

BLUE

Formaldehyde/Methylene Glycol

CIR EXPERT PANEL MEETING

JUNE 27-28, 2011



# Cosmetic Ingredient Review

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## Memorandum

To: CIR Expert Panel and Liaisons  
From: Director, CIR  
Subject: Formaldehyde and Methylene Glycol  
Date: May 23, 2011

At the March meeting, the Panel issued a tentative amended safety assessment for formaldehyde and methylene glycol that addressed the safety of these ingredients in light of uses in hair smoothing products and available safety data. In this tentative conclusion, the Panel:

- 1. reiterated that formaldehyde/methylene glycol are safe for use as preservatives in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should formaldehyde equivalents exceed 0.2%*

Much of the presentation of newly available toxicology and epidemiology data on formaldehyde toxicity was from a draft EPA report issued for comment. In assessing the available data in March, the Panel considered the suggestion that formaldehyde-induced nasopharyngeal cancers were best characterized as a linear, non-threshold phenomenon and that there are sufficient data to link formaldehyde to hematopoietic cancers. Since then, that EPA report has been reviewed by the National Research Council and this additional perspective that formaldehyde toxicity should be viewed as dependant upon threshold phenomena (i.e., cytotoxicity-compensatory cell proliferation), as well as mutagenicity, is now incorporated into the report. Submissions from the Nail Manufacturers Council and the Professional Keratin Smoothing Council urged that CIR rely on the additional perspective provided in the NRC comments. We expect further input from the American Chemistry Council on this aspect of the review.

Some discussion may be warranted regarding the basis for the 0.2% concentration limit on formaldehyde/methylene glycol used as a preservative. The data used to set that limit were from sensitization studies in which formaldehyde was tested at 0.2%. It appears likely, however, that 0.2% formalin was tested and not 0.2% formaldehyde equivalents. If formalin is considered to contain 37% (w/w) formaldehyde, then the level of formaldehyde equivalents in those studies was actually closer to 0.07%.

It remains the case that the limit for formaldehyde use as a preservative in Europe is 0.2% (0.1% in oral hygiene products), calculated as free formaldehyde. For individuals not sensitized to formaldehyde, the Panel should consider if a 0.2% upper limit is sufficiently protective.

In the tentative conclusion, the Panel also:

- 2. stated that it cannot be concluded that formaldehyde/methylene glycol are safe in cosmetic products intended to be aerosolized or in which formaldehyde/methylene glycol vapor or gas will be produced under conditions of use*

Additional data were found regarding measured levels of formaldehyde associated with salon use of hair smoothing products. The available data form a consistent picture of formaldehyde/methylene glycol levels in these products in the 5 – 10% range, if measured using DNPH derivatization and HPLC.

In addition to the data already available from Health Canada on adverse event reports, FDA's adverse event reports have been received and the information has been incorporated. In addition to the state OSHA hazard alerts we already knew about, the U.S. OSHA recently has issued a Hazard Alert and identified rigorous safeguards that should be in place to keep the levels of formaldehyde below the U.S. OSHA occupational exposure limit. FDA recently has received a request from several members of Congress to take regulatory action to protect the public from formaldehyde in hair smoothing products.

The Professional Keratin Smoothing Council (PKSC) has provided a large submission regarding the use of formaldehyde and methylene glycol in hair smoothing products. Among the positions taken by the PKSC raised in this submission are: methylene glycol is the added ingredient, not formaldehyde or formalin; methylene glycol should be measured using NMR, not the OSHA derivatization procedure; methylene glycol is the predominant form in the formaldehyde/methylene glycol equilibrium, even at high temperatures; and methylene glycol is the active ingredient in hair smoothing products that binds with hair to add straightening cross-links. The PKSC makes several recommendations relating to restrictions on the use of hair smoothing products that they believe are needed to ensure their safe use.

What was not received from the PKSC were the levels of methylene glycol in hair smoothing products. They argued that the exposure measurements they provided show very low exposures to formaldehyde in use situations. Recall that one MSDS included methylene glycol at 5%. It appears that formaldehyde/methylene glycol used in hair smoothing products must be in these products at levels higher than 0.2% in order to be effective. It is also clear that such use is associated with adverse reaction reports that are consistent with exposure to formaldehyde vapor. While it may be possible to put safeguards in place to preclude harmful exposures resulting from the use of hair smoothers as recommended by U.S. OSHA, and supported by the Professional Kerating Smoothing Council, it may be that safeguards are not always in place and that salon employees and customers may be injured, suggesting that the use of formaldehyde/methylene glycol in hair smoothing products could be considered unsafe.

Finally, in the tentative conclusion, the Panel also:

- 3. indicated that the available data are insufficient to determine the safety of formaldehyde/methylene glycol used as hardeners in nail care products, unless data are provided regarding nail exposure levels and the FDA position allowing use in nail care products up to specified concentrations is clarified*

The Nail Manufacturers Council of the Professional Beauty Association provided an extensive submission addressing the use of formaldehyde/methylene glycol in nail care products. This submission argues that

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methylene glycol is the active ingredient in these products. The International Cosmetic Ingredient Dictionary and Handbook recites artificial nail building as a function for methylene glycol, but not for formaldehyde.

Because methylene glycol reacts with nail proteins, the Nail Manufacturers Council further argued that the amount of free formaldehyde that might exist from an equilibrium (that highly favors methylene glycol at room temperature), is much lower. The Nail Manufacturers Council provided information that the use concentration of formaldehyde (methylene glycol?) as a nail hardening ingredient is less than 5% and that there is no history of adverse events associated with such use.

The Personal Care Products Council noted, and CIR's search of the FDA website confirmed, that the current "Guide to Inspections of Cosmetic Product Manufacturers" provided by FDA to its investigators and other personnel does specify an action level of 5%; i.e., FDA will not object if levels of formaldehyde are less than 5%. See <http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074952.htm> .

Comments on the tentative amended safety assessment were submitted by the Nail Manufacturers Council and the Personal Care Products Council and are provided for your review. Each of the comments has been addressed and additional data provided have been referenced.

The task for the Panel at this meeting is to finalize each of the 3 parts of the tentative amended conclusion.

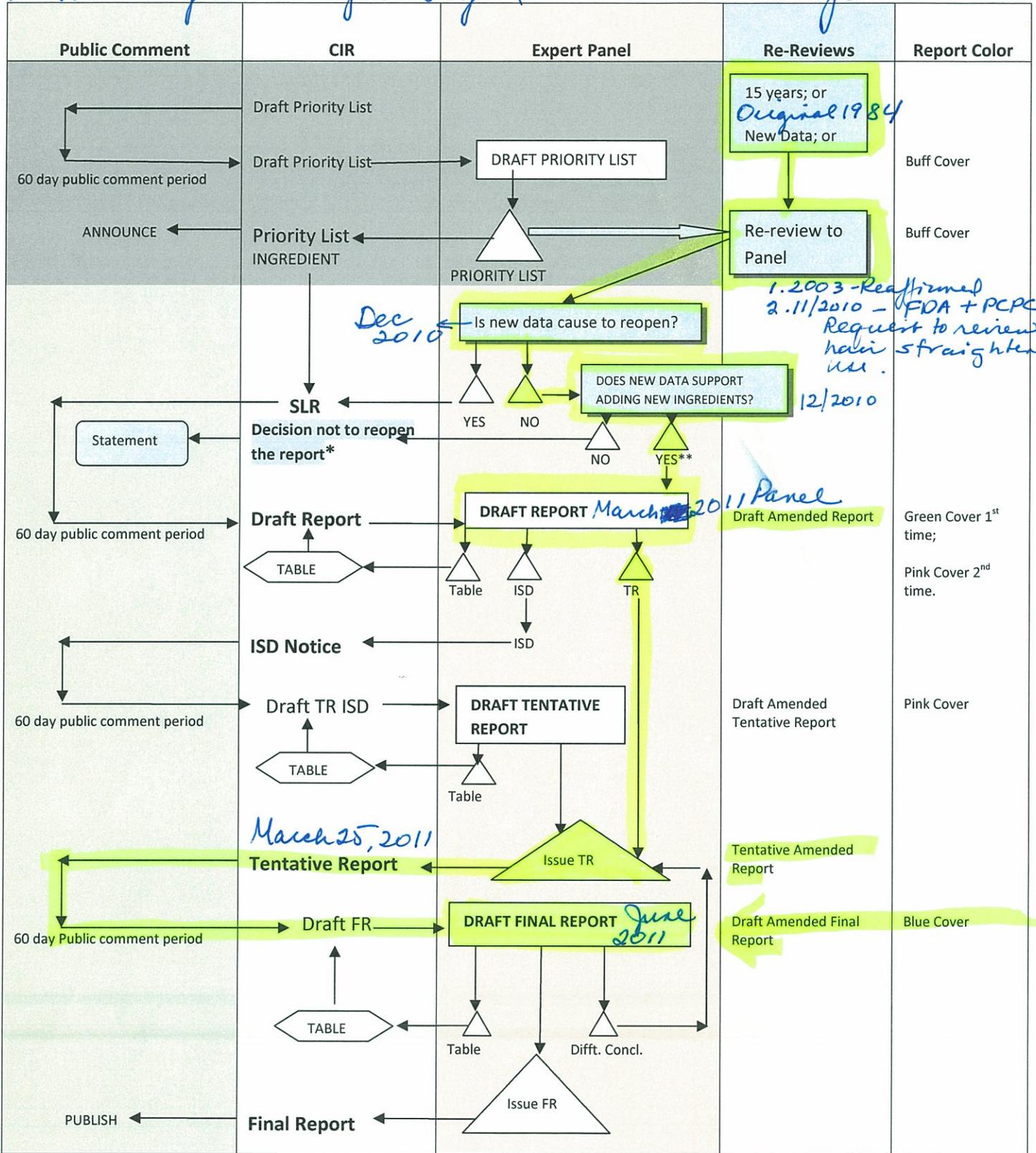
If the changes from the conclusion issued in March are primarily editorial and/or were contemplated in the report provided for public comment, then a final amended safety assessment can be issued at this meeting.

If the changes are substantive and/or were not contemplated in the report provided for public comment, then the Panel should issue a revised tentative amended safety assessment for an additional 60-day comment period.

# SAFETY ASSESSMENT FLOW CHART

*Formaldehyde + Methylene Glycol*

*June 2011*



\*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.



## 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 can't 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.

### 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.



March, 2011

Belsito's Team:

DR. BELSITO: Okay, it's 1:20, so why don't we resume. And we're starting with formaldehyde and methylene glycol, and we decided to reopen this largely because of a Brazilian hair care product that, while it doesn't contain formaldehyde on the label, it contains methylene glycol that we've **learned** when heated drives the equilibrium back to formaldehyde. What we don't know are what levels of formaldehyde are generated in that process of heating. And I'm not really very comfortable with all the, quite honestly, the chemistry since that's not my area of expertise.

So I think I will throw this over to Dan and any of my fellow teammates who can help me comment on this report and how to get a handle around particularly the chemical methylene glycol, which as I understand when you search for you don't find any hard data on methylene glycol because it's really formaldehyde. So help us out, Dan and Curt and Paul, and anyone else other than me.

DR. LIEBLER: Okay, it looks at first glance like this is tremendously complicated, but actually it's not really that complicated. And I'd like to compliment Bart and Ivan for their work on the chemistry section. So having said that, I actually did a lot of edits on the chemistry section, and I hoped that'd be helpful, but I think they did capture the main points. I just wanted to make them stand out even more clearly. And I'll just start by sort of setting the tone for this discussion so that everybody in the room's on the same page. And Bart and Ivan, correct me if you disagree on anything here.

Essentially, formaldehyde when it hits water, it hydrates. I debated hydrolysis versus hydration; just set it on hydration because usage is not entirely clear here. But basically formaldehyde hydrates to form methylene glycol, and this is an equilibrium reaction. So anytime you -- if you could take pure formaldehyde and put it in water, you're going to get an equilibrium mixture of about formaldehyde and methylene glycol, immediately. And if you were to make methylene glycol and put it in water, you would get an equilibrium mixture of the same two compounds, again, immediately.

Now in addition to methylene glycol, methylene glycol can form polymeric chains, and these polymeric chains can be shorter or longer. As you drive the process of chain length formation longer and longer by pulling water out of the mixture, you can form longer length polymeric chains, which are commonly known as paraformaldehyde. But paraformaldehyde is an imprecise name for essentially a mixture of longer length chains. But basically what you've got is sort of three broad chemical species. You've got formaldehyde, methylene glycol, and then the polymers. And I think the nice schematic you have, Scheme 1, sort of captures that very clearly. And my suggestions were not to change anything there, but mainly to edit the text a little bit to clarify this. You also introduced the term "formalin," which is simply an aqueous solution that contains all these things.

Let's see what else. So this section on the chemistry occupies the scheme and I think four paragraphs. And my revised version is still the scheme and four paragraphs, but I've done a lot of edits to the paragraphs. If you want to go through the language, we could, but unfortunately since it's a.pdf, I'm using this markup stuff. It's very hard to read all the changes back from that. It's not like reading a track-changes Word document. So I could pick through it if you want to hear that, but I think we might have other issues to discuss.

DR. BELSITO: But it's -- was not really substantive. It was more editorial, like hydration versus hydrolysis and things like that?

DR. LIEBLER: Well, yeah, and I think the most important thing is when we first started talking about this, it was clear that there was either confusion or a lack of understanding even among some members of the Panel as to what the difference was between methylene glycol and formaldehyde and how they relate to each other chemically. And essentially there's a phrase, I think -- well, the second or third, I guess it's the third paragraph, "the solubility of formaldehyde and water is actually the good solubility of methylene glycol and water." I reworded that, but essentially that indicates that these two compounds -- when you put formaldehyde in water, you get methylene glycol and formaldehyde. When you put methylene glycol in water, you get both as well. It's always an equilibrium mixture. So any product that's formally formulated with methylene glycol actually has formaldehyde in it and vice versa.

DR. BELSITO: Okay, but having said that, which I said I've appreciated, then how do we go about regulating methylene glycol when the amount -- I mean, what we want to regulate, right, presumably is formaldehyde, and when the amount of formaldehyde -- when the equilibrium can be affected by so many factors such as how much water, the temperature, I'm presuming the pH, and a whole bunch of other factors, how do we go about doing that? Are we going to come to some type of conclusion that it's up to the formulators if they include methylene glycol in a product to assure that it doesn't release under conditions of use, which would cover the heat application of a hair straightener, so much formaldehyde? Is that how we're going to come to this or how do we come to grips with the notion that we've in some way regulated formaldehyde and then that brings us to how do we want to regulate formaldehyde? So maybe we should look at formaldehyde first, but when I was going through the documents and sort of a sidebar discussion I had with Ivan before the meeting started today is that I was willing to accept that it was point-of-entry toxicity because of the reactivity. But then you have to explain the male repro effects that we're seeing and are those -- are we comfortable saying those were simply very high levels that overwhelm the defense mechanism because obviously the male reproductive tract was not the portal of entry of formaldehyde in those repro studies?

DR. LIEBLER: Okay, so that latter point, the male reproductive toxicity, is I think a separate issue from the chemistry. I think one of the things that -- from the standpoint of the chemistry, I think -- I would suggest the Panel takes the view that formaldehyde and methylene glycol are equivalent in these products. So if you have a stated amount of methylene glycol as part of a product formulation, that should be viewed as equivalent to the same amount of formaldehyde. In other words, to say that you've added methylene glycol to avoid saying you've put in formaldehyde is simply a dodge. I think if you have put methylene glycol in a product, it thus contains formaldehyde because of all the equilibria. If you put formaldehyde in a product, it thus contains methylene glycol, so they should be equivalent. So the toxicity data, the safety considerations, all of those things should be viewed as if we were talking about formaldehyde because these substances, when either substance included in any aqueous-containing product formation or applied in any environment that contains water, the equilibria take over and both of these things should be viewed as equivalent.

DR. BELSITO: So then if you go back to our original conclusion that we affirmed in 2003, we said that -- published concluding that "this preservative is safe for use in cosmetics if free formaldehyde was minimized, but in no case greater than 0.2 percent." So would you say your conclusion would be that these preservatives, i.e., formaldehyde and methylene glycol -- and then we'll get back to the word "preservative" because that doesn't seem to be the way they're being used in this hair care product -- but these

DR. LIEBLER: These ingredients --

DR. BELSITO: These cosmetic ingredients are safe for use in cosmetics if free formaldehyde was minimized, but in no case greater than 0.2 percent?

DR. LIEBLER: Right, free formaldehyde or methylene glycol.

DR. BAILEY: In this morning's discussion, we talked a little bit about the term "free formaldehyde" and what exactly that means. And I think that one of the things that the Panel will probably have to do is to just clarify that. I mean, it can mean simply the free formaldehyde -- the formaldehyde that is on one side of the equilibrium between methylene glycol and formaldehyde. When you're in an aqueous solution, the balance -- most of that is going to be in the form of methylene glycol, and you'll have a very small fraction of that -- it may be 1 percent or it may be less than 1 percent -- is actually free formaldehyde. And that's one way to interpret free formaldehyde. On the other hand it could mean that -- free formaldehyde could mean the total amount of formaldehyde that could be released from a product, from an aqueous solution or a product. And so we really need to be specific about what we mean by free formaldehyde.

DR. BELSITO: I think it would be the amount released under conditions of intended use. I think particularly with this Brazilian hair product you have to do that because as I understand it, the amount of free formaldehyde in the product coming off the shelf maybe low. But then when you put it on the hair and you apply heat, the amount of free formaldehyde that's coming out of that product is significantly higher. Am I not correct?

DR. BAILEY: That's correct.

DR. BELSITO: So you wouldn't -- you'd have to say that free formaldehyde in the product as intended for use.

DR. ANSELL: I think that's missing just how rapid this equilibration is. I think the hair treatment may well, I don't know, vaporize. But it's probably still that equilibrium, depending on the humidity in the air. I think the idea of the -- what Dan was saying as it relates to -- it's the combination of both when we talk about these things. It's the combination, very much like we talk about when we report lead even though if you look at the analysis, it's all heavy metals in the lead family even though we say "reported as." So when we look at a number of these things, I think "reported as" is probably a better way of thinking about it.

DR. LIEBLER: When I was a little kid, my little brother used to like to go -- we had this backyard on a little slope and we had a little wading pool. And my brother would go with a cup to the deep end of the wading pool, and he'd take a cup of water and he'd walk around and he'd pour it into the shallow end. And then he'd go get another cup. And he'd do this. This is why these equilibria are alike essentially. If you have methylene glycol as added if you could, if you added methylene glycol as a part of your formulation, as soon as you add it, you actually have a mixture of methylene glycol and formaldehyde. So any product that contains these -- that contains either formerly methylene glycol or formaldehyde has an equivalent amount of both. All you have to do is if you heat it, more formaldehyde is going to come off in a gas phase. It's going to be released as formaldehyde. If you chill it down, more of it's going to condense back into the solution and hydrolyze to methylene glycol. I think perhaps the way to think of these, this free formaldehyde business, is to think of these as essentially formaldehyde equivalents because that's what all of these are. So a polymeric form would be one polymer molecule that contains several equivalents of formaldehyde. One molecule of methylene glycol is one equivalent of formaldehyde. One molecule of formaldehyde, of course, is one equivalent of formaldehyde. So I would say that if you wanted to have sort of a common basis for expressing the formaldehyde content would be to simply refer to .2 percent as formaldehyde equivalents and that captures all of the other forms that are in equilibrium with formaldehyde, but are still chemically distinct.

DR. BELSITO: Okay, I mean, I understand that point. I guess the point -- and I don't want to keep beating a dead horse -- is that I think what raised this whole issue and the reason why we're reopening this and relooking at it is this particular product that is not only applied, but is applied and then heated so that the amount of gaseous formaldehyde that's being released is higher than the formaldehyde in the product. So are you saying that what you would do is limit -- you would just set the limit at .2, which is the respirable limit that we set for all products, and that might -- .2 of formaldehyde or methylene glycol? And then we don't need to worry about whether it's heated or what the equilibrium is or whatever, the assumption would be that it could release 100 percent formaldehyde, but if it's at .2, then it's below the limit that we're concerned about for the respirable rate?

DR. LIEBLER: Right. You talked about releasing formaldehyde --

DR. BELSITO: For the rate of free formaldehyde rather. The respirable rate we never said was safe.

DR. LIEBLER: There's a very important distinction between the formaldehyde-methylene glycol equilibria that we're talking about and the release of formaldehyde from the so-called formaldehyde-releasing compounds like quat- 15. That reaction goes in one direction, practically speaking, and it's very slow compared to what we're talking about here. So I would not look at methylene glycol like a formaldehyde-releasing compound, which slowly bleeds out a little bit of formaldehyde over time under the right conditions. Methylene glycol is essentially formaldehyde with water added to it. And that reverse reaction -- to go back to formaldehyde -- is so fast that these things -- even though they're chemically distinct in any snapshot in time, all of the methylene glycol can go to formaldehyde under the right conditions almost instantaneously. So I think that it makes more sense to simply refer to formaldehyde, methylene glycol, and polymeric compounds in terms of formaldehyde equivalents --

DR. BELSITO: Okay.

DR. LIEBLER: -- and consider that methylene glycol -- whatever number restrictions we want to apply to formaldehyde, we apply to methylene glycol and to polymeric forms. But I don't think polymeric forms are being referred to as ingredients here, so maybe we can leave that out.

DR. BELSITO: Okay.

DR. LIEBLER: Methylene glycol, I suggest -- it's probably most chemically honest to simply refer to the methylene glycol as formaldehyde. We note that there are two products in equilibrium with each other, but from a regulatory or a safety standpoint, we consider methylene glycol as being formaldehyde.

DR. BELSITO: Okay, so now then maybe instead of focusing on the chemistry, we need to go back and then look at the original conclusions and the reasons, and then maybe then go back to the chemistry and decide if we still need to set a limit. So, again, our original conclusion was that "free formaldehyde not greater than 0.2 percent" I believe was based on skin sensitization. Is that correct? And the lack of data to support safety in aerosolized products was generated by the nasopharyngeal carcinoma issue. So am I right?

DR. ANDERSEN: I think that's correct on both scores.

DR. BELSITO: Okay, so then the sensitization data for formaldehyde has not changed, so we can say okay, 0.2 percent formaldehyde or methylene glycol based upon sensitization. Then the issue becomes has the carcinogenicity data changed at all? We have a lot of arguments that there were misinterpretations of that data and that it's not a nasopharyngeal carcinoma and –

DR. LIEBLER: Of the epidemiology you mean?

17 DR. BELSITO: Right, and misinterpretations of the data linking formaldehyde to lymphoproliferative disease and a lot of the lymphoproliferative stuff was the fact that well, it's not going to get to the bone marrow because it's so highly reactive. But then you have all that male repro stuff that somehow affected male repro. So that throws a little bit of a kink on the argument that you discount the hematopoietic data simply because it wouldn't be a target endpoint because it's so reactive. So are we still concerned -- and, again, this is not my area of expertise -- are we still concerned about lack of safety for aerosolized based upon nasopharyngeal carcinomas?

DR. SNYDER: Well, I can specifically talk to the repro question. So we do have some new data -- 2007-2010 publications -- looking at some inhalation exposures and some questionable endpoints regarding testicular effects. I don't think those data supersede the more robust EPA studies that were done, 2-year bioassays, in which they dosed them, albeit orally, and didn't see any testicular effects, at least reported no testicular effects. And so I don't have much weight or much confidence in the testicular effects that were recorded because there are things like increase in heat shock protein, seminiferous tubule size, and not very robust evidence of actual toxicity. Whereas I think the EPA studies, which were much more robust, larger groups of animals, larger doses, and things like that. And so the one study that they did see, what was maybe the most significant testicular effect, was that inhalation study and it was at 6 parts per million in which there were noted sperm alterations, but I'm not even certain what they meant by that in the manuscript to know. So I don't think those are very robust data regarding the testicular effects in light of much more robust studies done by the EPA looking at formalin. And again, it was -- the portal of entry was where they saw the effects, the fore-stomachs where the exposures were just the same way with inhalation being the nasal passages. So, again –

DR. BELSITO: So that would all be –

DR. SNYDER: And that in combination with the Lu, et al about the distant site effects, I think, in my mind gives me pretty good confidence that those are not significant effects.

DR. BELSITO: So you believe portal of entry is the issue?

DR. SNYDER: Yes.

DR. BELSITO: Then that gets rid of all of the carcinogenicity concerns except nasopharyngeal.

DR. SNYDER: Yes.

DR. BELSITO: So then what do you feel about the controversy surrounding the interpretation of data that epidemiologically links formaldehyde to nasopharyngeal carcinoma in humans and then the rodent data that we also have on nasopharyngeal carcinomas?

DR. SNYDER: So the data then you're talking about is the data we received today? The specific dataset? That dealt specifically with I thought --

DR. BOYER: That was with the same study?

DR. SNYDER: That was all the hematopoietic tumors, right?

DR. BOYER: Exactly.

DR. SNYDER: So do we have data that suggested that nasopharyngeal carcinomas are not? I'm not aware of any.

DR. BOYER: No.

DR. SNYDER: We can discount those.

DR. BOYER: I think we're pretty sure that it causes nasopharyngeal cancers.

DR. SNYDER: Right. The new data that we got today that questioned the epidemiologic studies were all rated to the amount of hematopoietic tumors. So there still is an issue related to the nasopharyngeal carcinomas, and I think that there's data there suggesting relative risk increased --

DR. BAILEY: And there's also the issue of just at what level of exposure you're going to start seeing these effects. It's a very important issue, and it probably also would speak to the reproductive effects as well. You see the reproductive effects at exposure levels that are actually **quite** high. So the animals are pretty well stressed --

DR. SNYDER: Correct.

DR. BOYER: And so it could be a secondary effect. There are just a lot of questions that surround those issues.

