

BLUE

Formaldehyde/Methylene Glycol

CIR EXPERT PANEL MEETING

SEPTEMBER 26-27, 2011

Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel and Liaisons
From: Director, CIR
Subject: Formaldehyde and Methylene Glycol
Date: August 26, 2011

At the June meeting, the Panel issued a revised tentative amended safety assessment for formaldehyde and methylene glycol with the conclusion that: (1) formaldehyde and methylene glycol are safe for use in cosmetics applied to the skin when formulated to ensure use at the minimal effective concentration, but in no case should formaldehyde equivalents exceed 0.074% (w/w); (2) the available data are insufficient to determine the safety of formaldehyde and methylene glycol as used in nail hardening products, until additional data on use concentrations are available from FDA or industry; and (3) formaldehyde and methylene glycol are unsafe for use in hair smoothing products, the use of which involves application of high temperatures.

While comments on that revised tentative amended report have been received from the Personal Care Products Council, the expected inputs from the Nail Manufacturers Council and the Professional Keratin Smoothing Council have not been received and will be provided separately when they arrive.

The issues addressed at the last meeting included a change in the stated maximum concentration of formaldehyde equivalents in products applied to the skin. You determined that the proposed safe level of formaldehyde and methylene glycol of 0.2% formaldehyde equivalents was based on dermal safety testing using formalin, which contains only 37% (w/w) formaldehyde equivalents. Accordingly, the level that should be given as the safe level is 0.074% (w/w) formaldehyde equivalents.

While concern had been expressed in comments that the term “formaldehyde equivalents” was not the best term to convey essential identity of formaldehyde and methylene glycol, you considered 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 release of formaldehyde from so-called formaldehyde releaser preservatives that are not addressed in this safety assessment, yet are widely used. Comments from the Council’s CIR Science and Support Committee again question this approach, so, once more, this matter should be addressed at the meeting.

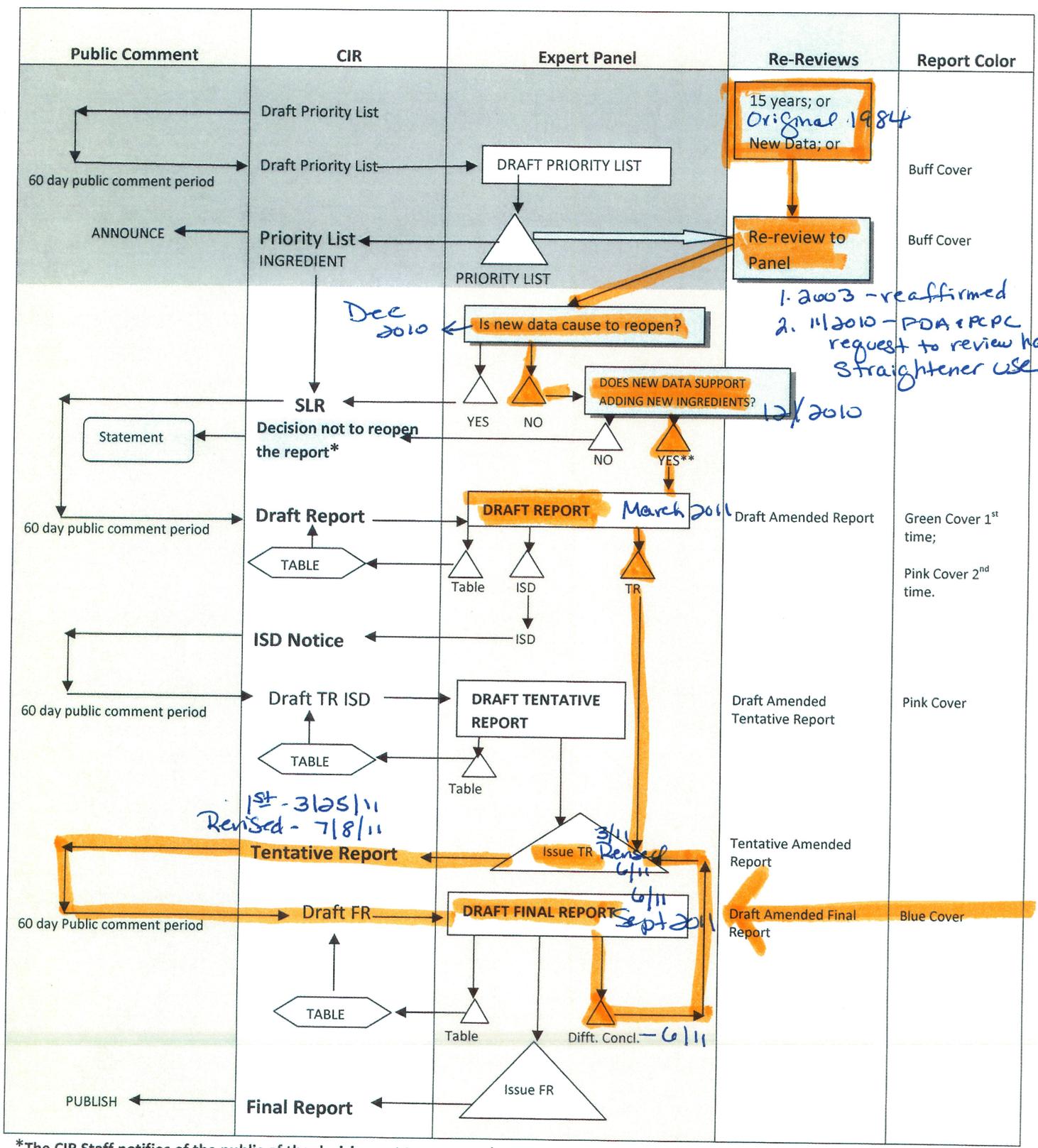
You also reviewed the available data on air measurements of formaldehyde in nail salon settings and determined that the levels were consistent with the absence of adverse reaction reports to manufacturers and to the FDA. Clinical experience of eyelid dermatitis, however, was reported with 2 patients using one brand of formaldehyde-containing nail hardener and the National Healthy Nail Salon Alliance provided other self-reported adverse events after use of that same brand. FDA testing of formaldehyde levels in that brand found a level of 2.2%. Other data may be forthcoming.

Formaldehyde and Methylene Glycol – page 2

After extensive discussion in each team meeting and in the full session, you were concerned about sensory irritation adverse reports consistent with measured air levels of formaldehyde in salons using hair smoothing products containing formaldehyde/methylene glycol. While an approach was suggested to place a burden on industry to manufacture products that would not produce sensory irritation, a concern remained that use of hair smoothing products with formaldehyde/methylene glycol should not be considered safe, even in salons where some ventilation appears to be in place, but especially given the inability to ensure adequacy of ventilation. Based on the unique circumstance of formaldehyde/methylene glycol use in hair smoothing products intended to be heated, the likely production of substantial amounts of formaldehyde gas, and the absence of any assurance that adequate ventilation could/would be available, you determined such use of formaldehyde and methylene glycol to be unsafe. The vote was 4 in favor and 3 against that motion. The Consumer Federation of America, FDA, and PCPC liaisons all supported the conclusion that formaldehyde and methylene glycol are unsafe for use in hair smoothing products, the use of which involves application of high temperatures.

The task at this meeting is to finalize this amended safety assessment.

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SAFETY ASSESSMENT FLOW CHART



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

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

- Expert Panel Decision
- Document for Panel Review
- Option for Re-review

CIR History of Formaldehyde

1984

- CIR published its original safety assessment of formaldehyde, concluding that this preservative is safe for use in cosmetics if free formaldehyde was minimized, but in no case > 0.2%. The Panel also said that it cannot be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized.

2003

- The Panel re-reviewed formaldehyde, confirming the original conclusion. That finding was published in the International Journal of Toxicology in 2006.

2010

- U.S. EPA National Center for Environmental Assessment (NCEA) released a lengthy, 4-volume draft toxicological review of formaldehyde for external review on 2 June 2010

- FDA asked CIR to consider the safety of formaldehyde given its detection in hair smoothing products, to consider additional data, and to address the safety of methylene glycol in cosmetics. The Personal Care Products Council and the Professional Beauty Association have supported such an effort

- at the December meeting, the CIR Expert Panel agreed to reopen the safety assessment of formaldehyde to address (1) formaldehyde and/or methylene glycol exposure from hair smoothing products; (2) nasopharyngeal cancer dose-response; and (3) hematopoietic cancers associated with formaldehyde exposure

2011

March Panel meeting - CIR issued a tentative amended safety assessment with the following conclusion:

- Formaldehyde/methylene glycol are safe in cosmetic products when formulated to ensure use at the minimal effective concentration, but in no case should formaldehyde equivalents exceed 0.2%.
- It cannot be concluded that formaldehyde/methylene glycol is safe in cosmetic products intended to be aerosolized or in which formaldehyde/methylene glycol vapor or gas will be produced under conditions of use.
- The available data are insufficient to determine the safety of formaldehyde/methylene glycol in nail care products, pending receipt of additional information: (a) clarifying the U.S. FDA position on allowed levels of these ingredients in nail care products and (b) nail salon exposure levels.

Technical comments were received from the Personal Care Products Council and comments with additional data were provided by both the Nail Manufacturer's Association and the Professional Keratin Smoothing Council.

June Panel meeting – CIR issued a revised tentative amended safety assessment with the following conclusion:

- Formaldehyde and methylene glycol are safe for use in cosmetics applied to the skin when formulated to ensure use at the minimal effective concentration, but in no case should formaldehyde equivalents exceed 0.074% (w/w).
- The available data are insufficient to determine the safety of formaldehyde and methylene glycol as used in nail hardening products, until additional data on use concentrations are available from FDA or industry.
- Formaldehyde and methylene glycol are unsafe for use in hair smoothing products, the use of which involves application of high temperatures.

Technical comments again were received from the Personal Care Products Council and comments with additional data were provided by a coalition of consumer interest groups, the Nail Manufacturer's Association and the Professional Keratin Smoothing Council.

Literature Search on Formaldehyde

Studies were identified primarily from the 2 June 2010 U.S. Environmental Protection Agency (U.S. EPA) Toxicological Review of Formaldehyde – Inhalation Assessment, external review draft. Supplemental searches of PubMed, U.S. EPA's Integrated Risk Assessment Information System (IRIS), Oak ridge National Laboratory's Risk Assessment Information System (RAIS), and the Agency for Toxic Substances and Disease Registry (ATSDR) website were also conducted between December 3, 2010 and 4 February, 2011 to obtain the most recent information.

Introductory Panel Session 06/27

DR. ANDERSEN: Okay, thank you. A couple of pieces of information. You notice Dr. Hill's seat is vacant. He is having trouble making flight connections; he's expected to be in late morning so we'll be patient and he'll join the Marks Team when he can get here.

Bob Bronaugh is sitting in for Linda Katz, and Linda Loretz is sitting in for John Bailey. Enjoy, both of you.

We have some new material. As is our wont, it's not zero but the good news is not huge either. There was the Wave 2 material that was sent out to the panel Tuesday or Wednesday of last week for a look at and then I guess if we had a Wave 3 this would have been Wave 3. It is additional information from the American Chemistry Council relating to formaldehyde. This reiterates the American Chemistry Council view that when you get right down to it formaldehyde isn't a cosmetic ingredient.

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 6/27

DR. BELSITO: Okay. Are we all assembled here? Those who are interested in, I guess, formaldehyde is the first topic. So we have three little new pieces of information here and maybe before we begin our discussion we can take a look at it. And so the first is from the American Chemical Council. And their number one point seems to be arguing to re-label what the ingredient is called. I don't think that's really our purview. Right? That would be up to the Personal Care Product Council and the dictionary people. So I think we can just tell them we appreciate their input but they're speaking to the wrong group of individuals. Is that a fair assessment?

DR. ANDERSEN: Well, I think that's correct. I don't know from Carol's perspective whether the Council has any interest in tackling that question but I don't disagree with Don's remarks.

DR. EISENMANN: Well, I have shared the information with the people at the Council who are responsible for the INCI Committee. It's something -- the process would take a while for that to get complete for that change to be considered.

DR. BERGFELD: Can I ask a question? How do you get in the dictionary? Did not the company file it as formaldehyde?

DR. EISENMANN: Formaldehyde's been in the dictionary for a long time. That would have happened a long time ago so I don't know if it was one of the few ingredients that was in the dictionary to start with. So it may not have had that process at that point.

MR. STEINBERG: Yeah, I'm the one who filed methylene glycol in the dictionary just so everyone knows.

DR. ANDERSEN: What took you so long?

MR. STEINBERG: What took me so long was basically being sent to ECA's meeting in Espera, Italy, about five years ago when they were discussing formaldehyde. And one of the people from -- I want to say it was Great Britain -- said "but formaldehyde is an anhydrous gas, CAS No. 50-00-0. And all this information is methylene glycol." So I came back and that's when I was asked by various parties to file for an INCI submission for methylene glycol citing both the CAS number, the European chemical number, and a report by the CIR in 1993 when you mentioned that we really should have called it correctly. We filed for it. We got the CAS, the INCI designation, but at the same time we did not make any comments that the monograph on formaldehyde should really be removed and shifted over to methylene glycol because that is what is found in cosmetics, not the anhydrous gas.

DR. BELSITO: Okay, but again, I think our panel or team, rather, feeling is that's not something for CIR to be addressing. That's something that goes back to PCP and the people that do the dictionary.

So the second point is to clarify the percentages. And I guess that would go out to the writers. Are all the percentages being done by weight or by volume or do we have any clue as to how those are -- the percentages were reporting?

I always presumed they were weight-weight.

DR. BOYER: And that was my assumption as well.

DR. BELSITO: So if we could just make sure that, in fact, that's what it is as we go forward with the document. Again, the next to the third point has to do with formaldehyde in solution is not formaldehyde. Formaldehyde is a gas. We appreciate that. They don't like formaldehyde equivalents. I really think at this point I like formaldehyde equivalents because I think it forces you to think that. At least when I hear formaldehyde equivalents I immediately think both formaldehyde and methylene glycol. And I think that's what we're trying to get across in this report. That's my own personal view but I'd like to hear from other people here.

DR. LIEBLER: I agree. I was the person who suggested using the term formaldehyde equivalents and I think it's the best way to represent the chemistry of the ingredients.

DR. SNYDER: Don, I just had one question. There was mention of timonacic trioxane and timonacic acid as formaldehyde releasers. Are those two ingredients in the dictionary? Do we know?

DR. HELDRETH: The acid that you spoke of I know is listed but it's just listed as timonacic. It doesn't have acid as part of the INCI name.

DR. SNYDER: Should we be including those since they are considered formaldehyde releasers in this report?

DR. HELDRETH: We're not actually necessarily looking at formaldehyde releasers here. We're looking at two different forms of formaldehyde, whereas there is a list of other formaldehyde releasers that we've talked about in the past.

DR. SNYDER: Is that an agreement on the other panel members that we're looking -- I mean, do we consider methylene glycol a formaldehyde releaser?

DR. BELSITO: No.

DR. SNYDER: No?

DR. BELSITO: Methylene glycol is aqueous formaldehyde. In other words, when you have formalin, my assumption is most of what's in formalin is methylene glycol and not formaldehyde unless you heat it and then formaldehyde comes out of it. It's just a reaction.

DR. SNYDER: Right. I agree.

DR. BELSITO: Formaldehyde releasers, Paul, like quaternium-15 we just reviewed or, you know, DMDM hydantoin, things like that. So I don't think we need to add anything here beyond just formaldehyde.

DR. SNYDER: I agree.

DR. BERGFELD: Can I ask an "I'm not a chemist" question? Why couldn't you say formaldehyde/methylene glycol and take the two --

DR. LIEBLER: Instead of formaldehyde equivalents?

DR. BERGFELD: I think that would be better.

DR. LIEBLER: You could. But of course, in addition to methylene glycol there are the higher polymers --

DR. BELSITO: Paraformaldehydes.

DR. LIEBLER: -- that are derived from formaldehyde that would not be included in that. But that are present in the solution when you have formalin or products derived from formalin.

DR. BERGFELD: Well, we're not talking about any of those in this document.

DR. LIEBLER: Well, they're in equilibrium with, I mean, they're in equilibrium with formaldehyde and methylene glycol. The current version of the report, the chemistry section actually has I think Figure 1 which nicely explains that. So the downside of saying formaldehyde/methylene glycol is that it's probably about 98 percent correct.

DR. BELSITO: Because you have that paraformaldehyde formation to that is going on so there are some other issues. Okay.

DR. BERGFELD: So we're okay with formaldehyde equivalent?

DR. BELSITO: Yes, ma'am.

MS. VERAN: I think the problem that we had at the American Chemistry Council with using formaldehyde equivalents is this will be problematic when you're discussing other forms of formaldehyde methylene glycol as you consider other cosmetic ingredients that might be donor molecules. We understand that in the context of formaldehyde methylene glycol and in the context of cosmetic

ingredients that you are predominately going to be talking about what we call methylene glycol. As you address concerns about things like paraformaldehyde and some of the oligomers, basically again because of the way the equilibrium works and because you do have inhibitors of the formation of these materials in there, and from a practical working perspective, you are predominately talking about methylene glycol in this context.

