DR. BERGFELD: Is that a motion or do you have it for discussion?

DR. BELSITO: No, that's a motion.

DR. BERGFELD: A motion.

Dr. Marks?

DR. MARKS: So this would be another re-revised tentative amendment?

DR. BELSITO: No. We actually indicated I think the only thing that's changed substantively, not editorially, is that we're now saying that nails are safe and before we said they were insufficient for use concentration which we got. So it's not a change, at least I don't think it's a change, in the conclusion at all. We indicated that if we got the concentration and it was acceptable, it would be fine.

DR. MARKS: I'll let Alan make that decision as to whether going from insufficient to safe is enough to have another review.

Probably the only thing in the first portion that you mentioned also from the scientific council, there was the suggestion that methylene glycol level could be established at 0.118 percent, so we might want to include that in that first part.

Then the last part, that's where our team also wrestled with how to deal with the hair-smoothing products fully well knowing that they're going to be used and if we didn't somehow recognize that that it might be used in ways which we were concerned…

DR. BERGFELD: The Belsito team's response?

…DR. MARKS: Alan, is this going to be a re-revised or final because there were changes in the nail hardeners and we would have another shot at this again if there were more data from the use in hair salons.

DR. ANDERSEN: I don't think so. I think that the changes to part one of the conclusion that addresses the expanded discussion of formaldehyde equivalence to include what will turn out to be very useful information for manufacturers referring to formalin because that's what they actually add so now we've got that link, all of that is editorial.

On the nail hardeners' conclusion, it was contemplated that these data would come in and that if the concentrations were now known and the panel was comfortable, they would put a number and in this case it's understood that the data are consistent so present practices of use is a fine way of characterizing it and that was one of the expected results.

And the unsafe for hair smoothers as the motion was made didn't change, so this could be issued as a final safety assessment. The further emphasis that Paul Snyder made and that Jim Marks is suggesting including an expanded discussion of how it could be used safely in the discussion part is also from my standpoint editorial. So I think this can go final.

Final Amended Report

Formaldehyde and Methylene Glycol

December 7, 2011

The 2011 Cosmetic Ingredient Review Expert Panel members are: Chair, 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. This report was prepared by Ivan J. Boyer, Ph.D., D.A.B.T, and Bart A. Heldreth, Ph.D.

1101 17th Street, NW, Suite 310 ◊ Washington, DC 20036-4702 ◊ ph 202.331.0651 ◊ fax 202.331.0088 ◊ cirinfo@cir-safety.org
www.cir-safety.org

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ABSTRACT

Methylene glycol is continuously converted to formaldehyde, and vice versa, even at equilibrium, which can be easily shifted by heating, drying, and other conditions to increase the amount of formaldehyde. This rapid, reversible formaldehyde/methylene glycol equilibrium is distinguished from the slow, irreversible release of formaldehyde resulting from so-called formaldehyde releaser preservatives, which are not addressed in this safety assessment (formaldehyde releasers may continue to be safely used in cosmetics at the levels established in their individual CIR safety assessments).

Formaldehyde and methylene glycol may be used safely in cosmetics if established limits are not exceeded, and are safe for use in nail hardeners in the present practices of use and concentration, which include instructions to avoid skin contact. In the present practices of use and concentration (on the order of 10% formaldehyde/methylene glycol, blow drying and heating, inadequate ventilation, resulting in many reports of adverse effects), hair smoothing products containing formaldehyde and methylene glycol are unsafe.

INTRODUCTION

In 1984, CIR published its original safety assessment of formaldehyde,[1] concluding that this ingredient is safe for use in cosmetics applied to the skin if free formaldehyde was minimized, but in no case > 0.2%. This conclusion was based on data from numerous human skin irritation and sensitization tests (number of subjects ranging from 8 to 204) of cosmetic products (skin cleansers and moisturizers and a hair rinse) containing 0.2% formalin (37% w/w aqueous formaldehyde solution). Except for a few mild, equivocal, or inconsistent reactions, the results of these tests showed that such products have little potential to irritate or sensitize the skin. The Panel also said that it cannot be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized.

The Panel re-reviewed the safety assessment of formaldehyde and confirmed the original conclusion in 2003.[2]

Since that re-review, methylene glycol has been listed as a cosmetic ingredient and CIR has become aware of increasing uses of formaldehyde/methylene glycol in hair smoothing products intended to be heated. In addition to the issues related to increasing uses and identification of methylene glycol as a cosmetic ingredient, the U.S. EPA National Center for Environmental Assessment (NCEA) released a draft toxicological review of formaldehyde for external review on 2 June 2010, including interagency comments on an earlier draft of the document.[3] The NCEA Risk Assessment provides a comprehensive summary of the toxicological literature, including both human and animal studies and all of the major exposure routes of concern (inhalation, ingestion, and skin contact). The U.S. National Research Council (NRC) has released their review of the draft assessment.[4] Much of the significant new toxicology data are related to genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

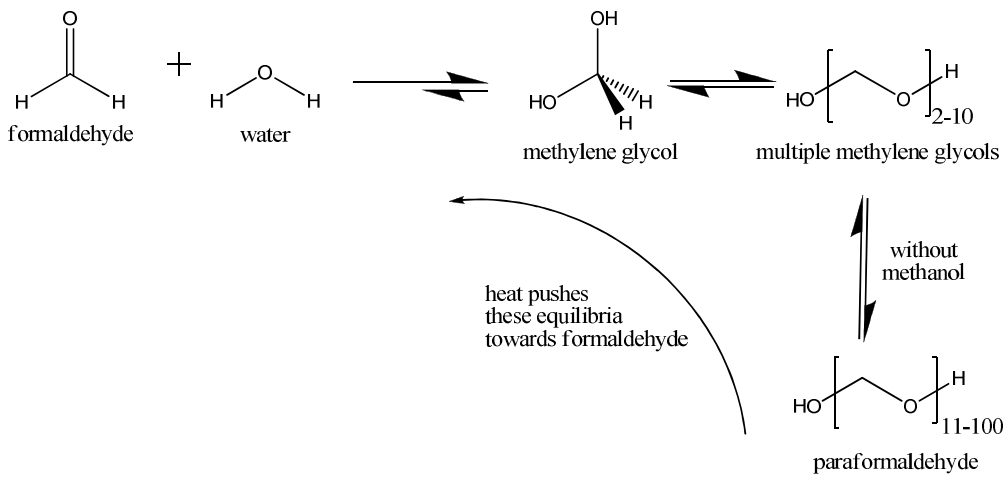
Data and analysis were provided by the Nail Manufacturer's Council (NMC) the Professional Keratin Smoothing Council (PKSC), the Personal Care Products Council, and the American Chemistry Council. Additional data from the U.S. Food and Drug Administration's (FDA's) adverse event reporting system and results of FDA laboratory product analyses are included.

CHEMISTRY

Formaldehyde – Formalin –Methylene Glycol

Formaldehyde, a gas, is not used in cosmetics in its pure, anhydrous form, but is instead most commonly produced as an aqueous solution called formalin.[5] Formalin is industrially produced from methanol. First, a mixture of vaporized methanol and steam is passed over a catalyst bed, where the methanol is oxidized to formaldehyde gas. Since this reaction is highly exothermic, the gas stream is cooled directly after passing over the catalyst to prevent thermal decomposition. Next, the formaldehyde reacts with water in an absorption column, because formaldehyde in its pure, gaseous form is highly unstable. Formaldehyde quickly reacts with water to produce methylene glycol and, without a polymerization inhibitor (eg, methanol), polymethylene glycols via a series of reversible reactions (Scheme 1). In the absence of methanol, these reactions proceed to form a mixture of long chain polymethylene glycols, which are referred to as paraformaldehyde.

Scheme 1 – Equilibria in aqueous formaldehyde solutions such as formalin



Methylene glycol, as a pure and separate substance, is not commercially available, but is instead produced as an aqueous solution called formalin, as denoted above for formaldehyde. Methylene glycol is a *geminal* (*gem*) diol, or a diol with both hydroxyl groups on the same carbon. *Gem* diols are typically unstable compounds. Indeed, methylene glycol exists only in aqueous solution, where it is stabilized by hydrogen bonding with water molecules. Thus, the high solubility of formaldehyde in water is due to the rapid hydration of formaldehyde to methylene glycol and the capacity of the aqueous solution to stabilize methylene glycol and small polymethylene glycols (ie, two to ten methylene glycol units long).[6] The rate of the hydration reaction is very fast (the half-life of formaldehyde in water is 70 milliseconds) and the equilibrium between methylene glycol and formaldehyde strongly favors methylene glycol at room temperature and neutral pH.[7] The equilibrium is dependent on temperature, solution density, pH, and the presence of other solutes. Increased temperature favors formation of formaldehyde. While the concentration of methylene glycol in formalin is much greater than formaldehyde, at room temperature, neutral pH stasis, this says nothing about the reversibility of this equilibrium shift or about the rate of dehydration when this stasis is disrupted (eg, formalin is exposed to air or a formulation containing formalin is heated). This reaction is reversible. The dehydration of methylene glycol to formaldehyde happens rapidly and can be catalyzed by lower pH.[8]

The formation of the higher polymethylene glycols is much slower than the rates of hydration and dehydration, and can be inhibited by methanol. Accordingly, a typical solution of formalin consists of water (~40-60%), methylene glycol (~40%), methanol (~1-10%), small methylene glycols (eg, dimers and trimers; ~1%), and a very small amount of formaldehyde (~0.02-0.1%). The multiple equilibria between these components favor methylene glycol at room temperature.[9] However, removal of water, increase in solution density, heating, reduction of pH, and/or the reaction of the small amount of free formaldehyde in the solution will drive the equilibrium back toward formaldehyde.[10] Moreover, a product formulated with either of the ingredients methylene glycol or formaldehyde actually contains an equilibrium mixture of the components: methylene glycol, polymethylene glycols and formaldehyde. While it can be pointed out that formaldehyde and methylene glycol are different and distinct molecules, the ever present equilibrium between the two makes this distinction of virtually no relevance to ingredient safety.[11] Due to the equilibria demonstrated above, any aqueous formulation that reportedly contains formalin, formaldehyde, or methylene glycol, actually contains both formaldehyde and methylene glycol. Accordingly, the ingredients formaldehyde and methylene glycol can be referred to as formaldehyde equivalents. Under any normal conditions of cosmetic use, including at room temperature and above, methylene glycol is not stable in the gas phase and very rapidly dehydrates to formaldehyde and water.[12] Accordingly, heating of a formulation containing formaldehyde or methylene glycol will primarily off-gas formaldehyde. For this reason, the hazards of formaldehyde equivalents in a heated solution are the same as the hazards of gaseous formaldehyde, since the solution so readily releases gaseous formaldehyde.

Formaldehyde Equivalents

Formalin, as recited above, is an aqueous solution of formaldehyde, methylene glycol and polymethylene glycols, all in equilibria and often stabilized with methanol. Formalin, *per se*, is not listed as an ingredient in the International Cosmetic Ingredient Dictionary and Handbook (INCI Dictionary) but is often recited herein as the material tested (therefore representing formaldehyde/methylene glycol). Of special importance is an understanding of the meaning of percent formalin. "100% formalin" means an aqueous solution wherein formaldehyde has been added to water to the saturation point of these equilibria, which is typically 37% (by weight) formaldehyde equivalents in water. Accordingly, a 10% formalin solution contains approximately 3.7% formaldehyde equivalents. More specifically, an aqueous solution which is 3.7% of formaldehyde (by weight) relates directly to a solution which is 5.9% methylene glycol (because the molecular weight of formaldehyde is 30 g/mol and the molecular weight of methylene glycol is 48 g/mol).

All of the toxicity studies relied upon for determining the current 0.2% limitation in cosmetic products are based on the idea of "free formaldehyde," what we now are calling formaldehyde equivalents. However, it seems quite probable that this number actually meant 0.2% formalin. Accordingly, based on the average formalin solution being 37% formaldehyde equivalents, this represents a true limit of 0.074% formaldehyde equivalents.

Moreover, the ingredients in this review are not to be confused with "formaldehyde releasers," which are not analogous to formaldehyde or methylene glycol, but release small amounts of formaldehyde over considerable intervals (eg, Diazolidinyl Urea), acting as preservatives.

Analytical Methods

Most commonly used analytical methods for qualitative and quantitative detection of formaldehyde are non-specific to non-hydrated formaldehyde, but can accurately describe formaldehyde equivalent presence and quantity. A typical method, for example the method used by the Oregon OSHA Laboratory, can detect formaldehyde equivalents present in a formulation, or released into the air, via a two stage process: 1) derivatization of a sample with a hydrazine (which reacts with formaldehyde or methylene glycol, in a formulation sample or in an air sample), and 2) detection of the resultant hydrazone (ie, the reaction product of the hydrazine and formaldehyde) with a diode array, after separation on a column (eg, high performance liquid chromatography (HPLC) separation followed by ultraviolet/visible light (UV/Vis) detection).[11] Accordingly, published values for "formaldehyde" levels should be taken to mean formaldehyde equivalents.

While other formaldehyde/methylene detection techniques are known, the methods used by OSHA are the most common methods and are what current regulations, globally, have been based on. These techniques would find that a typical formalin solution contains approximately 37% formaldehyde equivalents. Some may argue that using nuclear magnetic resonance (NMR) spectrometry techniques would demonstrate that this same formalin solution is only 0.037% formaldehyde.[13] This is a technically correct interpretation of the amount of non-hydrated formaldehyde molecules present in the static environment of an NMR sample tube. This scenario, however, exists only in the highly controlled experimental system where the conditions (room temperature, neutral pH, closed NMR tube) maintain an artificially constant level of non-hydrated formaldehyde. This does not represent the conditions under which formaldehyde or methylene glycol are used in hair smoothing products, and as such, drastically underestimates the exposure risk. In use, hair smoothing treatments containing formaldehyde or methylene glycol involve elevated temperatures (eg, 450 degrees F) and reduced pH formulations (eg, as low as pH = 4).[13] Further, the solutions are used in a system where the bottle is opened, the solution is poured, applied, and allowed to partially evaporate/off gas. Focusing on the equilibrium between formaldehyde and methylene glycol in a closed system that artificially favors a liquid state is not representative of the conditions of use of these ingredients in hair smoothing products.

An alternative technique has also been proposed for specifically addressing the vapor/gas present in the headspace above an aqueous formaldehyde/methylene glycol solution, which involves trimethylsilyl (TMS) derivatization of those moieties present, followed by detection of the resultant derivatives.[13] However, the chemical specificity for this method is not conclusively defined. The resultant derivatives detected could have arisen from a variety of constituents present in the headspace. Furthermore, no standards were recited which validate this method's ability to detect non-hydrated formaldehyde.

COSMETIC USE

As given in the INCI Dictionary,[14] formaldehyde functions in cosmetic products as a cosmetic biocide, denaturant, and preservative. According to the 2010 13th Edition of the INCI Dictionary, methylene glycol is reported to function as an artificial nail hardener.[14]

In the FDA's Voluntary Cosmetic Registration Program (VCRP),[15] there are 77 uses of formaldehyde and formaldehyde solution (formalin) reported. Since these all are probably the same ingredient as added to cosmetics, they are combined in Table 1.[2,15,16] Industry surveys of formaldehyde use concentrations and an FDA reports yielded data shown in Table 1.[16-19] No uses of methylene glycol are currently reported to the VCRP, but the use concentration in nail hardeners containing methylene glycol reportedly ranges from 0.8% to 3.5% (corresponding to 0.5% to 2.2% calculated as formaldehyde).[16-19]

The Material Safety Data Sheet (MSDS) provided by Brazilian Blowout for their salon product, however, does include methylene glycol.[20] The list of ingredients provided by the manufacturer is shown in Table 2, with methylene glycol listed at <5.0%.

From a high of 805 reported uses of formaldehyde/formalin in 1984, VCRP data from 2001/2002, 2006/2007, and 2009/2010 show that uses have decreased to less than 100 uses, as shown in Figure 1. The VCRP, however, does not include reporting of ingredients used in cosmetics labeled "for professional use."

In Europe, formaldehyde is also permitted for use in cosmetics at concentrations ≤0.2% (the limit for oral hygiene products is ≤0.1%).[21] Products containing >0.05% formaldehyde must be labeled "contains formaldehyde." The maximum authorized concentration in finished nail hardeners is 5%, provided that the product is labeled "Protect cuticles with grease or oil. Contains formaldehyde" These limits are expressed as "free formaldehyde" or "calculated as formaldehyde." Formaldehyde is prohibited for use in aerosol dispensers. Canada, Australia, China and ASEAN nations have regulatory limits very similar to those of the European Union.[22-27]

Use of Formaldehyde/Methylene Glycol in Nail Hardening Products

The FDA Guide to Inspections of Cosmetic Product Manufacturers[28] states that nail hardeners often contain formaldehyde as the active ingredient and that the Agency has not objected to its use as an ingredient of nail hardeners if the product 1) contained no more than 5% formaldehyde, 2) provided the user with nail shields that restrict application to the nail tip (and not the nail bed or fold), 3) furnished adequate directions for safe use, and 4) warned consumers about the consequences of misuse and potential for causing allergic reactions in sensitized users. Based on comments given at the June 27-28, 2011 CIR Expert Panel meeting, it appears that nail shields are no longer supplied with nail hardeners in the U.S. because consumers did not use the shields.

As noted above, in Europe, formaldehyde is permitted for use in nail hardeners at concentrations ≤5% "calculated as formaldehyde," and the product label must instruct the user to protect cuticles with grease or oil.[29] If the formaldehyde concentration in the product exceeds 0.05%, the label must also state "contains formaldehyde."