DR. BELSITO: Okay, so then if I'm reading everyone right, so we have -- we believe that formaldehyde can be linked to nasopharyngeal carcinoma. We don't know the threshold.

DR. BOYER: Right.

DR. BELSITO: And, therefore, the safety in an aerosolized product is "the data are insufficient."

DR. BOYER: Yeah, there's no doubt in experimental **stages studies** that formaldehyde will produce nasopharyngeal cancers. There's no doubt about that. The questions revolve around the epidemiological studies and whether or not they really showed that there is a cause- and-effect relationship between the levels of formaldehyde exposure estimated in those studies and the incidences of nasopharyngeal cancer. That's an open question.

DR. BELSITO: Right.

DR. BOYER: The EPA has recently done its draft risk assessment, and they have assumed that those levels as reported in the epidemiological studies show a cause-and- effect relationship, and they have proposed some toxicity values based on that assumption. And they're also assuming -- the other issue is the mechanism of action. Is it -- no doubt it causes nasopharyngeal cancers, but how does it do that? Is it a matter of stimulating cellular proliferation or is it the result of injury to the tissue in which case you're dealing with a threshold effect? It's not your clean non-genotoxic effect because there's no doubt that genotoxicity plays a role in that. Or is it a linear at low dose type of extrapolation that they should be doing? And EPA has decided on the latter. And so you get some very, very conservative -- could be viewed as very conservative estimates of what might be carcinogenic to humans.

DR. SNYDER: On page 9, Don, of the -- Panel Book page 21, page 9 of the report, under the Nasopharyngeal Cancers Mode of Action -- I think the third paragraph I think has a mistake. Shouldn't that be -- and Ivan, can you co-verify this -- they reported "specifically significant increases in nasal proliferation only at" -- shouldn't that be "greater than" equal to 6 parts per million?

DR. BOYER: Yes, yes, yes, actually and Carol picked up on that.

DR. SNYDER: So that is --

DR. BOYER: Both of those should be "greater than," -- "greater than 6 ppm" and "greater than 10 ppm."

DR. SNYDER: So the 0.2 is still well below that in regards to the sensitization issue.

DR. ANDERSEN: Paul, my concern would be those threshold numbers for the endpoint for nasopharyngeal cancers when EPA is hinting that maybe it's linear and not threshold.

DR. SNYDER: Okay.

DR. ANDERSEN: At some point if it is linear non- threshold, then some finite increase in nasopharyngeal tumors could be expected below 6 parts per million. You would disbelieve these results as being maybe not enough animals looked at or whatever. We've always approached nasopharyngeal tumors as we've looked at them as being a clear threshold effect, and while I understand that EPA is positing a more conservative approach, I'm not sure that's based in data. I just don't see it. These results seem to be pretty clear.

DR. BELSITO: Well, they're clear in the sense that it's a statistically significant increase in nasal cell proliferation, but it doesn't say that there was no nasal cell proliferation at less than 6 ppm. And proliferative stimulants are one of the links to carcinoma. So it may be non-threshold linear aggravated by other factors as to whether you have seasonal rhinitis as well as formaldehyde exposure, et cetera, et cetera.

DR. ANDERSEN: Yeah.

DR. BELSITO: But I don't think we know.

DR. ANDERSEN: Well, if we do that then though, then my question for Ivan is what the EPA numbers for what you should be using to set a value for exposure that's dangerous.

DR. BOYER: And that's a tough question. Depending on the assumptions, they are proposing limits of parts per trillion.

DR. BELSITO: Yeah, 63 ppt.

DR. BOYER: Right. And, in fact, if you take into account the assumption that exposure during childhood is particularly -- represents a particularly vulnerable period, then -- then it goes down to something like 7 parts per trillion or so, which others have criticized as being unrealistic. Of course we have formaldehyde, endogenous levels of formaldehyde, even in unexposed -- formaldehyde unexposed individuals, you're going to get a certain amount of formaldehyde in the tissues and in -- even in the breath, and those levels are calculated based on their risk assessment, EPA's risk assessment, are well below what has been estimated as the excretion or the release of formaldehyde in breath of an unexposed individual. So, I mean, this risk assessment has been under review by the NAS, and based on what I heard this morning, we're expecting to get something from them within the next couple of months. There are basically two camps, and they are arguing either side of these issues. And EPA has come down on one side, and others have criticized EPA's approaches, and assumptions, and so forth; and that's an ongoing discussion.

DR. BELSITO: But then it's safe to say, as we did in our original conclusion, that it can't be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized. Is that a --

DR. BOYER: I think that's true.

DR. BELSITO: That's fair.

DR. BOYER: Yeah.

DR. BELSITO: I mean, we -- the data we have does not allow us to say one way or the other.

DR. BOYER: That's right.

DR. BELSITO: So then --

DR. KLAASSEN: And here we need to say maybe not just aerosolized but evaporated.

DR. BELSITO: Well, products -- I think we need to wordsmith it so that we include this hair straightening product that -- the panel also said that it can't be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized or where the product could be aerosolized under conditions of use.

DR. KLAASSEN: Yeah. We have to --

DR. LIEBLER: Which release formaldehyde under conditions of use.

DR. KLAASSEN: Right.

DR. LIEBLER: Aerosolized is overly limiting I think in terms of mechanism.

DR. BOYER: And the appropriate word would probably be vaporized or the vapor. It's really the vapor that we're concerned about.

DR. BELSITO: Okay.

DR. ANSELL: And I will point out that the conclusion is not simply 0.2 percent. It's 22 percent as currently used with the concern about aerosolization. So there's some question in mind as to whether this product falls within the broader conclusion, which is in cosmetics as currently used and reviewed in this report.

DR. BELSITO: Well, this -- that product would essentially be -- would not have sufficient data to support safety because we don't know the amount of formaldehyde release, but we know as intended to be used and heated, it's releasing -- what's the term you -- gaseous formaldehyde, vaporized formaldehyde, so that it would fall in an insufficient category. It would also fall probably in an insufficient category because at 5 percent methylene glycol it probably contains in the bottle itself more than 0.2 percent formaldehyde. So you would --

DR. LIEBLER: It would contain as much as 5 percent formaldehyde depending on --

DR. ANSELL: Right.

DR. LIEBLER: -- what you do to it.

DR. BELSITO: Right. Exactly. But, I mean, it would probably contain more than 0.2. So this particular product that brought up this whole discussion would likely be unsafe either because it contained more than 0.2 formaldehyde in the product itself or would have insufficient data because it's releasing vaporized formaldehyde.

DR. ANSELL: I think the issue in my mind is not that the toxicology has changed since you did this original review. It's the end use application no one envisioned is that it would be used in such an application that the product would be vaporized resulting in airborne concentrations in excess of what was considered within -- in the review.

DR. ANDERSEN: I'd like to take off from that point. We need to grapple with that fundamental understanding of this new end use that we're talking about. The formaldehyde produced, whether it's methylene glycol added to the formulation or formalin added to the formulation. How it gets there doesn't change the fact that something can subsequently happen to it. If it's being used as a preservative, one of those things is it can react with the bugs that it's supposed to kill, and that is probably a largely irreversible reaction. You're pulling that formaldehyde out, but bless it's pea picking little heart, there's more methylene glycol there to convert to formaldehyde as soon as that's pulled out of solution. And it remains effective as a preservative. It's a simply wonderful equilibrium dynamic for doing its job. I'm not sure I understand what its job is in a hair smoother. I think, at least we had some hint methodologically that it's binding to hair or binding to the keratin and cross-linking to hair. In concept then, that becomes the same paradigm as killing bugs. It's reacting and probably isn't hugely available subsequently to react with much. But I don't understand that process fully, how fast, how much, and could it -- could that process influence how much formaldehyde at a point of concern, which is I think we've been saying once you start to heat it, how much is really available to do anything. And I just don't know the answer to that. I think we have some feel for that for the preservative use, and it's not going to be heated subsequently. It's just for the preservative use, there's a wonderful dynamic equilibrium that work so that it has its intended function. For hair smoothers, I'm not sure we understand it.

DR. LIEBLER: So just to address the point you raised, the scenario you raised. You put this stuff on your hair. I think the reason this ingredient is in there is to pickle your hair, proteins basically, so that they stay straight, and to do that, pickling in this case means that the formaldehyde reacts with lysine residues or cystine residues or histidine residues on the proteins. And those reactions are reversible.

DR. ANDERSEN: Okay.

DR. LIEBLER: They start with one reversible, rapidly reversible step, and then there are subsequent slower steps that make the overall reaction less reversible. In other words, subsequent steps make those (inaudible) more stable. But if you had just put this stuff on your hair and then you apply heat or blow drying I think is what -- you know, then you're -- you could easily release that.

DR. ANDERSEN: Okay.

DR. LIEBLER: So I don't think the scenario intends to add any significant ambiguity to our earlier discussion about this. The fact that some percentage of the applied material could end up irreversibly bound to the hair after 1 minute, 2 minutes, 10 minutes, a half an hour, probably doesn't change the fact that there's a lot of formaldehyde applied in the product. A lot of formaldehyde could be released, particularly when you're starting with something that's like 5 percent methylene glycol.

DR. BELSITO: And we know that there must be -- I mean, the product very quickly came to attention because of consumer complaints. So there's got to be -- we don't know the amount, but there's probably a significant amount of formaldehyde coming out of that product when it's heated. I mean, consumers put up with a lot to get nice hair, including the horrible smell of permanents from thioglycolates. So to -- and the horrible smell of acrylates to get beautiful nails -- no offense, Doug -- but the fact that these consumer complaints came out suggest to me that there's a considerable amount of vaporized formaldehyde from this product. And then hearing about what Dan said about the fact that it can be reversible for some period of time, I think -- our conclusion I think can stay the same. I don't think it has to change. We just have to add methylene glycol and formaldehyde, and then we have to get rid of the word preservative because clearly they're not being used as preservatives. I think the most concerning thing to me is also beyond that Brazilian product is Table 2 with the Health Canada reports of what the use concentrations are. Unless these are typos, they have leave-on concentrations that they've detected up to 10 percent formaldehyde. They have rinse off concentrations that they've detected up to 30 percent formaldehyde. That's hugely in excess of what we previously had stated.

DR. LIEBLER: That's like an explosive.

DR. BELSITO: I'm just reading what I'm reading.

DR. LIEBLER: Are these typos?

DR. BELSITO: You know, my comment is 30 correct? Are their decimal points screwed up?

22 DR. KATZ: That's what they found.

DR. BELSITO: Ouch.

DR. LIEBLER: Literally, itch. Ouch and itch.

DR. SNYDER: That seems like it's got to be a typo because the other two are much different. The one -- it doesn't seem like --

DR. BELSITO: Well, you know, for frequency and concentration use Table -- for formaldehyde is Table 1B. Everything we have is not stated. So, you know, then we have the current historical use we have is from, concentration is from 2002. We have no industry reported concentrations from 2010. The only concentrations we have are -- and I don't know when this survey was done. Linda, do you know when that was done?

DR. KATZ: My understanding is that they did the survey shortly after the first Brazilian Blowout complaints came through. So that would have been about a couple months ago and maybe a little longer than that. Now I'm not sure they got up to 30. I had seen numbers up to about 10 previously in that range, and I think that was the highest we had seen from what we -- they had shown us. But we haven't seen all of their data, and some of it that's been shared with us has been proprietary of nature. So it's nothing that I can necessarily share. But it was our understanding that some of what they were reporting was not that dissimilar to other reports that have been circulating around over the last several months in terms of the levels. Thirty seems a little high, but, you know, I'm sure we could probably go back and ask them where the 30 came from. But numbers in the range of about 10 would not be inconsistent.

DR. LIEBLER: The 10s even strike me as very high.

DR. KATZ: That's right. That's why I'm saying it's not inconsistent with other numbers that we've seen in other reports in this country as well.

DR. BELSITO: In the U.S.?

DR. KATZ: That's correct.

DR. BELSITO: And those reports came from?

DR. KATZ: Those are data that's currently being done by states by OSHA and EPA. And, again, I can't really share that data because I don't have the final results, but from preliminary results we seem to be in fairly good agreement of the things that have been tested in this country and what Canada has found.

DR. BELSITO: And are these from -- I mean, God forbid, are these from manufacturers that are part of the PCPC, members of PCPC?

DR. KATZ: That I don't know. We don't know that information.

DR. BELSITO: I mean, because that's ludicrous. They're way in excess of the limits we had previously set.

DR. SNYDER: Well, I can't -- trust me, I work with a lot of formalin and 10 percent is barely -- you can hardly stand it if you're not in a --

DR. LIEBLER: Yeah.

DR. SNYDER: -- ventilated area; 30 percent it would be -- your eyes would be -- I mean --

DR. BELSITO: But 30 percent was rinse off.

DR. SNYDER: Yeah. But I don't – I mean, even that is –

DR. ANSELL: Not in my shower.

DR. SNYDER: Yeah.

DR. ANDERSEN: Unless you're cleaning the walls.

DR. ANSELL: Check with Carol, but the numbers I have are 0.15, 0.04 in rinse off; 30 percent would be staggering.

DR. BELSITO: I agree. But, I mean, that's the number we have in Table 2 from the Health Canada report.

DR. ANDERSEN: Yeah. I think the dichotomy that we're seeing here is the – the longstanding use of formaldehyde/methylene glycol as a preservative. The industry has a pattern of use that as Jay describes it is consistent with CIR's limits. It's the use in hair- smoothing products that's creating an outlier.

DR. LIEBLER: Could it be an exchange rate thing where 10 Canadian formaldehydes make 1 U.S. formaldehyde?

DR. BELSITO: Okay. Well, the Health Canada reports aside, I mean, it just shows what may be happening out in the environment. So are we going to go with this document and open it to add methylene glycol?

DR. LIEBLER: Yes.

SPEAKER: Yes.

DR. BELSITO: But continue essential with the same conclusion that formaldehyde and methylene glycol are safe for use in cosmetics if free formaldehyde is minimized but in no case greater than 0.2 percent. And the panel could not conclude that formaldehyde is safe in cosmetic products intended to be aerosolized or where vaporized formaldehyde could be released under conditions of use.

DR. ANSELL: Formaldehyde slash.

DR. LIEBLER: Slash methylene glycol.

DR. BELSITO: Okay.

DR. LIEBLER: So we would change the formaldehyde to formaldehyde/methylene glycol.

DR. ANDERSEN: Every place.

DR. BELSITO: Okay. So that's what we're going to do? Is everyone -- Doug?

MR. SHOON: Yes. If I could make a quick statement. Doug Shoon, representing Nail Manufacturers Counsel, Professional Beauty Association. I just want to remind the panel that formaldehyde nail hardeners are currently allowed and have been accepted as safe as used at up to 5 percent by the FDA, which I believe they were probably talking about formalin at the time. Five percent -- if you take 5 percent formalin, figure that's in a nail hardener, which is only applied to the nail plate and not to the skin itself. So we don't have a lot of the issues that you discussed. But if you look at that 5 percent formalin and you take the equilibrium constant calculation and determine how much methylene glycol versus formaldehyde is in the product, you'll find there's 2.96 percent methylene glycol and 23 parts per million formaldehyde. So my concern would be if you make them equivalent and lower the limit, you're really lowering the limit of methylene glycol to 0.2 percent, and you're limiting the use of these products for nail hardeners.

DR. BELSITO: So then we could yet add another caveat to our conclusion I guess. It would have to be that formaldehyde/methylene glycol in products intended to be applied solely to the nail are safe as used or safe up to 5 percent. Would there be a reason why you would go above 5 percent formalin?

MR. SHOON: Never.

DR. BELSITO: So I open that up for discussion as another part of our already convoluted conclusion.

DR. LIEBLER: I think I'd be okay with that.

DR. BELSITO: Paul?

DR. SNYDER: So where's the data to support that percent safety limit? Do you –

MR. SHOON: The FDA. The FDA actually says "formaldehyde," which is kind of part of the problem. CIR says "free formaldehyde" and gives one level, and the FDA says "formaldehyde" 5 percent. So that's -- if I may, that's really created a lot of confusion.

DR. ANDERSEN: So if we go to the formaldehyde equivalents terminology, that may indeed help the situation, but I think of more use would be to describe to the reader much as Doug just described it. Here's what's happening and that most of it is methylene glycol, small parts per million formaldehyde, but we've chosen to -- to apply a limit that will keep a lid on the combination of the two. So if it's 5 percent formaldehyde equivalents and don't care whether it's methylene glycol or whether it's formaldehyde, that would allow the use, as Doug described it, of 2.9 percent methylene glycol and 23 parts per million formaldehyde, which doesn't sound far from what the equilibrium legitimately ought to be. So it's seems consistent.

DR. ANSELL: I think the concern that he's raising is if we remove the word preservative, we then open a class of materials which had been handled under an FDA guidance as opposed to a CIR guidance, which was specifically nail polishes.

DR. BELSITO: But nail polishes and hardeners are cosmetic products that fall under our purview as well. So then what will we say? That, you know, we're reviewing formaldehyde as a preservative and -- rather formaldehyde/methylene glycol as a preservative and some unknown function in a hair straightener, but we're excluding its use in nail products? I'm not sure that makes sense. You know, we need to look at all of the cosmetic issues.

DR. ANDERSEN: Yeah. I'm not sure I know how we would not comment on it because the current use listed in the international cosmetic ingredient dictionary and handbook says artificial nail products. So it would be hard to duck that issue.

DR. BELSITO: Okay. Back to the drawing boards. We have a conclusion for all aspects, except for nail care products. So how do we deal with the nail care product issue where it said that it's -- that formalin, which is typically, what, 37 percent formaldehyde and the rest water at 50 percent. So it's 50 percent of 37 percent?

MR. SHOON: Well, formalin is actually 59 percent methylene glycol.

DR. BELSITO: Okay.

MR. SHOON: And about 466 parts per million. It's 59 percent methylene glycol, 466 parts per million free formaldehyde at room temperature.

DR. BELSITO: And then we're taking 5 percent of that mixture.

MR. SHOON: Correct. And this is based on the work that Professor Winkelman did determining the equilibrium concentration. It can be measured by <sup>13</sup>C-NMR, but I don't know that that's been done with a nail hardener.

DR. BELSITO: Because it's actually not percent formaldehyde/methylene glycol. It's 5 percent formalin, which is not 100 percent.

MR. SHOON: That's where the 2.96 percent methylene glycol comes in. That's what the FDA in a sense is backing.

DR. BELSITO: So then we would have to say up to x percent formaldehyde/methylene glycol is safe in nail products not intended -- or products intended for application solely to the nail? I mean, how do we craft the ethyl methacrylate issue? It was -- but that was by trained professions. That was a whole -- here we're not talking about trained professionals, right? These are products that are put out into the marketplace for ladies to apply to their nails to make them harder.

MR. SHOON: That's correct.

DR. BELSITO: And men. I'm a sexist. I know.

MR. SHOON: And I wanted to point out quickly that the CR document said nail builders. It's actually for nail hardeners, two different categories.

DR. LIEBLER: So formalin, what percent is a formaldehyde/methylene glycol equivalents?

MR. SHOON: Five percent formalin?

DR. LIEBLER: Fifty-nine percent. Right. So approximately 60 percent.

MR. SHOON: Well, that's of 37 percent.

DR. LIEBLER: I'm just good at round numbers. Yeah.

MR. SHOON: Formalin. It comes in different strengths as you all are well aware of.

DR. LIEBLER: Okay. So the nail-hardening product, you're talking about limits out at 5 percent of this 37 percent formalin --

MR. SHOON: Correct.

DR. LIEBLER: -- component? Okay. That's the FDA approved limit for that type of product.

MR. SHOON: Maximum. Yes.

DR. LIEBLER: Right. So you can actually calculate using these numbers. You can calculate the formaldehyde or the methylene glycol/formaldehyde equivalent amount in a product.

MR. SHOON: Correct. Which would --

DR. LIEBLER: And I know that you're saying that it's -- you're emphasizing that it's almost all methylene glycol and a little bit of formaldehyde because the equilibrium constant; that's in the solution. As soon as you put it on the nail, stuff happens, right? As soon as it starts to evaporate you also got formaldehyde being formed again. So I think -- I get your point about in the solution the equilibrium favors methylene glycol by leaps and bounds, but we -- I still think we should deal with the methylene glycol by essentially referring to it in equivalent to formaldehyde.

DR. ANDERSEN: With the argument that every methylene glycol potentially can dissociate, every molecule could, any molecule.

DR. LIEBLER: Once you apply the product; once it's applied to the skin; once it's applied to the nail; once it's applied to the hair and it begins to evaporate or you do other things.

DR. BELSITO: Doug or Linda, can you comment on how and why the FDA got to this 5 percent formalin concentration?

MR. SHOON: I'll let Linda do that.

DR. KATZ: I really have no idea how the FDA arrived at that. I can kind of plead that it was before my time, which it was, but I really don't know how they derived at that number. And I'm presuming it must have been based on whatever data was available at that point in time.

DR. BELSITO: So another option since we're flying blindly as to how this 5 percent came would be to table this to get the original FDA documents to look and see so we can resolve. I think we've resolved all of the issues, if I'm correct, except the nail issues. So we're left trying to figure out what the caveats we put on for nail-only use. We don't have the data. We don't have the data –

DR. SNYDER: Right.

DR. BELSITO: -- in the original report. We don't have the data here. So I would say at this point that we table it for insufficient for FDA data, one or the other.

DR. KATZ: And what we will do is we will try to go back to see if we can figure out where that conclusion came from for that 5 percent. Obviously we won't have that answer for you tomorrow.

DR. BELSITO: I understand.

DR. KATZ: But we will go back to look.

DR. BELSITO: So, Alan, do you have a preference for tabling or safe, yadda, yadda, yadda, but insufficient for nail use pending this?

DR. ANDERSEN: Actually my feel for this one is the table is somehow the appropriate thing to do.

MS. WEINTRAUB: I have a question. You know, this is something where consumers are using this product. They are having sensitization from it. So I think we need to be as aggressive and as timely as we possibly can given that there's consistent exposure happening, and it seems like, you know, we're going to be coming out -- or the panel is going to be coming out with a conclusion that may -- that will likely impact the continued use. I mean, obviously, you know, we're not a regulatory body, but it seems like we should act as quickly as we can since consumers are being exposed.

DR. BELSITO: You're specifically talking about the Brazilian hair care product?

MS. WEINTRAUB: Yeah.

DR. BELSITO: Yes. I agree. That's --

DR. KATZ: What I was going to say is we can make a commitment to have the information available by the next meeting. It may be that we won't find the information, but we will make every effort to come up with at least the background information as to where the 5 percent came from before the next time.

DR. ANDERSEN: I think for purposes of providing information to the public and to manufacturers, et cetera, in all fairness 90 percent of the conclusion you have captured, and I don't think -- assuming that both teams generally agree tomorrow, I don't think there's any problem with the announcement pointing out that the panel was in substantial agreement that all of the things that you talked about in terms of formaldehyde equivalents being limited to 0.2 percent, inappropriate to use in products intended to be aerosolized or where formaldehyde vapor may form are the points on which the panel reached agreement. One element of uncertainty is the basis for and the use of a limit in nail-building products, and data had been requested to resolve that. But that would put a substantial part of the question, which is the use in the hair smoothers. Folks, here is what the panel thinks.

DR. LIEBLER: Can I ask an informational question about the nail-hardening product in the role of formaldehyde/methylene glycol in that product? Is that consumed during the chemistry that ensues for nail-hardening? We had a similar discussion I remember about a year or two ago about a hydroquinone I think that was

completely used up during the polymerization reaction, and it was used I think to control the kinetics of polymerization or something like that. What's the role of methylene glycol in the nail- hardening process?

MR. SHOON: Well, good question. That's actually the active species I believe. In fact, if you just look at tissue-hardening chemistry. It's the same thing. Keratin tissue reacts the same way; I think you'd said before between lysine groups, et cetera. Definitely what you're seeing is cross-linking going on, on the surface of the nail. There's hardly, virtually no penetration through the nail plate.

DR. LIEBLER: Yep.

MR. SHOON: So you get surface hardening on the nail plate, which takes the very rigid weak nail plate and makes it more -- less bendable, less flexible.

DR. LIEBLER: Okay.

MR. SHOON: And it is consumed in the process. What percentage is consumed and what percentage evaporates, that I don't know, but I don't believe very much evaporates. I think the majority of it's probably consumed.

DR. LIEBLER: Yeah. Because there would be no point in putting an ingredient like that into a product that's not --

MR. SHOON: If it's just going to evaporate.

DR. LIEBLER: -- contributing to the chemistry somehow by being incorporated or covertly modifying things.

MR. SHOON: Is it the -- **active** is not the right term. It is the workhorse ingredient.

DR. LIEBLER: I'd like -- the reason I'm asking about this is that let's just consider the Brazilian hair straightener. If the purpose of having methylene glycol in this product is to react with the proteins in the hair to alter their properties so that the hair is straighter, in a way that's an analogous function as it is in the nail- hardening product. It's to react with the proteins in the product -- or in the nail to influence their properties.

MR. SHOON: Well, certainly that's what's happening. The methylene glycol is reacting with the surface of the cuticle, hardening of the cuticle so that when you iron it down it stays in place for extended periods of time.

DR. LIEBLER: Right. And in the hair it's giving you straighter hair --

DR. BELSITO: Right.

DR. LIEBLER: -- by doing essentially the same chemistry --

MR. SHOON: Absolute, correct.

DR. LIEBLER: -- and being consumed to some extent --

MR. SHOON: Yes.

DR. LIEBLER: -- probably unknown in the case of the hair. So I want to avoid us getting into a situation where we make what is a seemingly arbitrary sort of exemption for a nail-hardening product, and then we come down really hard on a hair-straightening product. It's clear that people aren't complaining about their nail hardeners. I don't think, but they are complaining about their hair-straightener products.

DR. BELSITO: So the difference, Dan, is to get straight nails you just need to -- or harder nails, you just need to paint on.