I think the other part of our comment was really directed toward, you know, we really shouldn't be in terms of talking about these materials, methylene glycol is correct from the chemistry point of view but we certainly don't want anyone to ignore all of the data that have been generated in the past on what was formalin, again called formaldehyde at the time. But we do have major concerns about this comment - about this concept of formaldehyde equivalents because when you're talking about formaldehyde in methylene glycol in the context of other molecules, this is going to get really very confusing. And I think, too, those of us who read your document, even those of us who are pretty experienced in formaldehyde, it was extremely confusing and difficult to understand. And difficult to communicate to our sales people, marketing people, R&D people who are trying to understand the ingredients.

DR. BELSITO: For the purpose of the minutes could you please identify yourself?

MS. VERAN: I'm Jane Veran from International Specialty Products. Our company is also a member of the American Chemistry Council Formaldehyde Panel.

DR. BELSITO: Thank you. Dan, would you like to comment?

DR. LIEBLER: I don't think the issue is really confusion; I think the issue is that formaldehyde and methylene glycol are in equilibrium in any aqueous system. And formaldehyde has many deleterious effects. It's more attractive to represent formaldehyde as methylene glycol because it's present formaldehyde is largely present as methylene glycol and aqueous solution. I think the responses that we've gotten to the report from the American Chemistry Council and the other groups are trying to represent this mixture as methylene glycol and use this as a means of minimizing the hazards associated with formaldehyde. I think it misrepresents chemistry and it actually creates more confusion than I think the well written summary that's presented of the chemistry in the current draft of the report.

DR. BELSITO: So your vote would be to stay with the equivalent phrase?

DR. LIEBLER: Yes.

DR. BELSITO: Okay. Comment back there?

DR. GOLDEN: Yes. Hi. My name is Robert Golden. I'm a consultant with my own company, TaxLogic, but I represent the Protein Keratin Smoothing Council.

I just want to make the point that I think in the past the equilibrium has always been thought of as something that was going on at room temperature. But when this whole issue of heat, which is what these products take advantage of, then of course this equilibrium becomes very important because it is shifted. I mean, the heat does it. That's really -- and I have some

comments for later on, but I think that's something that was never anticipated. That heat would be involved and that equilibrium then obviously becomes different. It's shifted.

DR. BELSITO: Okay. Any other comments? Rachel.

MS. WEINTRAUB: Yeah, I just wanted to get us back one minute to the reason why the lexicon and the language here is actually important. And in terms of going back to the beginning, isn't the reason why we're all doing this and focusing on this so specifically and why there is such a big impact for consumers, because there are a number of products that contained high levels and stated that they contained methylene glycol but stated they were formaldehyde-free? So I think we are trying to get to the root of that in consistency which ultimately was a very confusing and not necessarily true statement for consumers and for all those involved in using and purchasing this product.

DR. BELSITO: Yes.

MR. STEINBERG: When we received the approval of the methylene glycol as the correct INCI designation for the reaction anhydrous formaldehyde gas with water, it was the intention of the manufacturers of nail products, which is the people who sponsored getting the INCI name, that all products be labeled, "Caution. If you're allergic or sensitive to formaldehyde you will be experiencing the same type of reaction with this product." It was never the intention to hide to the consumer like some people -- some marketers have done. It was always our intention to label it correctly scientifically and then also have the caveat that if you are sensitive, etc. And this I think should hold true to the preservative area and the other use of this chemical moiety in cosmetics.

DR. BELSITO: Thank you. Okay, so to return to how we referred to whatever it is we are referring to in this document, it's been suggested by Dan that it's his feeling that we proceed with formaldehyde equivalents having defined formaldehyde equivalents as being formaldehyde, paraformaldehyde, methylene glycol, everything that happens when you put formaldehyde gas into an aqueous phase. So again, that's a decision, we've heard input, that our team has to make. So Dan, you feel formaldehyde equivalent. I was happy with that.

DR. LIEBLER: Yes.

DR. BELSITO: Paul? Curt?

DR. KLAASSEN: Yes.

DR. SNYDER: Yeah, again, only in the context of what we're reviewing in this document. Because if you go to page, excuse me, page 268 and the information that was distributed by the --

DR. BELSITO: This is Panel Book page 268?

DR. SNYDER: Yeah. Panel Book page 268. That first big full paragraph after the bullet points has the last sentence there. And this is the issue I was trying to raise earlier in that while I understand that we're only obligated to what's in the dictionary but there are regulations that deal with the labeling of things as formaldehyde preservatives which encompasses a broad range. And I think we need to be careful that we're not inferring that we

are including those in this assessment. And I think that that kind of goes to what Rachel is talking about in regards to we need to define very clearly what we're evaluating in this document.

DR. BELSITO: Well, we're evaluating formaldehyde and methylene glycol and what we're looking at is the ability of those two chemicals to generate what we're calling formaldehyde equivalents, which are basically formaldehyde, methylene glycol, paraformaldehyde, and all the other stuff.

DR. SNYDER: But we're not categorically evaluating formaldehyde preservatives.

DR. BELSITO: No. Not at all.

DR. SNYDER: Okay. Just so we're all on the same page.

DR. BELSITO: Okay.

DR. ANDERSEN: I guess the question, Paul, would it help in the introduction if, in fact, we explained some fundamental differences? Certainly, methylene glycol and formaldehyde essentially form an identity. Whether we believe quaternium-15 is a formaldehyde releaser or not, it's a different ball of wax in terms of the behavior of quat-15 in producing formaldehyde. It doesn't look anything like what we're dealing with here in terms of methylene glycol and formaldehyde being the flipside of each other. And that -- I don't think it would be that difficult to explain that that's a different ball of wax and that we're not dealing with it in this report.

DR. SNYDER: I agree. I think we need to make it clear almost as important that what we are evaluating as what we're not evaluating.

DR. BELSITO: Okay. Point well taken. But if I'm hearing everyone correctly, to summarize we're staying with formaldehyde equivalents now as the discussion of the document.

Fourth point from the ACC, analytical methods. I have no comment. That's not my area of expertise. So people? Bart? Comments on their comments on analytical methods?

DR. HELDRETH: I mean, certainly from a synthetic organic chemist's perspective, we love NMR and that makes some sense to me to look at things with NMR. But the truth of the matter is whatever sample you take that you're going to put in the NMR and look at, you're going to put it in deuterated water. So even if you somehow got an anhydrous sample, you're still instituting the same equilibrium that's occurring whether or not you use the hydrazine method that OSHA is using or some other derivative method. So it just kind of pushes the matter back a point as to are you measuring methylene glycol or formaldehyde, whereas I don't think we really care so much which one it is. It's a formaldehyde equivalent regardless of the measurement method.

DR. GOLDEN: I'm sorry. Once again I think this issue of analytical -- and maybe this would be an appropriate time for me to just put my comments in because I'm going to have things to say about all of these points. Would it be permissible to do that?

DR. BELSITO: Sure.

DR. GOLDEN: Okay. Let me just get these. I think I have enough copies to give to everyone. I went through -- let me just pass those along. Do you need one more? Sorry.

As I had said just a few minutes ago, I'm here on behalf of the Protein Keratin Smoothing Council. We think that the CIR has obviously taken a reasonable and responsible approach to this whole complicated issue and this organization has also taken a reasonable approach to safety testing of these products because I think the, as I said, the introduction of heat is a big game changer here. Both OSHA and NIOSH emphasize that test methods need to be consistent with the nature of a product and we agree that testing methods also must be consistent with specific products and potential risks.

But that really isn't the case right now. Because the current test methods that are used to estimate the release of free formaldehyde or formaldehyde equivalents or however that's characterized, they rely on some analytical methods that use acidic pH conditions and these derivatives that were just mentioned. And obviously heat to create excess free formaldehyde and overestimate.

Now, we're talking about in the product itself, the potential for exposure to stylists and consumers. I think that this C13 NMR is really the only methodology, at least in terms of the analytical conditions, doesn't perturb the equilibrium in the way that the OSHA methods and the other methods that have been used because -- and if the HPLC methods are used, the proper equilibrium constant must be applied to be able to accurately account in the presence of heat free formaldehyde from methylene glycol.

But really the primary focus ought to be on salon air monitoring and not what's in the bottle, as measured by some inappropriate methods. The monitoring clearly demonstrates that when these kind of smoothing products are properly performed, exposure levels are below OSHA and ACGIH limits. Really, this air monitoring is the most important component of ensuring that the in use of these products does not exceed exposure levels capable of causing sensory irritation.

I think the warning labels have to explicitly state the manner in which these products should be used to avoid the symptoms of sensory irritation and stylists should be warned, operators should be warned that if sensory irritation occurs this is the warning. And these processes, these procedures ought to be discontinued until proper ventilation can be instituted. The idea of ventilation is key to this whole thing because these products are only formulated for use in salons where everyone is trained and knows how to do it. And I know a big issue is where people are using these products in their homes and in basements where ventilation isn't adequate and then, of course, sensory irritation does occur.

Interestingly, it is methylene glycol in these products, that is the active ingredient. It's not formaldehyde. Formaldehyde is generated as an incidental byproduct. Excess formaldehyde I should say just because of the use of heat because this does involve using flat irons to raise the temperature. I mean, that's the whole idea to try and get the curliness out of hair and then lock it in with this methylene glycol.

In the coming months the Council will utilize an independent testing laboratory that's being lined up as I speak to perform air monitoring studies

to measure workplace exposure as well as studies to empirically measure the free formaldehyde methylene glycol in the air when different keratin smoothing products are in use. In other words, formulations with different concentrations, starting concentrations of methylene glycol. And these data will be submitted to the CIR for consideration and for this reason we are requesting postponement of a final decision until this can be completed because this ought to get to the bottom of the analytical method and what the actual air concentrations in a salon would be from the use of these products.

This organization is ramping up the efforts to teach stylists and salon operators how to control exposure through proper ventilation and to eliminate sensory irritation and we'll be developing a training program and a manual for operators and stylists.

And then this whole idea of warning labels. They must explicitly state conditions under which products can be used in salons with appropriate ventilation to eliminate sensory irritation. And just a point which is in my area. I'm a toxicologist. Keep in mind that formaldehyde circulates in us as methylene glycol. I mean, that's the way it's there. For some reason it's called methanediol in biological systems. I don't know why that is but it's the same thing. And the formaldehyde that we're all exhaling right now is a result of this methylene glycol formaldehyde equilibrium and the little bits that leak out of tissues in the upper respiratory tract, we are exhaling around upper level about two parts per billion.

In the absence of sensory irritation there is no risk of nasal tumors or any other health effects. And I've put in a link here. I just had a very extensive review published in Critical Reviews in Toxicology. I would suggest maybe you'd be interested in seeing that. There are actually two papers there. They're online.

They're open access so anyone can get those. There's my paper and another one by Lorenz Rhomberg, who looked specifically just at the whole formaldehyde leukemia weight of evidence.

And my final point is that we suggest that the CIR recommend that cosmetic products not exceed 2.6 percent methylene glycol, which is equivalent to 0.002 percent free formaldehyde as measured by either ¹³C NMR or if by HPLC with the proper equilibrium constant to determine the concentrations of free formaldehyde and methylene glycol in the product as it sits on the shelf.

And of course, these amounts, that's in the bottle, and when a bottle is opened and actually used, that amount, whatever it is, is into the air of whatever the size room is and whatever the ventilation conditions are, which in a use situation, of course, is far less than what would be measured out of the bottle. And we think that this would help eliminate the confusion and over-reporting of potential for exposure when these measurements are made just of something in the bottle which can't be equated to actual inhaled concentrations.

Any questions?

DR. BELSITO: Question for you, sir.

DR. GOLDEN: Yeah.

DR. BELSITO: I understand where you got the 0.002 percent based upon our prior limits, but we also said that we couldn't assume that that level was safe for aerosol products. So why are you now assuming that that level would be safe for aerosol products?

DR. GOLDEN: Well, I would assume that they would be safe because of measuring -- in an actual use situation what the air measurements would be. And in our comments you will notice there was some extensive testing by E^xponent and there's more than just that. There's a lot of data that when these products are in actual use conditions where ventilation is adequate the measured amounts in the air all fall well below the applicable standards.

DR. BELSITO: I seem to recall that even some of the information that was submitted by your Council showed that they fell above applicable standards.

DR. GOLDEN: I don't think so. I think if you look in the comments, they were -- now, I think there were some data shown there where they weren't measured accurately or the amount measured was in the bottle but not in the salon air.

DR. BOYER: Well, CIR also summarized some of the data, the same data that you're speaking of. And granted, if the ventilation is adequate that there will be some substantial differences between the standards and so on. But that's not always the case. Even that data from those studies, exponent and so forth, if you look carefully at the data there are many instances where those concentrations approach the standards and in a few instances where they exceed the standards under the conditions of those studies.

DR. GOLDEN: Well, but isn't the key here to avoid sensory irritation? I mean, that's really the --

DR. BELSITO: The key is to avoid exceeding standards that have been set by various governmental agencies.

DR. GOLDEN: Well, and --

DR. BOYER: Just to clarify also, the standards we looked at were not just the standards for occupational exposure but there are also at least a couple that were applicable to -- that are applicable to residential exposures to avoid irritation. That's true and there have been several researchers' published papers. I think yours is one of them, Dr. Golden, indicating that if you protect people against the potential irritation from formaldehyde then there probably is no concern for the potential carcinogenicity of those exposures.

DR. GOLDEN: Right.

DR. BOYER: But that is still a matter of debate and a matter of which mechanisms or combination of mechanisms of carcinogenic action that you accept.

DR. GOLDEN: Well, and what I've recommended is consistent with what the World Health Organization has recommended as well. I mean, the same idea. And --

DR. BELSITO: Why don't we hold this and then get back to it when we have specific discussions on use in hair keratin products? Because what I'd like to do is address all the new information.

So for Point 4 what I'm hearing is NMR is one of the techniques and that we need to maybe have a little bit more discussion on the pros versus cons of different ways of measuring formaldehyde in the report. So maybe, Bart, when you do that you can make a little bit more explanation.

DR. HELDRETH: Just one other thing I would like to add is the standards that were set that we're comparing everything to were set using the hydrazine to hydrazone derivative formation.

DR. BELSITO: Okay, so then --

DR. HELDRETH: Comparing the NMR data to that data isn't necessarily a direct comparison.

DR. BELSITO: Okay. So --

DR. HELDRETH: I think the standards would have to be set by NMR data to use that as a limit. So I think that at this point it's kind of odd to step outside the method that I was just using and use a different method and say they're necessarily comparable.

DR. BELSITO: Okay. So I think that's an important point then that needs to be clarified that all government regulations, the WHO, yadda, yadda, yadda all were set with hydrazine methods. So then that should be stated and that always should be compared and we can mention NMR but obviously the gold standard here is to use hydrazine.

Toxicology. The ACC wanted us to include two references. Could someone comment on does that change our view of the toxicity of formaldehyde/methylene glycol? Or just to be complete? Was there a reason why we would add those two references? Is there something there that we haven't heard about in the current document?

DR. BOYER: In my opinion there's nothing new there. It's -- these are reviews. They do a very good job of supporting the argument that we're dealing with a threshold as opposed to a non-threshold mechanism of carcinogenicity and so forth. They're very well written papers and so on. But I think we've pretty much got all of that covered in our current draft.

DR. BELSITO: So we can include them but it's not going to change our opinion of anything that we've seen so far?

DR. BOYER: I would say that is correct.

DR. BELSITO: Dermal irritation, sensitization, that's a no brainer. So Point 7, clinical use, adverse reports in Canada, cosmetic ingredients in hair smoothing products should be changed from formaldehyde gas to methylene glycol. I mean, it's what is on the label so I guess I wouldn't have an issue with that change. Dan?

DR. LIEBLER: Fine.

DR. BELSITO: Okay. Non-cancer effects. Use appropriate scientific nomenclature. Experimental animal studies referred to in this section were dosed with a formaldehyde solution. No need to use quotes around formaldehyde. The others seem -- Point 9, exposure, line 2, urban air. Fine.

Ten. Formaldehyde methylene glycol as a preservative. So I guess the issue there is what to call what they used. Nasopharyngeal cancer, misleading. Was statistically associated with peak exposures of occupational workers based upon atypical grouping of peak exposures which were reported to be above 5 milligrams per meter cubed.

Okay. I don't recall this. I guess -- Paul.

DR. SNYDER: Yeah, I just have to relook at the wording on that and --

DR. BELSITO: Maybe do a little wordsmithing later.

DR. ANDERSEN: Don, there's an issue regarding the process of going through this stuff that's increasingly bothering me. By submitting something on the 23rd and then we'll get to the nail manufacturers on the 24th, these late arriving comments are getting detailed reviews that I'm not sure they're worthy of. I mean, not to suggest that the comments aren't decent; it's just we're focusing a huge amount of attention on that and we're not -- we probably wouldn't go through line by line the comments from the consumer group that submitted stuff a week earlier.