In the earlier CIR safety assessment of formaldehyde,[1] the CIR Expert Panel acknowledged reports of use of formaldehyde in nail hardeners at a concentration of 4.5%. It now appears that methylene glycol is considered to be the appropriate ingredient name to use to describe formaldehyde/methylene glycol in nail hardeners. [14] . Recent data provided by the Nail Manufacturers Council (NMC)[30] indicated that, to make a nail hardener nominally "1% formaldehyde"– which should be considered a typical marketplace level – a formulator would add 2.703% formalin (2.703% x 37% = 1%). Because of the well-recognized equilibrium relationship between formaldehyde and methylene glycol, the formaldehyde converts to methylene glycol. Therefore, a product with 2.703% formalin would contain 1.60% methylene glycol (2.703% x 59.2% = 1.60%). A recent survey of U.S. marketers conducted by the NMC indicated that formaldehyde/methylene glycol is not used in all brands of nail hardeners.[18] The survey results indicated that brands using methylene glycol/formaldehyde contain 0.7% to 1.85%, calculated as formaldehyde. Analyses of two finished nail hardener products (brand/origin not identified) indicated that they contained 1.9% and 2% formaldehyde equivalents, expressed as formaldehyde.[19] FDA recently reported finding 2.2% formaldehyde/methylene glycol in a nail hardening product that was cited often in a compilation of customer self-reports from Internet sites indicating adverse effects including skin irritation, burning sensation of nail beds and

exposed skin, and pain[17,31] and two cases of eyelid dermatitis reported by a member of the CIR Expert Panel. The cases reported by the Panel member patched tested negative for 1% formaldehyde equivalents (calculated as formaldehyde) in water; higher concentrations (eg, 2%) were not tested.

Use of Formaldehyde/Methylene Glycol in Hair Smoothing Products

The use of formaldehyde/methylene glycol containing hair smoothing products largely appears to take place in salons, but use in a home is not precluded. Workplace surveys conducted by the Oregon Occupational Safety and Health Administration (OSHA) uncovered a wide variety of ventilation approaches, including simply having a building HVAC system, propping the business's doors open, or operating ceiling fans.[11]

Although the purpose and mechanism of action of formaldehyde/methylene glycol in hair relaxers/straighteners is not well documented, formaldehyde (as part of a formalin solution) is known to induce a fixative action on proteins (eg, keratin).[32] This is at least in accord with formaldehyde's function as a denaturant, in the classic sense of the term (ie, reacting with biological molecules, such as disrupting the tertiary structure of proteins, not just making liquids non-potable). Purportedly, formaldehyde/methylene glycol hair straightening formulations, such as Brazilian-style or keratin-based straightening products, maintain straightened hair by altering protein structures via amino acid crosslinking reactions, which form crosslinks between hair keratins and with added keratin from the formulation.[33]

One proposed reaction scheme involves: 1) hemiacetal formation between a keratin hydroxyl group and formaldehyde, 2) reaction of two such hemiacetals, in a dehydration step, to form a methylene ether crosslink, and 3) formaldehyde elimination to finalize the new methylene crosslink.[34] Stoichiometricaly, this proposed scheme purports that some of the formaldehyde that initially reacts with keratin is eventually released as formaldehyde during the hair straightening process. Formaldehyde can react with multiple protein residue side-chains, although the principal reactions are with the epsilon amino groups of lysine residues.[35] Besides proteins, formaldehyde is known to react with other biological molecules such as nucleic acids and polysaccharides.[36] The action of formaldehyde in intramolecular and intermolecular crosslinking of macromolecules can considerably alter the physical characteristics of the substrates.

The U.S. OSHA has issued a hazard alert concerning hair smoothing products that could release formaldehyde into the air.[37] The alert stated that OSHA investigations uncovered formaldehyde concentrations greater than OSHA's limits of exposure.[38] One investigation reported such levels of formaldehyde even though the product was labeled "formaldehyde-free." The hazard alert stated that formaldehyde gas presents a health hazard if workers are exposed, described the other chemical names to look for on the label that would signal reason for concern, and told businesses what to do to reduce exposure when using formaldehyde-releasing hair smoothing products.

Canada issued health advisories informing consumers of the risks associated with hair smoothing products containing excessive levels of formaldehyde, and has recalled several such products.[39-42] Hair smoothing products with formaldehyde at levels >0.2% are not permitted for sale in Canada.[41]

France's health authority warned consumers and hairdressers against using hair straightening treatments that contain high levels of formaldehyde and has removed a number of such products from the market.[43] Germany's Federal Institute for Risk Assessment (BfR) advised against the use of hair straightening products that contain formaldehyde in high concentrations.[44] The Irish Medicines Board, which is the competent authority in Ireland for cosmetics, took action to remove hair smoothing products from the market if they contain greater than 0.2%, the level established by the European Commission (EC).[45]

TOXICOKINETICS

Formaldehyde is a highly water-soluble, reactive, rapidly metabolized chemical with a relatively short biological half-life. Inhaled formaldehyde is absorbed primarily in the respiratory epithelium lining the upper airways, where it undergoes extensive local metabolism and reactions with macromolecules. Based on the weight of the evidence, the NRC concluded that formaldehyde does not penetrate beyond the superficial layer of the nasopharyngeal epithelium, and is unlikely to appear in the blood as an intact molecule, except possibly at concentrations high enough to overwhelm the metabolic capacity of the epithelium.[4] The NRC concluded that formaldehyde is not

available systemically in any reactive form, and systemic effects are unlikely from the direct delivery of formaldehyde or methylene glycol to distal sites, except possibly in highly exposed people.

TOXICOLOGY

Previous CIR Safety Reports on Formaldehyde- Summary

> In low amounts, formaldehyde is generated and present in the body as a normal metabolite, and as such or when taken into the body, it is rapidly metabolized by several pathways to yield carbon dioxide. It is a very reactive chemical. Not surprisingly, formaldehyde is an irritant at low concentrations, especially to the eyes and the respiratory tract. Formaldehyde exposure can result in a sensitization reaction. Under experimental conditions formaldehyde is teratogenic, mutagenic and can induce neoplasms.
>
> Perhaps the single most important attribute common to these toxic effects of formaldehyde is that they are all concentration/time dependent. A higher concentration or duration of exposure than that which produces irritation, for example, induces degenerative changes in the tissues exposed to it. There was no evidence that formaldehyde can induce neoplasia at concentration/time relationships that do not damage normal structure and function of tissues, even under laboratory conditions.
>
> *From the Final Report on the Safety Assessment of Formaldehyde*[1]

> New clinical studies reviewed in 2003 confirmed that formaldehyde can be a skin irritant and sensitizer, but at levels higher than the 0.2% free Formaldehyde upper limit established by the CIR Expert Panel.
>
> The developmental toxicity, genotoxicity, and carcinogenicity of high doses of formaldehyde were also confirmed in the new studies (published between 1984 and 2003). These studies demonstrated that there is a threshold effect; that is, high doses are required before any effect is seen.
>
> *From the Published Re-Review of Formaldehyde*[2]

New Data on Safety of Formaldehyde

The U.S. EPA National Center for Environmental Assessment (NCEA) released a 4-volume draft toxicological review of formaldehyde for external review on 2 June 2010, including interagency comments on an earlier draft of the document.[3] U.S. EPA is conducting this assessment to support the development of new chronic inhalation toxicity values for formaldehyde. Ultimately, the final versions of these values will be incorporated into the U.S. EPA Integrated Risk Information System (IRIS).

The NRC recently released their review of U.S. EPA's draft assessment [4] and their findings are also summarized below, where appropriate. The NRC noted that the systemic delivery of formaldehyde may not be required for some of the systemic effects attributed to formaldehyde inhalation (eg, lymphohematopoietic cancers and reproductive toxicity). Instead, systemic effects could be secondary, indirect effects of the local effects of exposure, including local irritation and inflammation, and stress.

This document provides a summary of the toxicological literature, including both human and animal studies and all of the major exposure routes of concern (inhalation, ingestion, and skin contact). Much of the significant new toxicology data are related to genotoxicity, carcinogenicity, and reproductive and developmental toxicity. A comprehensive summary of the findings is presented in Tables 3 through 11.

Reproductive and Developmental Toxicity

Several potential modes of action of formaldehyde for reproductive and developmental outcomes have been suggested by animal studies, including endocrine disruption, genotoxic effects on gametes, and oxidative stress or damage.[46,47] However, the evidence for causality is weak. In addition, it is not clear that inhaled formaldehyde or its metabolites can penetrate past the portal of entry or cross the placenta, blood-testis barrier, or blood-brain barrier.

The findings of studies on male reproduction generally used concentrations that result in significant weight loss and overt toxicity. There are no multigenerational tests for reproductive function.[3] These deficiencies, particularly for

male reproductive effects, represent important data gaps in the assessment of risks of reproductive and developmental toxicity associated with inhalation exposures to formaldehyde.[4]

The NRC noted that a small number of epidemiological studies[48-51] suggest an association between occupational exposure to formaldehyde and adverse reproductive outcomes in women.[4]

Genotoxicity

Clear evidence of systemic mutagenicity does not emerge from animal inhalation bioassays, despite the reactivity and mutagenicity demonstrated in isolated mammalian cells.[52-54]

Similarly, the evidence that inhaled formaldehyde may be directly genotoxic to humans systemically is inconsistent and contradictory.[55-60]

Carcinogenicity

Nasopharyngeal Cancers (NPC)

The NRC agreed with EPA that there is sufficient evidence from the combined weight of epidemiologic findings, results of animal studies, and mechanistic data of a causal association between the inhalation of formaldehyde and cancers of the nose, nasal cavity, and nasopharnyx.[4] Formaldehyde is highly reactive, readily forms DNA and protein adducts and crosslinks, and is a direct-acting genotoxicant. Among the potential modes of action that have been considered for the development of NPCs through the inhalation of formaldehyde in animal studies include direct mutagenesis of cells at the site of first contact and cytotoxicity-induced cell proliferation (CICP), which correlates with tumor incidence.[61-68]

The subchronic or chronic inhalation of formaldehyde at high concentrations (eg, ≥6 ppm) clearly can cause NPCs in mice and rats. However, there is still debate in the scientific community about whether this effect should be considered to be a non-threshold effect or a threshold effect in cancer risk assessments.

The NRC concluded that these two primary modes of action contribute to formaldehyde-induced carcinogenicity in nasal tissues, including mutagenicity and CICP.[4] A mutagenic mode of action is generally the reason for adopting the default low-dose linear extrapolation methods in a quantitative cancer risk assessment. However, the NRC noted that formaldehyde is endogenous, that nasal tumors are rare in both rats and humans, and that no increases in tumor frequency are observed in animal studies at formaldehyde concentrations that do not also cause cytotoxicity. Further, the animal studies reveal a substantial nonlinearity in dose-response relationships among formaldehyde uptake, cytotoxicity, cell proliferation, and tumor formation.

Thus, the NRC recommended that the quantitative assessment of the risks of formaldehyde-induced NPCs incorporate the nonlinear phenomenon of CICP, as well as the mutagenicity of formaldehyde.[4]

Lymphohematopoietic (LHP) Cancers

The three proposed modes of action by which formaldehyde exposure may cause leukemia include:[69]

- Transport of formaldehyde/methylene glycol from the portal of entry through the blood to the bone marrow, followed by direct toxic action to hematopoietic stem cells in the marrow
- Direct toxic action of formaldehyde/methylene glycol on circulating blood stem cells and progenitors at the portal of entry, followed by return of the damaged cells to bone marrow
- Direct toxic action of formaldehyde/methylene glycol on primitive pluripotent stem cells at the portal of entry, followed by migration of damaged cells to bone marrow

Similarly, direct toxic action of formaldehyde/methylene glycol on lymphocytes in mucosa-associated lymphoid tissues (MALT) at the portal of entry may cause lymphoid cancers.[3]

Remarkably little evidence from animal studies indicates that formaldehyde exposure can cause LHP cancer. Studies have consistently failed to find elevated levels of free formaldehyde or methylene glycol in the blood of exposed human and animal subjects, or DPCs in the bone marrow of exposed animals.[70] Further, formaldehyde is a highly reactive, rapidly metabolized chemical yielding short-lived DPCs and DNA-adducts that are amenable to rapid reversal and repair.[71,72] These observations are consistent with conventional wisdom, which has been that the expected sites of action of formaldehyde are limited to portals of entry (eg, nasal epithelium), and would not likely include distal sites, such as the bone marrow, where leukemias originate.[70,73-75] Although several possible modes of action have been postulated to explain associations between LHP cancers and formaldehyde exposure in epidemiological studies, little scientific evidence supports these hypotheses, and there is some recent evidence against them. Thus, these proposals remain speculative and continue to represent a highly controversial topic in the scientific community.

The NRC noted that little is known about the potential modes of action by which formaldehyde might cause LHP cancers, other than mutagenicity.[4] A mechanism that would explain the occurrence of LHP cancers has not been established, the epidemiological data are inconsistent, the animal data are weak, and there is a growing body of evidence that formaldehyde is not available systemically in any reactive form. Further, the lack of consistency in exposure-response relationships between several exposure metrics and the LHP cancers in the epidemiological data could reflect the absence of causal mechanisms associating these cancers with formaldehyde exposure.

Irritation and Sensitization

As noted in the original safety assessment of formadehyde,[1] aqueous formaldehyde/formalin solutions can irritate the skin and cause contact urticaria and allergic sensitization in both occupationally and non-occupationally exposed persons. The North American Contact Dermatitis Group (NACDG) reported a 5% incidence of skin sensitization among 2,374 patients exposed to 2% formaldehyde in aqueous solution.[76] Aqueous formaldehyde solutions as low as 0.01% can elicit skin responses in some sensitized persons under occlusive conditions. Most sensitized individuals can tolerate repeated topical axillary application of products containing up to 0.003% aqueous formaldehyde solution on normal skin.[77] Cosmetic products containing 0.0005% to 0.25% formalin (0.000185%-0.0925% calculated as formaldehyde) were essentially nonirritating and non-sensitizing in 1,527 subjects in 18 studies summarized in Table 5 of the original safety assessment.[1]

Recent reviews addressing the human irritation and sensitization potential for aqueous formaldehyde/formalin solutions are consistent with the observations reported in the original assessment.[78,79]

Healthy volunteers (n=30; ≥18 years old) of either sex were exposed to 11 personal care products and 2 controls (ie, deionized water and 0.3% sodium lauryl sulfate) using an occlusive patch-testing protocol.[80] The products included 3 keratin hair straighteners containing methylene glycol (concentration not reported). All of the products were diluted to 8%, presumably with deionized water, before applying 0.2 ml of the diluted product to Webril© disks. Note that, based on the manufacturer's directions, hair straighteners are applied undiluted to the hair. The patches were applied to the skin of the upper arms of each subject and left in place for 23 hours, and removed and examined during the 24th hour, for 4 consecutive days. Each subject was exposed to each of the 11 products and 2 controls on patches applied to the same site of the skin each day. The specific site of application for each product/control varied from subject to subject, depending on the random assignment of each subject to one of 5 groups. None of the diluted products or the negative control elicited any more than minimal erythema throughout the study. In contrast, the positive control elicited substantial erythema.

CLINICAL USE

Adverse Event Reporting

Nail Hardening Products

A compilation of 33 customer self-reports from Internet sites and blogs of nail hardening products indicate adverse effects including skin irritation, burning sensation of nail beds and exposed skin, severe finger pain, scabbing under the nails, and drying, flaking, splitting, crumbling, or peeling of the nails.[31] Two additional reports noted that the product contained formaldehyde and has a strong odor, without noting any other adverse effects. Three reports indicated that the product contained 4%-4.5% formaldehyde.

Hair Smoothing Products

Canada
Some 50-60 individuals have reported adverse reactions to Health Canada resulting from use of hair smoothing products containing formaldehyde. These reports concerned burning eyes, nose, throat and breathing difficulties, with one report of hair loss,[41] but additional reports also were received of headache, arthritis, dizziness, epistaxis, swollen glands and numb tongue (Health Canada, personal communication).

USA
The Center for Research in Occupational and Environmental Toxicology (CROET) at the Oregon Health Sciences University (OHSU) has received numerous phone calls and emails from stylists from around the United States since first posting an alert on a hair product on September 16, 2011.[11] Many of the stylists reported health symptoms associated with the use of this product at work. The health symptoms reported include the following: burning of eyes and throat, watering of eyes, dry mouth, loss of smell, headache and a feeling of "grogginess," malaise, shortness of breath and breathing problems, a diagnosis of epiglottitis attributed by the stylist to their use of the product, fingertip numbness, and dermatitis. Some of these effects were also reported to have been experienced by the stylists' clients. CROET also received emails from persons who report hair loss after having the treatment. Oregon OSHA has received similar, although generally less detailed, reports from individuals who have contacted the agency as a result of recent media coverage.

The U.S. OSHA recently issued a Hazard Alert and identified safeguards that should be in place to keep formaldehyde concentrations below the U.S. OSHA occupational exposure limits.[37]

The FDA has been notified by some state and local organizations of reports from salons about problems associated with the use of Brazilian Blowout, a product used to straighten hair.[81] Complaints include eye irritation, breathing problems, and headaches. State and local organizations with authority over the operation of salons are currently investigating these reports.

The FDA adverse reporting system includes 33 adverse event reports from use of hair smoothing and straightening products from hair stylists, their customers, and individual users from 9/29/08 through 3/1/11.[82] The results clearly link the use of formaldehyde/methylene glycol-containing hair smoothing products to clinical signs and symptoms that would be expected from the vaporization and inhalation of toxic levels of this ingredient. These reported effects include irritation of the eyes, nose and throat, nasal discharge, nose bleeds, congested sinuses, hoarseness, persistent coughing, bronchitis, difficulty breathing, feeling of pressure, tightness, or pain in chest. Two reports note inhalation pneumonitis in a professional hair stylist. Other complaints include headache, dizziness, fainting, and vomiting. Reported effects potentially attributable to direct contact with these products include irritation, inflammation, or blistering of the skin, especially on the scalp, and hair loss. In addition to these 33 reports, there were 7 reports of hair loss that did not indicate whether other possible adverse effects also occurred.

RISK ASSESSMENTS

Carcinogenicity

In 2006, the International Agency for Research on Cancer (IARC)[83] concluded that there was *sufficient* epidemiological evidence that formaldehyde causes NPC in humans and *strong but not sufficient* evidence for a causal association between leukemia and occupational exposure to formaldehyde. They also elevated their evaluation of formaldehyde from probably carcinogenic to humans (Group 2A) to carcinogenic to humans (Group 1).