DR. LIEBLER: Right.

DR. BELSITO: To get straighter hair you need to apply heat --

DR. LIEBLER: Right.

DR. BELSITO: -- in the process. So I think it's --

DR. ANSELL: Do you heat the nail up too?

DR. BELSITO: No.

DR. ANSELL: You don't do that? Okay.

DR. BELSITO: Or maybe there is some UV cured acrylics --

DR. ANSELL: Yeah.

DR. BELSITO: -- but they're not nail -- I mean --

DR. KATZ: But the processing is really different.

DR. ANSELL: Okay.

DR. KATZ: One is you're inhaling from -- you're getting the vapors, the fumes that you're actually inhaling. And the person who is applying it is also getting the same vapors. The other one, you may get some of the -- you may inhale some of the product as you're putting it, but it's really not intended as a vapor.

DR. ANSELL: Right.

DR. KATZ: You're not getting the gaseous --

DR. ANSELL: Right.

DR. KATZ: It's not -- you're not --

DR. ANSELL: There's no blowout part.

DR. KATZ: Exactly.

DR. BELSITO: Right.

DR. KATZ: That's what the difference actually is.

MR. SHOON: And if you look at the OSHA data, they've done their monitoring, you can see that you're raising up into the irritation level clearly. So I think that's probably -- not that I'm an expert in that area.

DR. LIEBLER: Okay.

MR. SHOON: But it seems like you're just in irritation zone, and that's what the clients are suffering.

DR. LIEBLER: I just didn't want us to appear to be inconsistent in our dealing with these issues.

DR. BELSITO: I didn't --

DR. LIEBLER: Okay.

DR. ANSELL: Yeah. And it's not clear that a hair-straightening product could not be used safely, but, you know, from the occupational reports because of the difference in the end use application, it appears that they are resulting in methylene glycol/formaldehyde concentrations in the workplace in excess of those levels, inducing irritation.

DR. BELSITO: Okay. So then, to get back to Rachel's point and Alan's comment, if we table this, then how do we get out to the public and industry that we feel that a product like Brazilian Blowout that contains more than -- or 16 contains maybe 5 percent, maybe slightly less than 5 percent methylene glycol and that probably or almost certainly releases some amount of inhaled formaldehyde as used is either unsafe because of the concentration of methylene glycol or insufficient because of the aerosolized, vaporized formaldehyde?

DR. ANDERSEN: I'm convinced by the discussion that my previous aggressive persona was actually better. If the panel reaches a tentative conclusion with all of its findings about formaldehyde/methylene glycol in uses other than nail hardeners that's a pretty good position to have staked out, and it's your tentative conclusion. That has more power than my flacking it to death as part of a tabling, and then you I would say insufficient to gather additional data on the basis for a limit in nail hardeners with the clear expectation that, that's an issue that can be resolved. It's not a fatal flaw. It's one that we'll gather the data and deal with it when it comes back.

DR. BELSITO: Okay. So then what we are proposing is that formaldehyde/methylene glycol is/are safe for use in cosmetics if free formaldehyde is minimized but in no case greater than 0.2 percent. It cannot be concluded that formaldehyde/methylene glycol is safe in cosmetic products intended to be aerosolized or which under conditions of use could release vaporized formaldehyde. The safety of formaldehyde/methylene glycol in nail products is 5 insufficient for what? For the FDA data showing it's safe up to 5 percent for --

DR. LIEBLER: So the FDA has already said it's safe at 5 percent, formalin in the product.

DR. BELSITO: I understand, but we don't know why.

DR. ANDERSEN: We don't have any -- we don't know why.

DR. LIEBLER: But I don't know if knowing why actually changes our conclusion about that because it is what it is. The FDA said so, right?

DR. BELSITO: Good point.

DR. LIEBLER: We're not going to -- you know, what if the reason that the FDA set it at 5 percent is because that's what it's used at because that's optimal for purposes of formulating a product that does what it's supposed to do? I don't know, but, I mean, I'm just wondering if we think through -- what if the information is something like that?

DR. BELSITO: What if the information that the FDA based this on came from 1940 regulation, and looking at the new data we disagree with the FDA? So, I mean, I don't think that, you know -- and no offense to the FDA. I mean, the FDA has disagreed with our decisions sometimes and has decided to relook at data on their own, and I think we have the same reciprocal right. And I think we have a duty to at least look at the data. So I don't know that -- you know, I mean, you talked about getting into that slippery slope where the functions and now and here are really the same. It's the conditions of use that are different. But is there volatilized formaldehyde when you put on a nail hardener that oftentimes -- I mean, it contains, what, acetone. I mean, there are volatiles in nail hardeners, right, when you put them on that then allows the product to harden on the nail as that solvent vaporizes.

MR. SHOON: Well, I think that's fair to say, but the other thing to remember they're film formers. So a film forms very quickly. So the bulk -- it's designed to hold the bulk of the material against the nail plate for an extended period of time.

DR. BELSITO: Right. I agree. But, you know, it's just --

MR. SHOON: But I'm sure there is some vaporization, which is why I would be a little uncomfortable with you simply talking about vaporization at room temperature.

DR. BELSITO: Right. So, I mean, that's why I think we need to really see that data again. So I would say insufficient. I mean, I think you can deal with the sensitization data similar to, you know, labeled to state that it

should be applied to the nail only and protection against cutaneous application, but I think it's probably the, you know, issues of vapor –

DR. ANDERSEN: Go ahead, Curt.

DR. KLAASSEN: Doesn't your organization have some OSHA type data that says that the concentration that people are exposed to when they do this is belong such and such?

MR. SHOON: Actually, yes. We do. We did a -- because of Prop 65, we did a pretty large study in California, and what we found out in the use of these products that typically the measured amount of formaldehyde in the air was highest in the morning when the salon was first opened; and then the concentration dropped during the day. They attributed that to outgassing from carpeting, et cetera, would build up overnight, and there was virtually no additional formaldehyde created in the use of these products in the salon area.

DR. BELSITO: And these were nail salons, strictly nail salons or generalized -- general salons?

MR. SHOON: Well, I'd have to look and see. I think the focus was nail salons. There may have been other things going on, but they were done in winter, and summer, and done northern and southern California. It was a very extensive and very expensive study.

DR. BELSITO: Well, that kind of data would be very helpful in our evaluation of the safety in nail products. So I think that we should go insufficient for any data that the FDA can supply us on why they chose 5 percent and insufficient for data on air analysis of nail salons in California. And in the discussion simply point out that it's assumed that these products are applied to the nail and do not have cutaneous applications.

MR. SHOON: And one other fact I'd throw in there. Actually, the State Attorney General of California concluded at the end of the study that there was no reason to warn under Prop 65.

DR. BELSITO: I mean, that's all very helpful information for us. So then let me restate where we're going. Formaldehyde/methylene glycol, safe use in cosmetics if free formaldehyde is minimized but in no case greater than or equal to free formaldehyde/methylene glycol is minimized –

DR. ANDERSEN: Didn't we decide to go to formaldehyde equivalents?

DR. SNYDER: Yes.

DR. BELSITO: Okay. So formaldehyde/methylene glycol is safe for use in cosmetics if free formaldehyde equivalents are minimized but in no case greater than 0.2 percent. The panel cannot conclude that formaldehyde/methylene glycol or free formaldehyde equivalents?

DR. ANDERSEN: No. It's formaldehyde.

DR. BELSITO: I guess... formaldehyde/methylene glycol is safe in cosmetic products intended to be aerosolized or where vaporized formaldehyde may be released under conditions of use.

MR. SHOON: Could I make one suggestion? The formaldehyde equivalent, that's a decision you have to make, but I think using the word "free formaldehyde" can be confusing because people think of free formaldehyde in chemistry terms as what is typically called unbound formaldehyde or the non-hydrated formaldehyde. So I think that word "free" creates some confusion.

DR. LIEBLER: I agree. I think it's imprecise to the point of being misleading.

DR. BELSITO: So use in cosmetics if formaldehyde equivalents are minimized but in no case greater than or equal to 0.2 percent.

DR. LIEBLER: Yeah.

DR. BELSITO: We cannot conclude that formaldehyde or methylene glycol are safe in cosmetic products intended to be aerosolized or when come under conditions of use, vaporized formaldehyde may be formed. And then the use of formaldehyde/methylene glycol in nail care products, the data are insufficient to support its safety. The data required are the FDA data that allowed use up to 5 percent and the California EPA data. Is that it?

MR. SHOON: No. California State Attorney General.

DR. BELSITO: California State Attorney General.

DR. ANSELL: Well, it's exposure data from –

DR. BELSITO: Exposure data –

DR. ANSELL: -- from California, and I wonder –

DR. BELSITO: -- from California nail salons.

DR. ANSELL: Could we make that and/or?

DR. BELSITO: I'd like to see both. It's insufficient. You can ask for everything. You can always decide to drop what you ask for.

DR. LIEBLER: So by going insufficient on the basis of the nail stuff -- so back up. We're asked to look at this because of the Brazilian Blowout, and we are inches from a clean getaway as Jack Nicholson said. And then we're hung up on the nail thing for which there is not apparently a problem.

DR. BELSITO: But it's a cosmetic use.

DR. LIEBLER: And it puts us off. It is a cosmetic use. Now, I mean, I'm not ignoring the possibility that a nail product with that much formaldehyde might actually not be as good as we think it is. The FDA might be wrong. But I'm just -- I'm still thinking about Rachel's point earlier that we got into this in the first place to deal with this sort of acute pressing issue with a product that's causing a lot of irritation to people. I don't think anybody was complaining about the nail products. People were complaining about the Blowout products. So by doing this insufficient we're essentially setting ourselves back a period of time, another review cycle essentially to get the insufficient data.

DR. BELSITO: No. We're not. We're not. We're on the same cycle. What can happen is it comes back to us again as a tentative final –

DR. LIEBLER: Uh-huh.

DR. BELSITO: -- and we either have the nail data and we say, fine, it's safe in nail products up to 5 percent; or we don't have the nail data, and we decide to change our mind because the FDA has already approved it; or we decide to continue to go insufficient with nail data. So we're on the same time track.

DR. LIEBLER: Okay. So we don't lose time.

DR. BELSITO: We don't lose any time.

DR. LIEBLER: Okay. I'm fine with it then. We'll get the FDA data.

DR. BELSITO: Other comments?

DR. SNYDER: So in the report, I'm still kind of confused on this. On page 3, under number 1, where we talk of the issues, and so here – are we going to change then -- because now we're saying formaldehyde functions as a cosmetic biocide, denaturant, or preservative. Then we say methylene glycol functions as the artificial nail builder in cosmetics. So is all that going to be changed to formaldehyde/methylene glycol?

DR. ANDERSEN: Those are simply quotes from the dictionary.

SPEAKER: And the dictionary is wrong.

DR. LIEBLER: Okay.

DR. ANDERSEN: To what the two ingredients function as.

DR. LIEBLER: Okay.

DR. ANDERSEN: And it was done that way simply to frame the issue. When we make the transition from this version of the report, I think all of that disappears. It did for triclosan, and we then substituted with "here is what's really going on." So we frame these questions. Now we'll be framing what the answers are.

DR. LIEBLER: Okay.

DR. ANDERSEN: And that I think is the logical transition.

DR. BELSITO: And also I think, you know, since Paul, and I, and I'm sure a lot of other people reading this report were struck by the absence of any "data" on methylene glycol. I think in the introduction when it comes back to us it has to really hit the reader over the head that, you know. Really there is -- when you search for methylene glycol you don't find anything because, again, it's formalin. It's an equilibrium, et cetera, et cetera. So people aren't going, oh, my God, how are these people reviewing methylene glycol when I don't see a single data point for methylene glycol.

DR. ANDERSEN: We probably can't say it too frequently.

DR. BELSITO: Yeah.

DR. LIEBLER: I think that draft introduction that Bart and Ivan wrote is very good, and we can improve it, tighten it up a little bit more and make the logic flow just a little bit more clear. I tried to do that with some of my edits, and I think we can really make that clear enough to the average reader.

DR. BELSITO: I know. I'm a sub-average reader. It wasn't clear to me.

DR. LIEBLER: You can even make it clear to the dermatologists.

DR. BELSITO: We're bringing it down to third grade level now.

DR. LIEBLER: That was a belt-high fastball, Don.

DR. SNYDER: And to that point I think, including something like along the lines of what Doug shared with us, that 37 percent formalin what that means; that is specifically means 59 percent methylene glycol, 446 parts per **million**. And I think that's very telling to me.

DR. BELSITO: Yes.

DR. SNYDER: That really helps clarify that because I too was struggling with that intro part.

DR. BELSITO: Anything else on formaldehyde/methylene glycol?

DR. LIEBLER: That could be included in the introduction. One of those paragraphs I suggested condensing a little bit, but one of those paragraphs could be sort of for example and framing it just as Paul said. That would be a nice way to illustrate, you know, 37 percent formalin includes at neutral pH let's say whatever that, whatever your numbers are from -- yeah.

DR. BELSITO: Okay. Okay. Any last comment before we close the book on formaldehyde?

DR. SNYDER: Has anybody else noticed an inverse relationship between the number of carbons in a molecule and the amount of time we spent talking about it?

### **Dr. Marks' Team**

DR. MARKS: Okay. Formaldehyde and methylene glycol in the Green Book. We just got a lot of information on a handout.

SPEAKER: Yes, we did.

DR. MARKS: Can somebody summarize it, or do we need to take time to read it first?

DR. SHANK: I didn't read it yet either.

DR. MARKS: Good. Did you read it?

DR. HILL: You said blessedly short, but that didn't apply in this particular case.

DR. EISENMANN: It's really not that long. It's a single-sided copy. It just concerns the one study essentially.

SPEAKER: Swenburg?

DR. EISENMANN: Yes. So if you already have -- I mean there's already some concerns expressed in the report. This is just additional concerns about that study. The submissions are above.

DR. MARKS: So as background, in the December meeting, the Panel reopened the safety assessment of formaldehyde to address the chemistry between formaldehyde and methylene glycol and water, the safety of methylene glycol if we're going to add this, especially in hair-smoothing products, and the adequacy on the current limit on formaldehyde. In my notes, we moved, we reopened it to add methylene glycol, but probably we'll have the same conclusions.

And as you may recall, the, I think, precipitating event was the Brazilian Blowout epidemic of adverse reaction in humans, and this cosmetic or personal care product had markedly high concentrations of formaldehyde. So my notes actually, to go through the chemistry and toxicology, I want to ask Ivan or Bart if you have any -- besides the prelude you gave about this most recent document, did you guys want to comment first about formaldehyde and methylene glycol?

DR. BOYER: Well, I think --

DR. MARKS: How's that for putting you on the stage?

DR. BOYER: Well, I think that actually, the Panel has a major challenge because there is such contradictory information out there, and there, basically you can divide the camps into two diametrically opposed points of view. And in spite of the very large amount of research that's been done over the years, there are still some major issues that haven't been resolved, and there are still major controversies that still exist. EPA has recently conducted a risk assessment geared toward developing toxicity values for inhalation for that particular group, but they basically reviewed much of the literature. They've covered several, all of the major routes of exposure that EPA anyway is concerned with. And they, I thought, did a very good job in summarizing the literature and even bringing out some of the most recent reports, some of the most recent epidemiological studies and meta-analyses and so on, but interestingly enough, leaving out some others. So what we tried to do to prepare at least the toxicity, toxicology section for this report is to use the EPA report as the source of information, help us to identify critical papers that are in fact the center of -- at the center of what EPA is trying to do at the moment. The risk assessment, by the way, is

in NAS's hands and has been in their hands since June 2nd. They're anticipating about a 14-month review process. EPA has taken a good deal of criticism for their tox values, their proposed tox values.

DR. HILL: Because they're too high or too low?

DR. BOYER: Because they're way low. They're very low, and the bases of their tox values also are in question, and even in terms of the way that they estimated the cancer risks. They assumed a linear, at low dose model, and they've done that before. They did that back in 1993, and even that is still a matter of controversy at this point. Is it linear at low dose? Do you consider it to be a non-threshold effect, the carcinogenicity, both in terms of the solid tumors in the nasal passages of rats and even the assumption that formaldehyde exposure can cause leukemia? So I mean that's a big issue. And we've got some really nice work. I think it was Curt Klaassen who may have mentioned it at the last meeting, by Swenberg's group, the paper by Lu that came out in late 2010 – very nice biochemistry that showed pretty clearly, at least in terms of the DNA adducts and DNA-DNA cross-links, adduct formation. Basically, those are local effects. You see that at the site of contact. You don't see those effects migrating to places like the bone marrow to cause leukemia, and so forth. And given the questions that have been raised with the epidemiological studies and so forth, it looks to be the case that in one camp, from their perspective in any case, the EPA has really jumped the gun and they are proposing some toxicity values that are so low. Someone has even indicated that the air concentrations that they're proposing to regulate is on the order of the concentrations that you would see in the breath in an unexposed person simply because formaldehyde is an endogenous metabolite and it is produced in the body at certain levels, and so on. So it's not going to be an easy, easy task for the Panel from that perspective.

I think it's going to be a matter of looking at the studies. I think we've captured most of, if not all of, the major studies, the most important ones in the report. And then determining just on the basis of the quality, the relative quality of these studies, what conclusions you'd like to reach at this point.

DR. MARKS: Okay. Thank you for that background. Bart, do you have anything on the chemistry. You mentioned formalin in here, but on the Scheme 1 formalin doesn't appear. Is that purposeful?

DR. HELDRETH: Well, essentially, formalin is everything in Scheme 1.

DR. MARKS: Everything.

DR. HELDRETH: In an aqueous environment, like the human body or the planet, it's somewhat disingenuous to say that you have either formaldehyde or methylene glycol. You're going to have an equilibrium of both of them. So if you're worried about one, you've got to think about the partner to it. This whole mixture, you know. You put formaldehyde in water, and that's how it's generated. Methanol and water, like I laid out there, produces methylene glycol, and the reaction is very fast. You know, microseconds. The reaction in the reverse direction is also very fast, but it's temperature-dependent. So if you heat this stuff up around the boiling point of the solution you're starting to push towards more formaldehyde formation. You always have some of both at room temperature in a water solution. It's going to be a very small amount of formaldehyde, but that equilibrium is always there, and there's always a list of things that could shift that equilibrium and produce formaldehyde.

DR. HILL: And then you have the extended polymers which form more slowly, but they're definitely there.

DR. HELDRETH: Right, right. There can be some stabilization of the solution with certain other alcohols; methanol can do it. But other alcohols have the same potential to stabilize the solution to some extent. But yeah, you're going to get the smaller polymethylene glycols. The larger ones, if you have the right amount of stabilizer in there, you're not going to produce a lot of because that's a much slower reaction, and if you have a stabilizer in there you don't really go there as much. But certainly, you're going to have a mixture of methylene glycol, the short polymethylene glycols and, of course, water and a tiny amount of formaldehyde at room temperature in any formalin solution.

DR. HILL: There was a question, while we're on this subject, that a couple of places you put a higher density. Do you mean under high pressure there? Is that what you're really intending to say because I don't understand how you would get higher density in an aqueous solution of formaldehyde?

DR. HELDRETH: I mean the direct reference is for density. So if you had a higher dense solution, it's hard to kind of imagine that. I totally agree.

DR. HILL: I guess what I'm asking is can we go back and look at where those original statements come from and what they actually were referring to. I didn't take time to do that.

DR. HELDRETH: They were referring to a denser type of solution. So if you –

DR. HILL: No, I mean dense could be you're stirring in some silica, or dense could be it's at a lower temperature as opposed to higher temperature.

DR. HELDRETH: Right.

DR. HILL: And that's not the way this goes. So I guess what I'm asking is we're talking about compression here which to me, chemically, I can see exactly what that would do.

DR. HELDRETH: No, I --

DR. HILL: I wondered if that's where that was coming from, in which case we can make that totally irrelevant to cosmetics or because we're not going to have even -- no. I mean anything, even an aerosol can, is not going to be under those kinds of pressures. So it would be irrelevant.

DR. HELDRETH: No. Specifically there, the density refers to those solutions that would perhaps be more concentrated with other solutes to create a higher density solution. It does have an effect on equilibrium.

DR. HILL: Well, okay. I mean higher density because it's packed with, nearly saturated with sodium chloride should be a very different situation than higher density because it's packed with propylene glycols.

DR. HELDRETH: Certainly.

DR. HILL: And I'm thinking that the equilibria with two very different things. I doubt that that would be a consistent result at all. So that's why I'm saying clarification is needed here if this is truly relevant or not.

DR. HELDRETH: Well, the density will differ depending on what the solutes are, for sure, but we're not going to be able to have a picture of what the density differences are for each and every solute that might come –

DR. HILL: Well, I'm proposing that this is totally irrelevant to the discussion because I doubt that cosmetically -- I think it probably traces back to under pressure versus not under pressure when we're talking about density here. If that's not true, I would think high density, again saturated with inorganics like sodium chloride, would be very different than high density because it's got polypropylene glycols in there or something else that makes the density very high -- simple syrup, a lot of sucrose.

DR. HELDRETH: Yes.

DR. HILL: That, I would envision to be a very different scenario than it's very dense because it's got a high concentration of inorganics. I think the equilibria would do very different things. I'd be stunned if that wasn't the case. And in terms of assessing what's going on here, I guess I need to know, and perhaps I should do the research, but –

DR. HELDRETH: Well, I can tell you that I can recall that the reference has nothing to do with pressure.

DR. HILL: Okay, so it's density. So the question is where is -- how is the density varied in that particular reference? What's actually varying the density? Is it varying concentration of sucrose, something like a simple syrup –

DR. HELDRETH: Yes, it's just different solutes. Right.

DR. HILL: -- or is it a varying concentration of sodium chloride? I mean I think it would not do the same thing.

DR. HELDRETH: Sure.

DR. HILL: Maybe it will.

DR. MARKS: Go ahead, Ron. Ron Shank.

DR. SHANK: What is being asked of the Panel regarding the formaldehyde methylene glycol?

DR. BRONAUGH: I think the concern is that with products like Brazilian Blowout the formaldehyde is mostly in the form of methylene glycol. But when it's heated, when it's put on the hair and heated, then it's converted to formaldehyde and gas is formed and people are having reactions to the formaldehyde gas.

DR. SHANK: Skin reactions or respiratory reactions?

DR. MARKS: Both.

DR. BRONAUGH: Both, even though as a liquid at room temperature there's very little formaldehyde. It's not in the form of formaldehyde. It comes in the form of formaldehyde when the product is used and heat is applied.

DR. MARKS: I thought that actually when they did the measurements of formaldehyde it was like 40 times greater in the product itself, and then you heated it and it even dried out more formaldehyde. I'd have to go back to that.

DR. SHANK: I thought it was under three digits.

DR. MARKS: Yeah, 8 or 10 percent, just as a -- which was much higher, 40 times higher than what the Panel had recommended as in their conclusion in '84. So I think it was a higher concentration of formaldehyde to begin with, and the heating even made it worse.

DR. BRONAUGH: I think maybe in analytical process, some of it even passed the level of formaldehyde. It's maybe converted back to formaldehyde during the analytical process.

DR. BOYER: Right. It may be present in the aqueous solution, in the aqueous product largely 99 percent of it, or more, as methylene glycol. But when they do the analyses, it comes out as formaldehyde. That's basically what they're measuring it as.

DR. SHANK: But our task is not to review a commercial product, is it?

DR. MARKS: Well, I think it was the idea was we had never addressed methylene glycol was my understanding.

DR. BRONAUGH: The concern is under these conditions of use where this, where the products are converted, like with heat, to a high level of formaldehyde. This is something different than a topical product that's not heated, and the form is not in formaldehyde, but it's in methylene glycol.

DR. BRONAUGH: So I mean let me just say that the aerosol now becomes important.

DR. SHANK: Okay.

DR. BRONAUGH: And previously, the Panel had ruled that there was, I guess, a concern there was (sic) no data to show that it was safe. But now we have products where aerosols are being formed. Where before it was maybe a theoretical concern, now it's an actual concern about aerosol exposure.

DR. MARKS: And it says here –

DR. BERGFELD: Well, vaporization – is it aerosol, true aerosol, or vaporization?

DR. MARKS: I'm not sure –

DR. BERGFELD: Well, what the differences are.

DR. BRONAUGH: I would call it a vaporization as opposed to --

DR. BERGFELD: Anyhow, it's in the air.

DR. BRONAUGH: Right.

DR. BERGFELD: Inhaled.

DR. BRONAUGH: Right.

DR. BERGFELD: Deposited on the skin and mucosa. So we've gone from a 2 percent, less than 2 percent, to 10 plus.

DR. SHANK: So we haven't gone.

DR. BERGFELD: I mean to consider.

DR. SHANK: A product is out there that's way over what we have recommended, and it's also potentially aerosolized or vaporized, and we said we have no data to support the safety for that.

DR. MARKS: Right.

DR. SHANK: So why are we reviewing this product?

DR. MARKS: I think it's the fourth paragraph.

DR. SHANK: But we're interested in ingredients, not products.

DR. MARKS: Recognizing –

DR. SHANK: And we're in the formaldehyde document.

DR. BRONAUGH: Right.

DR. SHANK: So are we re-reviewing the safety of formaldehyde or a product?

DR. BRONAUGH: We're re-reviewing the safety of formaldehyde as an ingredient in a product because now we're concerned about the volatility of it in a product whereas before there was not that concern.

DR. BOYER: Yeah.

DR. SHANK: But we already took care of that years ago when we said we don't have sufficient data to establish the safety of aerosolized formaldehyde.

DR. BRONAUGH: But maybe the Panel needs the data now to determine one way or the other whether it is safe.

DR. SLAGA: To make a reemphasis.

DR. MARKS: Well, yeah. So Ivan -- well, Halyna, you're first, then Ivan, and then I'll refer to Panel Book page 14.