This is a process question not relating to the validity of the comments. I'm just a little bothered by the attention that they're getting. We, of course, have to consider all of this as input in looking at each and every section in the report in whatever its next incarnation is going to be. But there's a level of detail here that unless there's something fundamental that the panel thinks needs to be talked about or your dean thinks needs to be talked about, I wouldn't spend much time.

DR. BERGFELD: It's almost done.

DR. BELSITO: Well, I guess the only reason that I --

DR. ANDERSEN: Yeah, but there's nail manufacturers to follow.

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.

But I guess my point is this is a final, Alan.

DR. ANDERSEN: Yeah.

DR. BELSITO: You know, the whole purpose of going out for 60-day comments are to get comments. And, you know, this is going to be our last chance to discuss all the comments that have come in and decide what to do. So, I mean --

DR. ANDERSEN: It's a frustration that these are legitimate comments. Ostensibly they are provided within a comment period. I didn't look at the dates that closely but it's just the phenomenon that the last stuff coming in seems to get the most attention is just -- it perplexes me.

DR. BELSITO: I'm not sure that it's getting any more attention than what came in earlier. The difference is the attention that what came in earlier was given to it last night and Saturday night and Friday night and Thursday night.

DR. BERGFELD: I think if it was longer and it wasn't so short --

DR. BELSITO: We'd table it.

DR. BERGFELD: -- you'd table it.

DR. BELSITO: Yeah. Okay. So I think, Paul, you'll look at that aerosol.

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. LIEBLER: Don, I don't think all the products that are used for hair straightening actually contain methylene glycol.

DR. BELSITO: This was Brazilian Blow-Out.

DR. LIEBLER: Oh, it was Brazilian Blow-Out?

DR. BELSITO: When I called the salon operator afterwards I said your product doesn't contain formaldehyde? He said no. I said what does it contain? He said methylene glycol.

DR. LIEBLER: Yeah.

DR. BELSITO: So, you know, he had no clue. He did know that it needed proper ventilation and it appears, at least from her sensory experience, that that occurred at the salon she used. But --

MS. WEINTRAUB: I have a number of points to make about this but one that relates directly to yours, I've had a number of anecdotal experiences as well. During the week that we reviewed this last time both a good friend and my aunt, who is actually a pediatrician in New York, had this process done. And in New York, my aunt had this done in someone's home. And there was a child in the dining room sitting next to the person who was putting this on her hair. And this just happened, you know, it's just information that came to me. She was very excited about this new hair experience and it just is incredibly disconcerting because I think the ability to control how this product is used in the places is very difficult. And I think the manufacturers need to take responsibility for what is not only in the bottle but what is necessary for the proper use and the intended use of this product which obviously involves the use of heat.

Further, I've spoken to two different stylists who use this product and I've asked them about their ventilation procedures. And these are both well-respected salons and it varies widely.

One defines ventilation by being near a window that could be open; one involves having a fan. I think from my limited anecdotal experience, ventilation and what that means, how it's applied in different salons varies widely across the board.

DR. GOLDEN: Can I make a comment? Well, I think this speaks to exactly what I was talking about, that the professional users of this need to be the ones -- obviously, you can't control it if it gets into somebody's home and somebody's basement. But the professionals who do this, I think that they are committed to dealing with this through proper ventilation. I know there are devices that are coming on the market that would augment just in an area working other than this sort of thing doesn't control it properly. There have to be devices that are directly over a client's head to pull the fumes off with substantial higher efficiency than the typical HVAC system in a building.

But I will also -- you mentioned your daughter. My daughter had her hair straightened just recently in Florida, also in someone's home, with fans blowing and masks on and she still had some sensory irritation. But she did say to me, and I think this is really in a sense the bottom line here, she said, "Dad, I'd put up with a little more sensory irritation to get hair that looks like this." I mean, that's really what -- consumers want this and I think the challenge is to be able to not drive it underground, to have it in situations where the ventilation is adequate and it's controlled and where users and operators are cognizant of these kinds of issues.

MS. WEINTRAUB: If I may, I think what this conversation points to is exactly the opposite of what you're saying it points to. I think that what this shows is that as a cosmetic manufacturer and as our role as the Cosmetic Ingredient Review, we need to focus on what we can control in a use pattern where there are many factors that we cannot control. And I think our responsibility is to limit the chemical that's causing this harm as much as possible from the beginning stages of the use of this product which means, you know, in the bottle of your product but looking at what's going to happen when it's used as intended.

DR. GOLDEN: Oh, I agree. I agree completely. And I think that's why it has to be addressed in that way and that's through obviously controlling what's in the bottle. But where the rubber hits the road is when it's taken out of the bottle and it's heated and slightly differently but that's a ventilation issue because they are clearly products that people want.

DR. BELSITO: But, I mean, yes, of course, they're clearly products people want but then, you know, I have to go back to settle the point that Rachel is getting to, too. Even if you were to say, okay, this is for use by trained professionals then how do you regulate the ventilation systems that those trained professionals will use? Clearly, even the data that you submitted shows that, I mean, one has to assume that that could potentially be biased since it's coming from your Council and it certainly shows data somewhat better than we got from Oregon OSHA or Tennessee OSHA that it's going to be used in a salon under proper ventilation techniques. I think that that's the issue.

If we go out and say, you know, this is safe, what are you going to do? You're going to sell it only to someone who buys, I don't know, for lack of a better word, a P3 ventilation system for their salon and regulate it to those people?

I don't think you can do that. Then you have, you know, you have essentially a product that's out there and can be used in fashions that we have decided really it should not be used.

DR. LIEBLER: I propose that we really focus on what our role is in this overall situation. Dr. Golden's comments about his daughter really illustrate the larger issue before us in many areas of life in America which is the balance between regulation, personal choice, and risk. That's not what this panel is dealing with.

That's a larger issue that's going to have to be dealt with in other ways.

The issue before us is the safety of the ingredient used in a product. And the safety of the ingredient used in the product is in doubt depending on the

conditions of use. And, you know, we typically use the term "safe as used" or "in the present practices and conditions of use." The "present practices and conditions of use" for this product or for this family of products is going to vary tremendously and it's something that we don't have any way of knowing or controlling.

The PKSC has pointed out things that could be done to make the use of these products more safe but that doesn't really change the core issue of the safety of the ingredient and the product under the present conditions of use which are highly variable.

So I think that we ought to not be driven as much by our perception of how the product will be used as much as the available data which does speak to the issue of relatively high levels of formaldehyde under conditions of use as they currently occur.

DR. BELSITO: Okay. So then --

DR. BERGFELD: I'm sorry. What you're really stating is we should control the concentration?

DR. BELSITO: No, what he's stating is the data are insufficient for products that might be aerosolized.

DR. LIEBLER: Exactly.

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.

So then the issue becomes are we changing the concentrations? This is sort of like the other one that I picked up where it should have been 0.1 instead of 1.0 or something but our argument for setting the limit was based upon dermal sensitization and irritation and that was with, quite clearly when you read the document, 0.2 percent formalin, not formaldehyde.

DR. BERGFELD: I think you have to change it.

DR. LIEBLER: I agree.

DR. SNYDER: Sure.

DR. BELSITO: 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.

DR. EISENMANN: Back to the 0.07. Now,

if it's methylene glycol, isn't it a little bit higher? Isn't it 59?

DR. BELSITO: 0.074 percent formaldehyde equivalent.

DR. HELDRETH: Yeah, I mean, this is just --

DR. EISENMANN: Because isn't this by weight -- I mean (inaudible).

REPORTER: Your microphone.

DR. EISENMANN: I'm a little confused myself about, you know, if it's methylene. If it's by weight it might be a little higher.

DR. HELDRETH: Yeah, I think it just comes down to defining what we mean. It comes down to perception. I think at the time when we said 0.2 percent formaldehyde people were thinking formalin, you know.

DR. BELSITO: Right.

DR. HELDRETH: But we said it was formaldehyde. And I think that's common globally. I don't think it's a mistake. I think it's just the way the people referred about it at the time. But now we're kind of splitting the two hairs into methylene glycol and formaldehyde. And so I think if we change that from 0.2 to 0.074 I think she's right. I think we need to be clear. Are we talking about methylene glycol? Are we talking about formaldehyde? I mean, maybe we're talking about both but I think maybe some clarity would need to be instilled.

DR. LIEBLER: Well, we can deal with that by simply saying but in no case should formalin exceed -- formalin content exceed 0.2 percent. You could say that. You could also say parenthesis formaldehyde equivalents and then use the lower 0.74 number.

DR. BELSITO: I mean, 0.2 percent formalin is actually what was tested. So I mean, that's -- and formaldehyde put into water is what's called formalin and then there's methylene glycol in there and paraformaldehyde. So actually formalin may be the better way to say it.

DR. LIEBLER: Isn't that literally how these products are made?

DR. BELSITO: Yes.

DR. LIEBLER: Formalin is included as an ingredient? Or is anhydrous formaldehyde gas bubbled into the product during manufacturing?

MR. STEINBERG: No, it's always bought as the commercial solution of formalin which contains methanol, water. You can purchase anhydrous formaldehyde. It's a real interesting product to work with but no one in the cosmetic industry has a container of this at all.

DR. LIEBLER: Right. Right. Not surprising.

DR. SNYDER: My preference would be the latter. To stick to the 0.2 percent formalin. And I'll just reclarify what we're stating in formaldehyde equivalents.

DR. BELSITO: Okay.

DR. SNYDER: That way there's less -- maybe there will be less confusion.

DR. BELSITO: Okay. So at this point we're really not changing our conclusions at all.

So can we look at the nail products now? What do we want to do?

DR. BERGFELD: Could I ask a question about the -- you said formaldehyde equivalents. Now you're saying formalin?

DR. BELSITO: No, 0.2 percent formalin.

DR. BERGFELD: I know. I know. But you said --

DR. SNYDER: But in the intro we're clarifying what that represents.

DR. BERGFELD: Okay.

DR. SNYDER: In regards to formaldehyde.

DR. BERGFELD: You probably have to clarify it in other places.

DR. LIEBLER: I think actually the report -- I should say the report sections having to do with the chemistry are really beautifully written out. I mean, it's very nice. I want to offer my compliments to the staff, particularly Bart, who have done this. And I think it's very clear what the relationships are between formalin, formaldehyde, methylene glycol, and the other related chemical forms from our document.

So even though in our document in many cases we refer to formaldehyde/methylene glycol or formaldehyde equivalents, it's appropriate still to have formalin in the conclusion because that's literally the ingredient that's used to make the products.

DR. BELSITO: I think that's very good, Dan, to bring that up. Yes, David.

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 Shone 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. BERGFELD: I'm having trouble with the hair product in the fact that you're concerned with what is aerosolized or vaporized because of the nasal irritation and the carcinogenicity of that over long term. We have never looked at a device associated with a product. We have dealt with a chemical and its concentration, whether it be in vapor or in the product itself and what it does.

So what we have done is to limit it in such a way that we can stay confined to the safety, even if it was vaporized. So I'm not understanding why we can't go there now. Is there a concentration that's vaporized that's safe?

DR. BELSITO: No.

DR. BERGFELD: Zero?

DR. BELSITO: Well --

DR. LIEBLER: I think it's because we can't control -- what we're saying is we can't control the use and exposure.

DR. BERGFELD: But you can control what's in the bottle. So what would be vaporized from the bottle could be minimized.

DR. BELSITO: Yeah, I mean, I suppose we could do that but we would come up with such a low level. I mean, so what you're saying is come up with what is the ambient concentration of formaldehyde in the air and come up with a level of methylene glycol/formaldehyde that could be used in a product that even if the equilibrium was driven to 100 percent, it was all formaldehyde, it wouldn't make a difference. Well, that level of formaldehyde would be too low to be of benefit to anyone in the cosmetic industry. It would essentially, I think, be below the level we set for leave-ons. There was some, I mean, what is it, 30 parts per million is below sensory detection level. I don't remember all that data.

DR. BOYER: Yeah, I think the highest concentration that is associated with irritation based on the AEGL level is about 0.9 parts per million. And 0.08 parts per million is probably not going to cause any irritation.

DR. KLAASSEN: In the air?

DR. BOYER: In the air.

DR. BELSITO: Right.

DR. BOYER: And we also may want to consider that the risk assessments are really up in the air right now. We would have a great deal of difficulty pinning down just what the risks would be with any specific concentration of You could look at the backgrounds as you mentioned, the ambient air backgrounds of formaldehyde, but even those vary quite a bit depending on where you are and so forth. So it would be quite a challenge to do that.

On the other hand, if you have -- if you have 0.2 percent threshold, guideline level standard and so forth in the product, it seems pretty clear that you're not going to be altering the background air concentration for formaldehyde. We just haven't seen any reports. And it's just not likely that that's what's going to happen. So basically the risks, additional risks at that level would most likely be very, very low.

DR. BELSITO: I think the only time when we really got involved in control, for lack of a better word, was with the acrylates and nail enamels where it was simple to say it's a salon product and you need a shield and no cutaneous contact rather than an issue where we're trying to control heating and exposures to air and so many other variables.

DR. BERGFELD: Well, we didn't say what kind of shield. We didn't say what kind of training program. We were a little bit generic on that. So on this we could be generic with it should be, in some way the ventilation should be appropriate so that there was no risk or the consumer or the beauty salon operator.

DR. BELSITO: Yeah, but I think that the reality of that is if you go to, you know, a number of nail salons using acrylics they're not using nail shields and the downside of that, yes, is eczema in some cases with acrylics, some permanent paresthesia of the nail tips, but you know, here you're talking about risk of potential, you know, nasopharyngeal carcinomas in individuals who, you know, it's like secondhand smoke. You choose not to smoke but someone next to you is smoking and you suffer the consequence. You're at a beauty salon and someone next to you has agreed that they don't care about formaldehyde exposure but you might. So, I mean, I think these are all -- this is a much more difficult issue than we've tackled before, I think.

DR. GOLDEN: But sensory irritation, if that was the controlling variable, if sensory irritation did not occur, I mean, analogous with the nail situation in terms of air concentrations, wouldn't that be -- wouldn't that be where the rubber hits the road on this sort of thing? If no one could detect it through sensory irritation, eye irritation in particular, which is the most sensitive?

DR. BELSITO: I understand. But, you know, as your daughter said, I would put up with it. I mean, beauty salons, there's a lot of sensory irritating chemicals. If you're ever smelled a permanent solution, it's very sensory irritating. However, the inhalation of that product does not result in nasopharyngeal carcinomas or other toxicological endpoints of concern as potentially formaldehyde does. So I think, you know, I mean, I can't stand the smell of nail polish. You know, it's a highly sensory irritant to me but, you know, you go to a nail salon, that's all you can smell.

DR. GOLDEN: But if no one had sensory irritation from these products that would be a level that really couldn't be equated with, I mean, other than how EPA regulates it in a linear through zero model. But in a practical sense

and a biological sense, if there's no sensory irritation there is no risk of any adverse health effect.

DR. ANDERSEN: I think the question that's on the table is what number in terms of what's in the bottle does that correspond to?

MS. MASON: Thank you. I'm Ann Mason with the American Chemistry Council. In our comments of the 23rd that we've talked about, point number one asks a question about content. And I think it's relevant for this particular situation. What the right number is I personally cannot tell but OSHA has decided that if you have a -- if you have a product capable of releasing formaldehyde gas at concentrations reaching or exceeding 0.5 parts per million then you have to label that product within an occupational workspace.

What we would suggest is that whether you accept that 0.5 parts per million or not there at least is a standard that's out there by a governmental agency that's looked at the health of workers and that we would ask that you consider using that as one of the questions about content because you can say if a cosmetic product releases formaldehyde gas by whatever constituent it is inside the product, it's releasing the formaldehyde gas, which is, I think, what you're concerned about, that you would include the words "contains formaldehyde generating ingredients." And therefore, there would be a trigger that you have exceeded an OSHA standard. That at least is a suggestion of a possible way to go forward. This would be an additive to the 0.2 percent that you've just spoken about. Thank you.

DR. ANDERSEN: Taking that though to the next level as Dr. Bergfeld was suggesting that there is some concentration in hair-smoothing products that will without adequate ventilation exceed that number. And the question I think that Dr. Bergfeld is putting on the table is if we could define what that number is, higher than that would be unsafe. You know, cut right to the chase. And I'm not sure that I can figure out from the discussion so far what that number actually is. It's probably, if we applied the 0.2 percent formalin across the board, my guess is we don't have a problem with hair smoothers. I don't think that, as Don pointed out earlier, I don't think it becomes a viable product at that point but to some extent that's not our problem. The two-tenths of 1 percent formalin from a lot of different angles is a number that we're comfortable with. Maybe that's how you do it.

DR. BERGFELD: Well, if you would do it that way then it's up to the industry to come back and demonstrate safety if they want it higher.