In 2009, IARC[84] updated their evaluation to conclude that there is *sufficient* evidence for a causal association between leukemia, particularly myeloid leukemia, and occupational exposure to formaldehyde. This conclusion was based primarily on:

- The statistically significant association between embalming and myeloid leukemia, including statistically significant trends for cumulative years embalming and peak formaldehyde exposure.[85]

- The levels of chromosome 7 monosomy and chromosome 8 trisomy in myeloid progenitor cells and hematological changes in formaldehyde exposed workers.[69]

The IARC Working Group was almost evenly split on the prevailing view that the evidence was sufficient for formaldehyde causing leukemia in humans.[84]

The U.S National Toxicology Program (U.S. NTP) concluded that formaldehyde is *known to be a human carcinogen* based on epidemiological reports indicating that exposures are associated with nasopharyngeal, sinonasal, and LHP cancers and data on mechanisms of carcinogenicity from laboratory studies.[86-88]

In 1991, U.S. EPA classified formaldehyde as a B1 carcinogen (ie, a probable human carcinogen), based on limited evidence in humans, and sufficient evidence in animals.[89] They estimated an upper-bound inhalation cancer unit risk of 1.6×10^{-2} per ppm (1.3×10^{-5} per $\mu g/m^3$), using a linearized multistage, additional-risk procedure to extrapolate dose-response data from a chronic bioassay on male F344 rats. An upper-bound 10^{-6} human cancer risk would be associated with continuous inhalation of 0.06 ppb (63 ppt) formaldehyde over a lifetime, based on this unit risk.

Recently, U.S. EPA proposed to identify formaldehyde as carcinogenic to humans.[3] They proposed an upper-bound inhalation cancer unit risk for NPC, Hodgkin's lymphoma, and leukemia, combined, using log-linear modeling and extra risk procedures to extrapolate cumulative exposure estimates from the epidemiological studies.[90] The NRC agreed that the Hauptmann et al (2004) study[91] of the NCI cohort is the most appropriate for deriving cancer unit risk estimates for respiratory cancers and other solid tumors, but noted that this study is being updated.[4] The update will likely address the deaths reported to be missing from this study.[90] However, the NRC explicitly did not recommend that U.S. EPA wait until the release of the update to complete its assessment.

Non-Cancer Effects

In 1990, U.S. EPA published a chronic reference dose (cRfD) of 0.2 mg/kg/day for oral exposure to formaldehyde, based on the results of a 2-year bioassay in rats.[89,92] Formaldehyde (methylene glycol/formaldehyde) was administered to Wistar rats (70/sex/dose) in drinking water, yielding mean doses of 0, 1.2, 15, or 82 mg/kg/day for males and 0, 1.8, 21, or 109 mg/kg/day for females. Severe damage to the gastric mucosa was observed at 82 and 109 mg/kg/day in males and females, respectively, but no tumors were found. The NOAEL was 15 mg/kg/day in this study.

U.S. EPA released a draft risk assessment for formaldehyde for public comment and review by the NRC.[3] They proposed a chronic reference concentration for formaldehyde exposure by inhalation, based on three "cocritical" epidemiological studies. These studies reported associations between formaldehyde exposure and increased physician-diagnosed asthma, atopy[93], and respiratory symptoms,[94] and decreased pulmonary peak expiratory flow rate[95] in residential populations, including children. The NRC agreed with U.S. EPA's assessment of a causal relationship between formaldehyde and respiratory effects, except for incident asthma based on one of the "cocritical" studies.[4,93]

EXPOSURE ASSESSMENTS

Formaldehyde is ubiquitous in both indoor and outdoor air. Substantial sources of airborne formaldehyde include both natural and anthropogenic sources. Formaldehyde concentrations are generally greater in urban air than in agricultural areas, and greater in indoor air than in outdoor air.[3,4,83,96,97] It is estimated that the general population is exposed to an average of 0.016 to 0.032 ppm formaldehyde in indoor air.[98] In addition, formaldehyde is a natural metabolic intermediate in humans and other animals and is, thus, normally present in all tissues, cells, and bodily fluids.[96] The concentration of endogenous formaldehyde in the blood of rats, monkeys, and humans is about 0.1 mM.[99,100] Endogenous tissue formaldehyde concentrations are similar to genotoxic and cytotoxic concentrations observed in vitro.[70] In addition, formaldehyde is likely present normally in exhaled breath at concentrations of a few parts per billion (ppb).[4]

Standards and Guidance for Formaldehyde Inhalation Exposures

U.S. OSHA Enforceable Standards[38]

8-hour Threshold for Hazard Communication Requirements (Threshold-TWA)	0.1 ppm
8 hour Action Level (AL-TWA)	0.5 ppm
8-hour Permissible Exposure Limit (PEL-TWA)	0.75 ppm
15-minute Short Term Exposure Limit (STEL-TWA)	2 ppm

The 8-hour Threshold-TWA is the time-weighted average concentration (0.1 ppm) above which employers are required to meet U.S. OSHA's hazard communication requirements.[38]

NIOSH Recommended Exposure Limits

10-hour Recommended Exposure Limit (REL-TWA)	0.016 ppm
15-minute Recommended Short Term Exposure Limit (REL-STEL-TWA)	0.1 ppm

The U.S. National Institute of Occupational Health (NIOSH) standards and recommendations were developed to protect workers primarily from irritation of the eyes, nose, throat, and respiratory system.[101]

U.S. NAC AEGL Committee

Acute Exposure Guideline Level-1 (AEGL-1)	0.9 ppm

The U.S. National Advisory Committee for Acute Exposure Guideline Levels (U.S. NAC AEGL Committee) for Hazardous Substances interim acute exposure guideline level-1 (AEGL-1) for formaldehyde is defined as a concentration in air above which the general population (including susceptible individuals) could experience notable discomfort, irritation, or other adverse effects.[102]

> The AEGL-1 was based on the NOAEL for eye irritation in a study in which 5 to 28 healthy subjects previously shown to be sensitive to 1.3 or 2.2 ppm formaldehyde were exposed eye-only for 6 minutes to 0, 0.35, 0.56, 0.7, 0.9, or 1.0 ppm.[103] Subjective eye irritation responses ranged from none to slight at 0, 0.35, 0.56, 0.7 and 0.9 ppm. The 0.9 ppm AEGL-1 was applied across all acute exposure durations (10-min to 8 hours) because several studies show that there is adaptation to irritation at such concentrations and because in the absence of exercise, there are no decrements in pulmonary function parameters in healthy or asthmatic subjects inhaling 3 ppm for 3 hours.[104-106]

ACGIH

Threshold Limit Value-Ceiling (TLV®-C)	0.3 ppm.

The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value-Ceiling (TLV®-C) is defined as the concentration that should not be exceeded during any part of the working exposure.[107]

WHO

30-minute average indoor air guideline	0.08 ppm

The World Health Organization (WHO) 30-minute average indoor air guideline is for the prevention of significant sensory irritation in the general population.[108] WHO notes that this guideline represents a negligible risk of upper respiratory tract cancer in humans, because it is more than an order of magnitude lower than the threshold for cytotoxic damage estimated for the nasal mucosa. Recent reviews of the relevant epidemiological and animal studies concluded that this guideline is protective against acute and chronic sensory irritation, as well as for all types of cancer (including LHP malignancies).[73,108]

Formaldehyde Exposures During use of Nail Products

Time Weighted Average (TWA) formaldehyde exposures of nail technicians and customers were measured simultaneously, during normal operations at 30 nail salons throughout California in winter and summer.[109,110] Nail hardeners containing formaldehyde were used in some of these salons and other products containing formaldehyde resins were used in most, if not all, of the salons during the study.[109] 2,4-dinitrophenylhydrazine (DNPH)-treated silica gel absorption tubes and high-flow pumps were used to collect the samples. One sample inlet tube was placed close to the technician's breathing zone, and another close to the customer's breathing zone during the application of the nail products. A third sampler was placed in the salon about 10 feet from the work station to collect "area samples" to measure concentrations in the salon during the application of the nail products. A fourth sampler was placed inside the salon early in the morning before the salon opened, inside during the first two hours the salon was open, or outside the salon while the salon was open, to provide background data. Preliminary air samples were collected from two office buildings for comparison.

Most of the air samples were collected for approximately 4 hours, and some for about 2 hours or 8 hours.[109] The samples were analyzed using high-performance liquid chromatography (HPLC), in accordance with U.S. EPA method TO-11.[110] The measured concentrations were used to calculate 8-hour TWAs.

The authors reported 8-hour TWA formaldehyde concentrations in the breathing zones ranging from **0.0032 to 0.065 ppm** (median = 0.01 ppm; mean = 0.0187 ppm; SD = 0.0187 ppm) during the application of the nail products.[110] The corresponding area concentrations ranged from 0.0038 to 0.06 ppm (median = 0.01 ppm; mean = 0.0196 ppm; SD = 0.0195 ppm). The background concentrations, pooled, ranged from 0.0023 to 0.12 ppm (0.021 to 0.12 ppm early morning before opening; 0.014 to 0.081 ppm during first two hours after opening; 0.0023 to 0.013 ppm outside; overall: median = 0.014 ppm; mean = 0.033 ppm; SD = 0.038 ppm). The concentrations ranged from 0.015 to 0.021 ppm (mean = 0.018 ppm) in one office building, and was 0.043 ppm in the other office building. The authors did not determine the sources of the formaldehyde measured in the background samples.

Thus, the reported 8-hour TWA formaldehyde concentrations in the breathing zones during the application of the products appear to be indistinguishable from the salon area concentrations, and comparable to the background concentrations. In addition, the reported concentrations measured in the breathing zone, area, and outside background locations were uniformly lower than standards for formaldehyde, including the U.S. OSHA PEL-TWA (0.75 ppm), AL-TWA (0.5 ppm), and Threshold-TWA (0.1 ppm).

One of the 7 remaining inside background concentrations (collected during the first to hours after opening) exceeded the Threshold-TWA, and none exceeded the PEL-TWA, AL-TWA, or AEGL-1.

In another study, aluminum foil over a wooden support was used as the substrate for a nail hardening product in a chamber (1.43 m^3) under two conditions: "Typical:" 70 ºF, 1 air change/hour; "Elevated:" 80 ºF, 0.3 air changes per

hour.[111] Formaldehyde concentrations were measured at 5-minute intervals in the chamber air over a 10.5 hour period. The nail hardener (15 mg/cm^2) was painted on 70 cm^2 of the surface of the substrate (>7 times the total surface of nails on the on a person's 10 fingers, assuming ~1 cm^2/nail). The peak chamber air concentrations (5-minute samples) were 0.15-0.6 ppm under the "Typical" conditions and 0.2 – 0.24 ppm under the "Elevated" conditions. The peak concentrations measured in the chamber in this study are not directly comparable to the OSHA/ACGIH/WHO standards and guidelines, because they are not estimates of the concentrations of formaldehyde in the breathing zones of a customer or manicurist over relevant exposure durations. In any case, the 5-minute peak concentrations in the chamber were all about an order of magnitude less than the 15-min STEL-TWA of 2 ppm.

Formaldehyde Exposure during Use of Hair Smoothing Products

Air samples during use of hair smoothing products were measured in six separate studies. The results are summarized below and in Table 12.

Oregon OSHA and Center for Research in Occupational Toxicology (CROET) collected 15 air samples from seven beauty salons during the use of a "formaldehyde-free" hair-smoothing product.[11] They used DNPH-treated silica gel absorption tubes (SKC 226-119) and high-flow pumps, and analyzed the samples using NIOSH method 2016, which is comparable to U.S. EPA method TO-11. The concentrations of formaldehyde at the stylists' workstations ranged from **0.074 to 1.88 ppm** (median = 0.34 ppm; mean = 0.62 ppm; SD = 0.59 ppm) during sampling/exposure periods ranging from **6 to 48 minutes** (median = 19 minutes; mean = 23 minutes; SD = 12 minutes):

- 4 samples (ranging from 1.26 ppm for 34 minutes to 1.88 ppm for 26 minutes) exceeded the U.S. NAC AEGL-1 (0.9 ppm for ≥10 min).[102]
- 9 samples (0.303 to 1.88 ppm) exceeded the ACGIH TLV®-Ceiling (0.3 ppm).[107]
- All 3 samples collected for ≥30 minutes (1.26 ppm for 34 minutes, 0.34 ppm for 47 minutes, and 1.35 ppm for 48 minutes) exceeded the WHO 30-minute guideline (0.08 ppm).[108]

Further, 2 of 24 area samples collected during the procedures (**0.319 and 0.471 ppm**) exceeded the TLV®-C, and 10 of 12 area samples collected for ~30 minutes or more (eg, 0.226 ppm for 26 minutes and 0.255 ppm for 97 minutes) exceeded the WHO guideline.

Exponent® collected two 30-minute background air samples in a salon before the use of a hair smoothing product, and duplicate samples in the stylist's breathing zone, the customer's breathing zone, and within 3 feet of the customer's location during the application of the product.[112] They used U.S. EPA method TO-11 to collect and analyze the samples. The background formaldehyde concentrations were 0.024 and 0.025 ppm. The concentrations in the samples collected during the procedure ranged from **0.170 ppm for 141 minutes to 0.269 ppm for 95 minutes**. All of these concentrations were from 57% to 90% of the ACGIH TLV®-C (0.3 ppm), and all exceeded the WHO 30-minute guideline (0.08 ppm).

The Tennessee Occupational Safety and Health Administration (Tennessee OSHA) conducted an inspection of a salon, including the collection and analysis of air samples.[113] They used DNPH-treated silica gel absorption tubes (XAD-2) and high-flow pumps (SKC AirChek® 2000) to collect, apparently, one air sample every 15 minutes for 75 minutes during the use of the product. The analytical method was not specified. The 15-minute concentrations ranged from **0.3 to 1.07 ppm**. One of these values is equal to the TLV®-C (0.3 ppm), and the 4 others exceeded the TLV®-C (0.3 ppm) by up to nearly 4-fold. The highest value (1.07 ppm) exceeds the U.S. NAC AEGL-1 (0.9 ppm). In addition, the 75-minute TWA calculated from the reported series of 15-minute concentrations is 0.558 ppm, which is approximately 7-times greater than the WHO 30-minute guideline (0.08 ppm).

The Professional Keratin Smoothing Council (PKSC) submitted the results of the analysis of 15-minute air samples collected during the blow-drying or flat-ironing steps of 4 hair-smoothing treatments.[13,114] They used Sep-Pak® DNPH-Silica Cartridges to collect the samples. No further details were provided about the methodology. Formaldehyde was not detected (reporting limit 0.0082 ppm) in one of the samples collected during blow drying, and was not included in the PKSC summary table, presumably because of technical difficulties encountered with this sample. The 15-minute concentrations in the 7 remaining samples ranged from **0.761 to 1.71 ppm**. None of

these samples exceeded the 15-minute STEL-TWA. However, all of the samples exceeded the ACGIH TLV®-C (0.3 ppm) by 2.5 to 5.7-fold, and all but one of them exceeded the U.S. NAC AEGL-1 (0.9 ppm) by 1.3 to 1.9 fold. TWAs (30-minute) calculated from each complete 15-minute sample pairs (ie, blow drying plus flat ironing) ranged from 0.996 to 1.69 ppm, exceeding the WHO 30-minute guideline (0.08 ppm) by 12 to 21-times.

The PKSC submitted the results of air samples collected to estimate the stylist's and customer's inhalation exposures in a beauty salon during hair-smoothing treatments conducted on two separate occasions.[13,115] They used Sep-Pak® DNPH-Silica Cartridges to collect the samples. No further details were provided. The results ranged from **0.189 ppm for 117 minutes to 0.395 ppm for 86 minutes**. The concentrations in two of the samples (customer exposure to 0.355 ppm for 117 minutes; stylist exposure to 0.395 ppm for 86 minutes) exceeded the ACGIH TLV®-C (0.3 ppm). All of the air samples exceeded the WHO 30-minute guideline (0.08 ppm) by 2.4 to 5 times.

In another study, Exponent® collected 63 air samples at 6 salons where hair-smoothing treatments were performed.[116,117] These included 6 area (background) samples collected before any hair-smoothing procedures were conducted, and 35 samples collected in the stylists' breathing zones during a total of 9 treatments. An additional 22 area samples were collected in the salons within 5 feet of the stylists during and after the procedures. They used DNPH-treated silica gel absorption tubes (SKC 226-119) and followed NIOSH method 2016 to collect and analyze the samples. Following is a summary of the results:

- Concentrations in the 6 background samples ranged from 0.0068 to 0.032 ppm.

- Concentrations in the other 22 area samples ranged from <0.005 ppm for 45 minutes to 0.14 ppm for 73 minutes. The 3 highest area concentrations (ranging from 0.084 ppm for 69 minutes to 0.14 ppm for 73 minutes) were collected during the treatments, and exceeded the WHO 30-minute guideline (0.08 ppm).

- Calculated 8-hour TWAs ranged from 0.02 ppm to 0.08 ppm. The highest of these is equal to the WHO 30-minute guideline.

- Concentrations in 9 samples collected in the breathing zones during the procedures (including application of the product, blow drying and flat ironing) ranged from 0.11 ppm for 63 minutes to 0.33 ppm for 73 minutes. The highest concentration (0.33 ppm) exceeded the ACGIH TLV®-C (0.3 ppm), and all of them exceeded the WHO 30-minute guideline (0.08 ppm) by up to 4 fold.

- Concentrations in the 26 samples collected in the breathing zones during each of the separate steps the procedures ranged from **0.041 ppm for 43 minutes** (during flat ironing) to **0.76 ppm for 17 minutes** (during blow drying). The 4 highest concentrations (ranging from 0.66 for 20 minutes to 0.76 ppm for 17 minutes) were 73% to 84% of the U.S. NAC AEGL-1 (0.9 ppm). Concentrations in 9 of the 26 samples (ranging from 0.31 ppm for 32 minutes to 0.76 for 17 minutes) exceeded the ACGIH TLV®-C (0.3 ppm) by up to 2.5 fold. Concentrations in 6 of the 10 samples collected for 30 minutes or more during each step of the treatments (ranging from 0.084 ppm for 31 minutes to 0.31 ppm for 32 minutes) exceeded the WHO 30-minute guideline (0.08 ppm) by up to 4 times.