What drove me was methylene glycol is now listed as a cosmetic ingredient, and that was what drove this -- is are we going to reopen this because we now have methylene glycol listed as an ingredient. But Halyna, what do -- that's what I thought drove reopening it because we're going to have the same conclusion when we discuss it.

DR. BRESLAWEC: When the panel first reviewed formaldehyde, methylene glycol was not listed as a cosmetic ingredient. It now is. The second point is that the concentration of use data and the product categories in which formaldehyde and methylene glycol use are identified, based on the data we have from the FDA and the industry, are not indicative of the advertising that we've all seen. So we don't have product information. We don't have current information on how methylene glycol and formaldehyde are in fact being currently used in cosmetic and personal care products. The industry has gone out and got the data or asked for the data. It's not indicative of what we know, of how we know it as being used. So whoever is out there using it --

DR. BERGFELD: It's called Brazilian Blowout, Dr. Hill.

DR. BRESLAWEC: -- we don't have accurate information.

DR. MARKS: David Steinberg said yes. It's manufactured in Brazil.

DR. SHANK: The industry doesn't use formaldehyde gas, does it? It uses an aqueous solution of formaldehyde, i.e., methylene glycol.

DR. HILL: Methylene glycol and polymethylene glycol.

DR. SHANK: So I mean this is a new issue, and if methylene glycol is listed in the dictionary as a separate entity it's basically a part of the same picture of formaldehyde.

DR. BRESLAWEC: I think that's why you reopened it, to consider methylene glycol.

DR. MARKS: Yes. So I think one of the things, Ron, you're bringing up is should the team not reopen because I'll moving tomorrow what to do with this, so not reopen and then in the summary discussion capture a lot of this, but that's a little bit before. Ivan, you had something you wanted to add?

DR. BOYER: I basically was going to say, the same thing as Halyna just did but maybe just emphasize that in our current analysis, our current discussion, methylene glycol was I don't believe mentioned. It may have been briefly mentioned, but it didn't give -- the write-up didn't give a whole lot of attention to the chemistry. So that was an important --

DR. MARKS: Carol, when you list it, that was my question in notes. This hair-smoothing product, is this a new use because we capture under a use table not only was this product had excessive amounts of formaldehyde that would probably in and of itself could cause human adverse reactions, but then heating it, as you so elegantly discussed in the chemistry, drives even more formaldehyde was available. So I guess when we go back to the most recent review, which was published in 2006, and you look at use, the use table, would under hair products with heated smooth, smoothing treatments be included in that?

DR. BRONAUGH: I would also like to point out Ron said that the industry does not use formaldehyde gas, but if you prepare a product that's intended to be heated and form a gas they are using it.

DR. BERGFELD: I'm uncertain as how it's heated. Being in the beauty salon a lot myself, I don't see them heating anything. Does the mixture heat?

DR. BRONAUGH: No. They use a metal plate is what I understand and put it on the hair.

DR. BERGFELD: Yeah, well, it's a straightening product. What we call a flat iron. Thank you. Yeah.

DR. HELDRETH: A flat iron.

DR. SHANK: But in the manufacturing of the cosmetic, do they take a water solution of formaldehyde, whatever that could be, and heat that to formaldehyde gas to make the cosmetic product?

DR. BRONAUGH: They make a product that's intended to be heated to form the formaldehyde gas.

DR. SLAGA: Intended, but not --

DR. SHANK: You're talking about this hair smoother.

DR. BRONAUGH: Right.

DR. SHANK: I'm talking about cosmetics in general where we have said up to two-tenths of a percent is okay.

DR. BRONAUGH: I don't know how they make the product. They wouldn't need to heat it, I don't think.

DR. SHANK: Yeah.

DR. BRONAUGH: It's intended to make a product that's a traditional product.

DR. BERGFELD: Well, the intent is also different. This is a protein-changing event where the other is more a preservative.

DR. SHANK: Preservative.

DR. BERGFELD: Yeah. So the intent is totally different.

DR. HILL: And I also have a question while we're on the exact subject. When that limit was set as 0.2 percent, was that total carbon 2 percent, in other words, formaldehyde plus methylene glycol plus all polymethylene glycols that are present?

DR. MARKS: I was going to ask Ivan that. That was based on RIPTs that had 0.2 percent formalin in my notes from those.

DR. HILL: Formalin.

DR. MARKS: So basically, that would obviously -- if it's formalin, to me that would be the proxy for the safety of formaldehyde and then obviously for methylene glycol because methylene glycol was in the material they were testing. And I know we had the discussion before in terms of sometimes it's not always easy to determine what they were using for testing, but undoubtedly it had to be formalin because it was going to be an aqueous solution.

DR. SLAGA: There's a number of ingredients that I would worry about. I didn't take time to come up with them. But if they were heated too, I mean, you know, that adds a whole new relationship to a number of chemicals, not just methylene glycol.

DR. SHANK: When you say two-tenths of a percent formalin --

DR. MARKS: Yeah, and that's different.

DR. SHANK: -- my understanding was the formaldehyde --

DR. MARKS: That's what's in the conclusion.

DR. SHANK: -- content was two-tenths of a percent in a formalin base, or whatever you call it, medium.

DR. BOYER: And I think if we go back and check, what it says is that the 2 percent applies to free formaldehyde, which --

DR. SHANK: Right.

DR. MARKS: Free formaldehyde.

DR. BOYER: Right.

DR. MARKS: Well, that's in the conclusion.

DR. SHANK: If it's two-tenths of a percent formalin, that's a lot less.

DR. MARKS: Yes.

DR. SHANK: I would recommend that we don't reopen it for this product, but we have a pretty extensive discussion and separate the toxicity inhalation which is very, as you said, highly controversial at this time versus skin. And I went round and round and round on this, how to handle this, and I finally did a calculation. I don't know how good it is. But I took a cosmetic cream with two-tenths percent formaldehyde, HCHO, and ten grams of that on the skin. That's 20 milligrams of formaldehyde. I assume that was immediately absorbed into the blood, 3.5 liters of plasma in an adult. So that gave me a concentration of formaldehyde of 0.19 mM, which blood is normally about 0.1. Okay. So this would double the concentration of formaldehyde. But in fact formaldehyde enters the skin very slowly, or slowly, and not nearly 100 percent, more like 3 or 4 percent, over 24, 48 hours. So from a dermal application, the contribution to the total amount of endogenous formaldehyde is trivial, and that's what we're interested in is the dermal. Now this hair straightener thing brings in inhalation, and we've already said we don't have information to establish safety. And I would put this in the discussion: I don't think that's skirting the issue. I think it's facing it, but this is where we are. I don't think any of us would recommend inhaling formaldehyde.

DR. HILL: So that would put it into the insufficient data regime then?

DR. SHANK: No, not reopen.

DR. MARKS: No, not reopen.

DR. HILL: No, no. I'm talking about, you know, we have a new procedure with regard to the insufficient data conclusions. Right? I mean there's basically after three years, two years, it's the equivalent of being declared unsafe.

DR. BRESLAWEK: I guess let me back up a little bit and ask for what kind of information would you recommend or would you ask that be provided, so that the insufficient data could become sufficient?

DR. SHANK: The nasopharyngeal cancer, I think, can be handled fairly well. The Lu paper does a very good job in saying not only that the DNA out of the cross-links are limited primarily to the nasopharyngeal area, but you also need cytotoxicity to fix the mutations, so that combination of DNA damage plus cell turnover. So as long as you avoid a cytotoxic exposure nasally, it's okay. You don't get that systemically. I had a problem in saying that there's no distribution beyond the lung because there are three or four studies, most of them not in English, but on reproductive toxicity, on adverse effects of inhaled formaldehyde on the male reproductive system. So it must -- if you have a high enough concentration, it must go systemic. The leukemia issue, there is a redress to the Lu paper saying the adducts don't change by inhalation. Adducts, DNA adducts in bone marrow don't change. Okay, but there -- that's assuming that's the mechanism of action is DNA damage. There was a suggestion from a paper from Finland, a letter to the editor saying the enzyme that oxidizes formaldehyde -- formaldehyde dehydrogenase -- also oxidizes a nitro compound, which is a cell signaling intermediate. It changes proteins. It involves the loss of different cell signaling pathways and has been related -- its aberration has been related to the various diseases. So this is another mechanism that could be considered. They're not saying this is the mechanism. But if you perturb this enzyme by loading it with formaldehyde, do you also change the cell signaling pathways? Just a suggestion. Well, that opens up the question maybe you don't change the DNA adducts in the bone marrow, but you may change the metabolism of cell signaling processes.

DR. SLAGA: That's very nonspecific.

DR. SHANK: Very nonspecific. Very hard to handle.

DR. SLAGA: Yeah.

DR. SHANK: I don't think we want to go to the issue of inhaled formaldehyde. I don't think we have the information to say what would be a safe level. There must be some safe level because formaldehyde is an endogenous compound.

DR. SLAGA: Yeah, it is.

DR. SHANK: But what that is in terms of inhaled cosmetic generated formaldehyde, I don't know. I don't know how we can get that, and I don't know what question we would ask.

DR. SLAGA: Well, on one hand, I totally agree with you, with the nasalpharyngeal and the leukemias, how you stated that. However, if we don't open it, I don't see how we can effectively get across to, you know, in a discussion. We're not going to change any conclusion, but at the same time it seems that we could address this new issue and the relationship of heating and how that drives it and that's obviously not recommended.

DR. SHANK: But don't we reopen with the intent to change a conclusion?

DR. SLAGA: We can reopen to do add-ons, and that's why this makes it more complete with the methylene glycol. Right?

DR. SHANK: Okay.

DR. HILL: Nothing's changed.

DR. SLAGA: Nothing's changed.

DR. BRESLAWEC: -- I do want to point out as much as I like a structured precedent, this situation is an example where the Panel will do whatever it needs to do to evaluate the safety of this ingredient. So we'll deal with the procedures, but you're going to have to figure out the best way to deal with this.

DR. SHANK: Do I remember right; this issue was brought to us by FDA?

DR. SLAGA: Yeah.

DR. SHANK: They asked us to review it?

DR. SLAGA: Right.

DR. SHANK: Did they ask us to review formaldehyde or the hair straightener? I thought it was to review formaldehyde.

DR. BRESLAWEC: And methylene glycol.

DR. BRONAUGH: Well, yes, but now formaldehyde is being used as a vapor in certain products, and so we would like, we would hope that the CIR would consider the safety of that, of that usage.

DR. SHANK: Okay.

DR. SLAGA: That's a product

DR. SHANK: Well, any product. I hate to sound like I'm defending the product because I don't know anything about it, okay, but we've never talked about a particular product before, and I get a little nervous about that.

DR. BRONAUGH: It's the usage.

DR. SHANK: But a product that is used in a way that we had not considered before, and it's causing irritation, health effects.

DR. BRESLAWEC: We're not talking about one product. We're talking about multiple products, and we are talking about a new type of use. That was the request that FDA made to us. They asked us specifically to include methylene glycol as an ingredient.

DR. SHANK: For hair straighteners.

DR. BRESLAWEC: For a new type of use, yes.

DR. SHANK: Okay.

DR. HILL: And if the popular press is to be believed, this type of use has a very devoted body of users who refute any attempts to criticize the safety –

DR. BRESLAWEC: Well, that's not --

DR. HILL: -- and would really like this thing to be on the market, I guess.

DR. SHANK: Well, we don't want to go that path.

DR. HILL: I know.

15 DR. BERGFELD: It does.

16 DR. HILL: But stay on the market is what I was going to say.

18 DR. BRESLAWEC: No.

19 DR. BRONAUGH: Well, you're correct. If there's no -- if the Panel could not get sufficient data to find usage, safe or unsafe, then maybe it could be evaluated as insufficient for aerosol use.

DR. BRESLAWEC: But again, in order to –

DR. SHANK: And that would really change our conclusion.

DR. BRONAUGH: Yeah.

DR. MARKS: Yes. Oh, absolutely.

DR. SHANK: So then we open.

DR. SLAGA: We would have to open it.

DR. SHANK: Okay.

DR. SLAGA: And the level of heating too. I mean even if we said we couldn't go beyond, so it wouldn't drive off more formaldehyde gas, you can't control that in the public.

DR. BERGFELD: They're currently using fans at their stations when they use this.

DR. MARKS: Let's go back into the conclusion. The Panel also said it can't be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized. Does this cover this? We've already covered a safe limit. It's interesting; when I go back to the original report, what I –

DR. SHANK: 1984?

DR. MARKS: Yeah. When I go back here to the original report and I look at the point two, I can't find a direct correlation. I assumed it came from the RIPT and the skin irritation studies. And when you look at all those, it's all with formalin. So I don't know if that was translated in the conclusion to free formaldehyde or what.

DR. BERGFELD: Exactly, because it's free formaldehyde.

DR. MARKS: Oh, it's free formaldehyde in the conclusion. I'm just not sure.

DR. HILL: Alan's memo here from August 8th of 2003 says "ensure use." Let's see here. "The formulation and the manufacture of a cosmetic product should be such as to ensure use at the minimal effective concentration of formaldehyde, not to exceed 0.2 percent measured as free formaldehyde." So in other words, put formalin in there; the 0.2 percent is the measured free formaldehyde from a formalin preparation.

DR. SHANK: That was my understanding.

DR. HILL: From a formalin-containing preparation.

DR. MARKS: Okay. And would that go along then that that would derive from the RIPTs which use 0.2 percent. When you look at that consistently, it's 0.2 percent were found to be safe.

DR. HILL: So I guess I presume that the people who were assessing the concentrations of those preparations that they used for the study were measuring free formaldehyde by accepted protocols and using that to establish the basis of how much formalin was in there, basically. But I mean it begs -- that's why I asked the question about this density thing. It might have seemed irrelevant, but if it's truly density, that should depend on the nature of what's changing the density. What you measure as free formaldehyde could vary vastly, depending on what's really going on with those equilibria based on what's increasing or decreasing the density. So I mean you're measuring free gas in equilibrium with a product or preparation that you're using for the safety evaluation which could vary vastly in terms of how much formalin is actually in there. Then if the only concern, which I think maybe it is, is inhaled formaldehyde, then the use comes into play as the thing. But I agree; we're not sure we know where that level came from.

DR. SHANK: (Inaudible)

DR. MARKS: Yeah, maybe that. Obviously, this concentration was good because we didn't see adverse effects.

DR. SHANK: Well, that's what they got, isn't it?

DR. MARKS: Yeah, yeah. It's like how does -- yeah, I'm trying to go back and reconstruct how we got the free formaldehyde level, whether somehow the chemistry. We didn't have Bart here to really clarify.

DR. BERGFELD: We had David Kaufman here.

DR. MARKS: Yeah.

DR. BERGFELD: He was a good one.

DR. SHANK: Okay. So that 0.2 percent formalin was 0.2 percent of a 37 percent formaldehyde solution according to this table, Table 5, page 174 in the very first report.

DR. HILL: This is the old one.

DR. SHANK: So the actual formaldehyde concentration test was 0.0185. So we would have to clarify that in the conclusion.

DR. MARKS: If we reopen it, and I still haven't gotten a good consensus –

DR. SHANK: I think though --

DR. MARKS: -- among the team here whether or not we should reopen it, whether the wording, whether that needs to be clarified. And then the other is whether the wording concerning aerosolization, whether we should have an insufficient conclusion on it. And then obviously addressing this, as I asked earlier, this "new use," although if it's a hair straightening product and using heat that's really not a new use. Cosmetics, I guess you –

DR. BRESLAWEC: It was not a use for which formaldehyde was reported to be used previously –

DR. MARKS: Right.

DR. BRESLAWEC: -- because that's what I mean by new use, yes.

DR. MARKS: Right. Okay. So, Ron?

DR. HILL: Okay. What's here contrasts with what I said because this says was it's actually 0.2 percent formalin -- it's very clear here -- and then diluted to 25 percent in aqueous solution. So that's a much lower concentration than what I just suggested.

DR. HELDRETH: Right, depends on what is meant by free formaldehyde.

DR. HILL: It says 0.2 percent formalin. Formalin, I think, is pretty well defined. So if it's 0.2 percent formalin, that should translate to a very low level of free formaldehyde.

DR. HELDRETH: Right, like a normal solution of formalin off the shelf. You know, at full concentration is probably going to be less than 0.2 percent unhydrated formaldehyde molecules.

DR. SHANK: So I think we should reopen it and the idea of --

DR. MARKS: We've done that.

DR. SLAGA: We already did it.

DR. SHANK: We did?

DR. MARKS: Yeah, it is reopened.

DR. SHANK: Okay, it is reopened.

DR. MARKS: Right. So now we have to come to, you know, what kind of conclusion, what more do we need as the format of this. So we're going to -- the title is going to be Formaldehyde/Methylene Glycol. Is there -- you know. It's really heavy, obviously, on the issue of cancer. If the discussion in here, there's reproductive and development. In this new document we have, there really isn't going back to sensitization and irritation, and that's a big issue with formaldehyde. So are we going to not have that in here, or are we going to kind of refer back? If we reopen it, that means the whole document has to be redone.

DR. BRESLAWEC: We have in the past couple of years, when we've reopened and readdressed an issue, we've tended to focus on the issue of particular concern. So if you would like us to go back and reexamine sensitization, we could do that. What we tried to do was focus in on the issues that we believed the Panel was concerned about for this particular time, and that's why those –

DR. SLAGA: You're always referring back to the old documents.

DR. BRESLAWEC: Right. That's why it was not specifically addressed. It was focused just on what it was intended to.

DR. BOYER: And to the extent that we went beyond that focus, we identified some papers that addressed sensitivity that weren't addressed in the older CIR analyses, but they're all old papers, and we really didn't find too much that's new in the literature. And so what we did was include a few of the old papers that weren't addressed in the previous CIR reports. So right now, you have a fairly meager list of additional studies that were addressed, and that doesn't -- none of that would change the conclusions in that area.

DR. HILL: And I have a question that directly pertains to what you just said and following up on something that Dr. Shank said, and I'm going to expose my ignorance about aerosols here for a moment. Take liquid and expel it with propellant to make it an aerosol of liquid droplets. Okay. Then I presume evaporation will take over, and the droplets will come down to a certain size, and anything that's volatile in there will now be gaseous vapor. So how do we encapsulate if somebody squirts an aerosol and then somebody is nearby breathing it and now we have some free formaldehyde gas, then that definitely not limited to nasopharyngeal exposure. It should be able to get all the way down into the lungs. How do we encapsulate? And this falls into information needed. How much formaldehyde gas gets down into the lungs because it's now gas and not aerosol under these kinds of exposure conditions?

DR. SHANK: The inhalation studies were done on gas, not aerosols.

DR. BOYER: That's correct.

DR. EISENMANN: But formaldehyde is so reactive, I don't think it goes beyond. That's because it's reactive.

DR. HILL: In other words, well, under normal -- I mean the concentrations of exposure. I don't know how high they actually went. Yet, I mean I realize people react with the water there in the nasal passage. It will never make it all the way down to the lungs. I get that. Okay. But it can get a little farther or a little less far based on really how high those concentrations actually get.

DR. BOYER: And I think it is really going to depend on just to what extent the mist, basically the formalin droplets, evaporate before someone inhales them. And it's very likely that at least some fraction of what is aerosolized is going to enter the alveolar space if those particles are small enough, and so you might get some exposure.

DR. HILL: Well, and -- right. And I guess what I'm saying is the particles won't go to zero because eventually surface tension will take over, although I don't know the full extent of that science, but the droplets won't totally disappear at ambient temps.

DR. BOYER: Right.

DR. HILL: For body temperature.

DR. BOYER: Right. And I don't think --

DR. HILL: But yeah, I mean I think if you've got formaldehyde gas, while I will say that it is reactive, I think not every bit of every gas molecule that passes into the lungs when we draw a rapid breath is going to hit the walls of the tubes going down until it gets into the lungs. I think it will get into the lungs. But how far, I don't know.

DR. BOYER: And all of the studies that we have are assuming that what someone is exposed to is the gases, the vapor, not the -- not aerosolized aqueous.

DR. HILL: Well, and see, I don't know because of course it will react with whatever water is there in the air. So depending on the concentration of formaldehyde, how much is actually there in the air as methylene glycol probably also varies.

DR. BOYER: Probably.

DR. HILL: But it's still a gas, which means if we take a bigger breath it could get down into the lungs. And if the concentration is high enough, quite a bit could get down in the lungs, I think.

MR. BOYER: Depending on particle size, I guess that's the point. In the boilerplate, we make the –

DR. HILL: Well, what I guess I'd really like to see is take radiolabeled formalin and find out where the carbon goes.

DR. EISENMANN: They have done that.

DR. HILL: Yeah? Those studies are there?

DR. EISENMANN: Those kinetics, yeah, recently.

DR. HILL: And at a high concentration. I mean they've run the concentration up with radiolabeled formalin and see where the carbon goes in aerosolized.

DR. EISENMANN: They haven't been able to find it further than the nose is my understanding. I think they're doing studies in monkeys.

DR. BOYER: Right, that was the vapor.

DR. MARKS: So we are at the point now we've reopened this. Now we have to come up with a tentative conclusion which is going to be obviously enhanced, different from the previous one. That's easy. We could just plug in methylene glycol, and that's a different conclusion.

We were having a sidebar when you were doing the aerosolized, and Ron and I believe that the previous conclusion where they used 0.2 percent free formaldehyde should have been formalin, not free formaldehyde, because when you look at all the RIPTs it's 0.2 percent formalin, and then they give free formaldehyde in the table. So we gotta change that conclusion. Either we gotta change from free formaldehyde to formalin itself because I don't -- I was looking at discussion to see how they came to that conclusion, whether there was anything else, any other tox data that suggest it shouldn't be 0.2 would land on that, and there really wasn't. It's all from the skin. So what tentative conclusion do we want?

Do we want to go at so the old one again, which we reaffirmed actually -- just let me see.

DR. SLAGA: In 2003.

DR. MARKS: Yeah, seven years ago, didn't pick it up then. From 1984, again, it says safe for use in cosmetics if free formaldehyde is minimalized but in no case greater than 0.2 percent. We obviously want to set a level. There's no new data that suggest that level should be altered. But it probably should be, do you think, 0.2 percent formalin, or do you want to use free formaldehyde but use the lower?

DR. BRESLAWEC: I just want to point out that formalin used to be a cosmetic ingredient. It is no longer a cosmetic ingredient. However, as Bart tells me, formalin is listed as an alternate name for formaldehyde.

DR. MARKS: Oh, interesting. Oh, so now maybe this is -- yeah.

DR. HILL: As the density gets higher, the plot thickens.

DR. MARKS: So Bart, as being the chemist, what would be the cleanest way of making sure that the cosmetic formulator knows how much free formaldehyde should come out of this?

DR. HELDRETH: Well, if we're talking about a formalin solution, we're talking about mostly methylene glycol.

DR. MARKS: Mostly methylene glycol.

DR. HELDRETH: Yeah. So if you're going to talk about those HRIPT studies –

DR. HILL: Right.

DR. HELDRETH: -- those were methylene glycol that they were studying. Now when it gets to the tissue --

DR. MARKS: That's not in the table as to what was measured, was it?

DR. HELDRETH: When it gets to the tissue, the reactivity is probably the formaldehyde. If you think about fixing tissues, it's a whole clock reaction. Methylene glycol goes into the skin really fast, but the fixation takes time, and that said, equilibrium shifting towards formaldehyde. So what's in the bottle is methylene glycol, but what's doing the action is probably the formaldehyde. So they're both there. It's hard to say one and not the other.

DR. HILL: So why was the name formalin abandoned? I mean that's the question here because to me that would be the right name for this ingredient. Then it encapsulates everything.

DR. HELDRETH: I don't know.

DR. BOYER: Well, actually, I think formalin is a defined solution.

DR. HILL: That's why.

DR. BOYER: And there's a certain percentage of methylene glycol actually.

DR. HILL: That's why.

DR. MARKS: Pardon?

DR. BOYER: It's a defined solution of methylene glycol and formaldehyde.

DR. HILL: It's 37 percent.

DR. BOYER: About 40 percent methylene glycol, or so. So if you dilute it, you don't really have -- strictly speaking, you don't really have formalin.

DR. HILL: That's why.

DR. HELDRETH: So once it's diluted, it's really methylene glycol/water solution.

DR. MARKS: Okay. So, Bart, how would you suggest we word this conundrum in the new, in the amended conclusion because we want to set a limit of how much? You know, the test back before 1984 showed that 0.2 percent formalin tested at that time was neither an irritant nor a sensitizer.

DR. HELDRETH: I think it has to be an either/or. I think it has to be we say that there's a certain percentage safe of either of these ingredients because they're inextricably linked. When we talk about one, we're talking about the other to some extent. So just make the percentage for both ingredients, and I think that's the beauty of reopening this to add methylene glycol because it should have always been part of the conversation.

DR. BERGFELD: The hidden part.

DR. HELDRETH: Right, right. And it was there in the original report, but hidden to some extent.

DR. HILL: Well, right. And then when you hit the blowout with the flat iron, probably the vast majority is converted to free formaldehyde.

DR. HELDRETH: Right.

DR. HILL: A conservative assumption would be assume it's all converted.

DR. MARKS: So how would you word that? If free formaldehyde/formalin/methylene glycol was minimized but in no case greater than 0.2 percent, how would you word that?

DR. HELDRETH: I don't think we can put formalin in there because it's not an ingredient.

DR. MARKS: Yeah. So it sound like we've got to interpret from this what they measured, free formaldehyde which was point -- what was it?

DR. SHANK: 0.07.

DR. MARKS: 0.07.

DR. SHANK: Yeah, I think you should do it on the basis of formaldehyde as far as the limit rather than getting into this --

DR. SLAGA: Which was a function of --

DR. SHANK: -- the different forms because that's what you're interested in is the formaldehyde basically.

DR. MARKS: And this one was 0.07. They're all 0.07 basically. Right?

DR. SHANK: Yes. Some were lower, but they were also nonsensitizing.