DR. GOLDEN: Well, I was going to say exactly that. As I mentioned, and it was very brief, we're in the process of designing studies that would actually test that. Different concentrations of methylene glycol, what are the consequences in the air, not in the product itself. But I think that goes to exactly what we're discussing. What are the consequences? It would have to be in a situation with adequate ventilation and the room size. I don't know how that would exactly be done but it's to test that exact proposition. There could be collaboration on what concentrations ought to be tested. I think that would be fair but then we would not have the dilemma that obviously you're facing right now as to trying to use the word that Alan used to try and define something. There could be actual data.

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. BELSITO: Okay. Any other comments from the team? Let's move on.

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. ANDERSEN: I think as the tentative report went out, everything that you're now saying was included. So any interested party had ample opportunity to provide input. We understand there are more data to come, but there's a 60-day clock on this. We're trying to move this stuff along. So I think there is no reason that you couldn't issue a final amended safety assessment. The only downside to doing that is that it sounds to me like you are going to get more data later this year, and you may have to reopen it to deal with those data. And I think for purposes of informing consumers as to what the heck's going on, issuing a final amended safety assessment is an accomplishment that we should strive for.

DR. BELSITO: Well, our next meeting is -- well, we have 60 days now? Is that it? So --

DR. BERGFELD: September.

DR. BELSITO: Well, we have 60 days now? Is that it?

DR. ANDERSEN: Yes, the comment period is 60 days.

DR. BELSITO: So this could come back in September?

DR. ANDERSEN: Yes.

DR. BELSITO: Okay.

DR. ANDERSEN: Or you could finish it now and reopen it when new data are available.

DR. BELSITO: Right. Let's finish it. But I would like to stress, though, I guess in my comments also is that perhaps -- I don't know if Consumer release or CIR or both of you. Is that when your hairdresser says that that straightening product has no formaldehyde in it? Please ask them if it has methylene glycol in it because they don't know that methylene glycol becomes formaldehyde when it's heated because this guy -- I mean, you know, I mean he's very honest. I asked him, any formaldehyde? Oh, no. I said, what are the ingredients? He goes, methylene glycol. I said, well, that releases formaldehyde. No one told me that.

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 -
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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: Okay. Anything else with the benzyl alcohol, acids, salts, and esters? If not, we'll move onto methylene glycol, which is the cosmetic ingredient, and the formaldehyde, which is not.

DR. ANDERSEN: It's in the dictionary.

DR. MARKS: Okay. And did Ron, Ron, and Tom, did you get to review the American Chemical Council --

DR. HILL: I didn't.

DR. MARKS: -- letter dated June 23rd that was given to us this morning. Let me give you this. And there's also a letter dated June 24th from the Nail Manufacturers Council.

DR. HILL: I didn't see either one of these, did you?

DR. SHANK: Yes.

DR. HILL: You saw them?

DR. SHANK: Mm-hmm.

DR. MARKS: So I think we look at the -- so at the March meeting, a tentative amended safety assessment of formaldehyde and methylene glycol was put forth with a three-part conclusion. And in the memo from our fearless director dated May 23rd in our Blue Book, the first has to deal with the formaldehyde/methylene glycol safe for use as a preservative in cosmetics when formulated to ensure use at a minimum effective concentration, but in no case should formaldehyde equivalent succeed 0.2 percent.

My question there was should it be 0.7 percent? But there's also, when you read the comments from the American Chemical Society or Council concerning the use of formaldehyde equivalents.

So how do you -- shall we go down each parts of these conclusions? That's really the meat of it is, one, the limit and how do we identify that limit? Do we use formaldehyde equivalents? Do we use methylene glycol? When we set that limit and then, again, as I recall when I looked through the sensitization studies, they were with formalin. And so that's how, in reality, if you take 37 percent of 0.2 percent, you come up with 0.07 percent, which is closer to what the sensitization level would have been in those studies in a safe level.

DR. SHANK: I agree. Has it been confirmed that those sensitization studies were formalin?

DR. ANDERSEN: Yes.

DR. SHANK: Okay. Good. Then that should be changed from 0.2 to 0.07.

DR. MARKS: Mm-hmm.

DR. SHANK: I like the term "formaldehyde equivalents." It's explained very clearly at the beginning of this report, and I think we should stick to that. Formaldehyde is a dictionary term. I think we have to use that. So I don't see any point in discussing calling everything methylene chloride.

DR. MARKS: Mm-hmm.

DR. SHANK: I think "formaldehyde equivalents" is a better term.

DR. MARKS: And that alerts the reader to delve into more what is meant by formaldehyde equivalents rather than switching over now after the historic and what the public -- and is Rachel here or somebody? -- what the public would think in terms of interpreting them.

So Ron Hill, Tom, do you like the formaldehyde equivalents?

DR. SLAGA: I do, too.

DR. SHANK: A lot of the toxicology literature is under the formaldehyde not under formalin, not under methylene glycol, methanediol.

It's under formaldehyde, even though they didn't use the gas.

DR. MARKS: Right.

DR. SHANK: So I think we should keep it.

DR. HILL: The difficulty comes for agents that have formaldehyde equivalents in their structure but where formaldehyde is not quickly released kinetically. So an example would be hexamethylene diamine. So I'm not sure exactly how that gets dealt with in the writing because there can be a large number of formaldehyde equivalents there, but they're inconsequential in terms of toxicology.

DR. ANDERSEN: Well, there are other cosmetics preservatives that are generally understood to function as formaldehyde releasers.

DR. HILL: Right.

DR. ANDERSEN: They are substantially different as we look at them in terms of that whole dynamic equilibrium between the releaser and formaldehyde. It's not like it is for methylene glycol and formaldehyde. I mean, they're similar in that it's an equilibrium, but it is a slow process, not the essential identity between methylene glycol and formaldehyde in water.

DR. HILL: Correct. Yes. I agree.

DR. ANDERSEN: So it makes sense to add something in the introduction that alerts the reader to what we're not talking about.

DR. HILL: Right. And then we're good. Yeah.

DR. ANDERSEN: We tend to stay away from telling people what we're not talking about, but in this case --

DR. HILL: We need to clearly.

DR. ANDERSEN: -- that may have some utility.

DR. HILL: Good point.

DR. ANDERSEN: And we talked about that last time. I'm just making sure we think about it again.

DR. MARKS: Any other comments about the first portion of the conclusion?

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DR. SHANK: Yes.

DR. MARKS: Okay.

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: This is the first bullet.

DR. MARKS: Yeah. Are we looking at the same page?

DR. SHANK: No. I'm under Conclusion, the last page.

DR. MARKS: I'm sorry.

DR. SHANK: Page 76 of the book, page 18 of the report.

DR. MARKS: Seventy-six. Yes. Okay. Now I got you. I was looking at the memo.

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. ANDERSEN: Change the number to?

DR. MARKS: 0.07.

DR. SHANK: 0.07 percent. Right.

DR. MARKS: Okay. Shall we move on? Now I understand why I was trying to -- what you were saying. 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, -

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DR. MARKS: Yeah.

DR. ANDERSEN: I'm having trouble with what the group titles were -- did present antidotal 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, error 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 antidotal 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.

And the third, "It cannot be concluded that formaldehyde, methylene glycol is safe in cosmetic products intending to be aerosolized in which formaldehyde, methylene glycol vapors or gas would be produced under conditions of use." Did we want to say it cannot be concluded or it's unsafe?

DR. SHANK: I don't think that "It cannot be concluded" really works,

DR. MARKS: Mm-hmm.

DR. SHANK: For every other ingredient we have either said safe, insufficient, or unsafe. So hashed this around quite a bit. A lot of this

we can handle in the discussion, but I'd change -- the third bullet I'd change to, "Cosmetic products which release respirable formaldehyde equivalents, under conditions of use, are safe as concentrations of respirable formaldehyde equivalents -- or when concentrations of respirable formaldehyde equivalents are not irritating to nasopharyngeal tissues." And that relies on the NRC review of the inhalation data on formaldehyde conclude that the carcinogenicity of formaldehyde relies not only on genetic damage, but there must be cytotoxicity as well.

DR. SLAGA: Irritation.

DR. SHANK: Irritation. So if the formulations are not irritating to nasopharyngeal tissue, you would not have to complete carcinogenic mechanism data.

The other cancers that EPA has suggested, leukemias and things, I think we can handle in the discussion. The NRC report did not support those.

DR. BOYER: If I can make just one suggestion on terminology. You might want to use the term "inhalable" as opposed to "respirable."

DR. SHANK: No. I chose respirable very specifically.

DR. BOYER: And the reason for that?

DR. SHANK: For deposition into the lung.

DR. BOYER: Okay.

DR. SHANK: Exposure into the lung.

DR. GOLDEN: Can I come up and have a few words?

DR. MARKS: Of course. Come right here so we can get in the mic.

DR. GOLDEN: Hi. I'm Robert Golden. I'm with ToxLogic, and I'm here on behalf of the Protein Keratin Smoothing Council, which is a group that was formed recently of these hair smoothing products. And I want to just give you a sense of what they're all about in terms of really in agreement with what you have just said about sensory irritation.

And it's their position, and I have - I can pass out these statements. I hope there's enough here.

DR. MARKS: We can share. Does anybody need it in the back.

DR. GOLDEN: I have two more.

DR. MARKS: Two more. Give Dr. Shank one.

DR. GOLDEN: I don't want to just read everything I've written here, but I do agree with what Ron said, that the bellwether for the use of these products is whether or not they produce symptoms of sensory irritation. And if the levels that are emitted, and I'll get into some more specifics about that, are below what causes these symptoms, then there is no risk of, well, obviously sensory irritation. And then with it goes pretty much every other

adverse health consequence from formaldehyde. It literally just doesn't get into the body.

Some of the problem that's arisen with these products is two-prong. It has to do with how these formulations have been tested for the presence of free formaldehyde. And the methodologies that have been used, and they're standard methodologies, but they were never intended -- well, number one, they were never intended for use with heat, which obviously creates conditions that perturb that methylene glycol, formaldehyde equilibrium. The other thing is that the methods themselves for getting heat as the products are used create conditions of lowering the pH using some of these derivatives.

And most importantly the high temperature used in HPLC ends up with showing formaldehyde potential in a product that literally doesn't exist in it as it's used. And really the only methodology is the C13-NMR, which doesn't perturb the equilibrium in the cosmetic product and gives a more accurate assessment of which actually is there.

Really the primary focus should be on salon air monitoring and not what's in the bottles, as measured by some of these test methods. And this organization wants there to be warning labels that explicitly state how these products should be used and who should be using them and, most importantly, what kind of ventilation ought to be in place if a salon is going to use these things. Then if sensory irritation occurs, the process ought to be stopped, and they shouldn't be doing these procedures until they make these symptoms of sensory irritation disappear. So appropriate ventilation is obviously key in the safe use of these products.

Interestingly, the ingredient in these products is methylene glycol. It's not formaldehyde that is the active ingredient. Formaldehyde is just an unwarranted byproduct, but obviously it has to be dealt with.

And what we have already started thinking about and contacting the appropriate testing laboratories is to measure workplace exposures as well as a lot of different methylene glycol formulations to be able to ascertain accurately in a real world kind of a situation, what the formaldehyde emissions would be under actual use conditions. And right now there's a lot of data in salons where proper ventilation is used that it shows that the emission levels are below OSHA or ACGIH standards where sensory irritation does not occur. Now clearly, there has been a lot of sensory irritation. I don't know how much. It's been reported, but this is an indication that products are, number one, are not formulated correctly in terms of what's on the label or that the ventilation is inadequate. So when -- and there's thousands and thousands of applications of these and there is no sensory irritation. I just want to stress that this testing will be done. The data will be submitted to CIR. I understand that there will be some additional time. It won't be finalized right away, and we would send all this data to you for your consideration.

And then also to just mention that formaldehyde is existing in us and all living systems in this formaldehyde methylene glycol equilibrium, and we breathe off formaldehyde, which is a consequence of how much formaldehyde escapes the equilibrium just at 98.6 degrees.

So this is the biology, and I agree with what Ron said. I think the NRC report was pretty explicit in disagreeing with the EPA that the levels that

don't produce sensory irritation are really inconsequential. And not to blow my own horn, but I have a website here. It's not my website, but I just recently published a paper. There's another paper there as well by Lorenz Rhomberg if you know him that I think is the state of the art on this issue. This is in critical review of toxicology. It's open access. It doesn't cost anything. You can just click on it and get this, and I think this took a long enough time to get timely accepted for publication that it contains the salient points that were made by the NAS committee on all of these issues. And I would suggest maybe that you get this and put it in the record in the same way that some other papers have gone into your record.

And finally, the PKSC suggests that the 2.6 percent methylene glycol or 0.002 percent free formaldehyde is measured by C13-NMR is an acceptable level of formulation as a product sits on a shelf. Obviously the only way to really show the safety of these is with air monitoring and avoiding the symptoms of sensory irritation.

DR. MARKS: Thank you. So, Ron Shank, would you repeat your conclusion again?

DR. SHANK: Well, it's a suggestion for the third bullet.

DR. MARKS: That sounded good, Tom, to you for the --

DR. SHANK: For the third bullet?

DR. SLAGA: If you want inhalation inhalable, I'll go for that.

DR. BOYER: And I can explain what I think about that if you're --

DR. SHANK: Okay. I'll use that for now.

DR. MARKS: Okay.

DR. SHANK: Cosmetic products which release inhalable formaldehyde equivalents.

DR. MARKS: Hold on a second. So this has really changed a lot from this.

DR. SHANK: It's changed entirely.

DR. MARKS: So cosmetic --

DR. SHANK: Products which release inhalable formaldehyde equivalents under conditions of use are safe --

DR. MARKS: I'm sorry.

DR. SHANK: Under conditions of use.

DR. MARKS: Conditions of use. I must just ask you tomorrow, but at any rate I'll write it down here. Yes.

DR. SHANK: At concentrations of inhalable formaldehyde equivalents that are not irritating to nasopharyngeal tissues.

DR. MARKS: Okay.

DR. SHANK: Then in the discussion they can talk about the NRC assessment about chronic toxicity as a necessary component to induce nasal cancer.

DR. MARKS: Now you're addressing just the -- in there the inhalation and the irritation nasopharyngeal. With the Brazilian Blowout they had also eye irritation with it. I can't remember if there was skin. So do you want to just - do you still think just limiting it to --

DR. SHANK: The first one handles that.

DR. MARKS: Right.

DR. SHANK: The first bullet. I don't deal with ocular.

DR. MARKS: Okay.

DR. SHANK: I didn't have any feel for that at all.

DR. GOLDEN: Eye irritation is the most sensitive endpoint, even more sensitive than nose and throat irritation. That's the first thing that people start detecting --

DR. SHANK: Uh-huh.

DR. GOLDEN: -- is in their eyes.

DR. MARKS: Why don't we just say they're not irritating?

DR. SHANK: Okay.

DR. MARKS: Do we want to say to nasopharynx or eye or just say nonirritating?

DR. SHANK: This is where I am. I do have one after saying this.

DR. MARKS: Yeah.

DR. SHANK: Does this mean formulators and manufacturers have to demonstrate that their products are not irritating?

DR. HILL: I see a lot of heads shaking yes.

DR. ANDERSEN: I would argue that it then becomes the obligation of Dr. Golden and the Professional Keratin Smoothing Council to demonstrate that their numbers of 2.6 methylene glycol --

DR. MARKS: Mm-hmm.

DR. ANDERSEN: -- match "not causing irritation" under conditions of use.

DR. SHANK: Okay.

DR. ANDERSEN: That would translate then the Panel's expectation into a number.

DR. SHANK: Okay. That's all right with me. I've tried to come up with a number by myself, and I just had to rely on NIOSH and OSHA.

DR. MARKS: Well, if I understood what you said, it's still dependent on proper ventilation.

DR. GOLDEN: Totally.

DR. MARKS: So no matter what standard you set, unless it's nonexistent, sounds like there could be buildup of free formaldehyde and an irritation. It might not be irritating, say, to the operator for the first five hours, but if there are seven hours, there might be irritation.

DR. GOLDEN: Well, first of all, formaldehyde doesn't follow Haber's law like a lot of chemicals, so it's just concentration dependent. It's not time.

DR. MARKS: Okay.

DR. GOLDEN: It's a crazy thing with formaldehyde, but this has been endorsed by NAS as well. So if they're not having it done -- if it doesn't affect them in the first hour and it's the same, it won't build up.

DR. MARKS: Okay.

DR. GOLDEN: And I think the occupational standards are perfectly good indicators. I mean, if you're below -- there's very little sensory irritation at 0.75. Some people occasionally, but 1 ppm is the lowest concentration that unequivocally causes symptoms of sensory irritation to everyone.

DR. BOYER: And the element of exposure duration does come into play in terms of the standards as well because they're -- typically the standards are time-weighted averages for an eight-hour workday.

DR. GOLDEN: Same. Yeah.

DR. BOYER: And what we're also concerned about is the acute exposure, the effects that it might have at exposure to a fairly large but short --

DR. GOLDEN: A spike.

DR. BOYER: A spike.

DR. GOLDEN: Like a stealth.

DR. BOYER: Exactly.