ChemRisk collected air samples at a salon during 4 consecutive keratin hair smoothing treatments performed by a licensed cosmetologist (stylist) on 4 separate human hair wigs mounted on mannequin heads over a 6-hour period.[118] Four different hair-smoothing products were used, in random order, during this 1-day study. The mean aqueous formaldehyde concentration was below the limit of detection (LOD <5 x 10^{-7}% w/w) in one product and 3%, 8.3% and 11.5% (w/w) in the others, as measured using a modified NIOSH 3500 method. Background air samples were collected in the stylist's breathing zone immediately before each treatment. Treatment-duration and task-duration samples were collected in the stylist's and mannequin's breathing zones, in areas representing the breathing zones of potential bystanders, and in the salon's reception area. The samples were collected on DNPH-treated silica gel absorption tubes (SKC 226-119) using sample pumps (SKC AirChek® 52) with low-flow adaptors. All of the samples were analyzed using a modified NIOSH 2016 method coupled with high performance liquid chromatography (HPLC) and ultraviolet (UV) detection. Following is a summary of the results:

- The concentrations of formaldehyde in the air samples collected during the treatments were directly related to the concentrations measured in the bulk samples.

- The mean concentrations in the treatment-duration breathing-zone samples for the three products containing measurable concentrations of aqueous formaldehyde ranged from **0.11 ppm for 82-84 minutes** to **1.17 for 56-57 minutes**. The concentrations in 4 of these 16 samples (ranging from 1.13 ppm to 1.21 ppm) exceeded the U.S. NAC AEGL-1 (0.9 ppm), and the concentrations in 8 of them (ranging from 0.58 ppm to 1.21 ppm) exceeded the ACGIH TLV®-C (0.3 ppm) by up to 4 fold. The concentrations in all 16 of these samples (ranging from 0.09 ppm to 1.21 ppm) exceeded the WHO 30-minute guideline (0.08 ppm) by up to 15 times.

- The highest mean concentrations in the treatment-duration samples collected 6-10 meters from the stylist were 0.37 ppm for 51 minutes and 0.52 ppm for 56 minutes. These values exceed both the ACGIH TLV®-C (0.3 ppm) and the WHO 30-minute guideline (0.08 ppm).

- The highest mean concentrations in duplicate samples collected in the breathing-zones during the blow-drying step (task) of the treatments were 2.35 ppm and 3.47 ppm for 10 minutes. The corresponding TWAs of the mean concentrations reported for the blow-drying and flat-ironing steps, combined, approached the OSHA 15-minute STEL-TWA (2 ppm) in the stylist's breathing zone (1.65 ppm for 23 minutes) and exceeded this standard in the mannequin's breathing zone (2.1 ppm for 23 minutes).

- ChemRisk estimated 8-hour TWA concentrations over all 4 treatments conducted sequentially over the 6-hour period. The 8-hour TWAs ranged from 0.25 ppm 6-10 meters from the stylist to 0.46 ppm in the stylist's breathing zone. None of the 8-hour TWAs exceeded the OSHA PEL-TWA (0.75 ppm). However, they approached the OSHA AL-TWA (0.5 ppm) by up to 92%, and they all exceeded the OSHA Threshold-TWA (0.1 ppm).

Simulated Use; Calculated Formaldehyde Levels

Berkeley Analytical placed 0.0946 grams of a hair smoothing product in a glass Petri dish, placed the dish in a small-scale, ventilated environmental chamber (0.067 m^3), and followed ASTM D 5116 procedures for measuring organic emissions from indoor materials and products.[119,120] They collected three consecutive 1-hour air samples from the chamber (1 air change/hour), at room temperature (73.4 ºF), using Sep-Pak XPoSure samplers. They reported emissions factors for formaldehyde ranging from 1,020 µg/gram-hour for the first hour to 1,670 µg/gram-hour for the third hour. Indoor Environmental Engineering calculated formaldehyde concentrations in a hypothetical hair salon (240 ft^2; 8-ft ceiling) from single 90-minute emissions of formaldehyde from the hair smoothing product. They conservatively assumed a 1,020 µg/gram-hour emission rate at room temperature, likely underestimating the emissions during actual use.[34] The emission rates are most probably much higher when the product is heated (eg, during blow-drying and flat-ironing). They modeled TWA exposure concentrations for the customer (110 minutes) and the stylist (8 hours), assuming 3 outdoor air ventilation rates (0.13 to 0.6 ft^3/min-ft^2) and three different amounts of the product applied the customer's hair (12.6 to 37.8 grams). The amounts were selected from recommendations provided in the manufacturer's training video for using the product on short, medium and long hair.

The 110-minute formaldehyde concentrations ranged from 0.033 ppm (12.6 grams product; 0.6 ft^3/min-ft^2) to 0.269 ppm (37.8 grams product; 0.6 ft^3/min-ft^2). Two of the three 110-minute estimates assuming 25.2 grams of product (0.096 to 0.18 ppm at 0.38 and 0.13 ft^3/min-ft^2, respectively) and all of the estimates assuming 37.8 grams (0.098 to 0.269 ppm), exceeded the WHO 30-minute guideline (0.08 ppm). The highest estimate (0.269 ppm) was about 90% of the ACGIH TLV®-C (0.3 ppm). In addition, the highest estimated 8-hour TWA was 0.108 ppm (37.8 grams; 0.13 ft^3/min-ft^2), which exceeds the U.S. OSHA 8-hour Threshold-TWA (0.1 ppm).

DISCUSSION

Based on the available data, the CIR Expert Panel (Panel) considered that formaldehyde and methylene glycol are safe for use in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should the formalin† concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. Additionally, formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardening products. However, formaldehyde and methylene glycol

are unsafe in the present practices of use and concentration in hair smoothing products. This is a final amended safety assessment.

The Panel emphasized that a large body of data has demonstrated that formaldehyde gas exposure can cause nasopharyngeal cancers (NPCs). While debate is ongoing regarding the dose-response relationship for the induction of NPCs, the Panel continues to believe that formaldehyde gas can produce such cancers at high doses. Epidemiology studies have suggested a weak association between exposure to formaldehyde and lymphohematopoietic (LHP) cancers. The reported association of formaldehyde exposure with LHP cancers is just that, an association, and the Panel is not aware of a plausible mechanism by which formaldehyde exposure could be causally linked to LHP tumors. Based on the testicular effects observed in rats exposed to formaldehyde, the CIR Panel acknowledged that a mechanism of action by which formaldehyde might cause the testicular effects is not known and these effects may be secondary to local effects, such as irritation and inflammation, and stress at high doses.

The Nail Manufacturers Council, the Professional Keratin Smoothing Council (PKSC), the American Chemistry Council, the Personal Care Products Council, and one individual provided new data and comments. After reviewing the comments and additional data, the Panel determined that the data were sufficient to support the safety of these ingredients in nail hardeners.

The additional data confirmed the current use concentration of formaldehyde/methylene glycol in the 1 – 2% range in nail hardeners (one product tested had a value of 2.2%). Given the rapid reaction on the nail surface and the use of nail hardeners at room temperature, the Panel did not consider that formaldehyde/methylene glycol at 1 – 2% in nail hardeners would present a risk of sensory irritation to the eyes, nose, or throat of users. The Panel noted that the present practices of use of nail hardeners include instructions that cautioned users to limit application of the material to the top surface of the nail only, to allow it to dry fully, and to not get the material on the skin.

The Panel noted that the OSHA occupational safety limits include a time-weighted average permissible exposure level of 0.75 ppm for a work day and a short-term exposure limit of 2 ppm. Air monitoring and medical exams are triggered when formaldehyde concentrations in workplace air exceed 0.5 ppm averaged over an 8-hour shift, and ventilation and training when concentrations exceed 0.75 ppm averaged over 8 hours or 2 ppm averaged over 15 minutes. Formaldehyde must be listed in a company's MSDS if formaldehyde is present at 0.1% or more, or if the product releases formaldehyde gas above 0.1 ppm.

While such requirements are mandated by OSHA, the Panel remained concerned about adverse reports of sensory irritation consistent with measured air levels of formaldehyde in salons using hair smoothing products (a.k.a. hair straightening products) containing formaldehyde/methylene glycol. Because the use of these products involves the application of heat, the Panel remained concerned about the amounts of formaldehyde vapor that can be released. The reported levels of formaldehyde gas measured in the air around salon work stations can be below occupational exposure standards and guidelines, but also may be at or only marginally below occupational exposure standards and above indoor air quality guidelines. The Panel noted that the PKSC suggested that these products are manufactured with the expectation that adequate ventilation would be provided during use; ie, safe use requires adequate ventilation. OSHA and other inspections, however, reported a range of ventilation controls, many of which were inadequate.

Additional use studies were done on behalf of the PKSC to demonstrate that exposure to formaldehyde could be minimized with proper procedures and use of personal ventilation devices. The Panel acknowledged that formaldehyde levels in air samples were lower in the most recent data compared to data submitted earlier, but proper safety procedures, including positioning of personal ventilation devices, were not uniformly followed.
In concept, therefore, limits on the concentration of formaldehyde/methylene glycol in hair smoothing products, control of the amount of product applied, use of lower temperatures, and approaches to mandate adequate ventilation, are among the steps that could be taken to ensure that these products would be used safely in the future. However, in the present practices of use and concentration (on the order of 10% formaldehyde/methylene glycol, blow drying and heating up to 450 ^{o}F with a flat iron, inadequate ventilation, resulting in many reports of adverse effects), hair smoothing products containing formaldehyde and methylene glycol are unsafe.

The Panel adopted a suggestion to include limits for formalin concentration because formalin is what formulators actually add to cosmetic products. Formalin is an aqueous solution typically containing 37% (w/w) formaldehyde.

Formalin contains both formaldehyde and methylene glycol because of the equilibrium between formaldehyde and methylene glycol in aqueous solution.

While retaining the concept that formaldehyde and methylene glycol should be used only at the minimal effective concentration, the Panel stated that in no case should the formalin concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. While these numbers appear to be disparate, they are not. The value of 0.074 % (w/w) of formaldehyde simply reflects that formalin typically contains 37% formaldehyde (0.2% (w/w) formalin multiplied by 0.37 = 0.074% (w/w) formaldehyde). The value of 0.118% (w/w) for methylene glycol simply reflects the difference in molecular weight between formaldehyde and methylene glycol.

The Panel recognized that the most commonly used analytical methods for the detection and measurement of formaldehyde are not specific for non-hydrated formaldehyde, but can accurately indicate the presence and quantity of formaldehyde equivalents. A typical method, for example, can detect formaldehyde equivalents in a formulation, or released into the air, via a two stage process: 1) derivatization of a sample with a hydrazine (which reacts with formaldehyde or methylene glycol, in a formulation sample or in an air sample), and 2) detection and measurement of the resultant hydrazone (ie, the reaction product of the hydrazine and formaldehyde) with a diode array, after separation on a column (eg, high performance liquid chromatography separation followed by ultraviolet/visible light (UV/Vis) detection).

While other formaldehyde/methylene analytical techniques are known, such as nuclear magnetic resonance (NMR) spectrometry, the Panel found that the methodology used by OSHA and FDA produces consistent results that are directly and meaningfully comparable to regulatory standards and guidelines. As the conditions under which formaldehyde is measured in products can affect the results, the method used to measure formaldehyde in products should be appropriate for the conditions, such as temperature and pH, under which the product is used.

The Panel reasoned that the term “formaldehyde equivalents” best captures the idea that methylene glycol is continuously converted to formaldehyde, and vice versa, even at equilibrium, which can be easily shifted by heating, drying, and other conditions to increase the amount of formaldehyde. Any other term would not distinguish the rapid, reversible formaldehyde/methylene glycol equilibrium from the slow, irreversible release of formaldehyde resulting from so-called formaldehyde releaser preservatives (eg, diazolidinyl urea). Formaldehyde releaser preservatives are not addressed in this safety assessment. The formaldehyde releasers may continue to be safely used in cosmetics at the levels established in their individual CIR safety assessments.

CONCLUSION

The CIR Expert Panel concluded that formaldehyde and methylene glycol are safe for use in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should the formalin† concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. Additionally, formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardening products. However, formaldehyde and methylene glycol are unsafe in the present practices of use and concentration in hair smoothing products (a.k.a. hair straightening products).

†Formalin is an aqueous solution wherein formaldehyde (gas) has been added to water to a saturation point, which is typically 37% formaldehyde (w/w). Because of the equilibrium between formaldehyde and methylene glycol in aqueous solution, formalin is composed of both formaldehyde and methylene glycol.

TABLES AND FIGURE

Table 1. Frequency and Concentration of Use Table Formaldehyde, Formalin and Methylene glycol

	No. of Uses (2010) [15]	*Conc. of Use (2011) (%)*[16-19]	*No. of Uses (2010)* [15]	*Conc. of Use (2011) (%)*[16-19]
	formaldehyde (and formaldehyde solution (formalin))[a]		**methylene glycol**[b]	
Totals[c]	**77**	**0.04 – 2.2**	**NR**[d]	**0.8-3.5**
Duration of Use				
Leave-On	*33*	*0.056 – 2.2*	*NR*	*0.8-3.5*
Rinse Off	*44*	*0.04*	*NR*	*NR*
Product Category				
Bath oils, tablets and salts	1	NR	NR	NR
Bubble baths	1	NR	NR	NR
Hair conditioner	16	NR	NR	NR
Permanent waves	2	NR	NR	NR
Shampoos (non-coloring)	13	0.04	NR	NR
Hair grooming aids	6	0.056	NR	NR
Other hair preparation	7	NR	NR	NR
Other hair coloring preparation	2	NR	NR	NR
Manicure basecoats and undercoats	2	NR	NR	NR
Nail Hardeners	6	<0.5-2.2	NR	<0.8-3.5
Bath soaps and detergents	7	NR	NR	NR
Other personal care products	2	NR	NR	NR
Shaving cream	1	NR	NR	NR
Depilatories	2	NR	NR	NR
Body and hand (excl. shave prep.)	2	NR	NR	NR
Skin moisturizing preparations	1	NR	NR	NR
Paste masks (mud packs)	1	NR	NR	NR
Other skin care preparations	5	NR	NR	NR

[a]Reported as formaldehyde
[b]Calculated as methylene glycol
[c]Totals = Rinse-off + Leave-on Product Uses
[d]NR = Not Reported

Table 2. List of ingredients in Brazilian Blowout from the Brazilian Blowout MSDS dated 10/26/10

Ingredient	Percentage
Water	≤85%
Methylene glycol	<5%
Behenyl methylammonium methosulfate/N-hexadecanol/butylene glycol	≤5%
Isoparaffin	≤3%
Cetrimonium chloride	≤2%
Petrolatum	≤1%
Hypnea musciformis extract/Gellidiela acerosa extract/Sargassum filipendula extract/sorbitol	≤1%
Theobroma grandiflorum seed butter (cupuacu butter)	≤0.5%
Panthenol	≤0.25%
Hydrolyzed keratin	≤1%
Fragrance (parfum)	≤1%
Methylchloroisothiazolinone	≤0.1%
Methylisothiazolinone	≤0.1%

Table 3. Skin irritancy/sensitization studies of formaldehyde/methylene glycol in test animals

Species (n)	Concentrations; volume; duration	Results	Reference
		Multiple dose studies	
Hartley guinea pigs (n = 5/group)	1%, 3%, 10% formalin; 100 µl/d,10 days	Dose-dependent increase in skin-fold thickness was observed, with shorter latencies at higher concentrations; e.g., erythema on treatment day 6 for 1%, day 5 for 3%, and day 2 for 10% formalin.	121
English smooth-haired guinea pigs (n = 4 or 8 males/group)	**Induction, Dermal:** (a) 100% formalin; 100 µl/d, 2 days (b) 50% formalin w/50% adjuvant; 200 µl/d, 1 day (c) 0.13, 1.3, 13, 54, 100% formalin; 25 µl/d, 1day **Induction, Inhalation:** (a) 6, 10 ppm; 6 h/d, 5 days (b) 10 ppm; 8h/d, 5 days **Challenge, Dermal:** 5.4% formalin; 20 µl/d, 1 day	Dose-dependent contact sensitivity was observed in all of the animals exposed dermally during the induction phase and challenged on day 7 of the experiment. Two of the 4 guinea pigs challenged on day 31exhibited signs of contact sensitivity (mild) after inhalation of 10 ppm, 8 h/d for 5 days. No contact sensitivity was observed in the other inhalation groups or in any of the control groups.	122
Wistar and BN rats (n = 4 females/group)	2.5, 5, 10% formalin in 4:1 acetone/raffinated olive oil; 75 µl/d, 3 days	Increase in the weights of the lymph nodes and dose-related increase in the proliferation of paracortical cells were observed in both strains in response to 5% and 10% formalin (1.9% and 3.7% formaldehyde equivalents) in a local lymph node assay (LLNA). No statistically significant increase in serum IgE concentrations were observed in BN rats (high IgE responders) in a parallel experiment.	123

Table 4. Genotoxicity inhalation studies of formaldehyde/methylene glycol in test animals

Species (n)	Concentrations; duration	Results	Reference
		Multiple dose studies	
Sprague-Dawley rats (n = 10 males/group)	0, 5, 10 ppm; 6 h/d, 5 d/wk, 2 weeks	Statistically significant, dose-dependent increases in Comet Olive tail moments were observed in blood lymphocytes, liver cells, and lung tissue. **Comment:** A critical review noted that formaldehyde-induced formation of DNA-protein crosslinks (DPCs) and DNA-DNA crosslinks (DDCs) in the cells should have decreased, rather than increased, DNA migration in these assays.	52,53,124
F344/DuCrl rats (n = 6 males/group)	0, 0.5, 1, 2, 6, 10, 15 ppm; 6 h/d, 5 d/wk, 4 weeks	No statistically significant differences were found between the exposed and negative control groups in Comet tail moment or intensity, or sister chromatid exchange (SCE) and micronuclei (MN) frequencies in peripheral blood samples. The results of the Comet assay were negative even after irradiating the blood samples to increase sensitivity for detecting DNA-protein crosslinks (DPCs). Statistically significant effects were observed in the positive controls (ie, orally administered methyl methanesulfonate or cyclophosphamide), demonstrating the sensitivity of the tests.	54