DR. MARKS: In no case greater than 0 point, what was it, 07.

DR. BRESLAWEC: Dr. Marks?

DR. MARKS: Yes.

DR. BRESLAWEC: Before we go on, could I ask Doug Schoon to make a comment? He reminds me that this product, these ingredients are also used in nail preparations, and I think that would be worth remembering.

MR. SCHOON: Yes, I'm Doug Schoon, Doug Schoon with the Nail Manufacturers Council, Professional Beauty Association. Thank you very much. Yeah, I just love your discussion -- very, very right on target. I just want to remind you that methylene glycol, formalin, whatever we called, is used as a nail hardener preparation. It's not heated. It's not applied to the skin. It is kept on the natural nail. The FDA has allowed up to 5 percent of formalin to be used, which roughly translates into about 2.96 percent -- not roughly, exactly at room temperature -- translates to about 2.96 percent methylene glycol and about 23 parts per million of free formaldehyde in equilibrium, which could be measured by C13 NMR. Which I thought was really interesting, another point that was made, is analytical techniques have changed quite a bit recently, and now it's a lot easier to measure the actual ratio between free formaldehyde and methylene glycol whereas before that could only be done by calculation using equilibrium constant to determine the ratio between the two. But you can get at the number of what is the free formaldehyde content, what is the methylene glycol content either by C13 MR or by use of equilibrium calculation. But you're correct when you say the analytical techniques dry all methylene glycol to free formaldehyde, to derivatize and measure as formaldehyde. But for my perspective, the real issue was again identified as what is free formaldehyde. That's what's creating the confusion.

DR. HILL: What was the percentage of free formaldehyde you just stated?

MR. SCHOON: If you use 5 percent, which is there are various concentrations of formalins, up to 55 percent I believe. If you use 5 percent of 37 percent formalin, you come up with 2.96 percent of methylene glycol and 23 parts per million of free formaldehyde, again if you use the equilibrium calculation and assume room temperature.

DR. HILL: So then –

MR. SCHOON: We've had a long history of safe use with free -- with this product on natural nails as a hardener. So I would certainly hate to see that usage go away.

DR. HILL: And then -- yeah. So we've got 2.9 percent. If 6 percent is methylene glycol, presumably then there will be some present as polymethylene glycol as well.

MR. SCHOON: Well, the methanol is there to prevent that from happening, but of course smaller amounts of that can occur and cyclization can occur too, but those are trivial contaminants.

DR. MARKS: So does this conclusion from 1984 conflict with what's actually used in nail products?

MR. SCHOON: I don't think it conflicts, depending on how you define free formaldehyde. That's really the heart of the issue in my estimation. That's what's causing all the confusion. And I've worked with -- I mean I'm not representing them, but I've worked with many of the companies that are making these products that you're considering now, and they're confused by this as well. So I don't think anybody wants to do the wrong thing. Everyone wants to do the right thing, but there's just not clarity in what is meant.

DR. MARKS: Okay, Bart, how do we make this clear?

DR. HELDRETH: Poor Bart.

DR. MARKS: Yeah, poor Bart.

DR. HILL: If I calculate it right, that 23 parts per million is 0.0023 percent.

DR. HELDRETH: So it was in it already.

DR. MARKS: Which is well below the 0.07 percent that we calculated was safe.

DR. SHANK: Well, I think you have to do it on the basis of free formaldehyde. Otherwise, we -- how do you get data on methylene glycol because the toxic form is going to be formaldehyde?

MR. SCHOON: There has been data generated on exposure in salons. These services are done by OSHA (inaudible).

DR. SHANK: What kind of data is this?

MR. SCHOON: Air inhalation.

DR. SHANK: Of what?

MR. SCHOON: Of when these treatments, the treatments –

DR. SHANK: For the nail?

MR. SCHOON: I represent the Nail Manufacturers Council, but there are data out there on what exposure is occurring in salons when these smoothing treatments are used as well, according to OSHA. Oregon OSHA has done that inhalation study.

DR. MARKS: So is it your sense the reason there wasn't a problem before the Brazilian Blowout product hit the market is because prior to that the concentrations of free formaldehyde actually were within what was recommended and you didn't get problems with aerosolization. And then they made this product with 8 percent formaldehyde in it, and because it was so high then it became a significant issue. It's not just the -- we use what we had formulated previously, which was safe, that the heating and this new use would not have been an issue.

MR. SCHOON: I think that's fair to say, and this definitely is a new use, and there are over 40 different companies making products in this category right now. So it's definitely a new use within the last several years.

DR. BERGFELD: Is the mechanism of hardening of the proteins, so to speak, the same for the nail and the hair.

MR. SCHOON: I think they're the same. In everything I've read, not to argue with what was said earlier -- I didn't have it ready -- it's actually that methylene glycol is the reactive species with the protein. Lysine, like lysine is the main amino acid that it reacts with and causes cross-linking, hardening. That's certainly the mechanism for the nail. And it's a surface hardening. There's virtually no penetration --

DR. MARKS: Yeah.

MR. SCHOON: -- through the nail plate into the nail bed.

DR. MARKS: Okay. Those comments are very helpful. So do we want to, again getting back to, since it's reopened, our tentative conclusion which changed the wording: "If free formaldehyde was minimized but in no case greater than 0.07 percent," or should we get rid of some of that wordage and just say "the free formaldehyde is not greater than 0.07 percent"? Oftentimes, when we set limits in our conclusions, we don't use words like "minimize." We just say this is your limit.

DR. SLAGA: And that's based on some predictor.

DR. MARKS: Yeah.

MR. SCHOON: You may also -- free formaldehyde is the vaguer term. I would also see that definition structure with chem abstract number, et cetera.

DR. MARKS: Yeah, that would be in the actual report, so that definition. And Bart's done a --

DR. BERGFELD: Are you comfortable with that lower concentration? I mean with all your calculations up here. I mean you're really dropping it almost in half.

DR. MARKS: Yet, we're basing it on --

DR. BERGFELD: I know. Are you comfortable with it?

DR. HILL: Well, the 0.2 percent seems to be traceable to 0.2 percent formalin that was tested. So you're really not dropping it. It's just --

DR. BERGFELD: A redefinition.

DR. HILL: Yeah.

DR. MARKS: Yes, exactly.

DR. BERGFELD: I know, but the line. You're going to have to explain that.

DR. MARKS: I think what Doug -- that's why I asked the question with the nails was this, and then if the 23 parts per million of free formaldehyde -- I didn't do the quick calculation, but that's way under that if it's 0.0023 percent. I mean that doesn't even come close. That's why I asked would that be a problem, and it should not be a problem.

MR. SCHOON: Well, I think it's hard for me to say whether it would be a problem or not, but I think the calculation is pretty precise. Definitely what happened before, with the confusion between what the FDA says and what the CIR is saying, I believe is in the definition and the calculation.

DR. HILL: Good. We have this sheet pertaining to the nail hardeners. I was trying to find where it was. It's in this free piece of paper and discusses the FDA position on these and has the 5 percent.

DR. MARKS: Five percent formalin?

DR. HILL: Five percent formaldehyde is what it says. One of the waves -- I think this came from Wave 2 that I printed; I'm pretty sure.

DR. MARKS: Oh, there's -- So really that's 5 percent formalin.

MR. SCHOON: I believe they were talking about formalin, but that's just my belief.

DR. SHANK: I haven't seen that.

DR. HILL: I knew I saw it, if I can find the piece of paper where it was.

DR. MARKS: Okay, team members, we've got to have -- we have to move a tentative conclusion tomorrow, or a tentative conclusion. Do you like changing that, "safe for cosmetics if free formaldehyde is less than 0.07 percent"?

DR. HILL: The thing that bugs me about this, and I'll just put it out there, is based on what Dr. Bronaugh was saying primarily, which is you could have this Brazilian Blowout product which may or may not safe, we really have no idea, but we are having people react to it. It could be analyzed as it sits there on the shelf, to have below that level of free formaldehyde in it, but yet when you put it on the hair and heat it up under a flat iron you're going to be generating way more formaldehyde. And we're not saying as used, are we?

DR. MARKS: No. That's in the second sentence is going to -- that's when we talk about aerosolized.

DR. HILL: Okay. All right.

DR. MARKS: And I think what one has to say then is when you heat it, it's becoming aerosolized. Does that it include that use or that result? But I think first we've got to figure out what we want to say is a safe limit.

DR. SHANK: I don't think we can for --

DR. MARKS: Not for that, but on the --

DR. SHANK: -- inhaled.

DR. MARKS: Right, right.

DR. SHANK: You can handle the heating issue in the discussion.

DR. MARKS: Right.

DR. SHANK: I wouldn't put that in the conclusion.

DR. MARKS: Right.

DR. SHANK: And I'm tempted to leave that part of the conclusion the same. We don't have -- if you say "insufficient," then we have to say what data we need. And you've got --

DR. MARKS: So you would --

DR. SHANK: -- a mechanism of action for carcinogenicity, a molecular mechanism of action.

DR. SLAGA: Yeah, but people have been working on that all their lives in chemicals.

DR. SHANK: Yeah, that's right.

DR. SLAGA: So you can't say that.

DR. BRONAUGH: In the EPA draft report, they talk about that, but it's only a draft report. It's mentioned in this.

DR. SHANK: Right.

DR. BRONAUGH: So I don't know how much you can -- there may be references in there. I don't know.

DR. BOYER: Yeah. In fact, they list four, at least four different mechanisms, but it's all proposed mechanisms. It's really just speculation at this point, including the mechanism that you mentioned as well.

DR. SHANK: The nitric oxide one. So we -- I guess have we ever done insufficient data and not said what is needed?

DR. SLAGA: We'd be eaten alive.

DR. BRESLAWEC: You need to have --

DR. SHANK: And just say what the need is.

DR. BRESLAWEC: You need to say what is needed.

DR. HILL: Probably everything he said, at least, seriously. Seriously, everything he said, at least, because I agree with it.

DR. MARKS: Do you want to do that? Insufficient?

DR. SLAGA: We'll be discussing what the insufficiency is for weeks.

DR. HILL: So be it. I mean really. And meanwhile, I, unfortunately, just read the transcript on the plane. Is the Swenberg work the Lu reference, basically?

DR. SHANK: Yes.

DR. HILL: Okay. Can you guys get me a copy of that because I don't have my laptop with me?

DR. SHANK: I have a copy.

DR. HILL: You have a copy? But if I take your copy, then you won't have it.

DR. SHANK: It's on my computer.

DR. HILL: Okay.

DR. MARKS: So safe free formaldehyde limited to 0.07 percent, I think we've landed on that. And now the next is how to deal with the aerosolized. Do we use the same wording, Ron, as you suggested, "can't be concluded," or do we be more bold and say "insufficient data for aerosolized" and then list a lot of data needs? You were suggesting --

MR. SCHOON: That part of the industry is anxious to provide that data, so you will probably get a transcript.

DR. BRESLAWEC: Really? That would be great. We were kind of hoping to get some of that data prior to this, but we really had very little product characterization data.

DR. BERGFELD: This version would be adequate.

DR. HILL: Well, and see, that may have been done. That's what she's telling me, and that's why I needed to look at this.

DR. SHANK: Okay.

DR. HILL: I want to see exactly what they did, exactly how they dosed, exactly how they aerosolized. And again I didn't see this. I read the capsule summary, but I didn't know the issue until now.

DR. SHANK: That was an elegant study where they used deuterated formaldehyde and it didn't go to the bone marrow. So they'd say okay, so it can't cause leukemia. That's fine, but if you look under reproductive toxicity, inhaled formaldehyde has as its target the male reproductive system. So how do you put these two together?

DR. BOYER: That does seem contradictory.

DR. SHANK: Right.

DR. BOYER: On the other hand, in the analyses you're dealing with very high exposures. So it's very likely that you're overwhelming whatever might be happening by way of protective mechanisms at the site of contact.

DR. SHANK: I think Swenberg used 6 ppm inhalation.

DR. BOYER: They used, I believe it was 6 ppm. It may have been 10.

DR. SHANK: The animal studies used 10 for reproductive.

DR. BOYER: They used -- yeah.

DR. SHANK: Ten and higher, up to forty ppm.

DR. BOYER: Exactly.

DR. SHANK: But still 10 was still effective.

DR. BOYER: And we know so little about what the mechanism for those reproductive effects are --

DR. SHANK: Right.

DR. BOYER: -- that, you know, it could be anything. It could be entirely secondary. At those very high exposures, you're likely to see a good deal of damage if these animals are stressed. There's at least one paper that does suggest that the damage is due to oxidative stress, but it could be something else as well that's happening.

DR. SHANK: Well, they --

MR. BOYER: Systemically, it's really indirect.

DR. SHANK: True, but there's a Chinese paper, unfortunately, in Chinese. So I'm out of the picture, but the abstract says that they got the male reproductive toxicity with formaldehyde, but if they supplemented with tocopherol, it protected the animal --

DR. BOYER: Right.

DR. SHANK: -- the male reproductive system, from the formaldehyde. That would suggest oxidative damage.

DR. BOYER: Exactly.

DR. SHANK: Totally indirect.

DR. BOYER: Yeah. And we did include a summary of that study.

DR. SHANK: Yes, you did.

DR. BERGFELD: Maybe you should ask for concentrations of use then, if you want the studies.

DR. BRONAUGH: Also, exposure, exposure of people to formaldehyde use.

DR. MARKS: Yeah. Well, I'm going to get to data needs. I want to get to the point that we want to say insufficient for aerosolized because I got sort of the -- well, I like the way it was. We can't be -- it can't be concluded that formaldehyde is safe in cosmetics intended to be aerosolized, but that's sort of dodging the issue.

DR. BERGFELD: It's called weak

DR. MARKS: Yeah. So I think we should put in "insufficient for aerosolized" and then give some data needs in the discussion obviously, or summary.

DR. SHANK: Some data needs.

DR. MARKS: Yeah, some, some.

DR. SHANK: Could you be more explicit?

DR. MARKS: Well, I don't know. That's what I'm asking. I can see that's what you're struggling with. Ron Hill earlier said, yeah, all those things. And what more? Is it the entire, basically the entire?

DR. HILL: Well, if we're suggesting that there is a threshold above which we swamp protective mechanisms, I mean glutathione levels leap to my mind. Then if we had some sense of what that is, then it would be possible, I think more possible, to proceed to evaluate the probability of remote effects.

DR. SHANK: But that's assuming we know the mechanism of action.

DR. HILL: Well, I know. That's what you said before, which is why I said what you said.

DR. SLAGA: We don't have any clue.

DR. MARKS: So, Ron, do you want to do an insufficient or not?

DR. SLAGA: I don't know what to come up with, other than mechanism of action and that's still --

DR. HILL: Well, my point is --

DR. SLAGA: We'll say the same thing as we did before, say nothing.

DR. HILL: -- if it's clear that it never leaves the nasalpharyngeal pathways, if it's clear that it -- I'm not sure that it's clear. If it's clear that it never gets anywhere down into the lungs, if it's clear that even if it does get into the lungs the amounts are small enough that whatever glutathione or whatever oxidated protection is there will take care of that, which it probably will, then you probably can proceed. Then you don't have to worry about mechanisms because it never gets anywhere where you have to worry about that. I guess if you could establish that, then in my mind you're done. It's okay.

DR. BERGFELD: It gets in the blood.

DR. MARKS: So the reports were burning eyes, nose and throat, breathing difficulties, hair loss. Interesting. I don't about the hair loss was.

DR. SLAGA: Hair loss is easy.

DR. MARKS: Yeah, that was. But at any rate, so let's get back. Do we want to wimp out with the old wording, or do we want to put insufficient? And we don't know.

DR. BRESLAWEC: (Inaudible)

DR. MARKS: Yeah. Do you have a solution for this?

DR. BRESLAWEC: I wish I did.

DR. MARKS: They're looking for this.

DR. BRESLAWEC: I just want to point out that OSHA has certain levels that are considered safe for formaldehyde in the work environment, and perhaps if we had more ingredient characterization in this use, if we had more information on that, that could provide an avenue for saying something along the lines that if the levels in this type of use do not exceed an OSHA limit then perhaps -- but we simply don't have enough information about how the product is used or how the ingredient is used in these new products right now. That's where I'm kind of --

DR. MARKS: But that's fascinating. So have we used other agencies' levels to --

DR. BRESLAWEC: Sure, we do.

DR. MARKS: And presumably, there's a lot of --

DR. SHANK: OSHA's is based on pulmonary irritation, I think. I think that's their end point.

DR. BRESLAWEC: You know, that's got to be something that you all are comfortable with. I'm just suggesting that that's something we want to look at.

DR. MARKS: Right. And you want the reproductive and lots of things.

DR. HILL: I would be comfortable with that, provided we are comfortable with their basis for establishing those limits.

DR. MARKS: Right.

DR. HILL: We would have to know how they came up with them. And if they're overly restrictive, we should be able to say that too.

DR. BOYER: And I think we started in that direction in some sense in this report.

DR. MARKS: So could we tentatively -- since this is a tentative amended, do we want to just say "safe for free formaldehyde limit?" I keep repeating this because tomorrow this is what's going to come up, and we're going to say how we get there. Well, look at the old tables. But do we now want to say concerning aerosolized product that we're going to -- you know. We don't have a conclusion at this point, but we're looking at possibly using OSHA limits as what we would make our conclusion. I don't know. What do you think about that? We obviously have to get what the OSHA limits. If it's only respiratory, then that may not be adequate.

DR. BRESLAWEC: Right. But also, we have to get more information about the products themselves, or the ingredients as they're used in the products and what perhaps levels they generate.

DR. MARKS: Well, I think as long as we just say this is what's the limit in the air --

DR. BRESLAWEC: Yeah.

DR. MARKS: -- it doesn't matter. The product has to -- they have to do some way of measuring what their product will release. And I presume we're going to be uniform and always use free formaldehyde in this because I guess that's back into the actual conclusion. There's going to be have to be, as you've already done, a robust -- since we label it formaldehyde and methylene glycol, there's going to have to be a robust discussion of what that really means, and formalin in all of this. What do you think? How do you like that tack of aerosols we're going to defer the conclusion at this point? I don't think we can propose a tentative amendment at this point. I think it almost has to be tabled with a direction because we can't send out a tentative amendment that we're going to look into the conclusion.

DR. HILL: If 14 months was the approximate review -- this is one we said was referred to National Academy of Sciences for input. If 14 months was the tentative time table, where are we at in that? Does anybody know?

DR. SHANK: I don't know.

DR. HILL: We're six months in? We're two months in?

MR. FISCHER: I'm happy to address that. My name is David Fischer. I'm with the American Chemistry Council Formaldehyde Panel. The NAS study is supposed to be released this month, perhaps this week, but probably next or the week after.

DR. SHANK: Thank you.

DR. MARKS: That's great. So how do you like handling this by tabling it?

DR. SLAGA: That's -- I was waiting for that.

DR. HILL: Well, that's why I asked. Well, we're going to have this. They probably won't like that. Alan won't like that.

DR. MARKS: Well, fortunately, there aren't 421 ingredients in this. It's only tabling two ingredients. But how can you release a tentative amended conclusion unless we handle aerosolized product with a conclusion? If we can't come to a conclusion right now, maybe our fellow team will come to a conclusion, but we're struggling with aerosolized.

DR. SHANK: There's one conclusion we haven't talked about.

DR. MARKS: Insufficient or no?

DR. SHANK: No.

DR. SLAGA: No.

DR. MARKS: Unsafe?

DR. SHANK: Unsafe for aerosol use. IARC, the International Agency for Research on Cancer, has now said by inhalation formaldehyde causes nasopharyngeal carcinoma and leukemia.

DR. HILL: Even if they're wrong.

DR. SHANK: Well, but I mean it's an international body.

DR. HILL: Yeah, it is.

DR. SHANK: And we can defend the safety for dermal application because so little gets through the skin. It doesn't change the endogenous level of circulating formaldehyde.

DR. BERGFELD: I think you have to go insufficient, and you have to state what you need in general concepts.

DR. SHANK: Well, that's the problem.

DR. BERGFELD: I know. In general concepts. I mean maybe you have to come at it to rule out the possibility of the nasopharyngeal tumors, cancers and systemic absorption. I mean there have to be inhalation tests that do allow for some of that.

DR. SHANK: You know, an indirect method, an indirect mechanism of action, be it reactive oxygen species or what, to produce leukemia and testicular toxicity is still an adverse health effect. And the fact that it's not a genotoxic or direct action between the chemical and the target cell, the adverse health effect is still there. And there are several mechanisms that are proposed for formaldehyde toxicity. I don't know which one to go to. The dermal is pretty easy, I think. It's just enough is going to get through the skin. There is a mouse study. I haven't seen it in our quarterlies. I don't remember. A two-year dermal skin feeding test on mice with formaldehyde, which was negative, so you don't have to worry about skin cancer.

DR. BOYER: I thought that was included in the previous.

DR. SHANK: Is that it? Okay. I can't remember seeing it, but I know it's out there.

DR. HILL: Well, we talk about insufficient data needs, but sometimes we've determined that for the purposes of the Panel discussion we have an information gap which is specifically: There are these proposed mechanisms. We don't have the literature about that. We can't reach a tentative conclusion because we don't have that information that we need to decide how to reach that tentative conclusion. So I don't know if that's a table or what that is, but I think that's a table.

DR. MARKS: Well, that's assuming we're going to get that information.

DR. HILL: Well, at least we know what research studies he's talking about, and we can evaluate that in the context of anything we get from the people who are using the products in terms of things like vapor concentrations and how 22 those relate. And we can see at least how those relate to the OSHA levels and how those were set. I don't see how you do anything other than not reopen, which it's already reopened.

DR. SLAGA: You mean tabled, reopened and tabled. Wait for the important OSHA data.

DR. HILL: Well, yeah, because meanwhile we get that information. We get that information. We get the National Academy input.

DR. SLAGA: There's no doubt there's no concern for the skin.

DR. MARKS: So, Panel Members, would you like to table it then? Tomorrow, do you want me to, move to table it and we are waiting for the NAS?

DR. SLAGA: Well, that's plenty.

DR. MARKS: Yeah. Well, do you think we'll get enough information that we can move from either insufficient or that we can –

DR. BERGFELD: Or unsafe.

DR. MARKS: Unsafe. Yeah, the unsafe is a real –

DR. SHANK: Well, I think we should wait for the Academy's report, especially since it's imminent. So that means table.

DR. HILL: Okay. But I know we can table and still put out there the data needs that we are interested in seeing. And the other things I mentioned were internal. In other words, finding the right papers and plugging them into this document, basically, or at least providing them to us for our deliberations.

DR. SHANK: Has anybody read that Chinese paper where they exposed mice to -- or, animals. I can't remember what. They exposed animals to formaldehyde by inhalation and had testicular toxicity which was protected by tocopherol? Has anybody actually read the paper, translated?

DR. BOYER: I read the paper, yes. Well, not --

DR. SHANK: Okay. Is that a strong enough step.

DR. BOYER: I read a paper that was in English, and it's not necessarily the paper that you are talking about. But the paper summarized 2 --

DR. SHANK: A translation?

DR. BOYER: No, it's a paper that's printed in English. I have --

DR. SHANK: Okay. Is that data strong enough to use that as the mechanism of action for systemic toxicity by inhalation, reactive oxygen species, that here is an end point, testicular toxicity, that is prevented by an antioxidant? Does it seem strong enough? Maybe we should consider that.

DR. BOYER: Well, let me take another look at it. It was --

DR. SLAGA: Do you have that paper here?

DR. SHANK: The Chinese one? No.

DR. SLAGA: No, I don't want the Chinese one.

DR. HILL: Because while it's proper to say tocopherol and the biological species that derived from it are antioxidant, what actually occurs is still not completely known, but then there's a diversity.

DR. BOYER: Right. I mean it still doesn't answer the question because it could be that the Vitamin E, the tocopherol was protecting what's happening in the respiratory system to some extent and may be protective at that level. So it's really not directly answering the question.

DR. HILL: Well, and there's another reason I ask this, which is that there's ample evidence from the Bhopal incident in 1984 that glucuronide species can be formed in the lungs, carried to remote sites in the body and then release **toxicant**. So that's exactly what happened with methylase **sesyaneisocyanate**; it delayed toxicity. I don't if anything analogous happens here with methylene glycol, but I mean hypothetically it could.

DR. BOYER: Right.

DR. HILL: And that would provide a mechanism for a local **insult** to be transferred to some place else like testes, as an example.

DR. MARKS: Okay. So may I summarize this? This has been a really robust discussion.

DR. HILL: Please.

DR. SLAGA: It's just the words you have to summarize?

DR. MARKS: Since I'm making the motion, you can say I keep harping on the end game here. So I'm going to move tomorrow we table the tentative amended conclusion until we see the NAS report, that what we're aiming at is a safe

free formaldehyde limit at 0.07 percent, as discussed, based on the original studies, RIPT studies in which it was 0.2 percent formalin, which they measured the free formaldehyde. And then we still have difficulty in determining the safety of these aerosolized ingredients -- formaldehyde and methylene glycol -- and that we were struggling with an insufficient versus unsafe conclusion. And we really try and clear up the mechanism of action, if possible, if it's cancer-producing. Does that sound, and shall I ask --

DR. SLAGA: Well, we also wanted the OSHA stuff.

DR. MARKS: Now is the OSHA -- yeah, okay. But the OSHA -- okay, OSHA.

DR. SHANK: The basis for their limit value.

DR. MARKS: OSHA. OSHA limits, okay. And that would be there, yeah.

DR. SLAGA: I wouldn't even mention a mechanism action because that's (inaudible)

DR. MARKS: Okay, because we aren't going to know that. So we're going to await the NAS report, and then we want to find the OSHA limits for free formaldehyde and see whether we can use that to come to a conclusion on aerosolized formaldehyde and methylene glycol. Does that sound like a good summary?

DR. HILL: The OSHA limits and the basis by which they were set.

DR. MARKS: Yeah.