DR. GOLDEN: Yeah. And, once again, a spike -- I don't want to equate the two, but it's like an onion. I mean, your eyes would sting and you have to get out of there, but it's a warning. If you get those spikes, it's a warning to stop it and stop doing the procedure until you get rid of it.

DR. MARKS: Okay. So cosmetic product which release inhalable formaldehyde equivalents. I'm sorry. Yes.

MS. MASON: I'll just stand back over there.

DR. MARKS: No. David, do you still need to be there?

MR. STEINBERG: I don't know.

MS. MASON: My name is Ann Mason. I'm with the American Chemistry Council. I'll just expand on what Dr. Golden has just mentioned.

OSHA has already set a number, and that is based upon the labeling that you have to have with any mixtures containing formaldehyde, and that is -- and I've adapted it for this purpose, but the label is: capable of releasing formaldehyde gas at concentrations reaching or exceeding 25 parts per million during the normal and/or expected use. then OSHA requires that you put in the words "containing formaldehyde generating ingredients."

So that's a way of relying on what another part of the U.S. Government has already done in terms of occupational safety, looking specifically at mixtures.

When you look at inhalation questions, I think the World Health Organization and the NRC Guidelines has done a nice monograph, really looking at what are the different levels that you see. And one could extract from that monograph, the guidelines, the number that you might be looking for in terms of sensory irritation. So you could add those numbers into the process if that served the Panel.

DR. SHANK: Thank you.

DR. MARKS: Okay. Your conclusion, Tom? Like the way Ron's wording for the full third bullet?

DR. SLAGA: The only thing --

DR. MARKS: There will be a discussion.

DR. SLAGA: -- that we - eye monitoring.

DR. MARKS: Pardon?

DR. SHANK: The eye irritation is kind of a bio- monitoring of --

DR. MARKS: I put in here -- I knew there would be discussion irritating to the nasopharynx and eye, particularly based on your comment that the eye is a sentinel organ --

DR. GOLDEN: Absolutely. Yeah.

DR. MARKS: -- which you initially -- and because that was a big issue with the Brazilian Blowout was eye irritation.

DR. SHANK: I see. Yeah.

DR. MARKS: Not from a --

DR. SHANK: Cancer point of view.

DR. MARKS: -- cancer point of view, but as a sentinel biologic monitor, so to speak. Yes.

DR. LORETZ: I guess just looking at the monitoring data that's available, but does that suggest we're already at a place where we can say you don't need further monitoring? Because it just seems because the fact that it's salons and it's -- everything is going to be different and the products are different. The heating is presumably different, the salon setup ventilation, et cetera. I mean, are we really in a place where we can say -- you know, do we not need more monitoring that really defines things rather than kind of, you know, using irritation as an endpoint that when you get there you've gone too far?

MR. GOLDEN: You're asking whether we need more monitoring?

DR. LORETZ: Whether we're really at a place where we define what conditions that can be used such that you won't get any kind of irritation. I mean, you talked about that your group is doing additional work, but those results aren't available this year.

MR. GOLDEN: No. Not yet. Well, because this has just sort of come up and -
-

DR. LORETZ: I mean, it's a very unique situation because usually we're talking about cosmetics use by consumers, and here you're talking about salons. And you can have every kind of, you know --

MR. GOLDEN: Sure.

DR. LORETZ: -- tiny debate to, a lot of these do next to none, et cetera. It just seems very complex to going to say, you know, as long as it's not irritating.

MR. GOLDEN: Well, I think it goes to what Ron said. This is what the NAS concluded when they reviewed EPA's assessment.

DR. LORETZ: Yeah. I don't have a problem with that.

MR. GOLDEN: Yeah.

DR. LORETZ: It's just more, again, you don't want to be irritating and say, okay, now we need to back off. It just seems like there needs to be more definition of what's problematic going forward so it's not, you know, saying, well, this didn't cause irritation, so I guess we're okay. Well, this did, so I guess we're not.

MR. GOLDEN: Well, I think if you don't have irritation, there's no reason to suspect that anything else would happen.

DR. MARKS: Should -- I'm going to go back to the third bullet just the way it was written on page 75, and we could use a word "unsafe" or whatever, that formaldehyde, it's unsafe in cosmetic products intended to be aerosolized. So do we -- is it unsafe in products? No.

DR. SHANK: I don't think so.

DR. MARKS: No.

DR. SHANK: Not at concentrations low enough.

DR. MARKS: Low enough to not be irritating.

DR. SHANK: Correct.

DR. MARKS: Yeah. Okay. That's an important point.

DR. SHANK: It's a normal metabolic emission.

DR. MARKS: As you said, we exhale it.

DR. SHANK: We need formaldehyde actually.

DR. MARKS: So we'll see how the discussion runs tomorrow. Ron Shank, I guess you're awake by -- I know you haven't left for the airport. It's early on in the discussion.

DR. SHANK: I know. Tell me.

DR. MARKS: Any other comments, Ron Hill or Tom? So I think we've done the three bullets.

Thanks for everybody's comments.

Okay. Anything else? So if it moves forward, it will be a tentative -- it will be --

DR. ANDERSEN: It could be final.

DR. MARKS: It could be final amended. Do you think it could be final amended changing the concentration in bullet one? Do you think that's an insignificant change in concentration?

DR. SHANK: No. That's not editorial.

DR. MARKS: Yeah. So it probably needs

DR. ANDERSEN: That's more in the category of "oops."

DR. MARKS: So I think we need to make it --

DR. ANDERSEN: So it could be a revised tentative.

DR. MARKS: Tentative amended. Yes.

DR. SHANK: But it's a great report.

DR. MARKS: Well, particularly, read the whole nomenclature there, Ron. There's a lot. I like the way you handled it with formaldehyde equivalents. I agree.

DR. HILL: However, ACC says --

DR. MARKS: No. They don't like it.

DR. HILL: -- the huge benefit to Ron's phraseology is that aside from it being brilliant, about very much is these products leaving the salon and going to home use.

This structure for the language can be used by the Consumer Federation or FDA or whoever wants to use it to say, look, if you experience sensory irritation using this stuff at home, stop using it immediately. It allows the endpoint of short-term sensory irritation to be used in a constructive way. It doesn't just limit the conclusion to a number the consumer would have no way of implementing.

DR. MARKS: Right.

DR. HILL: Hell, I could implement this. If it starts to burn, you don't use it anymore.

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DR. BERGFELD: Thank you. Then moving on to the third ingredient, which is formaldehyde/methylene glycol. Dr. Belsito.

DR. BELSITO: Okay, well, we decided to reopen this report primarily because of consumer complaints related to hair straightening products containing methylene glycol and we're very well educated in the equilibrium that exists between formaldehyde-methylene glycol and paraformaldehydes and water and at various pHs and various temperatures. 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 relooked at all of the data and kept in mind that when formalin is said to be used, it's actually 37 percent formaldehyde, and we had originally said that formaldehyde, and now we are saying formaldehyde/methylene glycol are safe in cosmetic products when formulated to ensure at the minimal effective concentration, but in no case should formaldehyde equivalence exceed originally we said 0.2 percent. That data was based on sensitization and irritation data for 0.2 percent formalin, which is actually 0.074 percent formaldehyde, so we reduced that level to 0.074.

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.

And lastly was the issue of formaldehyde/methylene glycol in hair straightening products and what we saw was even data from the Professional Keratin, I forget all the rest of it, that even in some of their salons where you'd think they would be ultra cautious, levels exceeded government levels.

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.

And then the last component in terms of an inhalant, what we felt we could use as -- and we agree that we are not going to control all the conditions in a salon as to is there proper ventilation, et cetera, how much heat is being used to vaporize -- that what we felt that the use -- it should be at a concentration of use formaldehyde equivalence that were not irritating to the nasopharynx or to the eye, so we used a biologic endpoint as we do in other conclusions, non-irritating to the skin, in this case it would be non-irritating to the nasopharynx and the eye.

And we felt because of the toxicology of formaldehyde that if it were not irritating, then we wouldn't be worried about the, say, potential carcinogenicity of formaldehyde. Right, Ron?

DR. BERGFELD: Do you want to comment on that, Don?

DR. BELSITO: Yeah, I guess, you know, again, you're putting a product out on the market that any salon can buy and it's going to be very difficult to regulate how they ventilate that product. So, if you want to use that line of argument, I would say that you would then have to go back and look at whatever it was -- I mean, there are values in the book, I don't know if it's 30 parts per million, less than 30 parts per million, as non-irritating or not noticeable, so if you want to say under conditions of use cannot release more than 30 parts per million, or whatever that level is, whether it's ventilated or not, then I guess I wouldn't have a problem. But I suspect, then, that those levels would not be useful for hair straightening.

DR. SHANK: But it would be much more difficult for a salon to measure the formaldehyde equivalent in the air than the irritation.

DR. BELSITO: No, but we're not asking the salon to do anything because the salons, quite honestly, Ron, if you've ever been in half the salons in New York City, really don't have the capability to do anything like that. So, what we're doing is, we're saying that the final product, under conditions of use, should not release anymore than whatever is the lowest acceptable limit of formaldehyde set by U.S. agencies.

DR. SHANK: How would they determine that?

DR. BELSITO: They would determine it by simply -- the way they determined formaldehyde in the air. They'd take someone and they put the product on the hair and they'd dry it and they'd measure the off-gassing of formaldehyde in the patient's breathing zone and the beautician's breathing zone, and if it came above that threshold -- and they do it without ventilation, because you can't assume that there will be appropriate ventilation in a salon -- then I

would agree with that. But I can't agree with putting a product out on the market where you're assuming that the salons will appropriately ventilate it.

I mean, I'm sure it can be done, but the problem is it's not a regulated industry.

DR. SHANK: Well, we're at the same point except your parameter is going to be a number for concentration and our parameter is a biological response --

DR. BELSITO: Right.

DR. SHANK: -- which is faster, cheaper, and can be done on an hourly basis, whereas if you set up a mass spectrometer in every salon, you're going to have --

DR. BELSITO: I'm not asking that that be done. What I'm asking is --

DR. SHANK: That's how you'd have to measure it.

DR. BELSITO: No. What I'm asking is that the mass spectrometer be set up by the manufacturer, that the process be done without ventilation, and that the levels of formaldehyde be measured in the breathing zone of the beautician and the client, and that those levels, without ventilation, as performed by the manufacturer using the product as it's supposed to be used, would be below acceptable levels for individuals.

I think when you do that what you're going to find is the level of formaldehyde and methylene glycol that could be used in these hair-straightening products is going to be well below a level that would be useful to that industry and I'm fine with that. But I don't think you can allow a product to go out and say, well, as long as it's more formulated not to be irritating, I mean, Rachel and I both have examples. My daughter actually had a Brazilian Blowout done a month ago in a very upscale salon in New York where literally her hair was sucked straight up with ventilation and she saw no odor. Rachel had a relative that had a totally different experience.

DR. BERGFELD: Rachel.

MS. WEINTRAUB: Yeah, and so my aunt who's actually a pediatrician had a hair-straightening procedure done and a well-respected woman who did it, but she does it in her home, so it was in her dining room with her child in the same room observing, you know, the whole procedure. So, I think the problem with -- and while I respect Dr. Marks' team's analysis, I think the problem with the consequence of your conclusion is that it could be interpreted to be the best situation such that it could be the salon where Dr. Belsito's daughter had her treatment where they had ventilation that literally, you know, went straight up, but we don't even have any sort of information for what percentage of salons have that type of ventilation system, we don't know what percentage of these treatments are done in peoples' homes. There's so much information that we don't have, and given the uncertainty, the inability for anyone to really control how this is used and where it's used, and even to understand the extent of ventilation systems in salons across the United States, I don't think we could have a biologic endpoint that really would assume a best case scenario which may be a very small percentage of actual use.

DR. SNYDER: I think the conundrum here for us is that we -- our conclusions are always based upon concentrations and use, and in this instance we cannot determine the conditions of use, and so, therefore, we're really at an impasse because the conditions of use can vary greatly whether it's well ventilated, not ventilated, heat, no heat, and I think that's really where our problem is. And so in our conclusion we can't say safe as used because we don't know the conditions of use, and I think that really what is obstructionary here.

DR. BERGFELD: Dan, did you wish to say something?

DR. LIEBLER: I agree. I think -- as I hear this I think the fundamental problem is whether we say we're going to measure the concentration with a mass spectrometer or a nose spectrometer, we basically are offloading the issue to the consumer in a way that is really hard to justify. So, I actually think that where we're going here is that the data are insufficient to support the safety of use in a product where methylene glycol and/or formaldehyde will be aerosolized during the use of the product. That's something that we just have not enough information about to be able to make a judgment that's safe.

DR. SHANK: And what information do you need?

DR. BELSITO: For the hair care products, I don't think --

DR. LIEBLER: We would have to -- so, the information that we would need, we would have to be able to know whether the extent to which the compounds presented a hazard to the users or people around the users. And the problem is, I think that that's largely unknowable because the circumstances are largely unregulatable. I mean, this is a product you can buy and use in your dining room, right, or you can use it in a salon with the cone thing over your head to, you know, whisk away all the vapors, and anything in between.

So, you know, I don't think we can really know what the concentration would be that would be in the air in somebody using this product. We have examples of high, we'd have examples of low. That means the safety is completely out of our control.

DR. BERGFELD: Ron, did you wish to respond? Ron Shank.

DR. SHANK: Perhaps then the product should only be used under professional care. That could be a recommendation.

DR. BERGFELD: Don.

DR. BELSITO: The problem here again with professional care is that salons vary from salon to salon and as Rachel pointed out, you can have a cosmetologist who's licensed in a state that practices out of their basement, and there are lots of those, so that you really cannot -- this is not like simply putting on a nail shield and painting acrylic on a nail. You know, this is airborne vapor that affects other people that are around the consumer, even if the consumer and the beautician want to take the risk to have straight hair, which according to my daughter, lasts for six months and she loves the process, I don't think it's fair to inflict risk on other individuals.

Essentially, the only way you could control that, again, would be to produce a product that under conditions of use, without ventilation, levels would fall within the safe levels as determined by governmental agencies. What we saw was in the OSHA reports from Tennessee, in the reports from Oregon, those levels were far exceeded in many cases and even what you would expect to be the cleanest data coming from Professional Keratin, those levels were exceeded in some cases.

So, quite honestly, I don't think you can release this product even for salon use and assume that it isn't going to create issues. It's created a huge amount of issues in Canada, it's created issues in California and a number of other areas. So, I just don't feel -- you know, as was mentioned, it's a tricky thing, because, yeah, under the right ventilation procedures, this might be safe as used. The problem is, we can't control how it's used and because of that and because of the data we've seen from environmental measuring in salons where this is being used, I think that it's either insufficient or unsafe.

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. BERGFELD: And hair?

DR. BELSITO: And hair, probably, you know, I guess I would say, you know, the way it's currently used, it should not be used. Because of the --

DR. BERGFELD: So, are you going insufficient or unsafe?

DR. BELSITO: Unsafe as currently used.

DR. SHANK: You're generalizing all airborne concentrations from any cosmetic based --

DR. BELSITO: No, I'm not.

DR. SHANK: Yes, you are.

DR. BELSITO: No, I'm not.

DR. SHANK: The issue is what is a safe level in inhalable formaldehyde equivalents --

DR. BELSITO: And in the hair --

DR. SHANK: -- not as particular product, and you're focusing on a product. We have to be more general than that.

DR. BELSITO: The -- at the concentration that this is used, methylene glycol, formaldehyde, in hair straightening products, the data clearly demonstrate that in many cases the levels in salons -- and, again, this is a salon where they know OSHA is coming in to measure things. I mean, you're going to be at your best.

It's just like, you know, when the Joint Hospital Commission comes to your hospital. For two weeks before, everything is cleaned up, okay, so people are going to be on their best behavior and levels were still exceeded.

So, I don't think -- that indicates to me that these products cannot be safely used.

DR. SHANK: But there are other uses for this ingredient where aerosolization may occur --

DR. BELSITO: And I mentioned that.

DR. SHANK: -- and we have to address that.

DR. BELSITO: I did.

DR. SHANK: You can't say it's unsafe just because of one product.

DR. BELSITO: I said it's unsafe in hair straightening products as currently used.

DR. SHANK: So, what about the other products where aerosolization may take place?

DR. BELSITO: I mentioned that. 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.

DR. BERGFELD: If I could bring us back, whatever the ruling of the panel would be at this time, there is significant change in the conclusions, so this would have to go out again for a 60-day review by the public, which would allow industry then to respond to whatever the decision is. So, yes, Alan.

DR. ANDERSEN: If it may help clarify the description of this third category of usage, I think, Don, adding the word "heat" --

DR. BELSITO: Mm-hmm.

DR. ANDERSEN: -- is the one factor that is different than either products for which dermal contact is intended or products for which nail contact is intended. In neither of those cases is it going to be heated to 450 degrees. If it is, we have other problems.

For the hair product, heat is the defining -- is a defining factor and that could be added.