Table 5. Genotoxicity inhalation studies of formaldehyde/methylene glycol in human subjects

Subjects (n)	Concentrations; duration	Results	Reference
(a) Workers at a formaldehyde manufacturing plant (n = 10) (b) Waiters (n = 16) (c) Students (n = 23)	(a) 0.80 ± 0.23 ppm 8-h TWA, 1.38 ppm Ceiling; average 8.6 years, range 1 to 15 years (b) 0.09 ± 0.05 ppm 5-h TWA; 12 weeks (c) 0.009 ppm 8-h TWA; not reported	Statistically significant increases in mononucleus (MN) and sister chromatid exchange (SCE) frequencies were found in nasal mucosa cells of the workers compared to student controls. The MN and SCE frequencies in nasal mucosa cells from the waiters were not different from the controls.	58
(a) Workers at two plywood factories (n = 151) (b) Workers at a machine manufacturing facility (n = 112)	(a) 0.08-6.42 ppm TWA (b) <0.008 ppm TWA	Exposure-related, statistically significant increases were found in Comet Olive tail moments and lengths and MN frequencies in lymphocytes from the plywood-manufacturing workers compared to controls (ie, machine-manufacturing workers).	59
(a) Pathology and anatomy laboratory workers (n = 59) (b) Individuals matched for gender, age, smoking (n = 37)	(a) 2 ppm 15-min TWA (range <0.1-20.4 ppm), 0.1 ppm 8-h TWA (range <0.1-0.7 ppm) (b) Not determined	No increase in DNA damage was observed in the lymphocytes of the pathologists/anatomists after one day of exposure, using a chemiluminescence microplate assay. Statistically significant increases in mono- and bi-nucleated lymphocyte frequencies were found in pathologists/anatomists compared to the controls using cytokinesis-blocked micronucleus (CBMN) & fluorescence in-situ hybridization (FISH) assay. No statistically significant differences were observed in the frequencies of centromeric or acentromeric MN. The authors suggested that the results are attributable to an aneugenic rather than clastogenic mode of action.	56
Volunteers (n = 10 women, 11 men)	0.15 to 0.5 ppm (concentration randomly assigned to each subject each day) w/ four 15-min 1-ppm peaks & three 15-min bicycling exercises during each exposure; 4 h/d, 10 days (Cumulative: 13.5 ppm-hour, 10 days)	A statistically significant decrease in MN frequency was observed in buccal mucosal cells collected 21days after the end of the exposure period compared with the control samples collected from the subjects 1 week before exposure. MN frequencies in samples collected immediately, 7 days, or 14 days after exposure did not differ from the control samples.	57
(a) Hospital pathological anatomy laboratory workers (n = 30) (b) Matched administrative personnel in the hospitals (n = 30)	(a) 0.44 ± 0.08 ppm mean 8-h TWA (range 0.04−1.58 ppm) (b) Not determined	Statistically significant increase in MN and SCE frequencies and Comet tail lengths were observed in lymphocytes collected from laboratory workers (employment duration averaging 11±7 years, ranging from 0.5 to 27 years) compared with controls. A statistically significant, positive correlation between exposure and both MN frequency and Comet tail length was found in the lymphocytes of the laboratory workers.	55

Table 5. Genotoxicity inhalation studies of formaldehyde/methylene glycol in human subjects

Subjects (n)	Concentrations; duration	Results	Reference
Healthy, non-smoking male volunteers (n = 41); 12 groups (n = 2 to 4/group)	Each subject exposed once to 0, 0.3 w/ four 15-min 0.6-ppm peaks, 0.4 w/ four 0.8 ppm peaks, and 0.5 ppm; 4 h/d, 5 days (subjects performed four 15-min bicycling exercises during each exposure period, including 2 during peaks)	A small but statistically significant increase in Comet tail intensity was observed in lymphocytes after the 5-day exposure period compared to the values determined before exposure. The authors concluded that this finding was not biologically significant, because formaldehyde-induced DPCs would be expected to decrease, not increase, Comet tail intensity. No statistically significant differences were found in Comet tail moments or SCE and MN frequencies in lymphocytes, MN frequencies in nasal epithelial cells, or biologically significant changes in gene expression in nasal biopsies collected after exposure compared with those collected before exposure.	60

Table 6. Nasal tissue studies of formaldehyde/methylene glycol in test animals

Species (n)	Concentrations; duration(s)	Results	Reference
		Multiple dose studies	
F344 CDF(F344)/CrlBr rats (n = 6 males/group)	0, 0.7, 2, 6, 10, 15 ppm; 6 h/d, 5d/wk, 1, 4, 9, 42 days (short-term) or 3, 6, 12, 18, 24 months (long-term)	Statistically significant increases in nasal cell proliferation were found only at ≥6.0 ppm (short-term) and ≥10.0 ppm (long-term). **Comment:** The authors and their co-workers interpreted these data to indicate that the dose-response curve is non-monotonic (ie, highly-nonlinear), because cell proliferation was diminished at lower doses and elevated at the higher, cytotoxic doses. This view is consistent with the hypothesis that formaldehyde exposure must be sufficient to stimulate regenerative cell proliferation, thereby increasing the likelihood that mutations that would otherwise be repaired will become permanent, and could then lead to tumor formation. Others have disputed this interpretation, because of the considerable uncertainty and variability in the data.	64-66,125,126
F344/CrlBR (n = 8 males/group)	0, 0.7, 2, 6, 10, 15 ppm; 6 h/d, 1,4,13 weeks	Transcriptional and histological changes at ≥6 ppm corresponded to doses for which pharmacokinetic modeling predicted substantial decrease in free glutathione (GSH) and increase in methylene glycol in nasal tissue. **Comment:** The authors concluded that formaldehyde exposure below 1 to 2 ppm in air would not perturb formaldehyde homeostasis in epithelial cells or elevate the risk of cancer in any tissue, consistent with a threshold for tissue responses and carcinogenicity.	127
F-344/NCrl rats (n = 5 males/group)	0, 0.7, 2, 6, 10, 15 ppm; 6 h/d, 13 weeks	Mutation levels were not elevated above the low spontaneous background levels, even in the rats exposed to 15 ppm formaldehyde, and showed no dose-related increases. Bromodeoxyuridine (BrdU) incorporation increased with dose and was statistically significantly elevated in the rats exposed to either 10 ppm or 15 ppm formaldehyde. **Comment:** The results support the view that cytotoxicity-induced cell proliferation (CICP) plays a pivotal role in the formation of NPCs in rats and, thus, formaldehyde-induced carcinogenicity is largely a threshold effect.	62
F344 (n = 10 to 30 males/group)	0.7, 2, 5.8, 9.1, 5.2 ppm; 6 hours	Formation of endogenous DNA adducts did not change in a dose-related manner in nasal epithelium. In contrast, the formation of exogenous adducts was highly non-linear, increasing 286-fold with a 21.7-fold increase in the exposure concentration. About 1% and 3% of the total number of adducts (endogenous plus exogenous) were exogenous adducts at 0.7 ppm and 2 ppm, respectively.	61
Cynomolgus macaques (n = 8 males)	1.9, 6.1 ppm; 6 h/d, 2 days	Endogenous and exogenous DNA adducts were detected in the nasal tissues at both exposure concentrations. **Comment:** The monkeys exposed to 6.1 ppm exhibited greater numbers of endogenous adducts and lower numbers of exogenous adducts in nasal tissues, compared with rats exposed to 5.8 ppm. Based on these results, the authors' suggested that the percentage of exogenous adducts would be lower in primates than in rats at equivalent exposure concentrations.	63,68

Table 7. Epidemiological studies of formaldehyde/methylene glycol and nasopharyngeal cancers

Study design; subjects (n)	Exposure metrics	Results	Reference
Retrospective Cohort mortality; Men employed after 1937 at six British factories where formaldehyde was produced or used, followed through 2000 (n = 14,014), compared with the general population	(a) Background: <0.1 ppm (b) Low: 0.1 to 0.5 ppm (c) Moderate: 0.6 to 2.0 ppm (d) High: >2.0 ppm	One nasopharyngeal cancer (NPC) mortality was identified among the factory workers, which included 3,991 workers exposed to >2 ppm. The single NPC case worked in a job with low exposure; two NPC cases were expected. Two sinonasal cancer deaths were identified, both having high exposures; 2.3 cases were expected. Fifteen pharyngeal tumor deaths were observed; 9.7 cases were expected.	128,129
Retrospective cohort mortality; Textile workers (82% female) employed after 1955 at 3 U.S. garment facilities, followed through 1998 (n = 11,039), compared with U.S. and local populations	(a) 8-h TWA (across all departments and plants) mean 0.15 ppm, range 0.09 to 0.2 ppm (b) Age at first exposure: median 26.2, range 15.2–79.8 years (c) Duration: <3, 3 to 9, ≥10 years (d) Time since first exposure: <10, 10 to 19, ≥20 years (e) Year first exposed: <1963, 1963 to 1970, ≥ 1971	No cases of NPC or nasal cancers were found; 1 case was expected.	129,130
Retrospective cohort mortality; Workers first employed before 1966 at 10 formaldehyde manufacturing plants (NCI cohort; Plants #1-#10) and followed through 1994 (n = 25,619)	(a) Average intensity: 0, ≤0.5, 0.5 to <1.0, ≥1.0 ppm (b) Cumulative: 0, >0 to <1.5, 1.5 to <5.5, ≥5.5 ppm-years (c) Duration: 0, >0 to <5, 5 to <15, ≥15 years (d) Ever vs. never exposed (e) Peak: 0, >0 to <2.0, 2.0 to <4.0, or ≥ 4.0 ppm	Nine deaths from NPC were identified in this cohort, including 7 classified as "ever exposed" and 2 as "never exposed." The highest relative risk (RR) estimates were 4.14 for ≥5.5 ppm-years cumulative exposure and 4.18 for ≥15 years exposure duration. Although confidence limits were not specified, the authors' footnotes indicate that they included 1 for these RR estimates. However, statistically significant dose-response trends were apparent for both peak exposure and cumulative exposure. **Comment:** Other researchers have demonstrated critical weaknesses in the model used in this study, including instability problems related to the data from Plant #1.	91,131-133
Retrospective cohort mortality; Workers employed in a plastics-manufacturing plant in Wallingford CT (NCI cohort; Plant #1) from 1941 to 1984 followed through 1998 (n = 7,328) compared with general population of 2 CT counties	(a) Average intensity: 0 to <0.03, 0.03 to 0.159, ≥0.16 (b) Cumulative: 0 to <0.004, 0.004 to 0.219, ≥0.22 ppm-years (c) Duration: 0 to <1, 1 to 9, ≥ 10 years (d) Duration exposed to >0.2 ppm: 0, 0 to <1, 1 to 9, ≥10 years (e) Short-term (<1 year) vs. long-term (>1 year) worker	Seven NPC cases were identified in this cohort, including 6 cases specifically identified as NPC and 1 case of pharyngeal cancer that was not identified specifically as NPC in the records. Several formaldehyde exposure metrics were associated with NPC for Plant #1, including "ever exposed," exposure duration ≥10 years, and cumulative exposure ≥0.22 ppm-years. The standardized mortality ratios (SMRs) estimated for these metrics were 6.03, 12.46, and 7.51, respectively, all with confidence limits >1. **Comment:** The authors suggested that their findings do not support a causal relationship between formaldehyde exposure and NPC mortality because elevated risks were seen in both short-term (<1 year; 4 cases) and long-term workers (3 cases), 5 NPC cases worked <5 years at the plant, the NPC cases among the long-term workers (>1 year) had relatively low average-intensity exposures (0.03-0.60 ppm), and the NPC deaths were concentrated among workers hired during 1947-1956.	134
Retrospective cohort mortality; Workers first employed before 1966 at 10 formaldehyde manufacturing plants (NCI cohort; Plants #1-#10) and followed through 1994 (n = 25,619	(a) Average intensity: <1.046, 1.046 to 1.177, ≥1.178 ppm (b) Cumulative: <0.734, 0.734 to 10.150, ≥10.151 ppm-years (c) Duration: <0.617, 0.617 to 2.258, ≥2.259 years (d) Highest peak: >0 to 1.9, 2.0 to 3.9, ≥4.0	Six of 10 NPC deaths (ie, identified specifically as NPC) in this cohort were associated specifically with employment at Plant #1, the remaining 4 cases distributed among 4 of the other 9 plants studied. A regional rate-based SMR of 10.32 (95% CI: 3.79-22.47) was estimated for exposed workers at Plant #1, compared to 0.65 (95% CI: 0.08 to 2.33) for exposed workers at Plants #2 through #10 combined. The statistically significant peak exposure-response relationship in the cohort was driven by excess NPC risk associated with the highest peak exposure category (≥4 ppm) at Plant #1. None of the exposure-response relationships for any of the four exposure metrics were statistically significant for Plants #2 through #10, combined. The authors concluded that the suggestion of a causal relationship between	135

Table 7. Epidemiological studies of formaldehyde/methylene glycol and nasopharyngeal cancers

Study design; subjects (n)	Exposure metrics	Results	Reference
	ppm	formaldehyde exposure and NPC mortality in previous studies was based entirely on anomalous findings at Plant #1.	
Retrospective cohort mortality; Workers employed in a plastics-manufacturing plant in Wallingford CT (NCI cohort; Plant #1) from 1941 to 1984 (n = 7,345) followed through 2003, nested case-control and comparison with general populations of U.S. and local counties	(a) Average intensity: 0 to <0.03, 0.03 to 0.159, ≥0.16 (b) Cumulative: 0 to <0.004, 0.004 to 0.219, ≥0.22 ppm-years (c) Duration: 0 to <1, 1 to 9, ≥10 ppm (d) Exposed vs. unexposed	SMRs of 4.43 (95% CI: 1.78-9.13) and 4.34 (95% CI: 1.74-8.94) were calculated for the 7 NPC mortalities among the exposed Plant #1 workers compared with local and U.S. rates, respectively. Four of the 7 NPC cases also held silver-smithing jobs, and 5 of the 7 NPC cases held silver-smithing or other metal-working jobs, and this type of work was relatively rare in the remaining study population. The authors noted possible exposures to several suspected risk factors for upper respiratory system cancer (eg, sulfuric acid mists, mineral acid, metal dusts and heat) associated with this type of work.	[136]
Nested case-control; Deceased embalmers and funeral directors (n = 6,808)	(a) Average intensity while embalming: 0, >0 to 1.4, >1.4 to 1.9, >1.9 ppm (b) Cumulative: 0, >0 to 4058, >4058 to 9253, >9253 ppm-hours (c) Duration in jobs involving embalming: 0, >0 to 20, >20 to 34, >34 years (d) Ever vs. never embalming (e) Lifetime 8-h TWA: 0, >0 to 0.1, >0.1 to 0.18, >0.18 ppm (f) Number of embalmings conducted: 0, >0 to 1422, >1422 to 9253, >9253 (g) Peak: 0, >0 to 7, >7 to 9.3, >9.3 ppm	Four cases of NPC were identified, only two of which had “ever embalmed” (Odds ratio = 0.1; 95% CI: 0.01-1.2). Exposure estimates for these 2 cases were indistinguishable from controls.	[85]

Table 8. Comparative tissue studies of formaldehyde/methylene glycol in test animals

Species (n)	Concentration(s); duration(s)	Results	Reference
		Multiple dose studies	
F344 (n = 30 males)	10 ppm; 6 h/d, 1 or 5 days	Exogenous formaldehyde-induced DNA monoadducts and DNA-DNA crosslinks (DDCs) were found exclusively in the nasal tissues after exposure. No exogenous products were detected in any other tissue even though, for example, the analytical method can detect ~3 monoadducts/10^9 deoxyguanosine (dG). This detection limit is ~30 times less than the endogenous monoadducts/10^9 dG measured in white blood cells (on-column detection limits ~240 and 60 amol for monoadducts and crosslinks, respectively). Endogenous products were found in all of the tissues examined, including blood and bone marrow. The levels of endogenous products were comparable across all tissues examined. The authors concluded: (1) Neither formaldehyde nor methylene glycol from formaldehyde reaches sites distant from the portal of entry, even when inhaled at high concentrations known to stimulate nasal epithelial cell proliferation and cause nasal tumors in rats. (2) Genotoxic effects of formaldehyde/methylene glycol are not plausible at sites distant from the portal of entry. (3) The idea that formaldehyde/methylene glycol transforms cells in the peripheral circulation or the nasal epithelium at the portal of entry, which can then migrate and incorporate into the bone marrow or other distant tissues to cause cancer, is not plausible.	137
F344 (n = 10 to 30 males/group)	0.7, 2, 5.8, 9.1, 15.2 ppm; 6 hours	Measurable numbers of endogenous adducts were found in both the nasal mucosa and bone marrow, and exogenous adducts in the nasal mucosa. No exogenous adducts were detected in the bone marrow (on-column detection limit ~20 amol).	61
Cynomolgus macaques (n = 8 males)	1.9, 6.1 ppm; 6 h/d, 2 days	Measurable numbers of endogenous and exogenous adducts were detected in the nasal tissues of both exposure groups, but only endogenous adducts in the bone marrow (on-column detection limit ~20 amol).	63

Table 9. Epidemiological studies of formaldehyde/methylene glycol and lymphohematopoietic cancers

Study design; subjects or studies (n)	Exposure concentration or metrics	Results	Reference
		Cohort, case-control and molecular studies	
Retrospective cohort mortality; Men employed after 1937 at six British factories where formaldehyde was produced or used, followed through 2000 (n = 14,014), compared with the general population	(a) Background: <0.1 ppm (b) Low: 0.1 to 0.5 ppm (c) Moderate: 0.6 to 2.0 ppm (d) High: >2.0 ppm	There were 31 leukemia deaths in this cohort, which included 3,991 workers exposed to >2 ppm; 34 cases were expected.	128,129
Retrospective cohort mortality; Textile workers (82% female) employed after 1955 at 3 U.S. garment facilities, followed through 1998 (n = 11,039), compared with U.S. and local populations	(a) 8-h TWA (across all departments and plants) mean 0.15 ppm, range 0.09 to 0.2 ppm (b) Age at first exposure: median 26.2, range 15.2–79.8 years (c) Duration: <3, 3 to 9, ≥10 years (d) Time since first exposure: <10, 10 to 19, ≥20 years (e) Year first exposed: <1963, 1963 to 1970, ≥ 1971	There were 59 leukemia cases in this cohort; 61 cases were expected.	129,130
Retrospective cohort	(a) Average intensity (8-h	This study reported and included 1,006 death certificates that a previous	90,138