DR. EISENMANN: You also want information on the products. Right?

DR. BRESLAWEC: Yes. Yeah, I would.

DR. MARKS: Information on the products.

DR. BRESLAWEC: What concentrations.

DR. EISENMANN: What level. When you use the product, what level gets in the air?

DR. MARKS: No, it doesn't matter. We're going to set a limit.

DR. EISENMANN: Okay.

DR. SHANK: It has nothing to do with the topic.

DR. EISENMANN: Okay. So you don't care about that. Okay.

DR. MARKS: No. We know what --

DR. SHANK: I'm sorry.

DR. MARKS: We know Brazilian Blowout is --

DR. HILL: Well, if we're going to use that rationale, we don't need it.

DR. SHANK: It's what is the safe exposure. It doesn't matter what product.

DR. EISENMANN: Okay.

DR. BOYER: Also, just by way of clarification and semantics, there is a formaldehyde vapor and there is a possibility of a formaldehyde aerosol, and some people make a distinction between an aerosol and a vapor. The

aerosol would be liquid mist, fine particulates. And it probably in this case would be better to use the word "vapor" or "vaporization."

DR. MARKS: In this, you mean in the final conclusion, or?

DR. BOYER: Right.

DR. BERGFELD: Your reference to aerosol.

DR. BOYER: Yeah. Rather than referring to aerosols, you probably need to refer to it as a vapor just to be precise.

DR. SHANK: In the conclusion.

DR. MARKS: So, vapor.

DR. SLAGA: That's a good point.

DR. BERGFELD: I'd like to see you start to develop a discussion in the fact that there are certain points that have to go into it that you've identified, so you don't forget them. And one is what formalin/formaldehyde definition, that to go in.

DR. MARKS: Oh, yeah. Bart is already –

DR. BERGFELD: The second thing is your recalculation of free formaldehyde and then the concerns over this vaporization. I mean these are highlights that you're going to have to have in there no matter which way you go.

DR. MARKS: Well, and then obviously it's got to be very clear what methylene glycol is in all this too because we're kind of using this.

DR. HILL: Well, and I was about to say we now raise the issue of what's the vapor phase equilibrium like. In other words, we know formaldehyde can exist as gas, but how about methylene glycol; surely, that can be gaseous. And so what's the equilibrium in the vapor phase as opposed to the liquid phase, which what you've dealt with thus far? And that's probably known, must be known. So we should probably -- and because our audience member said that at least the evidence suggested it doesn't have to be formaldehyde that reacts with lysines, for example. The methylene glycol can react directly.

DR. HELDRETH: Well, getting to the vapor phase, the equilibrium is shifting towards the free formaldehyde unhydrated form. So if we're talking about a product that has methylene glycol in it, a formalin-type solution, getting to the state where the methylene glycol could be vaporized, you're always pushing equilibrium towards free formaldehyde on the way there. So as you get closer to the temperature wherefore methylene glycol could vaporize --

DR. HILL: But it's like any other equilibrium. You've got an equilibrium in the liquid phase. You've got an equilibrium in the gas phase. Is that equilibrium in the gas phase 99.1? Is it 99.5? Is it 99.999?

DR. HELDRETH: But you're talking about given a liquid or a gas.

DR. HILL: So I know you're talking about on the way. At some point, you have a gas phase. If you've got droplets of --

DR. HELDRETH: But it's a complex gas phase.

DR. HILL: I don't think it's that complex. You've got droplets.

DR. HELDRETH: It's a complex solution. You have a solution of formaldehyde and methylene glycol in the liquid. When you go to the vapor phase, you're not getting just one.

DR. HILL: Okay. If you've got droplets evaporating, we're generating a vapor which is going to be some mixture of formaldehyde and methylene glycol. Probably nothing else because any of the polys are not going to be volatile.

DR. HELDRETH: Right, and they're going to be converting toward methylene glycol.

DR. HILL: Well, the question is are they when you're evaporating at room temperature as opposed to vaporizing thermally because you're not vaporizing thermally. So my point is there's got to be information about what goes on with the equilibria and the kinetics in the gas phase. People have been able to do that. That technology has existed for quite some time now.

DR. HELDRETH: Sure.

DR. HILL: See, what's there, please.

DR. BRESLAWEC: I just want to point out that if the report is tabled, we will come back with another draft report, but that will not be sent out for public comment.

DR. MARKS: Correct. And then I would include since we're changing the conclusion based on the RIPT and now what appears to really be the reference in the conclusion for free formaldehyde and the 0.07, we really need to have that in this report I think. I wouldn't put that back in the 1984 report without bringing it, so individuals can see this is exactly what we used. Any other comments? Thank you. Doug, any comments here? You predicted this was going to be a robust discussion.

DR. SHANK: It was.

#### Full Panel Discussion

DR. MARKS: Formaldehyde may have been the thinnest book we had, and it was inversely related to the length of the discussion about this ingredient. So, in December, the panel agreed to reopen the assessment of formaldehyde because of three reasons. There was new safety data, its use in hair-smoothing products, which had created a significant amount of salon user adverse events. And then lastly, to include methylene glycol, since that had not been in the original report, which was published in 1984. Which came to the conclusion that formaldehyde was safe in cosmetics if free formaldehyde was minimized, but in no case greater than 0.2 percent. And in the second sentence sort of equivocal in that conclusion, the panel also said it can't be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized. This was actually re-reviewed in 2003 by the panel, finding the same conclusion valid. And that was published in 2006. So, in light of these new developments at the end of last year, we reopened it, as I said earlier, and considered the new data, the use in hair smoothing products, and the elucidated chemistry of free formaldehyde, formalin, and methylene glycol, and the chemistry and bounce going between these chemicals. When we re-looked at the original report, it seemed like the conclusion was based on 0.2 percent formalin in skin irritation and sensitization studies, or repeat insult patch test. And that the amount of free formaldehyde was actually 0.074 percent. So that -- we had some difficulty in terms of deciding, well, what really is the level of free formaldehyde that would be safe. And then dealing with a second sentence in the conclusion. First of all, aerosolized it may be better to use the word "vapor" instead of aerosolized. And then we really didn't have enough data to decide on the respiratory route of toxicology, that being cancer and reproductive and development, and wanted to arrive at a conclusion of insufficient versus unsafe for the vaporized portion of this cosmetic ingredients. We found out that there is soon, meaning within a couple weeks, an NAS report which will be coming out. And then we also wanted to know what were the OSHA limits for exposure to formaldehyde that is in the air. So, with all that said, our team felt that we should table this at this point, awaiting the NAS report and the OSHA and finding out that OSHA limits to try and determine a basis for which we could come to the conclusion about the vaporized form as being insufficient or unsafe. I will ask Tom and the two Rons to elucidate better than what I said, if I left anything out.

DR. BERGFELD: Ron Shank?

DR. SHANK: Dr. Mark summarized it very well.

DR. BERGFELD: Ron Hill? Okay. Don?

DR. BELSITO: Yes. We took a slightly different tack, particularly because in our discussions there was a good amount of concern about the fact that this Brazilian hair care product is currently out on the market and currently creating problems. And to table this, we didn't think would be in the best interest of the consumer. We prefer to move this along. There's also a third point that you didn't address -- This is use in nail hardeners. And the FDA has approved its use in nail hardeners up to 5 percent.

DR. KATZ: Actually, when you're through with your comment, that needs to be corrected.

DR. BELSITO: Okay.

DR. KATZ: Because it is actually not approved. And when I've gone back -- and I can either make the mention now or later.

DR. BERGFELD: Probably now.

DR. KATZ: Okay. That it is actually not approved. There was a policy statement that was made back in 1974 via a warning letter that allowed its presence up to 5 percent. So, it actually is not approved at that level, but it is a policy statement. So I just wanted to clarify that the FDA has not approved it.

DR. BELSITO: Okay. So --

DR. BERGFELD: Thank you.

DR. BELSITO: -- you know, we viewed the issues as okay. Formaldehyde v. methylene glycol, the nasopharyngeal carcinogenicity issue, and then maybe setting a different limit for nail products as we have for other products that would contact only the nail. Thanks to Paul we did note that in 1993, actually, we looked at a higher concentration of nail products. And reading from the analysis of the submitted comments from the CIR compendium, it said, the expert panel publicly reviewed submitted comments relating to the use of formaldehyde at a concentration of 4.5 percent in nail hardeners. In its deliberation, the panel concurred that submitted evidence was inadequate to assure formaldehyde could be safely used above 0.2 percent in cosmetic products. And further information could be obtained from the -- from the published minutes of that panel meeting. So, it looked like we actually did look at some data at the higher concentration and could not arrive at safety. Having said all that, again in the interest of moving this forward, because of the issues with the Brazilian hair straightening product, we wanted to go out with a conclusion as follows. In that the -- we found that formaldehyde/methylene glycol is safe for use in cosmetics if formaldehyde equivalents are minimized but no case greater than 0.2 percent. The panel also said that it can't be concluded that formaldehyde/methylene glycol is safe in cosmetic products intended to be aerosolized or vaporized under conditions of use. The panel found that there was insufficient data to support the use of formaldehyde/methylene glycol in nail products. And the specific data that we had talked about getting was whatever data that FDA might have. So it would be of interest -- if it's just a letter -- but we're also informed that there is data from California nail salons regarding air levels of formaldehyde in these salons that might be helpful in assessing the safety of their use in a nail product. Because obviously if a product is labeled not for application to skin, sensitization goes away. But the issue would be the -- any volatility to the formaldehyde in air levels. So we wanted to move this ahead, again, in the interest of hopefully protecting the consumer from the Brazilian product that we feel would be considered unsafe because not only is its concentration greater than 0.2 percent methylene glycol, but also because there is vaporization with the heating process. So, our recommendation was safe methylene glycol, formaldehyde less than or equal to 0.2 for products. Insufficient data for aerosolized or vaporized and insufficient at this point for nail.

DR. BERGFELD: Comment? Or questions?

DR. MARKS: Two, a couple comments. One is, we weren't really sure that the 0.2 percent was really valid. We wanted to go back to the free formaldehyde, which now that there is several different analytical methods that we can be content that will actually measure the amount of free formaldehyde because that was one of the issues in the past. So, we would set a different limit of free formaldehyde.

And then we were really concerned about reacting specifically to a product versus coming to a conclusion that would cover. I know you did that, Don, when you talked about aerosolized or vaporized. But we didn't feel as compelled right now to come to a conclusion based on a product as to trying to get what would be the right limit for 8 aerosolized or vaporized formaldehyde. And we thought that data -- we could get that data potentially from the NAS report and OSHA limits.

DR. BERGFELD: Could I interfere and ask John Bailey a question? As the formaldehyde document exists today, the limit is 0.2 percent. And it is questionable in the vaporized or aerosolized -- so in fact, I don't hear any change in that with the various teams at this point. And -- except that there might be a reduction in the limit.

DR. BELSITO: Well, I mean the -- I think the -- when you're looking at formaldehyde you need to look at, you know, irritation under occlusion versus, you know, as used and open application and -- I mean, I think -- you know, we certainly can go back and re-look at that limit and change it. I guess I'll ask Rachel to comment on what she perceives as the public's need to have some immediate information on this Brazilian product.

MS. WEINTRAUB: Sure, thank you, Dr. Belsito. I think this is an instance where we know that consumers are having acute reactions to a product. There's numerous complaints about harms associated with receiving this treatment. So I think it's important that consumers understand that there are problems with the safety of this product. And in being in Dr. Belsito's team, it seemed very much like -- and I think what you're saying is consistent that it seems that this product is not consistent with safe use. So I think it's important to get the word out to consumers as soon as possible so that consumers understand the risks that they're taking by using this product.

DR. MARKS: Rachel, we concur. Certainly our team are certainly concerned about adverse effects on the consumer. I guess one could take the tack of, is it the panel's purview to get this out with some pending data which may be more accurate. And is it our role to really regulate this product? Or is it FDA's? And I guess I'd ask Linda about that. There's certainly enough in the literature now based on the Canadian action, based on an analysis that this material -- this Brazilian blowout has way over the concentration of formaldehyde as it's formulated now. And of course we know that heating it will drive more formaldehyde out. So we really wanted to come to a conclusion that maybe would be more accurate for the long run. And although we certainly know about the adverse events that are occurring now, the question is are we the right body to move forward to address this? I think there's enough information already to address it.

MS. WEINTRAUB: Well, if I may -- I mean, I think that both the FDA and the Personal Care Products Council have looked to CIR in both of their statements, they've said we want CIR to look at this. So, it's sort of been this circular -- well, almost circular sort of situation. So, you know -- and with -- there's been statements that have been put out to the public that sort of raise concerns but there's not certainty -- it's not necessarily clear. And I think from, you know, an average consumer looking at that information it's not clear what the conclusion is. So there's been a lot of looking to this body to make a determination.

DR. BERGFELD: Linda, do you want to respond, or?

DR. KATZ: Well, I'm not necessarily -- for a determination is the right word. I probably would say that we're looking to this body to get additional information so that we will have the information at hand that we need to be able to take an action. Right now we are not there. We are in the process of doing the research that we need to on the product specifically for which we've received complaints. But that there are missing pieces, and part of the missing piece is really the safety issue as to what one could expect or what one should look for in a vaporized product. And that was part of the reason why we asked for your help.

DR. BERGFELD: Ron Hill, then John.

DR. HILL: And that really was part of the -- excuse me -- we had yesterday because I think based on the science that's there I'm not sure we can reach a conclusion that it's unsafe if it's used properly. So I think, you know, the science suggests that in truth, we don't know. And I don't think we have enough information to conclude conclusively that it's not safe --

DR. BELSITO: Not safe in what regard, Ron?

DR. HILL: In using the product Brazilian blowout were it to be used in the proper circumstances. We know people are having reactions, we probably have some idea why. But I don't think we can conclusively say right now based on the science that it isn't safe and it shouldn't be used under any circumstances.

DR. BELSITO: You know, the issue is we haven't looked at methylene glycol. So, methylene glycol and formaldehyde have different functions listed in the Cosmetic Ingredient Dictionary. So, I think from a legalistic standpoint this panel has issued no regulations for methylene glycol, which allows this Brazilian blowout to use it what looks like at very close to 5 percent. Based on the information we now know, that methylene glycol is essentially formaldehyde, it just depends upon the state of the product it's in. And that when heated, formaldehyde is released and is going to be a certain amount of formaldehyde. At 5 percent, this product probably exceeds the limits that currently exist, number one. Number two, I think that we all can agree that the data for nasopharyngeal carcinoma, it's not clear, you know, whether it's a linear model or it's a, you know, genotoxic threshold model. We don't have that information. So if it's linear, as EPA is suggesting -- and we know from the chemistry that we've learned that we are vaporizing formaldehyde when we heat it -- then this product is probably unsafe or insufficient for vaporization and unsafe for concentration. But right now, that data is not even out there because we haven't looked at methylene glycol. I would also like to point out the next panel meeting is almost four months away, it's at the end of June. And then the panel meeting after that is the end of September. So if we table this we're not even going to get around to any announcements until June, and any possibility of final -- I don't even know if we can finalize it at September. It's 60 days now, right? Not 90? So we could finalize it September as opposed to if we do something today we can get the information, hopefully, since there's four months and go out with a final report, give the FDA -- this is a serious issue. And also more serious is, I call your attention to the reports from Health Canada with what their finding in terms of concentrations in formaldehyde on shells that totally exceed. I mean, cases are reported up to 30 percent, which many of us have trouble believing. Linda?

DR. KATZ: I went back to contact to see if that's actually correct, and I think the table may be wrong.

DR. BELSITO: Okay.

DR. KATZ: And it may be not quite that high. And the information that we've gotten was up to 7 percent. So that it may be that there -- one needs to check to make sure that it's really formaldehyde and not formalin or something else that's being measured in something. But -- so I'm not sure the table is correct as it's actually listed.

DR. BELSITO: Okay. But still, the report --

DR. KATZ: It's higher than what -- that's right.

DR. BELSITO: -- if it could be, are much higher than we've allowed. So I really -- I think, you know, I felt strongly before. Rachel has convinced me even more. So yesterday -- that we need to move forward with this document.

DR. KATZ: John Bailey?

DR. BAILEY: Yes, clearly this is a very complicated issue on several different levels. And not the least of which is nomenclature. And from our perspective formaldehyde gas is a rare material. It's actually pretty tough to make it and hold it. So, if it's around moisture at all it becomes methylene glycol. So, the way I kind of like to think of this is, formaldehyde equivalents. You know, you can take formalin, you can take methylene glycol, you can take paraformaldehyde, you can always calculate formaldehyde equivalents. And that's probably the best reference to use. Regarding looking to CIR, while we certainly respect FDA's position of having to look at it in the context of the Food, Drug, and Cosmetic Act, our expectation is that the CIR will review data, reach conclusions, publish those 7 conclusions, and industry will follow those. And certainly within the perspective of the council, our members -- most of them have signed on to a commitment -- the Consumer Commitment Code -- to follow the CIR guidelines. So I think, you know, I think perhaps we have a little more freedom and say in that than FDA might. Regarding the proper circumstances, I think it's possible to envision circumstances for properly ventilated facilities and properly trained individuals to use these hair smoothing products in a safe way. But the margin here is pretty narrow compared to an ordinary cosmetic. So I think you're dealing with an unusual situation. But it also harkens back to the alpha hydroxy acids, glycolic acid opinion where it was stated that anything used up to 10 percent or 30

-- I can't remember what it was, Alan. But nevertheless, it would be by trained professionals. So I think it's within the purview of the expert panel to make that kind of distinction. Regarding the need to do something sooner rather than later, I think there is a lot of confusion out there and I think Don, what you're talking about is to issue a conclusion and then let that force the submission of new data and information to clarify so that this would be dealt with in the June meeting. And I think that's certainly a viable way to do that. I think, though, the NAS and OSHA data will be very informative as to what is tolerable and maybe more information about how much is actually in the air. And perhaps a conclusion of unsafe if the formaldehyde levels in the air pass a certain threshold. And that would be set through that.

Regarding the -- I've been writing a list here. Regarding the 5 percent, it's certainly FDA policy. It's been that policy for a long time. It derives from some adverse events that go back to the 1970s. But also, in Europe they've done a similar assessment and have concluded that 5 percent in use in nail hardener products where there's protection shields and so forth -- because this is a polymerization reaction. So the formaldehyde is gone pretty fast. So, but steps do need to be taken. The 2 percent, whether we talk about 0.74 or 0.2 percent, again in Europe they've set it at 0.2 percent as calculated as formaldehyde. So they've had some basis for assessment. That and I, off the top of my head, I don't know how current or how available that is, but we can certainly find out more about that to see. So, anyway.

DR. BERGFELD: Don?

DR. BELSITO: Well, I mean, again I think, you know, if we proceed with this certainly, you know, that the two big issues are going to be sensitization, irritation, and inhalation. So, you know, it would be nice if very detailed summaries of what went before both with the initial review and the re-review that we did before that information be very nicely captured in the current document so we could look at it. I don't think that -- I didn't pick up on the fact that it was formalin, which is typically 37 percent formaldehyde. But I think what we'll find is that the studies are all over the board and it was probably irritation under occlusion. Because we all know that patch testing even with 1 percent aqueous formaldehyde induces a significant amount of irritation that you have to read through. But I've never really seen induction of allergy with patch testing with 1 percent aqueous formaldehyde. So I really doubt that that's going to be a significant sensitizer in humans. It would be more of an irritant under occlusion phenomenon. But again, I really feel very strongly that we need to move ahead with this document or we will not finish it until next year.

DR. MARKS: So read your conclusions again, Don. Because basically what you are recommending is we issue a tentative.

DR. BELSITO: A tentative with lots of insufficients.

DR. MARKS: Right.

DR. BELSITO: And so the conclusion was that formaldehyde/methylene glycol is safe for use in cosmetic products if formaldehyde equivalents are minimized but no case greater than 0.2 percent. The panel felt that it could not conclude that formaldehyde/methylene glycol is safe for use in cosmetic products intended to be aerosolized or vaporized under conditions of use. The safety of formaldehyde/methylene glycol in nail products where it would be used up to 5 percent is insufficient and the information we need to know for that -- because we can set the, you know, consumer guidelines about protection, et cetera. Where we were asking for FDA's information, which I gather may just be a letter. And also, we were told that studies were done in California nail salons as part of Prop 65 doing air analysis on formaldehyde in these salons. We would like to see what that is. And then obviously, the data you talked about before should come in and help us clarify that nail use.

DR. MARKS: I -- go ahead. I was going to say, I don't see a problem with moving forward hearing the discussion at this point, because we have plenty of opportunity to modify this conclusion. It's a tentative conclusion we're sending out. So I'd ask my other team members --

DR. SLAGA: I agree with that. I think -- in acids, we agree with Belsito's team. We just were hoping we could have the National Academy of Science data as well as the OSHA data to help formulate this a little better.

DR. MARKS: I would say, the difference is we didn't have Rachel at our meeting yesterday pressing the consumer's point of view, which we were very sensitive to.

DR. BERGFELD: Any other discussion? I'd like to have -- I know you've stated your -- is this going to be a motion, then?

DR. BELSITO: It's a motion.

DR. BERGFELD: Is there going to be a second?

DR. MARKS: Second.

DR. BERGFELD: Rachel?

MS. WEINTRAUB: I just have one statement. Or, one question. And that is, is there also an issue about terminology and measuring the formaldehyde? Which I think needs to be clarified. Because I think the issue of free formaldehyde or methylene glycol versus having a percentage limit, I don't think those are equal. So I think we need to figure out how to capture that and make those consistent.

DR. BERGFELD: Thank you. Dan?

DR. LIEBLER: So I think that in the draft report that Bart and I have -- the language that Bart and I have prepared was very helpful in defining -- describing the chemistry, defining the terms. One point that came up yesterday was in our discussion was that I think the term free formaldehyde is actually kind of ambiguous. Because to some people it might mean the formaldehyde side of the formaldehyde- methylene glycol equilibrium. To other people it might mean formaldehyde that is not covalently bound to proteins or other things, that some of those adducts could revert, and so forth. So, I think it would probably be good for us to avoid using the term 'free' formaldehyde in our language. And as John suggested, we discussed yesterday referring to formaldehyde equivalents, or very similar strategy where we said formaldehyde/methylene glycol to recognize the fact that these species are in rapid equilibrium. And one last thing, I mentioned that we probably need to pay attention to is, I believe that 5 percent number for the nail products is 5 percent formalin. Is that correct? Yes. So it's 5 percent formalin, so that translates actually to a different lower number for the formaldehyde/methylene glycol in those products.

DR. MARKS: We actually calculated, and it was below actually the -- whatever free formaldehyde is, it was below the .074 percent.

DR. HILL: Twenty-three parts per million, but the methylene glycol is about 3 percent, so.

DR. BERGFELD: Don? I'm sorry -- Ron, did you have something else? Don, did you have something else?

DR. BELSITO: No further comments.

DR. BERGFELD: John, please?

DR. BAILEY: Yes. I agree about the confusion between formaldehyde, you know, methylene glycol. And I think the form to present this in the report is actually -- is definitions where you've got a heading and a definition that follows it. Because that is something that we could use in communicating to everyone about, you know, how these are defined and how they relate to one another.

DR. MARKS: I agree, John. I termed it a "glossary."

DR. BAILEY: Right.

DR. BELSITO: Yes. Well, I mean, and as we discussed with Alan, I think throughout the report we need to keep hitting people over the head with the idea of this formalin, which is 37 percent formaldehyde, and this formaldehyde/methylene glycol. And that's going to exist in an equilibrium that is going to be very dependent upon

many factors, including the particular solutions it's in, the pH, the heat, yadda, yadda, yadda. So I think we need to keep emphasizing that throughout the document. Because, you know, both Paul and I were struck when we went through this by the total lack of absence on methylene glycol. And Paul actually went ahead and did a search and you really can't find anything in the literature about methylene glycol. It's all formaldehyde.

So, I think we need to make that clear up front, too. Because if you read this document you go, whoa. How did the panel decide on safety of methylene glycol when there's no data on methylene glycol here.

DR. BERGFELD: Alan, did you have a remark?

DR. ANDERSEN: I think the discussions yesterday demonstrated that it may not be possible to say often enough that methylene glycol and formaldehyde are in an equilibrium. It's part of the explanation for why many of the formaldehyde data likely informed methylene glycol safety, and vice versa. And it's just -- it's an understanding that in the original safety assessment, as I recall, got one sentence. It was there, if you wanted to read it. But it definitely needs to be emphasized. And, message received.

DR. BERGFELD: Paul, did you have a comment?

DR. SNYDER: No, no comment.

DR. BERGFELD: Then, Ron? Ron Hill, then Ron Shank?

DR. HILL: Let him.

DR. BERGFELD: Dr. Shank?

DR. SHANK: If we're changing the conclusion, I do not think we should perpetuate this 0.2 percent formaldehyde limit. Because the report was based on 0.2 percent formalin.

DR. BELSITO: I --

DR. SHANK: So we should change that now.

DR. BELSITO: Well, I don't know that we have the data to change it in this report. We can change -- it's not going out final, it's simply going out insufficient. So I think we -- that's why I asked that all of the data on sensitization, irritation -- all of the data that we saw on inhalation in the original report and our re-review be really very seriously summarized in the next iteration that we see, so we can actually re-look at the data on that -- on this 0.2 and get The minutes from the original meeting. I think what we'll find is the 0.2 percent is based upon irritation under occlusion, and is not really based on sensitization. But we'll see. We can change those. This is not a final. We can change everything, including saying that it's safe for use in aerosolized next time. This is just to get out to the public that, you know, we feel there's insufficient data for products that could be vaporized under condition of use. And that methylene glycol and formaldehyde are equivalent and whatever restrictions we place on one will be on the other. So, I'm not saying that 0.2 is going to be the final concentration, Ron. I just don't think we have all the data right now to set that.