DR. BELSITO: Plus the concentration, which is 5 percent to 10 percent in these hair products as opposed to nail products where we're being told that at least up to -- so far it's less than or equal to 2 percent. So, it's a concentration variable as well.

DR. BERGFELD: Can we recap what you're proposing then, just briefly?

DR. BELSITO: Safe as used in dermal contact 0.074 percent formaldehyde equivalents. Insufficient in nail products pending further analysis of what's out there in the market in terms of nail hardeners and the concentration of formaldehyde/methylene glycol/formaldehyde equivalents, whatever you want to call it. And unsafe for hair straightening products where levels of formaldehyde and methylene glycol are greater than 5 percent and heat is applied in the process of use, extreme heat, however you want to phrase that.

DR. BERGFELD: Okay. And Jim, can we have a comment from your team?

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(Discussion off the record.)

DR. SLAGA: I agree with Ron. I mean, it's dangerous if we only pick out one product. I think that what Alan stated about heating all products or something related to heating, that's a little different, which then the hair straightening comes under that. It needs to be broad.

DR. BELSITO: Well, that's -- I did make it broad, greater than or equal to 5 percent where the process involved heating.

DR. SLAGA: Yeah, but should --

DR. BELSITO: I didn't --

DR. BERGFELD: The question's being asked where you got the 5 percent.

DR. BELSITO: Because that's the level that was reported for methylene glycol in those products, correct?

DR. BRONAUGH: That's the level that was reported in the MSDS for one product.

DR. BELSITO: Okay.

DR. BRONAUGH: The ones where the measurements occur, we really don't know what the level of methylene glycol/formaldehyde is. So, I think I'd be more comfortable without that level.

DR. BELSITO: Okay, so where heat is applied. Fine. I'm comfortable with that.

DR. MARKS: So, our team doesn't second it. We still like the biologic endpoint, we use that for leave-on products, non-irritating, so we think aerosolized, if it causes irritation in whatever the conditions are, it shouldn't be used. So, that's where we come down on it.

DR. BERGFELD: Paul.

DR. SNYDER: Second.

DR. BERGFELD: You're seconding it? Any other discussion? I'm going to call for the question then, all those in favor? Four.

Against? Four. So, the chair makes the decision. I'm going to go for and so it is going out, as I understand it, at a concentration of formaldehyde of 0.074 percent, the nail, insufficient, and the hair-straightener with heat, unsafe.

DR. BELSITO: Application of any formaldehyde and methylene glycol product with heat.

DR. BERGFELD: Okay. And there's a 60-day review for industry to respond. Rachel?

MS. WEINTRAUB: Yeah, I applaud this decision. I think this is a very important decision for consumers, but another point that I think that needs to be made is that there's a lot of misinformation about these products. Dr. Belsito and I both discussed that in our anecdotal research when we spoke to both the people who applied this process. And consumers who asked whether these products contained formaldehyde, they were told that they do not, and the people in the salon say, you know, they'll look at the box, some of them even say formaldehyde free, and they say, no, there's no formaldehyde in these products, we were told there's no formaldehyde.

So there's a huge gap in information. There is a lot of need for education here. I think primarily it needs to come from the manufacturers of these products to make sure that the people who use these products and who interact with them for hours everyday understand what's actually in these products.

DR. BERGFELD: Thank you. Any other comments? A comment from FDA?

DR. BRONAUGH: Yes, I would just say that we support the Belsito proposal because we know there's a wide variety of conditions in the salons out there and it's just difficult to prevent, I think, people from continuing to have adverse reactions.

DR. BERGFELD: Thank you. Linda, any comments from the council?

DR. LORETZ: I would just say that we would also support that, and it is just the variables that exist in the applicators and in the salons.

DR. BERGFELD: Thank you. Any other comments from any of the team members? Dan?

DR. LIEBLER: Yeah, I'd just like to underscore one point that Rachel made, I think, about misinformation and misunderstanding about the nature of what's formaldehyde containing and what's not formaldehyde containing. And I think that any representation of a product that contains methylene glycol as not containing formaldehyde is a misrepresentation of the chemistry, and that should be made clear to industry that this is not just a matter of difference of opinion, this is a matter of chemistry and its interpretation and misinterpretation and misrepresentation, and I think it really is dangerous for the consumer.

DR. BERGFELD: Any other comments? Alan?

DR. ANDERSEN: I think it's not been said using these terms, but I'd like to take Dan's remarks and convert it to FDA-speak. It's called mislabeling. So, Bob, there's a hook on which to base FDA action.

DR. BERGFELD: Well, I think that all of the discussion will be well captured in the minutes and will be available for industry to review if they're not present, and I'm sure that we'll have a very hearty discussion at our next meeting.

We're going to move on to, then, reports advancing to the next level. Dr. Marks on the silylates.

Final Amended Report

Formaldehyde and Methylene Glycol as Used in Cosmetics

September 26, 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. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Ivan J. Boyer, PHD, DABT and Bart Heldreth, PHD, Chemist.

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ABSTRACT

Formaldehyde (cosmetic biocide, denaturant, and preservative) and methylene glycol (nail hardening ingredient and apparent cross-linking agent in hair straightening/smoothing products) exist in an equilibrium in aqueous cosmetic formulations whenever either one is present. Limits on the concentration of formaldehyde/methylene glycol in cosmetics used on skin have been established, but the available data are insufficient to support the safety of these ingredients in nail hardeners, and formaldehyde and methylene glycol are unsafe for use in hair smoothing products, the use of which involves application of high temperatures.

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

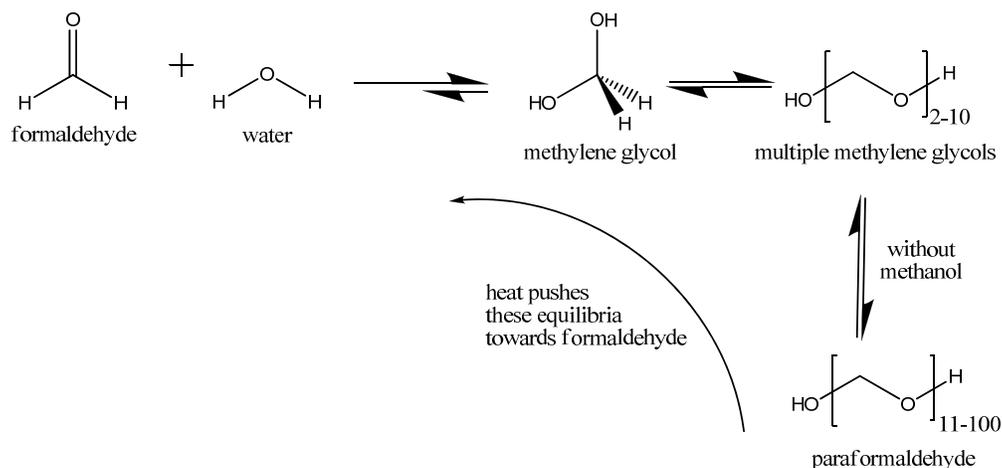
Since that re-review, methylene glycol has been listed as a cosmetic ingredient and CIR has become aware of increasing uses of formaldehyde/methylene glycol in hair smoothing products, intended to be heated. In addition to the issues related to increasing uses and identification of methylene glycol as 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 (U.S. 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.

Additional data from the U.S. Food and Drug Administration's (FDA's) adverse event reporting system and results of FDA laboratory product analyses have been obtained and added to this report. Lengthy submissions have been received from the Nail Manufacturer's Council (NMC) and the Professional Keratin Smoothing Council (PKSC).

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.

To make a paradigm shift from detecting formaldehyde equivalents to thinking about the detection of just the non-hydrated formaldehyde, would also require a paradigm shift from setting a limit of formaldehyde equivalents to thinking about a limit in terms of non-hydrated formaldehyde. In other words, if the current limit of 0.074% formaldehyde equivalents were to stand, a new limit (that would mean the same thing) would need to be set to 0.00074% formaldehyde. This seems to add nothing to the discussion of ingredient safety, but is a mere sidetrack.

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 C) 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 78 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.^{2,15-17} An industry survey of formaldehyde use concentrations yielded data shown in Table 1.^{16,17} No uses of methylene glycol are currently reported to the VCRP, but an industry survey reported a use concentration of <2%.

The Material Safety Data Sheet (MSDS) provided by Brazilian Blowout for their salon product, however, does include methylene glycol.¹⁸ 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 $\leq 0.2\%$ (the limit for oral hygiene products is $\leq 0.1\%$).¹⁹ 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.²⁰⁻²⁵

Use of Formaldehyde/Methylene Glycol in Nail Hardening Products

The FDA Guide to Inspections of Cosmetic Product Manufacturers²⁶ 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 $\leq 5\%$ "calculated as formaldehyde," and the product label must instruct the user to protect cuticles with grease or oil.²⁷ 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)²⁸ 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 ($2.703\% \times 59.2\% = 1.60\%$). The 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^{29,30} and two cases of eyelid dermatitis reported by a member of the CIR Expert Panel.

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).³¹ 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.³²

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.³³ Stoichiometrically, 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.³⁴ Besides proteins, formaldehyde is known to react with other biological molecules such as nucleic acids and polysaccharides.³⁵ 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.³⁶ The alert stated that OSHA investigations uncovered formaldehyde concentrations greater than OSHA's limits of exposure.³⁷ 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.³⁸⁻⁴¹ Hair smoothing products with formaldehyde at levels >0.2% are not permitted for sale in Canada.⁴⁰

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.⁴² Germany's Federal Institute for Risk Assessment (BfR) advised against the use of hair straightening products that contain formaldehyde in high concentrations.⁴³ 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).⁴⁴

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 U.S. 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 U.S. 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 Formaldehyde¹

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 Unpublished Re-Review of Formaldehyde²

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 U.S. NRC recently released their review of U.S. EPA's draft assessment⁴ and their findings are also summarized below, where appropriate. The U.S. 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 **Appendix 1**.

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.^{45,46} 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.

The U.S. NRC noted that a small number of epidemiological studies⁴⁷⁻⁵⁰ 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.⁵¹⁻⁵³

Similarly, the evidence that inhaled formaldehyde may be directly genotoxic to humans systemically is inconsistent and contradictory.⁵⁴⁻⁵⁹

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 nasopharynx.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.⁶⁰⁻⁶⁷

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 U.S. 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 U.S. 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 U.S. 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:⁶⁸

- 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.⁶⁹ Further, formaldehyde is a highly reactive, rapidly metabolized chemical yielding short-lived DPCs and DNA-adducts that are amenable to rapid reversal and repair.^{70,71} 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.^{69,72-74} 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 U.S. 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 formaldehyde,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.⁷⁵ 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% formaldehyde equivalents on normal skin.^{76,77} Cosmetic products containing 0.000185%-0.0925% formaldehyde equivalents were essentially nonirritating and non-sensitizing in 1,527 subjects in 18 studies summarized in Table 5 of the original safety assessment.⁷⁸

Recent reviews addressing the human irritation and sensitization potential for aqueous formaldehyde/formalin solutions are consistent with the observations reported in the original assessment.^{79,80}

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.⁸¹ 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.²⁹ 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.²⁹ 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,⁴⁰ 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 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.⁸² 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 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.³⁶

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 3/1/11.⁸³ 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)⁸⁴ 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, IARC⁸⁵ 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.⁸⁶
- The levels of chromosome 7 monosomy and chromosome 8 trisomy in myeloid progenitor cells and hematological changes in formaldehyde exposed workers.⁶⁸

The IARC Working Group was almost evenly split on the prevailing view that the evidence was sufficient for formaldehyde causing leukemia in humans.⁸⁵

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.⁸⁷⁻⁸⁹

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.⁹⁰ They estimated an upper-bound inhalation cancer unit risk of 1.6×10^{-2} per ppm (1.3×10^{-5} per $\mu\text{g}/\text{m}^3$), 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.⁹¹ The U.S. NRC agreed that the Hauptmann et al (2004) study⁹² 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.⁹¹ However, the U.S. 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.^{90,93} 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 U.S. National Research Council.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, atopy⁹⁴, and respiratory symptoms,⁹⁵ and decreased pulmonary peak expiratory flow rate⁹⁶ in residential populations, including children. The U.S. 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.^{4,94}

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.^{3,4,84,97,98} It is estimated that the general population is exposed to an average of 0.016 to 0.032 ppm formaldehyde in indoor air.⁹⁹ 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.⁹⁷ The concentration of endogenous formaldehyde in the blood of rats, monkeys, and humans is about 0.1 mM.^{100,101} Endogenous tissue formaldehyde concentrations are similar to genotoxic and cytotoxic concentrations observed in vitro.⁶⁹ 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 Standards³⁷

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.³⁷

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.¹⁰²

U.S. NAC AEGL Committee

Acute Exposure Guideline Level-1 (AEGL-1)	0.9 ppm
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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.¹⁰³

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.¹⁰⁴ 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.¹⁰⁵⁻¹⁰⁷

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.¹⁰⁸

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.¹⁰⁹ 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).^{72,109}

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.^{110,111} 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.¹¹⁰ 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.¹¹⁰ The samples were analyzed using high-performance liquid chromatography (HPLC), in accordance with U.S. EPA method TO-11.¹¹¹ 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.¹¹¹ 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 m³) under two conditions: “Typical:” 70°F, 1 air change/hour; “Elevated:” 80 °F, 0.3 air changes per hour.¹¹² Formaldehyde concentrations were measured at 5-minute intervals in the chamber air over a 10.5 hour period. The nail hardener (15 mg/cm²) was painted on 70 cm² of the surface of the substrate (>7 times the total surface of nails on the on a person’s 10 fingers, assuming ~1 cm²/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 five separate studies. The results are summarized below and in Table 3.

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).¹⁰³
- 9 samples (0.303 to 1.88 ppm) exceeded the ACGIH TLV[®]-Ceiling (0.3 ppm).¹⁰⁸
- 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).¹⁰⁹

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.¹¹³ 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.¹¹⁴ They used DNPH-treated silica gel absorption tubes (XAD-2) and high-flow pumps (SKC AirCheck 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.^{13,115} 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.^{13,116} 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.

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 m³), and followed ASTM D 5116 procedures for measuring organic emissions from indoor materials and products.^{117,118} They collected three consecutive 1-hour air samples from the chamber (1 air change/hour), at room temperature (73.4°F), 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 ft²; 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.³³ 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 ft³/min-ft²) 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 ft³/min-ft²) to 0.269 ppm (37.8 grams product; 0.6 ft³/min-ft²). 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 ft³/min-ft², 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 ft³/min-ft²), which exceeds the U.S. OSHA 8-hour Threshold-TWA (0.1 ppm).

DISCUSSION

The CIR Expert Panel received additional input from the NMC of the Professional Beauty Association, the Professional Keratin Smoothing Council (PKSC), the American Chemistry Council (ACC), the Personal Care Products Council (PCPC), and the National Healthy Nail Salon Alliance (comprised of the California Healthy Nail Salon Collaborative, Women's Voices for the Earth, and the National Asian Pacific American Women's Forum). The Panel also noted that U.S. NTP has now listed formaldehyde as a known human carcinogen and the U.S. NRC provided input to the EPA regarding approaches to formaldehyde risk assessment.

After reviewing the comments and additional data received, the Panel determined that revision of the previous tentative conclusion was appropriate and that issuing a revised tentative amended safety assessment for public comment was appropriate.

The Panel continued to emphasize that formaldehyde and methylene glycol exist in an equilibrium in aqueous cosmetic formulations whenever either one is present. That is, the addition of methylene glycol to a cosmetic formulation will rapidly yield formaldehyde and water on a one to one basis until an equilibrium is reached. Further reactions to produce other forms such as paraformaldehyde also are possible.

While comments had suggested that the term formaldehyde equivalents was not the best term to convey the Panel's intent, all parties agree that it is critical to use terminology that expresses the dynamic equilibrium between formaldehyde and methylene glycol in aqueous media. The Panel considered 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 release of formaldehyde from so-called formaldehyde releaser preservatives that are not addressed in this safety assessment, yet are widely used.

Both the NMC and the PKSC have noted that formaldehyde is not actually a cosmetic ingredient. When formaldehyde is added to a cosmetic, it is almost certainly in the form of formalin (nominally a 37% w/w dilution of formaldehyde in water). And because of the equilibrium described above, formalin is essentially methylene glycol and formaldehyde in water. There remains a history of cosmetic usage in which formaldehyde is identified as the ingredient, established limits all refer to formaldehyde, and the INCI Dictionary and Handbook identifies formaldehyde as an ingredient. Changing the naming convention does not appear necessary, especially when the chemistry of formaldehyde and methylene glycol is fully explained.

Formaldehyde/methylene glycol use in dermally applied cosmetics

The Panel considered the available data on the safety of formaldehyde/methylene glycol, noting that formaldehyde is a dermal sensitizer. There is a paucity of studies that report exposures using the term methylene glycol. However, in many cases, published studies of formaldehyde, given the chemistry of these two chemicals, actually determined the toxicity of both formaldehyde and methylene glycol.