Table 9. Epidemiological studies of formaldehyde/methylene glycol and lymphohematopoietic cancers

Study design; subjects or studies (n)	Exposure concentration or metrics	Results	Reference
mortality; Workers first employed before 1966 at 10 formaldehyde manufacturing plants (NCI cohort; Plants #1-#10) and followed through 2004 (n = 25,619), compared with U.S. population	TWA): 0, 0.1 to 0.4, 0.5 to <1, ≥1.0 ppm (b) Cumulative: 0, 0.1 to 1.4, 1.5 to 5.4, ≥5.5 ppm-years (c) Ever vs. never exposed (d) Peak: 0, 0.1 to 1.9, 2 to 4, ≥ 4.0 ppm (e) Peak frequency: hourly, daily, weekly, monthly	paper missed for this cohort. There were proportionally greater numbers of missing deaths among the un-exposed and low-exposed groups used as internal referents in the previous paper. There were 319 deaths from all LHP cancers (from a total of 13,951 deaths) in this cohort, including 286 "exposed" and 33 "non-exposed" cases. Based on U.S. mortality rates, neither of these groups showed statistically significant elevations in SMRs estimated for all LHP cancer, all leukemia, lymphatic leukemia, myeloid leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, or multiple myeloma. Statistically significant dose-response trends were reported for peak exposure and all LHP, all leukemia and Hodgkin's lymphoma deaths, as well as for average intensity of exposure and Hodgkin's lymphoma deaths. However, the relative risk (RR) for Hodgkin's lymphoma in workers with the highest average intensity was lower than for workers with lower average exposure. No statistically significant trends were found among the LHP cancers and peak frequency or cumulative exposures.	
Nested case-control mortality; Deceased embalmers and funeral directors (n = 6,808)	(a) Average intensity while embalming: 0, >0 to 1.4, >1.4 to 1.9, >1.9 ppm (b) Cumulative: 0, >0 to 4058, >4058 to 9253, >9253 ppm-hours (c) Duration in jobs involving embalming: 0, >0 to 20, >20 to 34, >34 years (d) Ever vs. never embalming (e) Lifetime 8-hour TWA: 0, >0 to 0.1, >0.1 to 0.18, >0.18 ppm (f) Number of embalmings: 0, >0 to 1422, >1422 to 9253, >9253 (g) Peak: 0, >0 to 7, >7 to 9.3, >9.3 ppm	There were 168 deaths attributable to LHP cancers in this cohort, including 99 lymphoid and 48 non-lymphoid cancers. Non-lymphoid cancers included 34 cases of myeloid leukemia. Statistically significant increases in risks of LHP cancers of non-lymphoid origin were found for several exposure metrics, including the highest levels of exposure for cumulative, TWA, and peak exposures, as well as for subjects who embalmed for >20 years. For myeloid leukemia, strong, statistically significant associations with exposure duration, number of embalmings performed, and cumulative exposure were found. Statistically-significant dose-response relationships were reported between myeloid leukemia deaths and both exposure duration and peak exposure. **Comment:** Several methodological issues have been identified for this study study. For example: (1) Myeloid leukemia cases among the study subjects were 50% more likely than controls to have begun employment in the funeral industry before 1942; This suggests that they belonged primarily to an older and earlier population than the controls and likely explains why they performed more embalmings (2) The single myeloid leukemia case in the control group yielded large, unstable confidence intervals; The odds ratios (ORs) were substantially reduced when the referent group included both the controls and the subjects performing <500 embalmings (3) The myeloid leukemia cases and controls had nearly identical mean estimated average, 8-h TWA, and peak exposures; The cases had higher estimated number of embalmings and cumulative exposure than the controls, which can be explained by their earlier first employment, younger age at hire, and longer average employment in the industry, compared with controls.	85,139-141
Molecular epidemiology of formaldehyde workers and frequency-matched controls in China (n = 43; 51 controls)	Median (10th-90th percentile): (a) Formaldehyde workers: 1.28 (0.63-2.51) ppm (b) Controls: 0.026 (0.0085-0.026) ppm	Statistically significant decreases were observed in mean red blood cell (RBC), white blood cell (WBC), granulocyte, and platelet counts in the subjects compared with the controls. Statistically significant increases were found in mean corpuscular volume (MCV) and in frequencies of chromosome 7 monosomy and chromosome 8 trisomy. No occupational co-exposures to benzene or other hemotoxic or genotoxic solvents were detected in this study. In a parallel experiment, statistically significant, dose-related decreases were observed in the number of colonies formed per plated cells from the subjects compared with controls. **Comment:** Numerous problems in this preliminary study have been identified. For example: (1) All of the blood counts in the exposed workers were within the reference range. (2) The frequencies of the aneuploidies reported were seen only after 14 days of in vitro incubation, were high for cells from both the workers	142-146

Table 9. Epidemiological studies of formaldehyde/methylene glycol and lymphohematopoietic cancers

Study design; subjects or studies (n)	Exposure concentration or metrics	Results	Reference
		and controls, and were not reported in either the factory workers or the controls in vivo. (3) The most frequent chromosome aberrations associated with myeloid leukemia are translocations, but this study investigated neither translocations nor aneuploidies other than monosomy 7 and trisomy 8. (4) Formaldehyde appears to be mutagenic predominantly by a clastogenic, not an aneugenic mode of action. (5) Formaldehyde has been shown to damage several cell types directly exposed in vitro, an effect therefore not unique to myeloid progenitor cells.	
		Meta-analyses	
Meta-analysis of cohort and case-control studies that reported leukemia rates in professional or industrial workers; (n = 18)	Not detailed	No statistically-significant associations were found between leukemia and exposure across all of the studies, across all cohort studies, or across all case-control studies. Slightly elevated risk of leukemia was reported among embalmers and pathologists/anatomists, but none for industrial workers, even those with the highest reported exposures.	147
Meta-analysis of cohort studies of professional or industrial workers through February 2007 (n = 25)	Not detailed	A "modestly elevated" pooled RR for LHP cancers was calculated for professionals (ie, embalmers, anatomists and pathologists; 8 studies), but not for industrial workers (4 studies). Similar results were reported for leukemia.	129
Meta-analysis of cohort and case-control studies that reported LHP cancer rates in professional or industrial workers (n = 26)	Not detailed	Summary RRs for professional and industrial workers combined were increased for all LHP cancers combined (19 studies). Statistically significant increases in RRs were reported for all leukemias (15 studies) and myeloid leukemia (6 studies). **Comment:** These authors attempted to increase the statistical power of their analysis by focusing only on the highest exposure groups in each study, selecting exposure duration from some studies, and peak, average, or cumulative exposure from others. They preferentially selected results for myeloid leukemia, rather than results for all types of leukemia combined, when available. They did not stratify the data to distinguish low-exposure professionals from high-exposure industry workers.	148
Meta-analysis of case-control and cohort studies that reported myeloid leukemia rates in professional or industrial workers (n = 14)	Not detailed	Statistically significant increases in summary RRs for professional and industrial workers combined were observed for leukemia and myeloid leukemia. Statistically significant increases in summary RRs were calculated for industrial workers (6 studies) and professionals (8 studies) considered separately. **Comment:** These authors attempted to increase the statistical power of their analysis by focusing only on the highest exposure groups in each study, selecting exposure duration from some studies, and peak, average, or cumulative exposure from others. They preferentially selected results for myeloid leukemia, rather than results for all types of leukemia combined, when available.	149
Meta-analysis of cohort and case-control studies of professional and industrial workers through May 2009 (n = 17)	Not detailed	For leukemia, no statistically significant increases in summary RRs were found in the cohort or the case-control studies for professionals (ie, embalmers and technical workers) and industrial workers combined. No statistically significant increases was observed in the summary RRs calculated specifically for professional workers (15 studies), for industrial workers (2 studies), or for myeloid leukemia from the cohort studies. Although the authors found that their summary proportionate mortality ratio (PMR) for leukemia was elevated (PMR = 1.44; 95% CI: 1.25- 1.67; 3 studies), they explained that PMRs are unreliable and sugested that the inclusion of PMR studies may have caused inaccurately elevated summary risk estimates in previous meta-analyses.	150

Table 10. Reproductive and developmental toxicity studies of formaldehyde/methylene glycol in test animals

Species (n)	Concentration(s); volume; duration	Results	Reference
		Multiple dose studies	
Wistar rats (n = 6 males/group)	0, 5, 10 ppm; 8 h/d, 5 d/wk, 91 days	Exposure to 5 or 10 ppm caused unsteady breathing, excessive licking, frequent sneezing, and hemorrhage of nasal mucosa. Statistically significant decreases in serum testosterone concentrations and seminiferous tubule diameters were found in both groups of exposed rats compared with controls. Hsp70 levels were increased in the spermatogonia, spermatocytes, and spermatids of the treated rats compared with controls.	46
Sprague-Dawley rats (n = 10 males/group)	8 ppm; 12 h/d, 2 weeks	Significant decrease in testicular weight was found in the exposed rats compared with the controls. Histopathological examination revealed seminiferous tubule atrophy, interstitial vascular dilatation and hyperemia, disintegration and shedding of seminiferous epithelial cells into azoospermic lumina, and interstitial edema in the testes of the exposed rats. Statistically significant decreases were reported in epididymal sperm count, percentage of motile sperm, activities of testicular superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), and in glutathione (GSH) levels, and increase in malondialdehyde (MDA) levels in the exposed rats compared with controls. All of these effects were markedly decreased in exposed rats that were also treated with Vitamin E. These authors did not report the overt toxic effects of the exposures.	151
Wistar rats (n = 7 males/group)	1.5 ppm; 4 h/d, 4 d/wk; 2 h/d, 4 d/wk; or 4 h/d, 2 d/wk; 18 weeks	Statistically significant decreases in diameter and height of seminiferous tubules/testis were observed in the exposed rats compared with controls. Severe decreases were found in the number of germ cells in the seminiferous tubules and evidence of arrested spermatogenesis after exposure 4 h/d, 4 d/wk, decrease in the number of germ cells and increased thickness of the tubule basement membrane after exposure 2 h/d, 4 d/wk, and disruption in the arrangement of Sertoli and germinal cells, with increased spacing between germ cells, after exposure 4 h/d, 2 d/wk. The authors did not report the overt toxic effects of the formaldehyde exposures.	152
Mice, strain not specified (n = 12 males/group)	0, 16.9, 33.8, 67.6 ppm; 2 h/d, 6 d/wk, 13 weeks	A statistically significant increase in the sperm aberration rate and decrease in mean live fetuses/litter in a dominant-lethal test were observed after exposure to 67.6 ppm. Resorption rates were statistically significantly increased for all groups of exposed rats. The English abstract of this Chinese paper does not detail the exposure method or report the overt toxic effects of the exposures.	153
Wistar rats (n = 10 males/group)	0, 6, 12 ppm; 6 h/d, 5 d/wk, 30 days	Lower numbers of both granular cells in the hippocampal dentate gyrus and pyramidal cells in the cornu ammonis of the hippocampus were observed at post-natal day 90 (PND90), compared to PND30, in rats exposed to 12 ppm. The authors did not report the overt toxic effects of the formaldehyde exposures.	47,154
Sprague-Dawley rats (n = 6 dams/group)	0, 6 ppm; 8 h/d, 6 weeks, starting on gestation day 1 (GD1), post-natal day 1 (PND1), or at 4 weeks of age or adulthood	Statistically significant decreased mean body and liver weights were observed in the offspring when exposure began on GD1. Liver weights were statistically significantly increased when exposure began at 4 weeks of age compared with controls. In the liver, statistically significant increases in catalase (CAT) activity and malondialdehyde (MDA) concentration, and decreases in glutathione (GSH) concentration and superoxide dismutase (SOD) activity were observed in the offspring when exposure began on GD1, PND1, or at 4 weeks of age. The authors did not report the overt toxic effects of the formaldehyde exposures.	155

Table 11. Epidemiological studies of formaldehyde/methylene glycol and reproductive effects

Study design; subjects or studies (n)	Exposure concentration or metrics	Results	Reference
Case control; Women who worked full-time in cosmetology and had a spontaneous abortion or a live baby during 1983−1988 (n = 376; 61 with spontaneous abortions, 315 with live births)	Exposed vs. unexposed	An association was reported between spontaneous abortion and use of "formaldehyde-based" disinfectants (crude odds ratio = 2.0; 95% CI: 1.1-3.8). The association was still apparent (adjusted odds ratio = 2.1; 95% CI: 1.0−4.3) after adjusting for maternal characteristics (eg, age, smoking, glove use, other jobs) and other workplace exposures (eg, chemicals used on hair, use of manicure products).	49
Case-control; Women occupationally exposed to formalin in hospital laboratories and having a spontaneous abortion, compared to controls who delivered a baby without malformations, during 1973−1986 (n = 208; 329 controls)	Mean: 0.45 ppm (range: 0.01-7 ppm) reported in similar laboratories	A statistically significant association was found between exposure to formalin/formaldehyde 3 to 5 d/wk and incidence of spontaneous abortions, after adjusting for employment, smoking, alcohol consumption, parity, previous miscarriage, birth control failure, febrile disease during pregnancy, and exposure to other organic solvents in the workplace. Exposures to toluene and xylene were also statistically significantly associated with the incidence of spontaneous abortions. No association was found between formalin exposure and congenital malformations in laboratory workers (n = 36) compared with controls (n = 5).	50
Case-control; Women occupationally exposed in woodworking industries, compared with employed, unexposed women (n = 602; 367 controls)	TWAs: (a) Low: 0.1 to 3.9 ppm (b) Medium: 4.0 to 12.9 ppm (c) High: 13.0 to 63 ppm	Statistically significant decrease was observed in fecundability density ratios (FDRs; ie, the average pregnancy incidence density of the exposed women divided by that of the unexposed women) for the high exposure group, and in the women in the high exposed group who did not wear gloves (n = 17). The reduced FDR among women in the high exposed group who wore gloves was not statistically significant (n=22). Associations were found between exposure and spontaneous abortions in 52 women who had worked in their workplace during the year of the spontaneous abortion and at the beginning of the time-to-pregnancy period. The odds ratios (ORs) were 3.2 (95% CI: 1.2−8.3), 1.8 (95% CI: 0.8−4.0), and 2.4 (95% CI: 1.2−4.8) for the low, medium, and high exposure categories, respectively. Endometriosis also appeared to be associated with exposure in women in the high exposure category (OR = 4.5; 95% CI: 1.0−20.0).	51
		Meta-analysis	
Meta-analysis of cohort, case-control and cross-sectional studies of professional or industrial workers through September 1999 (n = 8)	Up to 3.5 ppm	An overall meta-relative risk (meta-RR) estimate of 1.4 (95% CI: 0.9-2.1) was calculated, suggesting an association between occupational exposure and spontaneous abortion. However, no increased risk was observed after adjusting this estimate for reporting and publication biases (meta-RR = 0.7; 95% CI: 0.5-1.0).	156

Table 12. Measured formaldehyde levels during use of hair smoothing products

Test	Form Levels (ppm)	Exposure Time (min)	Samples ≥ Guidelines		
			US NAC AEGL-1[a] 0.9ppm ≥ 10 min	ACGIH TLV®-Ceiling[b] 0.3 ppm	WHO 30 min Guideline[c] 0.08 ppm
Oregon OSHA	0.074-1.88	6-48	Yes (4)	Yes (9)	Yes (All ≥30 min)
Exponent 1	0.170-0.269	95-141	No	No	Yes (All)
Exponent 2	0.041-0.76	17-43	No	Yes (9)	Yes (6 ≥30 min)
Tennessee OSHA	0.3-1.07	15	Yes (1)	Yes (5)	Yes[d]
PKSC 1	0.761-1.71	15	Yes	Yes (All)	Yes[e]
PKSC 2	0.189-0.395	86-117	No	Yes	Yes[f]
ChemRisk	0.11-1.17	56-82	Yes (4)	Yes (8)	Yes[g]

[a]National Advisory Committee Interim Acute Exposure Guideline Level-1 (concentration above which the general population could experience notable discomfort, irritation, or other effects)
[b]American Conference of Government Industrial Hygienists Threshold Limit Value Ceiling (concentration that should not be exceeded during any part of the working day)
[c]World Health Organization Guideline for Indoor Air Quality
[d]Calculated levels exceed by up to 4 fold
[e]Calculated levels exceed by 12-21 fold
[f]Calculated levels exceed by up to 5 fold
[g]Calculated levels exceed by up to 15 fold

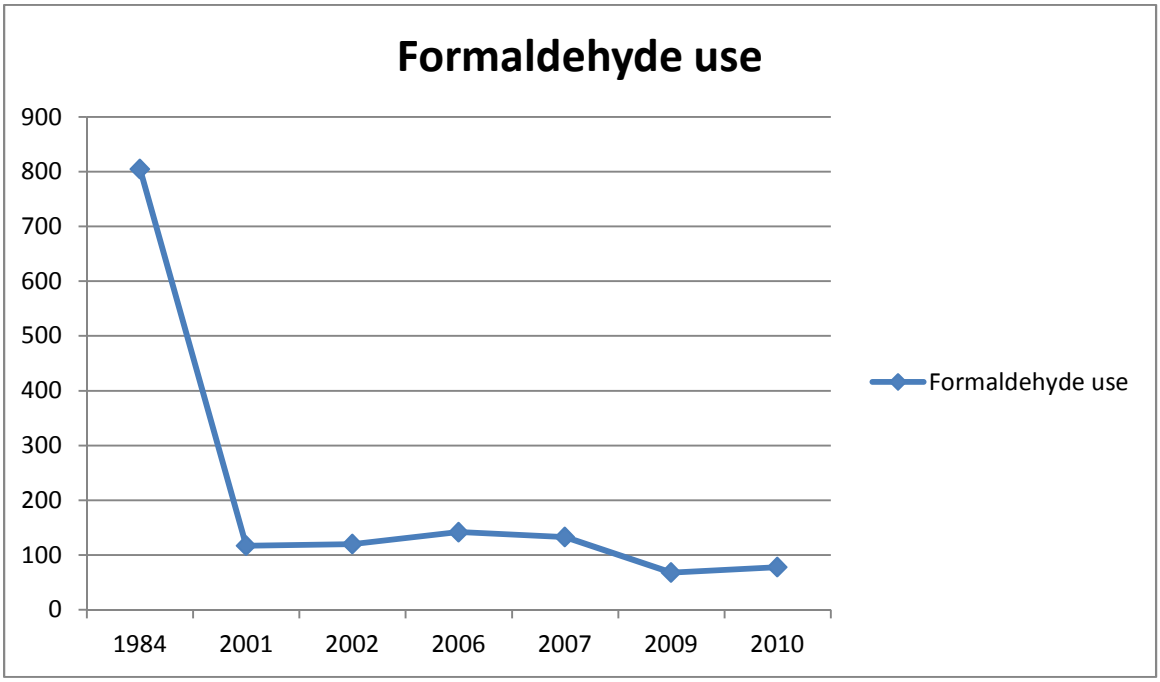


Figure 1. Declining use of formaldehyde in cosmetic products as reported to the FDA VCRP (The x-axis is not linear).