DR. MARKS: I think the clarification -- first of all, I agree, Don. I think that clarification is the 0.2 percent in these studies was formalin. And then when you look at the table, the free formaldehyde which, in the conclusion, it says that concentration of free formaldehyde should not be greater than 0.2 percent. So it's not an issue of whether the results of the studies were irritation or sensitization as what did they mean by -- was that a misprint and it really should have been formalin and is not greater --

DR. BELSITO: I mean, I understand. But we can change that concentration later.

DR. MARKS: No question. I just want to clarify, we were not concerned about the end results of the studies. It was, what did the 0.2 represent? Was it free formaldehyde or formalin?

DR. BERGFELD: Ron Hill?

DR. HILL: I just wanted to -- based on your wording, make sure that we are also pretty careful with the usage of formaldehyde equivalents. Because if you had dissolved formaldehyde present as paraformaldehyde then, yes, under conditions of very strong heating you could generate -- I hate to use the word now free formaldehyde, but molecular  $\text{CH}_2\text{C}=\text{O}$ . The carbonyl form, I guess that's unambiguous. You could generate the carbonyl form. But there are kinetics associated with that, and if you just put it based on formaldehyde equivalents, that we're going to start picking up things like quaternium, which has formaldehyde equivalents, and so forth. So we need to be pretty careful how that's used and make sure that wherever you use formaldehyde equivalents we're saying it very clearly. Because we spent time talking about things like the equilibrium in the liquid phase between the carbonyl form and methylene glycol is not necessarily the same as the equilibrium in the gas phase, and what are the implications of that. It also came up that it doesn't have to be in the carbonyl form to react with tissues. It can react as methylene glycol, apparently. So there are a lot of these things that need to be really clear.

DR. BERGFELD: Can the scientific council help us with that? The committee?

DR. BAILEY: Yes, we can put that on our agenda of things to work on and get back for the June meeting.

DR. BERGFELD: All right. So we have a motion and I believe we have a second.

DR. MARKS: We do, it's been seconded.

DR. BERGFELD: Second. And any further discussion? Seeing none, a call for a vote. All those in favor indicate by raising your hands. Thank you, so it will go out as an insufficient with -- as stated by Don. I guess it would be massaged and cleaned up a little bit. All right.



# Final Amended Report

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## Formaldehyde and Methylene Glycol as Used in Cosmetics

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**June 27, 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 smoothing products) exist in an equilibrium in aqueous cosmetic formulations whenever either one is present. Limits on the concentration of formaldehyde/methylene glycol used in cosmetics as a preservative and as a nail building ingredient have been established, but the safety of these ingredients in hair smoothing products is not assured.

## INTRODUCTION

In 1984, CIR published its original safety assessment of formaldehyde<sup>1</sup>, concluding that this preservative is safe for use in cosmetics 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.<sup>2</sup>

In addition to the issues related to new uses, the 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, including interagency comments on an earlier draft of the document.<sup>3</sup> In particular, Volume II – Hazard Characterization – of 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 toxicological information summarized in this Draft Final Report is from studies identified primarily in Volume II of the external review draft NCEA Risk Assessment.<sup>3</sup> Much of the significant new toxicology data are related to genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

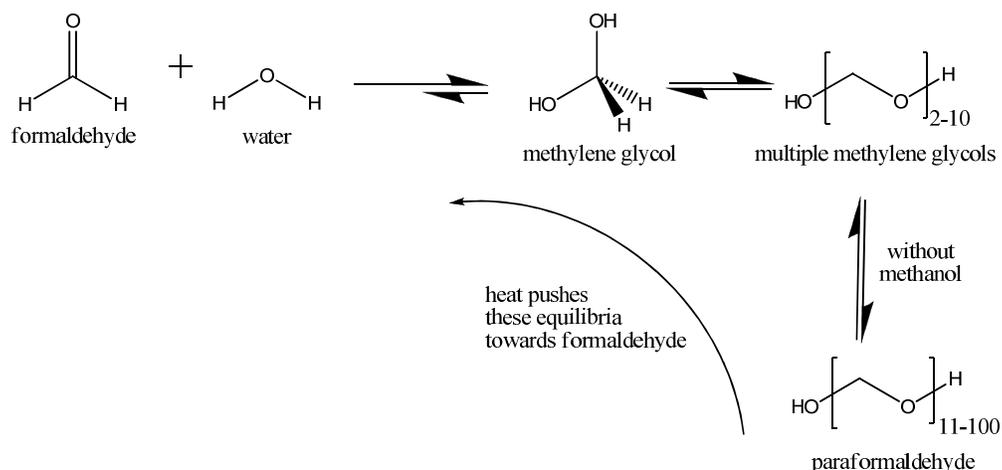
Based on the now available information, the CIR Expert Panel issued a tentative amended safety assessment of formaldehyde and methylene glycol, reaffirming the conclusion regarding formaldehyde used as a preservative, but asking significant questions about the use in hair smoothing and nail hardening products.

Additional data from the U.S. FDA's adverse event reporting system 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.<sup>4</sup> 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).<sup>5</sup> The rate of the hydration reaction is very fast (the half-life of formaldehyde in water is 70 ms) and the equilibrium between methylene glycol and formaldehyde strongly favors methylene glycol at room temperature and neutral pH.<sup>6</sup> 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.<sup>7</sup>

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.<sup>8</sup> 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.<sup>9</sup> 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.<sup>10</sup> 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.<sup>11</sup> 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 Nomenclature 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 0.2% (or 0.074%) formaldehyde equivalents were to stand, a new limit (that would mean the same thing) would need to be set to 0.002% (or 0.00074%) formaldehyde. This seems to add nothing to the discussion of ingredient safety, but is a mere sidetrack.

## 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).<sup>10</sup> 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.<sup>12</sup> 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).<sup>12</sup> 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.<sup>12</sup> 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,<sup>13</sup> formaldehyde functions in cosmetic products as a cosmetic biocide, denaturant, and preservative. According to the 2010 13<sup>th</sup> Edition of the INCI Dictionary, methylene glycol is reported to function as an artificial nail builder.<sup>13</sup>

In the U.S. FDA's Voluntary Cosmetic Registration Program (VCRP),<sup>14</sup> 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.<sup>2,14,15</sup> An industry survey of formaldehyde use concentrations yielded data shown in Table 1<sup>15</sup> 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.<sup>16</sup> 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 as a preservative in cosmetics at concentrations  $\leq 0.2\%$  (the limit for oral hygiene products is  $\leq 0.1\%$ ). Products containing  $>0.05\%$  formaldehyde must be labeled "contains formaldehyde." These limits are expressed as free 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.

### **Use of Formaldehyde/Methylene Glycol in Nail Strengthening Products**

The U.S. FDA Guide to Inspections of Cosmetic Product Manufacturers states the following regarding nail hardening products:<sup>17</sup>

"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."

In Europe, formaldehyde is permitted for use in nail hardeners at concentrations  $\leq 5\%$  “calculated as formaldehyde.”<sup>18</sup> The product label must instruct the user to protect cuticles with grease or oil.

### **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 OSHA uncovered a wide variety of ventilation approaches, including the presence of a building HVAC, simply propping the doors open, or having ceiling fans.<sup>10</sup>

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).<sup>19</sup> 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.<sup>20</sup>

One proposed reaction scheme involves: 1) hemiacetal formation between a keratin hydroxyl 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.<sup>21</sup> 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.<sup>22</sup> Besides proteins, formaldehyde is known to react with other biological molecules such as glycoproteins, nucleic acids, and polysaccharides.<sup>23</sup> The action of formaldehyde in intramolecular and intermolecular crosslinking of macromolecules can considerably alter the physical characteristics of the modified substrates.

Canada has issued health advisories informing consumers of the risks associated with hair smoothing products containing excessive levels of formaldehyde, and has recalled several such products.<sup>24-27</sup> Hair smoothing products with formaldehyde at levels  $>0.2\%$  are not permitted for sale in Canada.<sup>26</sup> Likewise, formaldehyde is approved for use in cosmetics in the European Union (EU) only up to a concentration of 0.2 percent; labeling requirements are prescribed if the concentration exceeds 0.05%. Accordingly, France’s health authority has 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.<sup>28</sup> Germany’s Federal Institute for Risk Assessment (BfR) advised against the use of hair straightening products that contain formaldehyde in high concentrations.<sup>29</sup> The Irish Medicines Board, which is the competent authority in Ireland for cosmetics, has taken action to remove hair smoothing products from the market if they contain greater than 0.2%, the level established by the European Commission (EC) for preservative safety.<sup>30</sup>

## **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 National Research Council (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.<sup>31</sup> The NRC concluded that formaldehyde is not available systemically in any reactive form, and systemic effects are unlikely from the direct delivery of formaldehyde or methylene glycol to distal sites, except possibly in highly exposed people.

## TOXICOLOGY

### Previous CIR Safety Reports on Formaldehyde- Summary

In low amounts, formaldehyde is generated and present in the body as a normal metabolite, and as such or when taken into the body, it is rapidly metabolized by several pathways to yield carbon dioxide. It is a very reactive chemical. Not surprisingly, formaldehyde is an irritant at low concentrations, especially to the eyes and the respiratory tract. Formaldehyde exposure can result in a sensitization reaction. Under experimental conditions formaldehyde is teratogenic, mutagenic and can induce neoplasms.

Perhaps the single most important attribute common to these toxic effects of formaldehyde is that they are all concentration/time dependent. A higher concentration or duration of exposure than that which produces irritation, for example, induces degenerative changes in the tissues exposed to it. There was no evidence that formaldehyde can induce neoplasia at concentration/time relationships that do not damage normal structure and function of tissues, even under laboratory conditions.

*From the Final Report on the Safety Assessment of Formaldehyde<sup>1</sup>*

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 Formaldehyde<sup>2</sup>*

### New Data on Safety of Formaldehyde

The 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, including interagency comments on an earlier draft of the document.<sup>3</sup> U.S. EPA is conducting this assessment to support the development of new chronic inhalation toxicity values for formaldehyde. Ultimately, the final versions of these values will be incorporated into the U.S. EPA Integrated Risk Information System (IRIS).

The NRC recently released their review of U.S. EPA's draft assessment<sup>31</sup> and their findings are also summarized below, where appropriate. The NRC noted that the systemic delivery of formaldehyde may not be required for some of the systemic effects attributed to formaldehyde inhalation (eg, lymphohematopoietic cancers and reproductive toxicity). Instead, systemic effects could be secondary, indirect effects of the local effects of exposure, including local irritation and inflammation, and stress.

The NRC concluded that formaldehyde does not penetrate beyond the superficial layer of the nasopharyngeal epithelium, and is unlikely to appear in the blood as an intact molecule, except possibly at concentrations that overwhelm the metabolic capacity of the epithelium.<sup>31</sup> The NRC concluded that formaldehyde is not available systemically in any reactive form, and systemic effects are not likely from the direct delivery of formaldehyde or methylene glycol to distal sites, except possibly in highly exposed people.

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.<sup>32-37</sup> 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.<sup>32,36</sup> There are no multigenerational tests for reproductive function.<sup>3</sup> 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 NRC noted that a small number of epidemiological studies<sup>38-41</sup> suggest an association between occupational exposure to formaldehyde and adverse reproductive outcomes in women.<sup>31</sup>

### **Genotoxicity**

Clear evidence of systemic mutagenicity does not emerge from animal inhalation bioassays, despite the reactivity and mutagenicity demonstrated in isolated mammalian cells.<sup>42-44</sup>

Similarly, the evidence that inhaled formaldehyde may be directly genotoxic to humans systemically is inconsistent and contradictory.<sup>45-50</sup>

### **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.<sup>31</sup> 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.<sup>51-58</sup>

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

The NRC concluded that these two primary modes of action contribute to formaldehyde-induced carcinogenicity in nasal tissues, including mutagenicity and CICP.<sup>31</sup> A mutagenic mode of action is generally the reason for adopting the default low-dose linear extrapolation methods in a quantitative cancer risk assessment. However, the NRC noted that formaldehyde is endogenous, that nasal tumors are rare in both rats and humans, and that no increases in tumor frequency are observed in animal studies at formaldehyde concentrations that do not also cause cytotoxicity. Further, the animal studies reveal a substantial nonlinearity in dose-response relationships among formaldehyde uptake, cytotoxicity, cell proliferation, and tumor formation.

Thus, the NRC recommended that the quantitative assessment of the risks of formaldehyde-induced NPCs incorporate the nonlinear phenomenon of CICP, as well as the mutagenicity of formaldehyde.<sup>31</sup>

#### ***Lymphohematopoietic(LHP) Cancers***

The three proposed modes of action by which formaldehyde exposure may cause leukemia include:<sup>59</sup>

- 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.<sup>3</sup>

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.<sup>60</sup> Further, formaldehyde is a highly reactive, rapidly metabolized chemical yielding short-lived DPCs and DNA-adducts that are amenable to rapid reversal and repair.<sup>61,62</sup> 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.<sup>60,63,64</sup> Although several possible modes of action have been postulated to explain associations between LHP cancers and formaldehyde exposure in epidemiological studies, little scientific evidence supports these hypotheses, and there is some recent evidence against them. Thus, these proposals remain speculative and continue to represent a highly controversial topic in the scientific community.

The NRC noted that little is known about the potential modes of action by which formaldehyde might cause LHP cancers, other than mutagenicity.<sup>31</sup> 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,<sup>1</sup> 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.<sup>65</sup> 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.<sup>66,67</sup> 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.<sup>1</sup>

Recent reviews addressing the human irritation and sensitization potential for aqueous formaldehyde/formalin solutions are consistent with the observations reported in the original assessment.<sup>68,69</sup>

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.<sup>70</sup> 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 Webri<sup>®</sup> disks. Note that, based on the manufacturer's directions, hair straighteners are applied undiluted to the hair.<sup>71</sup> 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 24<sup>th</sup> 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

#### 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,<sup>26</sup> 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.<sup>10</sup> Many of the stylists reported health symptoms associated with the use of this product at work. The health symptoms reported include the following: burning of eyes and throat, watering of eyes, dry mouth, loss of smell, headache and a feeling of “grogginess,” malaise, shortness of breath and breathing problems, a diagnosis of epiglottitis attributed by the stylist to their use of the product, fingertip numbness, and dermatitis. Some of these effects were also reported to have been experienced by the stylists’ clients. CROET also received emails from persons who report hair loss after having the treatment. Oregon OSHA has received similar, although generally less detailed, reports from individuals who have contacted the agency as a result of recent media coverage.

The U.S. 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.<sup>72</sup> 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.<sup>73</sup>

The U.S. 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. The results clearly link the use of formaldehyde/methylene glycol-containing hair-straightener 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. One report notes inhalation pneumonitis. 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

IARC (2006)<sup>74</sup> concluded that there was *sufficient* epidemiological evidence that formaldehyde causes NPC in humans and *strong but not sufficient* evidence for a causal association between leukemia and occupational exposure to formaldehyde. They also elevated their evaluation of formaldehyde from probably carcinogenic to humans (Group 2A) to carcinogenic to humans (Group 1).

In 2009, IARC<sup>75</sup> updated their evaluation to conclude that there is *sufficient* evidence for a causal association between leukemia, particularly myeloid leukemia, and occupational exposure to formaldehyde.<sup>59,75</sup> 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.<sup>76</sup>
- The levels of chromosome 7 monosomy and chromosome 8 trisomy in myeloid progenitor cells and hematological changes in formaldehyde exposed workers.<sup>59</sup>

The IARC Working Group was almost evenly split on the prevailing view that the evidence was sufficient for formaldehyde causing leukemia in humans<sup>75</sup>.

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.<sup>77</sup> They estimated an upper-bound inhalation cancer unit risk of  $1.6 \times 10^{-2}$  per ppm ( $1.3 \times 10^{-5}$  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.<sup>3</sup> 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.<sup>78</sup> The NRC agreed that the Hauptmann et al (2004) study<sup>79</sup> 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.<sup>31</sup> The update will likely address the deaths reported to be missing from this study.<sup>78</sup> However, the NRC explicitly did not recommend that U.S. EPA wait until the release of the update to complete its assessment.

### Non-Cancer Effects

In 1990, U.S. EPA published a chronic reference dose (cRfD) of 0.2 mg/kg/day for oral exposure to "formaldehyde," based on the results of a 2-year bioassay in rats.<sup>77,80</sup> "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 recently released a draft risk assessment for formaldehyde for public comment and review by the National Academy of Sciences (NAS).<sup>3</sup> 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<sup>81</sup> increased asthma, atopy, and respiratory symptoms,<sup>82</sup> and decreased pulmonary peak expiratory flow rate<sup>83</sup> in residential populations, including children. The NRC agreed with U.S. EPA's assessment of a causal relationship between formaldehyde and respiratory effects, except for incident asthma based on one of the "cocritical" studies.<sup>31,81</sup>

## 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 than in agricultural areas, and greater in indoor air than in outdoor air.<sup>3,31,74,84,85</sup> It is estimated that the general population is exposed to an average of 0.016 to 0.032 ppm formaldehyde in indoor air.<sup>86</sup> 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.<sup>84</sup> The concentration of endogenous formaldehyde in the blood of rats, monkeys, and humans is about 0.1 mM.<sup>87,88</sup> Endogenous tissue formaldehyde concentrations are similar to genotoxic and cytotoxic concentrations observed in vitro.<sup>60</sup> In addition, formaldehyde is likely present normally in exhaled breath at concentrations of a few parts per billion (ppb).<sup>31</sup>

## Standards and Guidance for Formaldehyde Inhalation Exposures

### U.S. OSHA Enforceable Standards<sup>89</sup>

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 above which employers are required to meet U.S. OSHA's hazard communication requirements.<sup>89</sup>

### 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.<sup>90</sup>

### 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.<sup>91</sup>

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<sup>92</sup>. 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.<sup>93-95</sup>

### ACGIH

Threshold Limit Value-Ceiling (TLV <sup>®</sup> -C)	0.3 ppm.
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The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value-Ceiling (TLV<sup>®</sup>-C) is defined as the concentration that should not be exceeded during any part of the working exposure.<sup>96</sup>

### WHO

30-minute average indoor air guideline	0.08 ppm
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The World Health Organization (WHO) 30-minute average indoor air guideline is for the prevention of significant sensory irritation in the general population.<sup>97</sup> 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).

### Formaldehyde Exposures During use of Nail Products

Time Weighted Average (TWA) formaldehyde exposures of nail technicians and customers were measured simultaneously, during the application of cosmetic nail products in winter and summer at 30 nail salons throughout California<sup>98</sup>. 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.

The samples were analyzed using high-performance liquid chromatography (HPLC), in accordance with U.S. EPA method TO-11.<sup>98</sup> However, the authors did not specify the sampling durations, except that some background samples were collected during the first 2 hours the salon was open, and they did not specify the averaging time or other assumptions that underlie the TWAs they reported.

The authors reported 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.<sup>98</sup> 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 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 and guidelines for formaldehyde, including the U.S. OSHA PEL-TWA (0.75 ppm), AL-TWA (0.5 ppm), and Threshold-TWA (0.1 ppm), the U.S. NAC AEGL-1 (0.9 ppm), and the WHO 30-minute guideline (0.08 ppm).

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

### 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.<sup>10</sup> 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  $\geq 10$  min).<sup>91</sup>

- 9 samples (0.303 to 1.88 ppm) exceeded the ACGIH TLV<sup>®</sup>-Ceiling (0.3 ppm).<sup>96</sup>
- 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).<sup>97</sup>

Further, 2 of 24 area samples collected during the procedures (**0.319 and 0.471 ppm**) exceeded the TLV<sup>®</sup>-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<sup>®</sup> 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.<sup>99</sup> 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<sup>®</sup>-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.<sup>100</sup> 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<sup>®</sup>-C (0.3 ppm), and the 4 others exceeded the TLV<sup>®</sup>-C (0.3 ppm) by up to nearly 4-fold. The highest value (1.07 ppm) exceeds the U.S. NAC AEG1-1 (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.<sup>101,102</sup> They used Sep-Pak<sup>®</sup> 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**. All of these samples exceeded the ACGIH TLV<sup>®</sup>-C (0.3 ppm) by 2.5 to 5.7-fold, and all but one of them exceeded the U.S. NAC AEG1-1 (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.<sup>102,103</sup> They used Sep-Pak<sup>®</sup> 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<sup>®</sup>-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, and followed ASTM D 5116 procedures for measuring organic emissions from indoor materials and products.<sup>104,105</sup> They collected three consecutive 1-hour air samples from the chamber, at room temperature, using Sep-Pak XPoSure samplers. They reported emissions factors for formaldehyde ranging from 1,020 µg/gram-hour for the first hour to 1,670 µg/gram-hour for the third hour. Indoor Environmental Engineering calculated formaldehyde concentrations in a hypothetical hair salon (240 ft<sup>2</sup>; 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.<sup>21</sup> The emission rates are most probably much higher when the product is heated (eg, during blow-drying and flat-ironing).

They modeled TWA exposure concentrations for the customer (110 minutes) and the stylist (8 hours), assuming 3 outdoor air ventilation rates (0.13 to 0.6 ft<sup>3</sup>/min-ft<sup>2</sup>) and three different amounts of the product applied to the customer's hair (12.6 to 37.8 grams). The amounts were selected from recommendations provided in the manufacturer's training video for using the product on short, medium and long hair.

The 110-minute formaldehyde concentrations ranged from 0.033 ppm (12.6 grams product; 0.6 ft<sup>3</sup>/min-ft<sup>2</sup>) to 0.269 ppm (37.8 grams product; 0.6 ft<sup>3</sup>/min-ft<sup>2</sup>). Two of the three 110-minute estimates assuming 25.2 grams of product (0.096 to 0.18 ppm at 0.38 and 0.13 ft<sup>3</sup>/min-ft<sup>2</sup>, 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<sup>®</sup>-C (0.3 ppm). In addition, the highest estimated 8-hour TWA was 0.108 ppm (37.8 grams; 0.13 ft<sup>3</sup>/min-ft<sup>2</sup>), which exceeds the U.S. OSHA 8-hour Threshold-TWA (0.1 ppm).

## DISCUSSION

The CIR Expert Panel emphasized 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.

Both the Nail Manufacturers Council (NMC) and the Professional Keratin Smoothing Council (PKSC) have noted that formaldehyde is not actually a cosmetic ingredient. When formaldehyde is added to a cosmetic, it is almost certainly formalin (nominally a 37% 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 International Cosmetic Ingredient Dictionary and Handbook identifies formaldehyde as an ingredient. Changing the naming convention does not appear necessary, especially when the dynamics of formaldehyde and methylene glycol are fully explained.

### Formaldehyde/methylene glycol use as a preservative

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 data on 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 nasopharyngeal cancers (NPCs) are produced by formaldehyde gas. While debate is ongoing regarding the dose-response for the induction of NPCs, the Panel continues to believe that formaldehyde gas does produce such cancers at high doses. Epidemiology studies have suggested an 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 from cosmetic products could be causally linked to leukemia.

Based on the testicular effects observed in rats exposed to formaldehyde, the CIR Expert Panel acknowledged that the mechanisms of the testicular effects are not known and these effects may be secondary to stress, irritation, or an increase in oxidative stress.

In consideration of these hazards, the Panel recalled that the original safety assessment published in 1984 had said that: (1) formaldehyde is safe for use in cosmetics if free formaldehyde was minimized, but in no case > 0.2%. This concentration limit, currently expressed as formaldehyde equivalents, is still considered sufficient to ensure safety of formaldehyde/methylene glycol as a preservative.

### **Formaldehyde/methylene glycol use as a nail builder/hardener**

The Panel noted that, as given in the International Cosmetic Ingredient 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 Panel was uncertain about the exposure levels of formaldehyde/methylene glycol vapor or gas for users of formaldehyde/methylene glycol in nail builder/hardener products and sought further information. The NMC argued that the ingredient added to nail builders/hardeners is methylene glycol and not formaldehyde and that the levels of formaldehyde gas that may be formed during the use of nail hardeners is extremely low (not even approaching established occupational exposure limits), and is not associated with any adverse reaction reports. Expressed in terms of formaldehyde concentration, the U.S. FDA does have an action level of >5% formaldehyde in nail care products, and the data submitted by the NMC confirms that the nail hardening products have less formaldehyde than that level.

As noted earlier, currently, the cosmetic functions for formaldehyde do not include nail hardening or nail building, yet formaldehyde continues to be reported to U.S. FDA's VCRP as being used in nail care products. The listed function of methylene glycol in cosmetics is nail building. No such uses have been reported to the VCRP, but use concentrations were reported in an industry survey. The Panel recalled that formaldehyde had been used in nail hardening products and that concern about sensitization resulted in a limitation of 0.2% in all cosmetic products. If exposure to skin is precluded, however, by shielding the skin, etc. then it may be that the use of formaldehyde/methylene glycol in nail hardeners can be considered safe as used. In Panel reviews of other nail care products, containing ethyl methacrylate for example, CIR has acknowledged that the risk of sensitization is low, in part because commercial fingernail enhancement products are applied by trained professionals and that directions for use can make it clear to any user that skin contact should be avoided.

### **Formaldehyde/methylene glycol use as a hair smoothing agent**

None of the reported functions appear to address the use of formaldehyde/methylene glycol in hair smoothing products. In such products, a solution containing formaldehyde/methylene glycol is applied to the hair, and the hair is dried and heated. The function of formaldehyde/methylene glycol in such products is not described, but it may be to react with the hair shaft to form linkages that contribute to the prevention of hair curling. The Professional Keratin Smoothing Council (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, 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 present in a cosmetic formulation such as hair smoothing products. Measurement methodology aside, the Panel was concerned with the reports of adverse reactions reportedly 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 found that the levels of formaldehyde approach and often exceed established occupational safety limits. The PKSC has recommended that keratin smoothing products be restricted to use by trained and licensed individuals and that proper ventilation be established as necessary to ensure that those applying the product and those individuals to whom the product is applied do not experience irritation of the eyes, ears, nose, and throat. Yet the testing submitted by PKSC was presumably done by trained and licensed individuals with proper ventilation. The Oregon OSHA workplace surveys uncovered a wide variety of ventilation approaches, including the presence of a building HVAC, simply propping the doors open, or having ceiling fans.