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 for the induction of NPCs, the Panel continues to believe that formaldehyde gas produces 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 is just that, an association, and the Panel is not aware of a clear 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 Expert 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 stress, irritation, or increased oxidative stress at high doses.

Considering these identified and potential hazards, the Panel recalled that the original safety assessment published in 1984 stated that: (1) formaldehyde is safe for use in cosmetics if free formaldehyde was minimized, but in no case > 0.2%. Reviewing the basis for the 0.2% limit, the Panel determined that the proposed safe level of formaldehyde and methylene glycol of 0.2% formaldehyde equivalents was based on dermal safety testing using formalin, which contains only 37% (w/w) formaldehyde equivalents. Accordingly, the level that should have been given as the safe level for formaldehyde and methylene glycol is 0.074% (w/w) formaldehyde equivalents.

This concentration limit, currently expressed as formaldehyde equivalents, is still considered sufficient to ensure the safety of formaldehyde/methylene glycol in dermally applied cosmetics.

Formaldehyde/methylene glycol use as a nail hardener

The Panel noted that, as referenced in the INCI Dictionary and Handbook, the cosmetic functions of formaldehyde are: cosmetic biocide, denaturant, and preservative; and that methylene glycol is reported to function as an artificial nail builder. The NMC refers to this use of methylene glycol as nail hardening.

The Expert Panel reviewed the available data on air measurements of formaldehyde in nail salon settings and determined that the levels were consistent with the absence of adverse respiratory reaction reports to manufacturers and to the FDA. The National Healthy Nail Salon Alliance provided a previously published study and suggested that air concentrations may not be low in all settings. In considering this question, the Expert Panel noted that the FDA inspection guide that describes 5% formaldehyde as a level below which action is not needed during inspections of nail hardener products/manufacturing sites, does not have a clear basis. Available data suggest current use of formaldehyde/methylene glycol at only 1 – 2% in nail hardeners. Given the rapid reaction on the nail surface and the use of nail hardeners at room temperature, the Expert 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.

However, recent clinical experience of eyelid dermatitis was reported with 2 patients using one brand of formaldehyde-containing nail hardener. The patients tested negative in a patch test with 1% formaldehyde. In addition, the National Healthy Nail Salon Alliance provided other self-reported adverse events relating to the skin, nail beds, and nails, many of which were reported after use of that same brand. Eyelid dermatitis is a common phenomenon seen by dermatologists and can be related to contact of the patient's hands with the eyelid area after application of a cosmetic to the nails. The Expert Panel was concerned that a better understanding of the current use concentrations of formaldehyde/methylene glycol in nail hardeners is needed. The FDA indicated that some testing to address this issue already has been done and could be extended to include the brand in question. Until such data and any additional relevant data are submitted, the Expert Panel determined that the data are insufficient to evaluate the safety of formaldehyde and methylene glycol in nail hardeners. Based on information provided, the Panel may determine that formaldehyde and methylene glycol are safe for use in nail hardening products in the present practices of use and concentration, or may establish a concentration limit for these ingredients in nail hardening products, without again offering this safety assessment for public comment.

Formaldehyde/methylene glycol use as a hair smoothing agent

In keratin-based hair smoothing products, a solution containing formaldehyde/methylene glycol is applied to the hair, and the hair is dried and heated. The PKSC suggested that the ingredient added to hair smoothing products is methylene glycol and that it functions to smooth hair by building additional structure to counteract disulfide linkages. Regardless of the specific function of formaldehyde/methylene glycol in hair smoothing products, concern exists that the high temperatures may lead to the formation of formaldehyde and/or methylene glycol vapor and/or gas.

Questions have been raised about the appropriateness of using DNPH derivatization and HPLC for measuring the amount of formaldehyde in a cosmetic formulation such as hair smoothing products. Measurement methodology aside, the Panel was concerned with the reports of adverse reactions linked to the use of hair smoothing products containing formaldehyde/methylene glycol, totaling some 50-60 people in Canada alone. The adverse effects reported most frequently, such as eye, nose, and throat irritation, are consistent with exposure to formaldehyde gas. Since most of the adverse reaction reports were the result of workplace exposures, this information was interpreted to mean that workplace controls to prevent exposures to toxic chemicals were not always effective. Apropos of this line of reasoning, CIR has reviewed the workplace air measurements provided by the PKSC and others and found that the levels of formaldehyde approach OSHA established occupational safety limits and often exceed WHO indoor air guidelines.

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. In addition, 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 also 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 Expert Panel was concerned about sensory irritation adverse reports consistent with measured air levels of formaldehyde in salons using hair smoothing products containing formaldehyde/methylene glycol. Because the use of hair smoothing products involves the application of heat, the Expert 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. These findings raised a concern that use of hair smoothing products with formaldehyde and methylene glycol may not be safe, even in salons where some ventilation appears to be in place. The Expert Panel noted that the PKSC suggested that these products are manufactured with the expectation that adequate ventilation would be provided when used; ie, safe use requires adequate ventilation. OSHA and other inspections, however, report a range of ventilation controls, many of which were simply opened shop doors or fans operated to distribute the air around the room. The Expert Panel also heard anecdotal information that hair smoothing products are used in home environments for which adequate ventilation cannot be assured.

Based on the unique circumstance of formaldehyde/methylene glycol use in hair smoothing products intended to be heated, the likely production of formaldehyde gas, and the absence of any assurance that adequate ventilation could/would be available, the Expert Panel determined such use of formaldehyde and methylene glycol to be unsafe.

The Expert Panel noted that some hair smoothing products may be labeled as “formaldehyde-free” and yet contain methylene glycol. Because the presence of methylene glycol ensures that formaldehyde will be present, the Panel joins OSHA and others in stating that a product with a “formaldehyde-free” label that contains formalin or methylene glycol or a chemical listed using any one of the technical names by which methylene glycol is called (eg, methylene oxide), is misleading.

CONCLUSION

The CIR Expert Panel concluded that:

1. formaldehyde and methylene glycol are safe for use in cosmetics applied to the skin when formulated to ensure use at the minimal effective concentration, but in no case should formaldehyde equivalents exceed 0.074% (w/w);
2. the available data are insufficient to determine the safety of formaldehyde and methylene glycol as used in nail hardening products, until additional data on use concentrations are available from FDA and/or industry; and
3. formaldehyde and methylene glycol are unsafe for use in hair smoothing products, the use of which involves application of high temperatures.

TABLES AND FIGURE

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

	<i>No. of Uses (2010)¹⁵</i>	<i>Conc. of Use (2010) (%)^{16,17}</i>	<i>No. of Uses (2010)¹⁵</i>	<i>Conc. of Use (2010) (%)^{16,17}</i>
	formaldehyde (and formaldehyde solution (formalin))		methylene glycol	
Totals	77	0.04 – 0.5	NR	<2
<i>Duration of Use</i>				
<i>Leave-On</i>	33	0.056 – 0.5	NR	<2
<i>Rinse Off</i>	44	0.04	NR	NR
<i>Product Category</i>				
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	NR	<2
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

NR = Not Reported;; Totals = Rinse-off + Leave-on Product Uses.

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. 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	0.170-0.269	95-141	No	No	Yes (All)
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

^aNational Advisory Committee Interim Acute Exposure Guideline Level-1 (concentration above which the general population could experience notable discomfort, irritation, or other effects)

^bAmerican Conference of Government Industrial Hygienists Threshold Limit Value Ceiling (concentration that should not be exceeded during any part of the working day)

^cWorld Health Organization Guideline for Indoor Air Quality

^dcalculated levels exceed by up to 4 fold

^ecalculated levels exceed by 12-21 fold

^fcalculated levels exceed by up to 5 fold

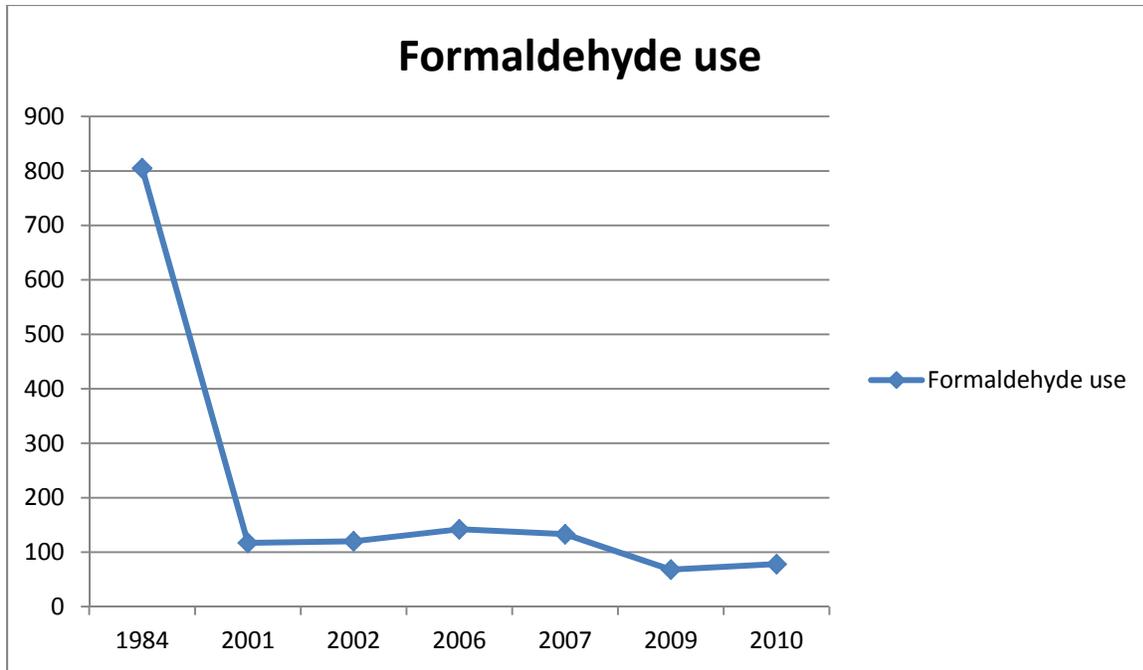


Figure 1. Declining use of formaldehyde in cosmetic products as reported to the FDA VCRP (The x-axis is not linear).

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APPENDIX

Review of Current Toxicology and Epidemiology Studies

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Table A1. 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 (0.4%, 1.1%, 3.7% formaldehyde equivalents); 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.	1
English smooth-haired guinea pigs (n = 4 or 8 males/group)	Induction, Dermal: (a) 100% formalin (37% formaldehyde equivalents); 100 µl/d, 2 days (b) 50% formalin (18.5% formaldehyde equivalents) w/50% adjuvant; 200 µl/d, 1 day (c) 0.13, 1.3, 13, 54, 100% formalin (0.048, 0.48, 4.8, 20, 37% formaldehyde equivalents); 25 µl/d, 1 day Induction, Inhalation: (a) 6, 10 ppm; 6 h/d, 5 days (b) 10 ppm; 8h/d, 5 days Challenge, Dermal: 5.4% formalin (2% formaldehyde equivalents); 20 µl/d, 1 day	Dose-dependent contact sensitivity was observed 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 31 exhibited 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.	2
Wistar and BN rats (n = 4 females/group)	2.5, 5, 10% formalin (0.9, 1.9, 3.7% formaldehyde equivalents) 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.	3

Table A2. 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.	4-6
F344/DuCr1 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.	7

Table A3. 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)	(a) 0.80 ± 0.23 ppm 8-h TWA, 1.38 ppm Ceiling; average 8.6 years, range 1 to 15 years	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.	⁸
(b) Waiters (n = 16)	(b) 0.09 ± 0.05 ppm 5-h TWA; 12 weeks		
(c) Students (n = 23)	(c) 0.009 ppm 8-h TWA; not reported		
(a) Workers at two plywood factories (n = 151)	(a) 0.08-6.42 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).	⁹
(b) Workers at a machine manufacturing facility (n = 112)	(b) <0.008 ppm TWA		
(a) Pathology and anatomy laboratory workers (n = 59)	(a) 2 ppm 15-min TWA (range <0.1-20.4 ppm), 0.1 ppm 8-h TWA (range <0.1-0.7 ppm)	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.	¹⁰
(b) Individuals matched for gender, age, smoking (n = 37)	(b) Not determined	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.	
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 21 days 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.	¹¹
(a) Hospital pathological anatomy laboratory workers (n = 30)	(a) 0.44 ± 0.08 ppm mean 8-h TWA (range 0.04-1.58 ppm)	Statistically significant increase in MN and SCE frequencies and Comet tail lengths were observed in lymphocytes collected from laboratory workers 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.	¹²
(b) Matched administrative personnel in the hospitals (n = 30)	(b) Not determined		
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.	¹³

Table A4. Nasal tissue studies of formaldehyde/methylene glycol in test animals

Species (n)	Concentrations; duration(s)	Results	Reference
Multiple dose studies			
F344 CDF(F344)/CrIBr 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.	14-18
F344/CrIBR (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.	19
F-344/NCrI 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.	20
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.	21
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.	22,23

Table A5. 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.	24,25
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.	25,26
Retrospective cohort mortality; Workers first employed before 1966 at 10 formaldehyde manufacturing plants 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.	27-30
Retrospective cohort mortality; Workers employed in a plastics-manufacturing plant in Wallingford CT (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.	31
Retrospective cohort mortality; Workers first employed before 1966 at 10 formaldehyde manufacturing plants (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	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.	32

	1.9, 2.0 to 3.9, ≥ 4.0 ppm	The authors concluded that the suggestion of a causal relationship between 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 (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	<p>(a) Average intensity: 0 to <0.03, 0.03 to 0.159, ≥ 0.16</p> <p>(b) Cumulative: 0 to <0.004, 0.004 to 0.219, ≥ 0.22 ppm-years</p> <p>(c) Duration: 0 to <1, 1 to 9, ≥ 10 ppm</p> <p>(d) Exposed vs. unexposed</p>	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.	33
Nested case-control; Deceased embalmers and funeral directors (n = 6,808)	<p>(a) Average intensity while embalming: 0, >0 to 1.4, >1.4 to 1.9, >1.9 ppm</p> <p>(b) Cumulative: 0, >0 to 4058, >4058 to 9253, >9253 ppm-hours</p> <p>(c) Duration in jobs involving embalming: 0, >0 to 20, >20 to 34, >34 years</p> <p>(d) Ever vs. never embalming</p> <p>(e) Lifetime 8-h TWA: 0, >0 to 0.1, >0.1 to 0.18, >0.18 ppm</p> <p>(f) Number of embalmings conducted: 0, >0 to 1422, >1422 to 9253, >9253</p> <p>(g) Peak: 0, >0 to 7, >7 to 9.3, >9.3 ppm</p>	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.	34

Table A6. 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	<p>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/10⁹ deoxyguanosine (dG). This detection limit is ~30 times less than the endogenous monoadducts/10⁹ dG measured in white blood cells (on-column detection limits ~240 and 60 amol for monoadducts and crosslinks, respectively).</p> <p>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.</p> <p>The authors concluded:</p> <ol style="list-style-type: none"> (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. 	35
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).	21
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).	22

Table A7. 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.	24,25
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.	25,26
Retrospective cohort mortality; Workers first employed before 1966 at 10 formaldehyde manufacturing plants and followed through 2004 (n = 25,619), compared with U.S. population	(a) Average intensity (8-h 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	<p>This study reported and included 1,006 death certificates that a previous 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.</p> <p>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.</p> <p>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.</p> <p>No statistically significant trends were found among the LHP cancers and frequency of peak or cumulative exposures.</p>	36,37
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	<p>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.</p> <p>For myeloid leukemia, strong, statistically significant associations with exposure duration, number of embalming performed, and cumulative exposure were found. Statistically-significant dose-response relationships were reported between myeloid leukemia deaths and both exposure duration and peak exposure.</p> <p>Comment: Several methodological issues have been identified for this study study. For example:</p>	34,38-40

	(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	(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.	
Molecular epidemiology of formaldehyde workers and frequency-matched controls in China (n = 43; 51 controls)	Median (10 th -90 th 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 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.	41-45
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.	46
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.	25
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.	47

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.	48
Meta-analysis of cohort and case-control studies of professional and industrial workers through May 2009 (n = 17)	Not detailed	<p>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.</p> <p>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 suggested that the inclusion of PMR studies may have caused inaccurately elevated summary risk estimates in previous meta-analyses.</p>	49

Table A8. 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.	50
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.	51
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.	52
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.	53
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.	54,55
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.	56

Table A9. 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).	⁵⁷
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).	⁵⁸
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).	⁵⁹
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).	⁶⁰

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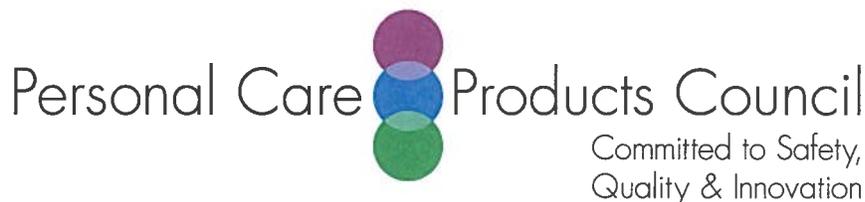
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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: John Bailey, Ph.D. *John Bailey 6-24-11*
Industry Liaison to the CIR Expert Panel

DATE: June 24, 2011

SUBJECT: Comments on the Draft Report on Formaldehyde and Methylene Glycol Prepared for the June 27-28, 2011 CIR Expert Panel Meeting

Cover - As additional changes will likely be made to this report after the meeting, the report should have been called a "draft" final.