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Women's Voices for the Earth
National Asian Pacific American Women's Forum (NAPAWF)
California Healthy Nail Salon Collaborative

Cosmetic Ingredient Review
1101 17th St. N. W. Suite 412
Washington D. C. 20036-4702

By email cirinfo@cir-safety.org and Certified Mail

June 21, 2011

To: F. Alan Andersen, PhD, Dr. James G. Marks, Dr. Donald V. Belsito, and members of the Cosmetic Ingredient Review,

We are writing to the CIR to provide information about nail hardeners containing formaldehyde for your consideration at your next meeting on June 27-28, 2011. Our organizations , the convenors of the National Healthy Nail Salon Alliance, are committed to strategically advancing the health, safety and workers' rights of the beauty salon sector. We have long been concerned about the presence of formaldehyde in nail products, and have led successful campaigns to influence the industry to produce effective formaldehyde-free products – including nail hardeners.

We have reviewed the transcripts of the CIR's March 10-11 meeting and are concerned about the characterization of the risks of formaldehyde in nail hardeners as was discussed at that meeting. Similarly we do not believe that the submission of data from the Nail Manufacturers Council provides a comprehensive view of the hazards of formaldehyde in nail hardeners.

Specifically:

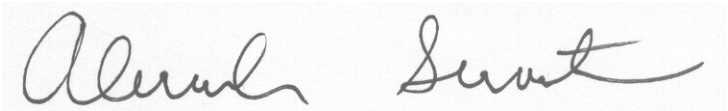
- We take issue with the claim that there is no history of adverse events associated with nail hardeners containing formaldehyde. While consumers may not be contacting manufacturers to report problems, they are reporting problems with these products frequently on customer review websites. Enclosed please find a compilation of customer reviews of nail hardener products containing formaldehyde which demonstrate a history of adverse events including skin irritation, burning sensation in fingers and hands, severe finger pain, strong unpleasant odor, coughing, dried out and peeling nails and other symptoms. These are all symptoms which are consistent with exposure to formaldehyde.

- We also disagree with the claim that formaldehyde vapor from the use of nail hardeners containing formaldehyde would be extremely low. While some of the formaldehyde may be fixed by the nail proteins, clearly there is a portion that will vaporize as well, despite being at room temperature. In fact, a 1999 study on formaldehyde emission rates from consumer products published in Environmental Science & Technology found that "fingernail polish and

hardener showed relatively high emission rates".[i] We have enclosed a copy of the study for your review.

We are concerned about the potential confusion to consumers if the CIR chooses to limit formaldehyde to .2% in all cosmetic products except nail hardeners. This will appear to be an arbitrary decision made merely to protect the commercial interests one particular sector of the industry at the risk of consumer safety. Given the wide availability of effective formaldehyde-free nail hardeners, we strongly encourage the CIR not to make an exception for nail hardeners, but rather to extend the same level of safety from formaldehyde for all cosmetic products.

On behalf of the National Healthy Nail Salon Alliance,



Alexandra Scranton
Director of Science and Research
Women's Voices for the Earth

CC: Linda Katz, Food & Drug Administration

Enclosures

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[i] **Thomas J. Kelly, Deborah L. Smith, and Jan Satola (1999) Emission Rates of Formaldehyde from Materials and Consumer Products Found in California Homes. Environ. Sci. Technol., 1999, 33 (1), pp 81-88. Available at:** http://pubs.acs.org/doi/abs/10.1021/es980592%2B

Nail Hardener Reviews

The following are customer reviews of various brands of nail hardeners submitted to online product review websites and posted on blogs. All websites were accessed on June 14, 2011. The 35 reviews quoted below clearly demonstrate a history of adverse events associated with nail hardener products containing formaldehyde. The reviews detail problems with nail hardener use including skin irritation, burning sensation in fingers and hands, severe finger pain, strong unpleasant odor, coughing, dried out and peeling nails and other symptoms.

1) From: http://www.amazon.com/review/R3MBSZQPZILGID

Quimica Alemana Nail Hardener

Not safe., August 15, 2010

Bufster3

This review is from: Quimica Alemana Nail Hardener 0.47 oz (Health and Beauty)

I saw all the wonderful reviews of this product and ordered it. I was so excited as my nails are very weak and brittle.

I noticed that there was a warning on the bottle stating that if a burning sensation occurs after application to remove it immediately. I figured it might sting a little but I was shocked when after 20 minutes or so I began to feel pain in my ring finger on my left hand. My finger tip and nail bed started to turn red and the pain traveled to the joint. Then as I was removing the product the pain began in other fingers on both hands. The pain continued and there was a rippling under my flesh that appeared on some fingers. The pain is mostly gone now after 2 days but this was a really scary experience.

2) From: http://www.amazon.com/Quimica-Alemana-Nail-Hardener-0-47/product-reviews/B00126IXLO/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

Works, but at a high cost, October 12, 2010

T. torrez "Kat" -

This review is from: Quimica Alemana Nail Hardener 0.47 oz (Health and Beauty)

I got this because I have extremely weak nails. I've tried tons of different nail strengtheners, and none have worked. I started using this and right away I experienced the burning. I took it off, waited for the burning to stop (it took a few HOURS), then did a very very thin coat. I kept doing his, and multiple times it burned and I had to take it off. After the third or forth time it burned me, I noticed I was getting these little black areas under

my nails. Tiny thin little lines or dots. When one grew out, I saw what it was...a SCAB. Whatever in this nail strengthener burns you, it's strong enough to burn through your nail and make under your nail actually bleed. My nails may be longer and a little stronger, but I threw it away when I figured out how bad it was for my nailbed. I'm trying out perfect formula now, and I really hope it works. At least it hasn't burned yet. *crosses fingers*

3) From: From: http://www.amazon.com/Quimica-Alemana-Nail-Hardener-0-47/product-reviews/B00126IXLO/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

NOT Natural, February 13, 2011

CM -

This review is from: Quimica Alemana Nail Hardener 0.47 oz (Health and Beauty)

Claims to be one of the more natural nail strengtheners, but it contains formaldehyde and DOES yeild a strong odor.
I am not stating that the product is not effective. I did try it (rather than throwing it away once reading the ingredients).
It does provide a hard layer to protect nails, so it would be useful if you do not care what the liquid contains.

4) From: http://www.amazon.com/Quimica-Alemana-Nail-Hardener-0-47/product-reviews/B00126IXLO/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

Be Careful!, December 26, 2010

SadiePoo (Arizona)

This review is from: Quimica Alemana Nail Hardener 0.47 oz (Health and Beauty)

I bought this product based on the reviews I read here. However, as a few of the reviewers stated, BE Careful! I used this daily and did notice a slight burning sensation. I must be allergic to one of the ingredients because the skin around my nails became EXTREMELY red and irritated, almost like a burn. I quit using the product and it took several weeks for the redness to go away. I would recommend you proceed slowly with this product to make sure you aren't allergic.

5) From: http://www.amazon.com/Quimica-Alemana-Nail-Hardener-0-47/product-reviews/B00126IXLO/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

1.0 out of 5 stars **Burning and red nail bed**, May 19, 2011

Stacy -

This review is from: **Quimica Alemana Nail Hardener 0.47 oz (Health and Beauty)**

I purchased this through my hair stylist and it did a great job at making my nails grow. Every 2 or so days I add a new coat but it peels off and I add another. I have been using it for about 3 weeks and my nails look great but then the burning started. I had pain in the nail bed of 3 nails, After a few days it went away but when I had to add another coat the burning returned in 2 nails. It feels like the nail is lifting from the nail but I don't think it is. I think the nail thinned out from the layers of the polish coming off and the chemicals seep into the nail bed and cuse pain. It has also turned parts of the nail bed red, like it is irritated. It really hurts and I will quite using this product.

6) From: http://www.amazon.com/Quimica-Alemana-Nail-Hardener-0-47/product-reviews/B00126IXLO/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

OUCH!!, April 8, 2011

Suzanne E. Burger "MountJoy Mama" (Mount Joy, PA United States) –

This review is from: **Quimica Alemana Nail Hardener 0.47 oz (Health and Beauty)**

I don't know what was in this stuff, but it BURNED under my nails!! It caused my nails to separate from the nailbed underneath and caused a few scabs, too. I used it once then threw it away. Be careful - it stings!!

7) From: http://www.amazon.com/Quimica-Alemana-Nail-Hardener-0-47/product-reviews/B00126IXLO/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

THEY ARE LYING!! DONT WORK @ ALL....IT'S BS!, May 15, 2011

Gabrielle_Love - See all my reviews

This review is from: **Quimica Alemana Nail Hardener 0.47 oz (Health and Beauty)**

OMG THIS NAIL POLISH WORKS GREAT, MY NAILS GROW STRONGER,FASTER & HEALHIER..??(FAIL!)..my nails still brake off ive use this for 2 weeks its a very good NAIL SHINER!!. BUT far as nail growth and hardner.. nope dosent work for me the polish peels off every once a while ..the first time ive use it my thumb nail just had broken off when i applied the "Quimica Alemana" <~ whatever that means. IT BURN THE HELL OUT OF MY NAIL!!! maybe because my nail just had been broken off but anyway it hurted. Just because you hear much good reveiws please dont be in a rush to buy it (like me..lol) I WAS REALLY TRYING TO FIND A GOOD NAIL POLISH TO HELP MY NAILS GROW!!! BUT THIS NOT

IT!!..(NOT SAYING U CANT TRY IT) but this didnt workout for me ...:(
p.s still going to use it for a shiner..LMMFAO!..SAD

8) From: http://www.amazon.com/Quimica-Alemana-Nail-Hardener-0-47/product-reviews/B00126IXLO/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

esmalte endurecedor para unas is horrible, May 10, 2011

Deanne D'imperio "book Deanne" (Rutherford, NJ) -

This review is from: Quimica Alemana Nail Hardener 0.47 oz (Health and Beauty)

This burned terribly on my nails... had to take it off immediately. And when I bought it in a nail salon, I paid $15! I'm throwing it out.

9) From: http://www.amazon.com/Duri-Cosmetics-00001-Rejuvacote-0-61oz/product-reviews/B000G33KEO/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

OOOUUUCCCHHH!!!, July 29, 2007

C. Davies (Washington, D.C., district of columbia USA) –

This review is from: Duri Cosmetics Rejuvacote 0.61oz (Misc.)

When I was getting my acrylic nails removed at the salon, my nail artist reccomended this product. I put a coat on when i got home and a few minutes later, I was in so much pain on my nails and finger tips it was unbelievable! I don't know if it was that my nails were so thin from the acrylic that the polish seeped through and irratated me under my nails or what but it was bad! The pain was indescribable! It was burning and stung and was sore all at once! I want strong, long nails so badly, but now I'm afraid to try anything else!

10) From: http://www.amazon.com/Duri-Cosmetics-00001-Rejuvacote-0-61oz/product-reviews/B000G33KEO/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

1.0 out of 5 stars **Damages the nail bed! Nails turned blue!**, July 12, 2008

Naomi

This review is from: Duri Cosmetics Rejuvacote 0.61oz (Misc.)

I had this on my nails for 3 days when they started to really hurt and turn blue. When I took the polish off, my nails looked bruised. It felt like needles had punctured the nail bed. I do

think the product is so heavy it cuts off all circulation and oxygen to the nails. My nails are on the thin side, so perhaps that is why I had that reaction, but I assume most people using this product have thin nails. Use with caution!!

11) From: http://www1.epinions.com/review/OPI_Matte_Nail_Envy_Natural_Nail_Hardener/content_32772034180

Nail Envy- not always for everyone

Written: Jul 23 '01

Product Rating: ★☆☆☆☆

Pros: Comes from a great manufacturer, but...

Cons: Wrecked my nails, more than once.

The Bottom Line: Try to find a mini-bottle and experiment first!

RVKMA's Full Review: Opi Matte Nail Envy Natural Nail Hardener

I realize that many many people swear by OPI Nail Envy, but I had a bad reaction to it. I've tried to use this product twice, a year apart, with the same results. My nails dried out, and peeled like I've never seen them peel before! They pretty much crumbled from the tips down - shredding like paper. I must be sensitive to some ingredient - I use OPI polishes with no problems, and I have used just about every other strengthener out there with no bad reactions, so it must be something unique to Nail Envy.
Since I love OPI's other products, I would suggest getting yourself a mini-bottle of this, especially since it's very expensive. You can usually find a mini bottle for $4-6 at the salon or beauty center, and they include a mini in most of their seasonal gift sets. Or, buy from a salon/store that will allow refunds.

12) From: http://www1.epinions.com/review/OPI_Matte_Nail_Envy_Natural_Nail_Hardener/content_378580209284

Another nail disappointment

Written: Jun 19 '07

Product Rating: ★★☆☆☆

Durability:

Pros: Shiny appearance to my nails

Cons: Made my nails peel worse than before, hard to find

The Bottom Line: Use with caution. If you're sensitive to chemicals, I would avoid this product.

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rjschweitzer's Full Review: Opi Matte Nail Envy Natural Nail Hardener

I was born with weak nails. No matter what I try--supplements, nail strengtheners, eating more Jello--my nails don't improve. A friend raved about OPI's Nail Envy, so I went to the mall and bought some at Trade Secret.

The instructions said to apply one coat every other day, so I applied it shortly before bedtime. What I wasn't sure about was how often to remove it. Using nail polish remover, even the acetone-free kind, is harsh on nails, so would it negate the effects of the Nail Envy? I ended up removing the buildup once per week, or whenever I felt it got too thick.

I used this product for six months, as directed. In that time, my nails actually got *worse* and peeled even more! I tried other methods of using this product, such as using it as a base coat or top coat only. This didn't seem to improve things. Once I cut out the Nail Envy, my nails went back to their sub-normal state.

I have since learned that OPI uses formaldehyde in their products, a carcinogen which is known to dry nails. Why would they use such a product in a nail hardener? I read a report from Women's Voices for the Earth, dated March 29, 2007, that OPI is removing other chemicals from their products but will keep formaldehdye in the nail hardeners.

I was disappointed in this product, especially for the price I paid.

Recommended:
No

13) From: http://www.makeupalley.com/product/showreview.asp/ItemId=53395/Nail_Magic/0/Treatments

Bfarris89 on 5/3/2011 5:04:00 PM More reviews by Bfarris89

Age: 19-24 Skin: Normal, Tan, Not Sure Hair: Brunette, Other, Other Eyes: Blue

Hoooooly Cow!!! After having acrylics for years my nails were very unhealthy and paper thin so I purchased Nail Magic which was recommended to me by a store associate. After applying the regiment, my nails started burning so bad that it was unbearable!! Immediately I started looking at reviews and found that others had experienced the same outcome with this product. After about an hour of thinking the pain would go away I removed it with finger nail polish remover and instantly felt better! I also see many people who are satisfied with this product but I'm undecided if I will give it another shot once my nails have healed.

14) From: http://www.makeupalley.com/product/showreview.asp/ItemId=53395/Nail_Magic/0/Treatments

Kunko on 3/13/2011 6:55:00 PM

Age: 19-24 Skin: Combination, Fair-Medium, Neutral Hair: Brunette, Other, Medium Eyes: Other

I love this product! I have always had nails that flake and break off if they grew even a little bit past my nail bed. I have tried the OPI nail treatments, and they have failed me miserably and was a waste of money.
So after seeing some good reviews on youtube I took the plunge and bought it. Just as a warning the first time I tried it my nails HURT like it was a mild burning sensation for the first few hours. The next time I tried it, it didn't hurt, so maybe that was the formula showing me just how weak my nails were? After using it once a week for a few months I had wonderfully strong and long nails that were the envy of all my friends, I was constantly asked if they were fake.
I would recommended this product to anyone who is trying to grow out their nails and having a hard time doing it, but just a warning if you have really weak nails like I did it will burn and hurt the first time you use it.
P.S. - they have a new "natural" formula I'm currently trying out to see if it is any better.
UPDATE: So I have been using the "natural" formula and I have to say don't waste your money on it, my nails went back to breaking and chipping so it wasn't worth it, just stick to the original formula if you want results.

15) From: http://www.makeupalley.com/product/showreview.asp/ItemId=53395/Nail_Magic/0/Treatments

Lizziex3 on 12/4/2010 3:14:00 AM

Age: 19-24 Skin: Acne-prone, Fair, Neutral Hair: Brown, Wavy, Medium Eyes: Green

This stuff works very well for me. You have to use it continuously for the full six weeks though before it works though.
This contains formaldehyde. YOU must make the decision whether its worth it to try.
If you want to wear polish with this treatment I suggest putting a base coat over the Nail Magic and under the color because this tends to peel off in big sheets after a couple days and will take your manicure with it unless you have something on top of it to keep it on.
Do not get this on your skin! It burns. Careful application is key with this product especially with the possible side effects of absorbing formaldehyde through your skin.
This product smells awful. Worse than a regular nail product. Keep that in mind.
The bottle doesn't last very long..eventually it thickens and becomes unusable..I got about three months out of my first bottle.
Overall I like it and will continue to use it but it might not be for you.

16) From: http://www.makeupalley.com/product/showreview.asp/ItemId=53395/Nail_Magic/0/Treatments

charstone on 11/10/2010 1:38:00 PM

Age: 44-55 Skin: Sensitive, Fair-Medium, Neutral Hair: Blond, Wavy, Fine Eyes: Hazel

I too have had the extreme burning reaction. I tried two coats as recommended and had to take it off within 5 minutes. I then tried one coat, being very careful not to get any on my cuticles and put oil around the edges immediately. Same TERRIBLE burning. I must be allergic. Someone else stated that if you are allergic to bees (I am) then probably best avoided. The problem is that you cannot have a test of these products before trying and it is not that cheap in the UK.
I have had a similar reaction to Nailtiques if it get too thick, but nothing like this!

17) From: http://www.makeupalley.com/product/showreview.asp/ItemId=53395/Nail_Magic/0/Treatments

famoushair on 4/4/2010 7:39:00 AM

Age: 36-43 Skin: Very Oily, Fair, Not Sure Hair: Blond, Other, Other Eyes: Blue

When I first purchased and used Nail Magic, I was pleased. It comes in a cute package and goes on thickly but evenly, with a pink appearance in the bottle but a clear appearance on the nail. I thought this would serve as a nice basecoat and hardener for my relatively wimpy nails.
I'm a couple of months into using it and my nails are worse than when I started using the product. After a bit of online research on the product, I realize this stuff is largely formaldehyde and therefore can be drying. I live in a very dry climate, and it's been pretty cold here. The end result: short, chippy nails, made worse by my attempts at filing them into shape, thus causing them to be painfully thin. Application of Nail Magic the last few times caused my nail beds to burn/sting with a fierceness I have no words to describe. My nail beds are way too soft and they ache.
Now I'm going to let my nails go "naked," and give them lots of moisture in the hopes that they can recover some of what was lost over the past couple months.
So despite all the successes listed here, Nail Magic was way less than magical for me. I'd rather have the wimpy (but relatively healthy) nails I started out with!

18) http://www.amazon.co.uk/product-reviews/B002EIHEI2/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

1.0 out of 5 stars **i'm not sure it worked?**, 29 April 2011

Miss Zoe Maskell -

This review is from: **Nail Magic Nail Treatment and Conditioner (Misc.)**

I brought this product after my nails started pealing which I was very unhappy about. It took about 10 days to arrive by which time I had brought myself new nail polish remover (that was meant to be kinder to my nails) and had left my nails unpolished for a week to try help them.

when the nail "treatment" arrive I put it on that evening, and after reading the back I did my very best not to get any on my skin. it took a long time to dry and then had to put a second coat on which took even longer. that night I was kept awake by the pain on the sides on my nails (not somewhere I thought that much pain could ever be felt!) even though I had made sure that the "treatment" had stayed away from any skin. but I carried on for 2 weeks only wearing it and putting on two layers 2/3 times a week (even though every time it still hurt!). Before deciding it was time to have coloured nails again.

nail polish doesn't seem to say on top of it and even though my nails are better than they were when I first brought the product I believe that it had more to do with the fact that I'm using better nail polish remover (that cost me about £3). If your having a similar problem I would defiantly recommend you try doing that first and then if it doesn't work then find another nail treatment, because this one doesn't seem to do any good.

19) http://www.amazon.co.uk/product-reviews/B002EIHEI2/ref=cm_cr_pr_viewpnt_sr_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

Hate this product!, 8 April 2011

E. Crane (South Yorkshire)
This review is from: **Nail Magic Nail Treatment and Conditioner (Misc.)**

I purchased this after hearing many good reviews, and when I recieved it and applied it, my nails and fingers were in server pain along with throbbing and burning sensations.

After hoping the pain would subside, it didn't and had to remove it as the pain was so bad :(

£[] (including p&p) was a waste of money!

20) From: http://www.makeupalley.com/product/showreview.asp/ItemId=6776/Nail-Hardener/Mavala/Treatments

Mavala Nail Hardener
FunkyMonkeyNOTaDonkey on 1/17/2010 7:52:00 PM

Age: Unknown Skin: Other, Other, Not Sure Hair: Other, Other, Other Eyes: Other

Love.Love.LOVE this product. It is 4% formeldehyde, not mostly form as others have mentioned. The concentration is considered high though in comp. to other cosmetics products. If you use ANY other nail treatment with form. in it then you should use only 1 at a time or overdrying will occur. Also use this 2-3 times a week at most. I have used this for about 2 months. I use a hydrating base coat in addition to this-nothing with extra protein or hardeners. I apply this to more than just the tips of my nails, but rarely, i have noticed it works better this way for me.
Due to this product i was able to FINALLY get really long nails, and they just do not break, they are hard but not brittle.
this is not a polish or base coat, instead it is in an actual treatment that is absorbed by the nail.
1 bottle lasts about a year if used according to directions, do *look* at your nails and use more sparingly when you see they are getting hard or brittleness will occur.

21) From: http://www.makeupalley.com/product/showreview.asp/ItemId=6776/Nail-Hardener/Mavala/Treatments

Gradle on 10/23/2009 5:13:00 PM

Age: 36-43 Skin: Combination, Other, Not Sure Hair: Red, Other, Other Eyes: Green

I hate to ruin the good reviews, but this stuff ruined my nails. I stumbled upon the reviews and decided to purchase based on the excellent ratings. My nails had finally grown out and looked nice, and based on the reviews this seemed like a good product to maintain the health of my nails. Almost immediately my nail tips started peeling and flaking off, but I kept using this weekly for about six weeks to give it a chance. The entire time I used it my nails were a flaky mess, and they've started growing a bit now that I've stopped. While using this, I continued to use the same base coat I'd been using, so really the only change was the Mavala Nail Hardener. I really wish that I got the results that everyone else got, but my search for a good nail strengthener continues. If this works for you, it's a great buy because this one bottle looks like it will last forever.

22) From: http://www.makeupalley.com/product/showreview.asp/ItemId=6776/Nail-Hardener/Mavala/Treatments

Taniaebj on 1/28/2011 8:23:00 AM More reviews by Taniaebj

Age: 36-43 Skin: Combination, Olive, Not Sure Hair: Brunette, Other, Other Eyes: Brown

I was so excited to get this after all of the wonderful reviews, but alas, it was not to be. I gave it a fair shot by using it for at least a month and also following the directions carefully. My nails became drier and more brittle than before. My nails went back to their original weak and fragile state as soon as I stopped using it. Will not buy again, did not work for me :(

23) From: http://www.folica.com/reviews/spa-and-body/manicure/mavala-scientifique-nail-hardener

Cathey, Tulsa, OK

It Works, Until It Ruins Your Nails! Beware of Formaldehyde

Warning! Warning! Warning! This product contains 4% formaldehyde. The maximum in cosmetics is usually .2% which does not require a warning label and anything over .2% with up to 3% requireing a warning label, but this doesn't have a warning label. This stuff worked great for me for about 2 months, I got amazing results, and then BAM BAM BAM peeling non stop. Peeling and splitting like crazy. My long nails reverted to the shortest they have been my entire life. That is the amazing power of formaldehyde. It works by making the keratin bonds in your nails have more threads which make the bonds harder,however there is no max to how many threads formaldehyde helps the keratins create. It can make the keratin bonds in your nails so strong that your nail will actually lift off from the nail bed. Use this at your own risk and be careful.

24) From: http://www.folica.com/reviews/spa-and-body/manicure/mavala-scientifique-nail-hardener

Anonymous

Didn't Work!

This didn't work for me at all. My nails are even more frail, brittle, and peel easily. I think this is actually drying my nails out more. I felt like I wasted my money on this product.

25) From: http://answers.yahoo.com/question/index?qid=20090901184730AAvPQ8o

Nail Magic" nail hardener makes my fingers ache.?

There is this nail hardener that I buy at Sally's. It's pink and it comes in a box and it's called Nail Magic.
I like it because it makes my nails strong and it makes them grow faster.
But I've noticed that whenever I use it, my fingers kind of burn.

The more I use it, the worse it gets.
I used it quite a few hours ago and my fingers still hurt. So much so that they feel like they are on fire and the ache has gone up to my elbows and into my wrists.
It hurts quite a bit, but the polish it dry.
When I run my hands under cold water, or put them right in front of the AC, the pain subsides, but as soon as that cold wears off, it comes back...

Any ideas as to why it's doing this or how I can make it stop?

(And don't say "Stop using it" because I've already decided that I'm going to if there's no other solution...)

26) From: http://answers.yahoo.com/question/index?qid=20090901184730AAvPQ8o

Best Answer - Chosen by Asker

OMG the same thing happened to me! I still have it, it comes in a purple box, with gold on it. I liked it for about the first week. Then it started burning my under my nails turned a reddish color... I was horrible..I left it on for another week, but I noticed it was just getting worse and my fingers began to swell, i even stopped being able to sleep! After I couldn't sleep I decided to take it off with nail polish remover and it kept burning for about another week. It hurt all the time, especially if I touched something. I went to my dermatoligist and she said that I had a chemical burn and actually had to prescribe an antibiotic ointment to rub into my nails. They finally healed. From previous use and pain I would say stop using this immediately! I know its great for awhile, but now I'm just using a sally hansen hard as nails and it works just fine too. Go see your local dermatoligist you might need an antibiotic too!

27) From:
http://www.makeupalley.com/product/showreview.asp/ItemId=20287/Witchcraft_Nail_Hardener/0/Treatments

Witchcraft Nail Hardener

summerrain1994 on 5/29/2011 10:14:00 PM

Age: 18 & Under Skin: Acne-prone, Fair, Neutral Hair: Brunette, Wavy, Coarse Eyes: Brown

I purchased this at Wal-mart for around $8 CAN I believe, and am really glad that I did!
For a girl that has brittle (they break easily) and flaking nails, I wanted something that would make my nails stronger. I work at a bookstore as well, and no matter what I did, sticking my hands in and out of the books also seems to ruin my nails.
Anyways, this stuff is great! I wear two coats underneath my regular nail polish, and one on top. It keeps

my nails strong, and my polish long lasting.
The only time I get breaking is when the polish begins to chip off the tips of the nails. I agree with the MUAer that said that when they don't wear this treatment, their nails get very brittle. This is the same for me, and though it's annoying, I just try to keep up with the treatments (applying at least once a week). The smell isn't that great either, it's super strong, but I just do my nails outside in this case.

28) From: http://www.makeupalley.com/product/showreview.asp/ItemId=20287/Witchcraft_Nail_Hardener/0/Treatments

selmf on 10/13/2007 8:26:00 PM

Age: 44-55 Skin: Combination, Other, Not Sure Hair: Blond, Other, Other Eyes: Blue

Bought this on ebay, could not find any other place. I am about 2/3 of the way through the bottle and it really has helped my thin nails. It keeps them from peeling and bending. If you try it be sure to use it in a well ventilated area. It is very strong.

29) From: http://thebeautybrains.com/bbforum/discussion/2024/mavala-scientifique-nail-hardener-formaldehide-dilema/p1

- georgia June 4

  Mavala Scientifique contains 4.5% formaldehyde. It's meant to be used only on the white portion of the nail. I've used it briefly when my nails have become too soft, but I try to avoid it. I find the odor very strong, so I use a mask when applying.

30) Fromn: http://www.amazon.com/Quimica-Alemana-Esmalte-Endurecedor-Hardener/product-reviews/B0038IA8XA/ref=cm_cr_pr_hist_1?ie=UTF8&showViewpoints=0&filterBy=addOneStar

1.0 out of 5 stars **Burns**, April 8, 2011

Nancy Mallory -

This review is from: Quimica Alemana Esmalte Endurecedor de Unas (Nail Hardener) 0.47 FL. oz (Health and Beauty)

Saw this on the Today show. Amazon is GREAT...I always receive my purchases timely. So I was excited to try this nail hardener, but almost immediately after I put this on, my nail beds began to tingle..and not in a good way. I left it on for about 15 minutes and the nail beds began to burn. I have natural nails, but used to have silk wraps 5 years ago. The

product has a high concentration of formaldehyde that is not allowed to be produced in the US. It seems to be OK for some people...it just didn't work for me.

31)
http://www.amazon.com/review/R12PPG91MKLESR/ref=cm_cr_pr_viewpnt#R12PPG91MKLESR

Good news & bad news, April 8, 2011

Helen James

This review is from: Quimica Alemana Esmalte Endurecedor de Unas (Nail Hardener) 0.47 FL. oz (Health and Beauty)

This nail hardener really works. It's like putting super glue over your flaky,layered, weak nails. The only problems I found were: If you get any on areas of cuticle or edges of nails it may throb for hours. Since the product is thick, it may hold to brush stem as pulled over edge of bottle and drop onto clothes, skin, etc. Lastly the stem with brush just fell out of cap the third time I used it, and made a mess....don't know if it will stay attached after I tried to secure it back into the lid.

32) From: http://www.justbeautysupplies.com/quimicaalemananailhardener.aspx

All women can't live without.
Denise Johnson *(Hartford, CT) 6/24/2010 1:17 AM*

After a relief from artificial finger and toenails period. My fingernails were being dinged up a lot: thin, peeling and ridged. The Quimica Alemana Nail Hardener certainly did what it claims, and in a matter of weeks with one night put in surface buffing and I discovered that my fingernails have transformed. It's important to understand, precisely how the active chemicals in nail hardener works, and this should affect how you put them to use. Quimica Alemana is a Colombian-made formaldehyde or formalin based nail hardener, while other products are reported to possess protein or nylon bases. The formaldehyde/formalin mixture means that the active chemical substances are really strong and efficient and consequently should be applied with extreme care and perseverance -- the latter of which is hard to have when you've just ripped away a set of acrylics and sworn them off for good! With very thin fingernails at the beginning, my two times coating on the first try was entirely too much and my nails were burning the whole evening and they were even super sensitive through the next day, especially to heat. Starting up a strategy, as I have, of every 4 to 5 days eliminating the old layers and reapplying another nice and single full covering coat. I think I used way too much too shortly, and some of my fingernails began to get opaque, whitish areas and marble, striated growth marks of the identical color. I'm nevertheless extremely delighted with the actual effect of considerably strong and tough nails within simply weeks; on the other hand, I'd advise the following, a more patient approach: Begin with one thin coat and reapply merely 1 thin layer every 4 days to one week for 3 weeks or so. In my instance, I believe the nail bed has been overstimulated with the formaldehyde process and

consequently over reacted in hyper-producing keratin's cross-linking fibers, which are the natural structures of nail strengthening.

33) From: http://www.justbeautysupplies.com/quimicaalemananailhardener.aspx

ESMALTE ENDURECEDOR PARA UÑAS

Patricia Santana *(New York City, NY) 6/13/2010 11:04 PM*

I've never ever made a critique prior to on Just beauty supplies site however after experiencing this nail hardener for a few weeks and realizing the improvement, I basically had to fill every person know how wonderful this product is. My fingernails would definitely always crack and were extremely weak until now. I have burned my money on any drug store nail strengthener and they never worked. Right after one week, I noticed the effects and after an complete month, my fingernails are longer and the tips are white. I ought to warn you that with my first several uses, my nail beds did hurt a little, but I assume I used too lots of layers. Other than that, this Quimica Alemana Nail Hardener is undoubtedly well worth the money! Make sure you get it on the net or here at Justbeautysupplies.com. $7.99 a bottle is better than $15 or $20 in nyc.

34) From: http://cydonianmakeup.blogspot.com/2010/03/nail-magic-review.html

Nail Magic Review

To start this off, my nails were in pretty sad shape about a month and a half ago. I had my hair professionally dyed purple (at the ends) and for whatever the reason, the color deposited itself heavily under my nails and all over the tops. So, after about a week, my nails were broken and fragile from all the chemicals.

So, I wandered into Sally's and asked for help... they had Nail Magic on special for $6.99 or so (about $6.50 with my Sally's card). The regular price is $8.49, $7.99 with your Sally's card…

I can see the improvements in them from this product, but I also have some major issues with Nail Magic as well…

3) Smell. The smell is pretty strong... it's a general chemical smell mixed with a teeny tiny bit of garlic. Weird, I know. I use this at night so it's not an issue but if I keep using it while my boyfriend is here, I'm gonna have to find something to cover it with. That just isn't an attractive thing to get into bed smelling like. It does dissipate after an hour or so, and I found that using a scented hand soap helps to mask it.

4) Pain. It is very painful when applied the first few times you use it. It feels like your nail beds are swelling -- literally. It's hard to describe how it feels... it's a general burning/aching feeling. I did notice after a few weeks that my nails were desensitized and it definitely didn't hurt as badly. Also, do not get this product on your skin! It hurts horribly. If you do, I found that washing my hands gently in cold water and soap helped to calm it. I was usually okay by the following morning.

35) From: http://www.tumblr.com/tagged/nail+harmony

Nail Magic Report: Day 1

I've decided to track my progress using Nail Magic. I have been using gel nail polish for over 2 months now. I started doing it myself about a month and a half ago after a HORRIBLE nail salon experience and I kept up with it because of the damage done by the "technician". (Who uses a metal scraper across the nail bed!?)...

So last night after removing Gelish I applied Nail Magic as directed. A thin coat over your clean nails. It dries to a satiny-matte finish like most base coats. I then applied two coats of color (I went with China Glaze Go-Go Pink) and then they recommend applying another coat of Nail Magic as your top coat. Because it dries matte-ish, I got a little nervous but it seems that over polish it dries nice and shiny! I should note - if your nails are week and brittle (as mine are) you may experience burning for a few hours after application. My ring finger nails were the damaged the worst (they are my weakest nail to begin with) and they did burn for a while. But it stopped. I would say if you experience extended burning (like more than a few hours) - remove it!