Abstract - Although the Dictionary uses nail building as a function, it would be better to refer to Formaldehyde/Methylene Glycol as a nail hardening ingredient.

Abstract, Conclusion - The original conclusion did not limit use of Formaldehyde to preservative, and the current conclusion does not include the preservative limit; "as a preservative" needs to be deleted from the abstract. The Abstract says "the safety of these ingredients in hair smoothing products is not assured", while the conclusion says "It cannot be concluded that formaldehyde/methylene glycol is safe in cosmetic products intended to be aerosolized or in which formaldehyde/methylene glycol vapor or gas will be produced under conditions of use" It would be helpful if the same language would be used in both places. Perhaps hair smoothing products should be added to the conclusion as an example of a product "in which formaldehyde/methylene glycol vapor or gas will be produced under conditions of use".

p.5 - Please delete "Nomenclature" as it is not included in the title of the Dictionary.

p.5 - The last paragraph of the Formaldehyde Equivalents section is not clear and does not seem to be necessary.

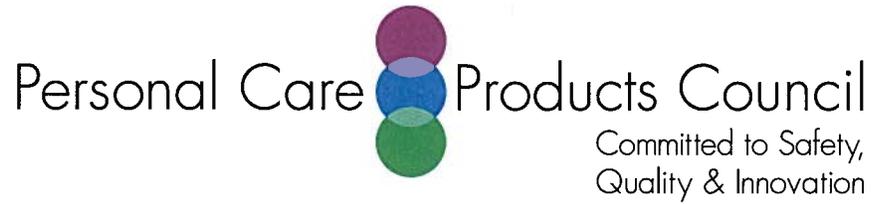
p.6 - If they are mentioned in the report, please provide references for Formaldehyde regulations in Canada, Australia, China and ASEAN nations.

p.6 - In the heading, please change "Nail Strengthening" to "Nail Hardening" to be consistent with what FDA is calling these products.

p.7 - The US OSHA hazard alert concerning hair smoothing products that could release Formaldehyde should be added to the section on Use of Formaldehyde/Methylene Glycol in Hair Smoothing Products. The alert (found at http://www.osha.gov/SLTC/formaldehyde/hazard_alert.html) states that salons "must follow the requirements in OSHA's Formaldehyde standard (29 CFR 1910.1048). The standard requires that employers test the air to find out the level of formaldehyde present in the air when the product is being used. If the test shows that formaldehyde is present at levels above OSHA's limits (0.75 parts of formaldehyde per million

parts (or ppm) of air during an 8-hour work shift or 2 ppm during any 15-minute period), then the employer must complete a number of requirements that serve to lower the levels of Formaldehyde in the air. Air monitoring and medical attention for workers is also required if “formaldehyde is present in the air at a level of 0.5 ppm during an 8-hour work shift or 2 ppm during any 15-minute period”.

- p.7 - The EU regulations for Formaldehyde in nail hardeners also state that products must be labeled with contains formaldehyde if formaldehyde is >0.05%.
- p.11 - Did the FDA adverse event report indicate if the inhalation pneumonitis was in a stylist or customer?
- p.12 - The NTP 12 Report on Carcinogens assessment should be added to this report.
- p.15 - As the OSHA value is the regulatory value for occupational settings, the PKSC 15-minute air samples also need to be compared to the 2 ppm 15-minute Short Term Exposure Limit (STEL-TWA). Although the 7 samples were above some limits, they were below the legal 2 ppm limit. The longer air collection samples should be compared to the OSHA 8-hour action level of 0.5 ppm. It should be noted that the WHO 30-minute guideline is intended for indoor air, not occupational settings.
- p.16 - The original CIR report on Formaldehyde did not indicate that the 0.2% concentration should be limited to use “as a preservative”. The heading “Formaldehyde/methylene glycol use as preservative” needs to be changed and “as a preservative” needs to be deleted from the last sentence of this section.
- p.17 - The PKSC air measurements primarily exceeded the WHO indoor air guideline. The WHO indoor air guideline should not called an “occupational safety” limit.
- p.17 - In the Discussion of the hair smoothing products, it would be helpful to note that the monitoring data suggest that OSHA values can be exceeded and that according to the OSHA hazard alert, this would require continued air monitoring and medical attention to workers.
- p.19 - The concentrations for nail products were for nail hardeners not for any other type of nail product. This would be better represented by adding a footnote to the concentration values rather than stating “(including Hardeners)” after the “Nail” category.
- p.20, Table 3 - If the WHO value is left in the Table 3, it should be made clear in a footnote to this table that it is a recommendation for indoor air, not an occupational limit. The legal OSHA occupational standards should be included as a comparison in this table.
- p.21, Figure 1 - If this Figure is left in the report, perhaps a bar graph would better represent this information.
- p.32-33 - Please check the calculations of Formaldehyde levels in formalin tested in the non-human irritation and sensitization tests. On p.5 of the report it correctly states that a “a 10% formalin solution contains approximately 3.7% formaldehyde equivalents”, while the skin irritancy/sensitization section (p.32-22) incorrectly states that 10% formalin contains 0.04% formaldehyde equivalents.



Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: John Bailey, Ph.D. *John Bailey* 7-19-11
Industry Liaison to the CIR Expert Panel

DATE: July 19, 2011

SUBJECT: Updated Concentration of Use: Formaldehyde

**Concentration of use by FDA Product Category
Formaldehyde and Methylene Glycol**

Ingredient	Product Category	Concentration of Use
Formaldehyde	Shampoos (noncoloring)	0.04%
Formaldehyde	Tonics, dressings and other hair grooming aids	0.056%
Formaldehyde	Other manicuring preparations ¹	0.5%
Methylene Glycol	Other manicuring preparations ¹	<2%

¹nail hardeners: at <http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074952.htm> in its GUIDE TO INSPECTIONS OF COSMETIC PRODUCT MANUFACTURERS, the FDA states the following regarding nail hardening products.

“Nail hardeners often contain formaldehyde as the active ingredient. Formaldehyde has been reported to be irritating to the skin or cause allergic reactions. In the past, the FDA has not objected to its use as an ingredient of nail hardeners provided the product:

1. Contained no more than 5% formaldehyde.
2. Provided the user with nail shields which 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.

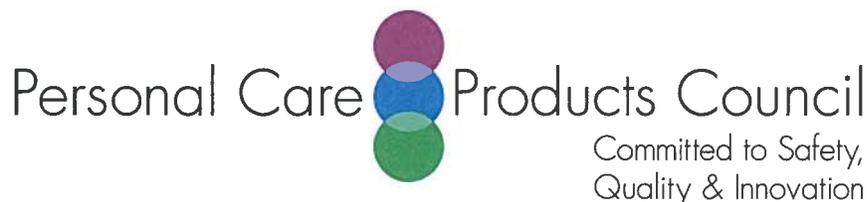
The safety of formaldehyde as a cosmetic ingredient was reviewed in 1984 by a panel of scientific experts appointed by the Cosmetic, Toiletry and Fragrance Association, a trade association representing a major portion of the cosmetic industry. The panel reported that available toxicological data and other information were insufficient to conclude that cosmetics containing formaldehyde in excess of 0.2% are safe. (J. American Coll. Tox., 3,3, 157-184, 1984).

Ascertain the concentration of formaldehyde, inspect the nail shields for proper design and construction. Review labeling for appropriate warnings and directions for use, and review consumer complaint files for the kinds and numbers of adverse reactions associated with this product.”

Concentration of use information collected in 2010

Table prepared January 10, 2011

Table updated July 19, 2011 - 0.15% in a hair grooming product was actually formalin, corrected to 0.056% formaldehyde



Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: John Bailey, Ph.D.  7-20-11
Industry Liaison to the CIR Expert Panel

DATE: July 20, 2011

SUBJECT: Comments on the Revised Tentative Amended Report on Formaldehyde and Methylene Glycol

p.3 - As the original report on Formaldehyde was published in 1984, it is not correct to state that the original conclusion was also confirmed in 1984. As the re-review was published in 2006, it is likely the original conclusion was confirmed in 2003 or 2004.

p.3 - The Introduction should mention the new use in hair straightening products. In the Introduction, it would also be helpful to note that this report does not address the use of formaldehyde-donor preservatives.

p.5, Formaldehyde Equivalents - Although one molecule (or mole) of Formaldehyde equals one molecule (or mole) of Methylene Glycol, Formaldehyde and Methylene Glycol are not equivalent by weight. As this section states: "the molecular weight of formaldehyde is 30 g/mol and the molecular weight of methylene glycol is 48 g/mol". Therefore, when expressed by weight, it is not appropriate to state that formalin is typically 37% (by weight) "formaldehyde equivalents". Formaldehyde is 37% by weight formaldehyde and 59% by weight methylene glycol.

p.5 - As the CIR Expert Panel has decided to reduce the limit of Formaldehyde in cosmetic products, the last paragraph of the Formaldehyde Equivalents section should be deleted.

p.6 - If regulatory information from other countries is included in the report, it should be cited to primary references. Please ask the Global Strategies department of the Council to provide appropriate references.

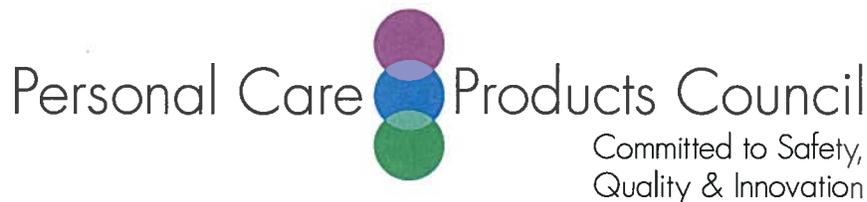
p.6 - Information about use concentration in nail hardeners from the Nail Manufacturers Council should be added to this report, e.g., comments provided on May 11, 2011 indicated a typical level of 1.6% Methylene Glycol (1% Formaldehyde).

p.10, Irritation and Sensitization section - When expressed as % by weight, Formaldehyde is not equivalent to Methylene Glycol. In the Irritation and Sensitization section, the concentrations (expressed as % by weight) should be expressed as Formaldehyde not as "formaldehyde equivalents".

p.17 - In the second paragraph under the heading Formaldehyde/methylene glycol use in dermally applied cosmetics, please delete "from cosmetic products" from the fourth sentence. The

studies concerning Formaldehyde exposure and LHP cancers do not concern exposure from cosmetic products.

- p.17 - In the third paragraph under the heading Formaldehyde/methylene glycol used in dermally applied cosmetics, it is not appropriate to provide % w/w values as “formaldehyde equivalents, as Formaldehyde and Methylene Glycol are not equivalent by weight. The value of 0.074% (w/w) represents Formaldehyde, not “formaldehyde equivalents”.
- p.19 - In the Conclusion, the 0.074% concentration should be expressed as Formaldehyde, not “formaldehyde equivalents” as Formaldehyde and Methylene Glycol are not equivalent by weight.
- p.19 - The first part of the conclusion states: “...safe for use in cosmetics applied to the skin...”. It is not clear if this part of the conclusion also applies to products applied to hair, such as shampoo and hair grooming aids (product categories for which concentrations of use were reported).
- p. 20, Table 1 - When ingredients have few reported use, the current use table summary is misleading. The Council concentration of use survey included 3 use concentrations for Formaldehyde, 0.04% in noncoloring shampoo; 0.15% (now corrected to 0.056% Formaldehyde) in hair grooming aids, and 0.5% in nail hardening products, and one use concentration for Methylene Glycol, <2% in nail hardening products. In this case more information would have been provided to the reader if the actual FDA product categories were presented. If Table 1 is left in the report in the current format, the 0.15% concentration (now corrected to 0.056%) should be included in the Hair - Non-coloring category. As the VCRP values for Hair-Non-Coloring and Dermal contact are not the same, it is not clear which of the hair products reported to the VCRP are not included under dermal contact.
- p.20, Table 1 compared to the Concentration of Use Table in the DEA and its salts report - The Use tables should be consistent between reports. The table in the Formaldehyde report includes the 0.04% concentration reported for shampoo use in the hair - non-coloring row and the dermal contact row, while the table in the DEA report, the 0.3% concentration reported for a shampoo is presented in the hair - non-coloring row, but not in the dermal contact row. Do hair products - non-coloring also belong under dermal contact? There should be a key to the use summary tables that is publically available.
- p.20, Table 1, footnote c - Please delete “dermal” from this footnote as the terms “leave-on” and “rinse-off” do not refer to just dermal products. If there has been a change and “leave-on” and “rinse-off” now refer only to dermal products, please provide an updated FDA product classification table, as nail products and some hair products would not fit into either “dermal” leave-on or rinse-off classifications.
- p.32-33, Skin irritancy/sensitization - When expressed as % by weight, it is not appropriate to use “formaldehyde equivalents” when the values actually represent % by weight Formaldehyde.
- p.34 - In the third paragraph under Non-Human (in vivo), the following does not make sense: “...should have increased, rather than increased,...”.
- p.36, p.39 - Although reference to tables in the draft EPA report may be helpful to the CIR Expert Panel, the draft report may not be available by the time this report is published.



Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: August 17, 2011

SUBJECT: Comments on the Revised Tentative Amended Report on Formaldehyde and Methylene Glycol

The CIR Science and Support Committee (CIR SSC) agrees with the overall findings of the Cosmetic Ingredient Review Expert Panel at 119th Meeting, June 27-28, 2011 concerning formaldehyde/methylene glycol but wishes to make the following comments:

Formaldehyde Equivalence

The CIR SSC agrees that formaldehyde gas in aqueous solution exists in equilibrium with formaldehyde, typically called free formaldehyde and methylene glycol. As such this equilibrium makes the distinction, in solution, between formaldehyde and methylene glycol of virtually no relevance to ingredient safety. However we believe that the wording in the draft report and in particular the conclusion should be clarified to avoid potential confusion.

The Expert Panel proposes that the term *formaldehyde equivalents* be used to best capture the idea that methylene glycol is continuously converted to formaldehyde and vice versa even at equilibrium, and the equilibrium may be shifted by some conditions. For example, heating may increase the rate of formaldehyde released from solution. Regardless, formaldehyde gas and methylene glycol are not identical and those differences, particularly in relation to analysis and the calculations, need to be acknowledged.

More specifically it is clear from the draft report that the revised 0.074% limit for cosmetics applied to the skin was derived by recognizing that the underlying safety data was based on formalin, "an aqueous solution wherein formaldehyde (gas) has been added to water to a saturation point, which is typically 37% (by weight) formaldehyde".

Therefore, when expressed by weight, it is not accurate to express the 0.074% (w/w) limit as "formaldehyde equivalents" (i.e., the equilibrium between formaldehyde and methylene glycol) but as formaldehyde.

We suggest the conclusion would more correctly be worded as:

Formaldehyde equivalents (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 concentration exceed 0.074% (w/w) as formaldehyde or 0.118% (w/w) as methylene glycol.

We also find the final paragraph in the Formaldehyde Equivalents discussion¹ to add to rather than clarify the confusion. Depending on the method of detection the analysis may indeed be looking at reporting the 'free' non-hydrated form. We do agree however that "(t)his seems to add nothing to the discussion of ingredient safety, but is a mere sidetrack" and so suggest that the paragraph be deleted.

Use Application

In addition to hair smoothing products, Formaldehyde is reported to be used in shampoo and hair grooming aids. Currently, the first part of the conclusion #1 states "...safe for use in cosmetics applied to the skin...". As shampoo and hair styling products are not applied to the skin, "applied to the skin" should be deleted from the first part of the conclusion.

Analytical Methods

As the conditions under which formaldehyde is measured in products affects the results, the CIR SSC recommends that the Discussion should note that 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.

Claims

The CIR SSC notes that the tentative final report includes a discussion of labeling on certain products that may include the claim "formaldehyde-free" and that in the "Panel joins OSHA and others in stating that a product with a "formaldehyde-free" label that contains formalin or methylene glycol or a chemical listed using any one of the technical names by which methylene glycol is called (eg, methylene oxide), is misleading."

While the CIR SSC does not dispute the statement we note that labeling claims are subject to review by national authorities' consistent with a substantial body of regulation and legislation and are very concerned that the Panel not include in final Safety Assessments opinions not specifically relevant to the scope of the CIR and the Panel demonstrated expertise: the safety of cosmetic ingredients.

We suggest that those sentences (page 18 & 19) be deleted.

¹ To make a paradigm shift from detecting formaldehyde equivalents to thinking about the detection of just the nonhydrated formaldehyde, would also require a paradigm shift from setting a limit of formaldehyde equivalents to thinking about a limit in terms of non-hydrated formaldehyde.