Previously, the Panel made it clear that it cannot be concluded that formaldehyde is safe in cosmetic products intended to be aerosolized. In regard to the use of the word "aerosolized," the Panel was of the opinion that

cosmetic products intended to be sprayed should not contain formaldehyde as a preservative. While cosmetic product sprays produce particle sizes too large to be respired, such particles can reach the nasopharyngeal cavity and that is the site at which formaldehyde carcinogenesis has been reported. The Panel considered that any such use of formaldehyde could not be considered safe.

In discussing the new exposure route that may result from the use of formaldehyde/methylene glycol in hair smoothing products and the release of gas, the Panel's concern was increased beyond the discussion of aerosols in the original safety assessment of formaldehyde. While workplace ventilation, in concept, could prevent the reported adverse effects, it is clear that methods currently in use have been ineffective in many instances. Accordingly, the Panel has tentatively concluded that use of formaldehyde/methylene glycol could not be considered safe in cosmetic products in which formaldehyde/methylene glycol is intended to be aerosolized and where vapor or gas will be produced under conditions of use.

## **TENTATIVE CONCLUSION**

The CIR Expert Panel determined that:

- 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%.
- Formaldehyde/methylene glycol are safe in nail care products at concentrations up to 5%, if provided with nail shields which restrict application to the nail tip (and not the nail bed or fold) and adequate instructions to use nail shields to preclude exposure of skin and the significant potential for allergic reactions if there is skin contact.
- 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.

## TABLES AND FIGURE

**Table 1.**  
**Frequency and Concentration of Use Table Formaldehyde and Formalin**

	<i>No. of Uses (2010)<sup>14</sup></i>	<i>Conc. of Use (2010) (%)<sup>15</sup></i>	<i>No. of Uses (2010)<sup>14</sup></i>	<i>Conc. of Use (2010) (%)<sup>15</sup></i>
	<b>formaldehyde (and formaldehyde solution (formalin))</b>		<b>methylene glycol</b>	
<b>Totals</b>	<b>58</b>	<b>0.04 – 0.5</b>	<b>NR</b>	<b>&lt;2</b>
<i>Duration of Use</i>				
<i>Leave-On</i>	<i>30</i>	<i>0.15 – 0.5</i>	<i>NR</i>	<i>&lt;2</i>
<i>Rinse Off</i>	<i>48</i>	<i>0.04</i>	<i>NR</i>	<i>NR</i>
<i>Exposure Type</i>				
Eye Area	NR	NR	NR	NR
Possible Ingestion	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR
Dermal Contact	24	0.04 – 0.15	NR	NR
Deodorant (Underarm)	NR	NR	NR	NR
Hair - Non-Coloring	44	0.04	NR	NR
Hair – Coloring	2	NR	NR	NR
Nail (including Hardeners)	8	0.5	NR	<2
Mucous Membrane	9	NR	NR	NR
Bath Products	2	NR	NR	NR
Baby Products	NR	NR	NR	NR

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

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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

<b>Ingredient</b>	<b>Percentage</b>
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%

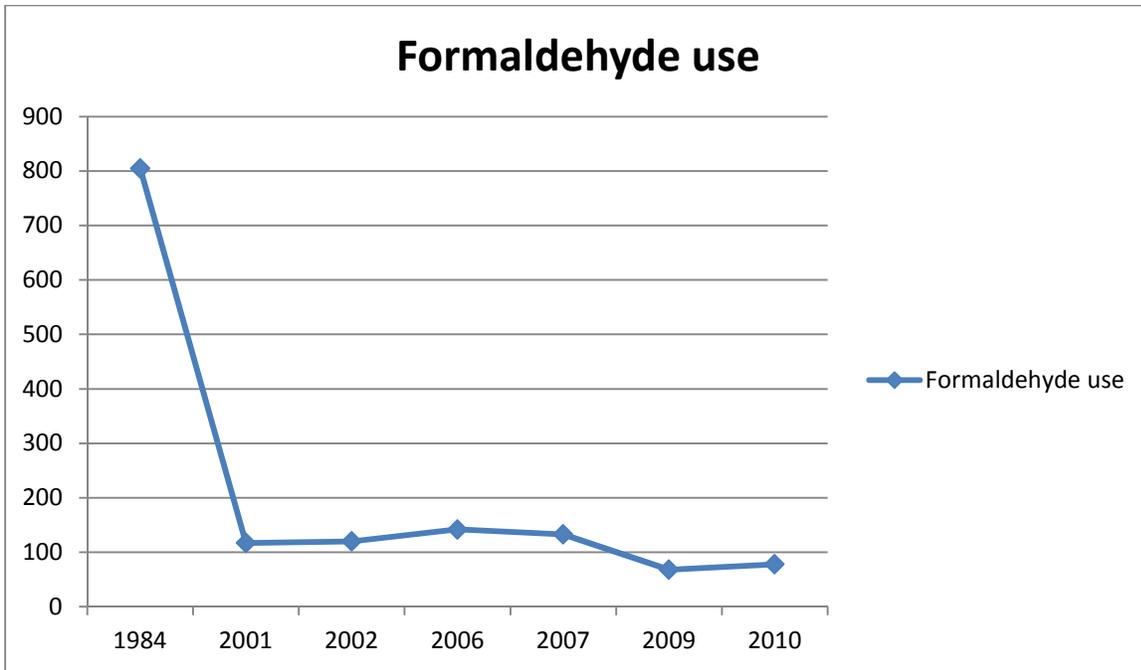
**Table 3. Measured Formaldehyde Levels During Use of Hair Smoothing Products**

<b>Test</b>	<b>Form Levels (ppm)</b>	<b>Exposure Time (min)</b>	<b>Samples ≥ Limits</b>		
			<b>US NAC AEGL-1 0.9ppm ≥ 10 min</b>	<b>ACGIH TLV®-Ceiling 0.3 ppm</b>	<b>WHO 30 min 0.08 ppm</b>
<b>Oregon OSHA</b>	0.074-1.88	6-48	Yes(4)	Yes(9)	Yes(All ≥30 min)
<b>Exponent</b>	0.170-0.269	95-141	No	No	Yes(All)
<b>Tennessee OSHA</b>	0.3-1.07	15	Yes (1)	Yes (5)	Yes*
<b>PKSC 1</b>	0.761-1.71	15	Yes	Yes (All)	Yes**
<b>PKSC 2</b>	0.189-0.395	86-117	No	Yes	Yes***

\*calculated levels exceed by up to 4 fold

\*\*calculated levels exceed by 12-21 fold

\*\*\*calculated levels exceed by up to 5 fold



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

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## **APPENDIX**

# Review of Current Toxicology and Epidemiology Studies

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## Review of Current Toxicology and Epidemiology Studies

The 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, including interagency comments on an earlier draft of the document.<sup>1</sup> 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). In particular, Volume II – Hazard Characterization – of this document 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 toxicological information summarized below is from studies identified primarily in the external review draft document. A few older reports and one new report addressing skin irritation/sensitization are also summarized below. In addition, the National Research Council (NRC) recently released their review of U.S. EPA's draft assessment ([http://www.nap.edu/catalog.php?record\\_id=13142#aboutpub](http://www.nap.edu/catalog.php?record_id=13142#aboutpub)),<sup>2</sup> and their findings are summarized below, where appropriate.

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 than in agricultural areas, and greater in indoor air than in outdoor air.<sup>1-5</sup> Salthammer (2010) estimated that the general population is exposed to an average of 0.016 to 0.032 ppm formaldehyde in indoor air.<sup>6</sup> In addition, formaldehyde is a natural metabolic intermediate in humans and other animals and is, thus, normally present in all tissues, cells, and body fluids.<sup>3</sup> The concentration of endogenous formaldehyde in the blood of rats, monkeys, and humans is about 0.1 mM.<sup>7,8</sup> Endogenous tissue formaldehyde concentrations are similar to genotoxic and cytotoxic concentrations observed *in vitro*.<sup>9</sup> In addition, formaldehyde is likely present normally in exhaled breath at concentrations of a few parts per billion (ppb).<sup>2</sup>

Formaldehyde is a highly water-soluble, reactive, rapidly metabolized chemical with a relatively short biological half-life. Inhaled formaldehyde is absorbed primarily in the respiratory epithelium lining the upper airways, where it undergoes extensive local metabolism and reactions with macromolecules. Based on the weight of the evidence, the NRC concluded that formaldehyde does not penetrate beyond the superficial layer of the nasopharyngeal epithelium, and is unlikely to appear in the blood as an intact molecule, except possibly at concentrations high enough to overwhelm the metabolic capacity of the epithelium.<sup>2</sup> The NRC concluded that formaldehyde is not available systemically in any reactive form, and systemic effects are unlikely from the direct delivery of formaldehyde or methylene glycol to distal sites, except possibly in highly exposed people.

The NRC noted that the systemic delivery of formaldehyde may not be required for some of the systemic effects attributed to formaldehyde inhalation (eg, lymphohematopoietic cancers and reproductive toxicity).<sup>2</sup> Instead, systemic effects could be secondary, indirect effects of the local effects of exposure, including local irritation and inflammation, and stress.

### Skin irritancy/sensitization

#### *Non-Human*

Wahlberg (1993) applied 0.1 ml of 1%, 3%, or 10% formalin (ie, 0.004%, 0.01% and 0.04 formaldehyde equivalents, respectively) in water to the shaved flanks of Hartley guinea pigs with a cotton-tipped applicator once a day for 10 days.<sup>10</sup> The skin was not occluded. They visually scored the animals for erythema and edema, and measured skin-fold thickness using Harpenden calipers. The diluted formalin solutions induced a dose-dependent increase in skin-fold thickness, with shorter latencies at higher concentrations. For example, erythema was observed on treatment day 6 for 1%, day 5 for 3%, and day 2 for 10% formalin solution.

Lee et al (1984) exposed English smooth-haired guinea pigs topically to 100  $\mu$ l formalin (37% w/v formaldehyde equivalents) applied to shaved depilated dorsal skin once/day for 2 days (total dose = 74  $\mu$ g), 25  $\mu$ l formalin dissolved in saline applied once to a 15-mm area of the dorsal skin (total doses 12  $\mu$ g, 120  $\mu$ g, 1.2 mg, 5.1 mg, or 9.3 mg), or by inhalation of 6 ppm or 10 ppm formaldehyde 6 hours/day or inhalation of 10 ppm 8 hours/day for 5

days.<sup>11</sup> They tested all of the animals for signs of contact sensitivity by applying 20 µl 2% formalin (0.007 formaldehyde equivalents) in saline over a 15-mm area of shaved dorsal skin. The sites were visually inspected for erythema 1, 6, 24, and 48 hours later, and reactions were scored.

These authors reported that all of the dermally-treated guinea pigs exhibited contact sensitivity, with scores increasing in a dose-dependent manner.<sup>11</sup> Of the animals treated via inhalation, only 2 of 4 guinea pigs tested on day 31 exhibited signs of contact sensitivity (mild) after 10 ppm formaldehyde 8 hours/day for 5 days. No contact sensitivity was observed in any of the control groups.

Arts et al (1997) applied 2.5%, 5%, or 10% formalin (0.009%, 0.02%, and 0.04% formaldehyde equivalents) in raffinated olive oil to the dorsum of both ears of female Wistar rats (low IgE-responders) and BN rats (high IgE responders) on days 0, 1, and 2 of the study.<sup>12</sup> They then used a local lymph node assay (LLNA) to measure response to the treatment. They first injected (IP) bromo-deoxyuridine (BrdU) on day 5 and euthanized the rats. Next, ear-draining lymph nodes were collected, fixed, and sectioned. Mitotic activity was monitored following successive incubation of the sections in anti-BrdU, biotin-labeled rabbit anti-mouse antibody, peroxidase-conjugated streptavidin, and 3,3-diaminobenzidine tetrahydrochloride. The authors reported an increase in the weights of the lymph nodes and a dose-related increase in the proliferation (BrdU positive) of paracortical cells, in both rat strains in response to 5% and 10% formalin (0.02% and 0.04% formaldehyde equivalents) treatment. They found no statistically significant increase in serum IgE concentrations in either strain.

### *Human*

As noted in the original safety assessment of formaldehyde,<sup>13</sup> 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.<sup>14</sup> 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.<sup>15,16</sup> 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.<sup>13</sup>

Recent reviews addressing the potential for aqueous formaldehyde/formalin solutions are consistent with the observations reported in the original assessment.<sup>17,18</sup> For example, de Groot et al (2009) noted that the frequency of sensitization to formaldehyde ranged from 6.8% to 9.3% in studies conducted from 1992 to 2005 in the U.S.<sup>18</sup> The prevalence rates in European countries ranged from 2% to 3%. The lowest concentrations of formaldehyde equivalents yielding allergic responses in formaldehyde sensitive patients were 0.02% to 0.03% in repeated open application tests (ROATs) of cosmetic creams and other products containing “formaldehyde releasers” on normal skin for up to 1 week.

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.<sup>19</sup> 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<sup>®</sup> disks. Note that, based on the manufacturer’s directions, hair straighteners are applied undiluted to the hair.<sup>20</sup> 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 24<sup>th</sup> 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 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.

## Genotoxicity

### *Non-Human (in vivo)*

Clear evidence of mutagenicity does not emerge from animal bioassays, despite the reactivity and mutagenicity demonstrated in isolated mammalian cells (Table 4-83<sup>1</sup>).

Im et al (2006) reported a dose-dependent increase in Olive tail moments (Olive TM) in blood lymphocytes from male Sprague-Dawley rats exposed to 0 ppm ( $1.24 \pm 0.04$ ), 5 ppm ( $1.72 \pm 0.11$ ;  $p=0.0019$ ), or 10 ppm ( $2.16 \pm 0.14$ ;  $p=0.0001$ ) formaldehyde via inhalation 6 hours/day, 5 days per week, for two weeks, using the Comet assay.<sup>21</sup> They reported similar results for liver cells. Using the same exposure and assay protocols, Sul et al (2007) observed a dose-dependent increase in tail moments in lung tissue in male Sprague-Dawley rats exposed to 0 ppm ( $0.75 \pm 0.07$ ), 5 ppm ( $1.11 \pm 0.17$ ;  $p<0.05$ ), or 10 ppm ( $1.32 \pm 0.34$ ;  $p<0.05$ ).<sup>22</sup>

In a critical review, Speit (2006) noted several issues with such studies, including the observation that the formation of DNA-protein crosslinks (DPCs) and DNA-DNA crosslinks (DDCs) in the cells should have reduced, rather than increased, DNA migration in the Comet assays conducted.<sup>23</sup>

Speit et al (2009) exposed groups of 6 F344 rats to 0, 0.5, 1, 2, 6, 10 and 15 ppm formaldehyde by whole-body inhalation 6 hours/day, 5 days/week for 4 weeks.<sup>24</sup> They obtained peripheral blood samples from each rat at the end of the exposure period by puncturing the retro-orbital venous plexus. They collected the blood samples in a randomized sequence, and the samples were coded by sequence number for blind evaluation. These authors conducted Comet, sister chromatid exchange (SCE), and micronucleus (MN) tests to evaluate the lymphocytes from each rat. They modified the Comet assay to include analysis both before and after irradiating the samples (2 Gy  $\gamma$ ) to increase sensitivity for detecting DNA-protein crosslinks (DPCs). Positive controls included 6 rats treated with a single 50 mg/kg dose of methyl methanesulfonate (MMS), and 6 rats treated with two 10 mg/kg cyclophosphamide (CP) doses, orally, before collecting blood. These authors reported no statistically significant differences between the formaldehyde exposed and negative control groups in any of the parameters examined. In contrast, statistically significant effects were found in the positive controls (MMS and CP), demonstrating the sensitivity of the tests.

### *Human (in vivo)*

Ye et al (2005) measured formaldehyde exposures and the frequencies of MN in nasal mucosa cells and SCEs in peripheral lymphocytes, and evaluated lymphocyte subsets collected from 10 non-smoking workers at a formaldehyde manufacturing plant in China (average exposure duration 8.6 years, ranging from 1 to 15 years).<sup>25</sup> They also exposed 16 non-smoking waiters to formaldehyde for 12 weeks in a ballroom that served as an exposure chamber. A group of 23 non-smoking students with no occupational exposure to formaldehyde served as control. The average age of the workers was  $29 \pm 6.8$  years, compared with  $19 \pm 2.3$  years for the controls. They measured an 8-hour time-weighted-average (TWA) of  $0.80 \pm 0.23$  ppm formaldehyde, with a ceiling of 1.38 ppm, for the workers. The waiters were exposed to a 5-hour TWA of  $0.09 \pm 0.05$  ppm. The 8-hour TWA in the dormitories of the control group was 0.009 ppm. Ye et al (2005) reported that the MN frequency was elevated in the nasal mucosa cells collected from workers ( $2.70 \pm 1.50$  per 1,000 cells;  $p<0.05$ ), compared with controls ( $1.25 \pm 0.65$  per 1,000 cells). Similarly, the SCE frequency was increased in peripheral lymphocytes from workers ( $8.24 \pm 0.89$  per 1,000 cells;  $p<0.05$ ), compared with controls ( $6.38 \pm 0.41$  per 1,000 cells). The frequencies of MN and SCEs in cells collected from the waiters were not different from controls.

Speit et al (2007) exposed volunteers (10 women, 11 men) 4 hours/day for 10 working days to 0.15-0.5 ppm formaldehyde (specific concentration randomly assigned to each subject each day), with four 15-minute 1-ppm peaks each day.<sup>26</sup> The subjects were required to perform three 15-minute bicycling exercises during each exposure. Cumulative exposure was 13.5 ppm-hour over the 10 days. Speit et al (2007) prepared smears of exfoliated buccal mucosa cells collected from each subject 1 week before starting the study (Control 1), just before the first exposure (Control 2), immediately after the 10-day exposure period, and 7, 14 and 21 days thereafter. Each subject served as his/her own control. They analyzed 2,000 cells from each smear, and MN frequencies were determined on slides coded by an independent quality-assurance unit. These authors reported a statistically significant decrease in MN frequency 21 days after the end of the exposure period ( $0.44 \pm 0.38$  per 1,000 cells;  $p<0.05$ ), compared with the

controls (Control 1:  $0.95 \pm 0.67$  per 1,000 cells; Control 2:  $0.86 \pm 0.84$  per 1,000 cells). MN frequencies in samples collected immediately, 7 days, or 14 days after the exposure period did not differ from controls.

Zeller et al (2011) exposed 41 healthy, non-smoking male volunteers to formaldehyde in an exposure chamber 4 hours/day for 5 working days.<sup>27</sup> Each subject was exposed once to 0 ppm (background = 0.01 ppm), 0.3 ppm with four 15-minute 0.6-ppm peaks, 0.4 ppm with four 15-minute 0.8-ppm peaks, 0.5 ppm, and 0.7 ppm formaldehyde during the 5-day exposure period. The subjects were assigned to 12 groups (n=2 to 4), and the sequence of exposure to these concentrations (with or without peaks) varied among the groups over the 5 consecutive days. The subjects performed four 15-minute bicycling exercises during each 4-hour exposure, including 2 exercise periods during the peak exposures. Zeller et al (2011) collected blood samples, nasal mucosal cells, and nasal biopsy samples from each subject once before the first exposure and again after the last exposure. They evaluated the blood samples using Comet, SCE, cytokinesis-block micronucleus (CBMN), QRT-PCR, and DNA microarray assays, the nasal epithelial cell samples using a MN test, and the nasal biopsy samples using microarray analysis. These authors reported a small but statistically significant ( $p=0.002$ ) elevation in Comet tail intensity after the 5-day exposure period ( $2.66 \pm 0.646$ ), compared to the values determined before the exposure period ( $2.28 \pm 0.492$ ). However, they concluded that this finding was not biologically significant, because formaldehyde-induced DPCs would be expected to reduce, not elevate, Comet tail intensity. Further, they found no statistically significant differences in Comet tail moments or SCE and MN frequencies, or biologically significant changes in gene expression in samples collected after exposure, compared with those collected before exposure.

Yu et al (2005) measured the workplace formaldehyde exposures and collected peripheral blood lymphocyte samples from 151 workers at two plywood factories and 112 workers at a machine manufacturing facility, which served as the control.<sup>28</sup> They used air samplers and gas chromatography (GC) to collect and analyze the air samples, a questionnaire to obtain personal information from the subjects, and a Comet assay and CBMN test to identify DNA and chromosomal damage in the lymphocyte samples. The TWA concentrations for the plywood factory workers ranged from 0.08 to 6.42 ppm, compared to  $<0.008$  ppm for the controls. The exposed workers were divided into two subgroups, including “low-exposed” and “high-exposed” workers. Yu et al (2005) observed an exposure-related increase in the average Olive TM measured in the lymphocytes from controls ( $0.93$ ;  $0.78 - 1.10$   $\mu\text{m}$ ), “low-exposed” ( $3.03$ ;  $2.49 - 3.67$ ), and “high-exposed” ( $3.95$ ;  $3.53 - 4.43$ ) workers.<sup>28</sup> The differences were statistically significant ( $p<0.05$ ). Similar statistically significant differences ( $p<0.05$ ) in MN frequencies (average number per 100 binucleated cells) were observed in the controls ( $0.27 \pm 0.13$ ), “low-exposed” ( $0.41 \pm 0.25$ ), and “high-exposed” ( $0.65 \pm 0.36$ ) workers. For controls, “low-exposed,” and “high-exposed” workers, respectively, the average Comet tail lengths were  $6.78$  ( $6.05 - 7.6$ ),  $11.25$  ( $10.12 - 12.5$ ), and  $12.59$  ( $11.8 - 13.43$ )  $\mu\text{m}$ . The authors report that the difference between “exposed” workers and the controls was statistically significant for this measure.

Orsière et al (2006) measured formaldehyde exposures using passive air-monitoring badges near the breathing zone of 59 pathology and anatomy laboratory workers for 15 minutes to 8 hours.<sup>29</sup> Mean formaldehyde concentrations for the 59 subjects were 2.0 ppm (range  $<0.1 - 20.4$  ppm) and 0.1 ppm (range  $<0.1 - 0.7$  ppm) for the 15-minute and 8-hour sampling times, respectively. A control group consisted of 37 individuals matched for gender, age, and smoking habits. These authors collected peripheral blood lymphocytes from 57 of the workers both before and after a 1-day exposure period. They found no increase in DNA damage in these workers after one day of exposure, using a chemiluminescence microplate assay to evaluate the lymphocytes. They used a CBMN assay combined with fluorescent in situ hybridization (FISH) and a pan-centromeric DNA probe to analyze the lymphocytes in 18 exposed and 18 control subjects randomly selected from the initial populations. Using this approach, they found statistically significant elevations in the frequencies of binucleated micronucleated cells ( $16.9 \pm 9.3$  vs.  $11.1 \pm 6.0$  per 1,000 cells;  $p=0.001$ ) and monocentromeric MN ( $11.0 \pm 6.2$  vs.  $3.1 \pm 2.4$  per 1,000 cells;  $p<0.001$ ) in pathologists/anatomists, compared to the controls. They found no statistically significant differences between these two groups in the frequencies of centromeric or acentromeric MN. Orsière et al (2006) interpreted their results to suggest that formaldehyde genotoxicity is attributable to an aneugenic rather than clastogenic mode of action.

Costa et al (2008) estimated the breathing-zone formaldehyde exposure of 30 pathology/anatomy laboratory workers at four hospitals in Portugal.<sup>30,30</sup> The mean exposure concentration was  $0.44 \pm 0.08$  ppm (range:  $0.04 - 1.58$  ppm). They selected 30 matched individuals working in administrative offices in these hospitals to serve as controls. These authors collected 10-ml venous blood samples from each participant at work, between 10 and 11 AM, and coded and analyzed the samples under blind conditions. They conducted MN, SCE, Comet and genotype analysis to evaluate the lymphocytes from each participant. Costa et al (2008) reported statistically significant elevation in MN

frequency ( $5.47 \pm 0.76$  vs.  $3.27 \pm 0.69$  per 1,000 cells;  $p = 0.003$ ), SCEs ( $6.13 \pm 0.29$  vs.  $4.49 \pm 0.16$  per 1,000 cells;  $p < 0.05$ ), and Comet tail lengths ( $60.00 \pm 2.31$  vs.  $41.85 \pm 1.97$   $\mu\text{m}$ ;  $p < 0.05$ ). In addition, they reported a positive correlation between formaldehyde exposure and both MN frequency ( $r = 0.384$ ;  $p = 0.001$ ) and Comet tail length ( $r = 0.333$ ;  $p = 0.005$ ).

## Carcinogenicity

### *Nasopharyngeal cancers – epidemiological studies*

Several reports evaluated the solid tumor mortality risks associated with formaldehyde exposures at 10 U.S. production plants in a National Cancer Institute (NCI) cohort study.<sup>31-33</sup> The occupational histories of 25,619 workers first employed prior to 1966 in the manufacturing of formaldehyde, formaldehyde resins, molding compounds, plastic products, film or plywood, were taken from company records, and formaldehyde exposure was estimated for each job category.<sup>32,34</sup> Exposure categories were defined for each of four exposure metrics, including highest peak exposure (0,  $>0$  to  $<2.0$ ,  $2.0$  to  $<4.0$ , or  $\geq 4.0$  ppm), average intensity of exposure (0,  $>0$  to  $<0.5$ ,  $0.5$  to  $<1.0$ , or  $\geq 1.0$  ppm), cumulative exposure (0,  $>0$  to  $<1.5$ ,  $1.5$  to  $<5.5$ , or  $\geq 5.5$  ppm-years), and duration of exposure (0,  $>0$  to  $<5$ ,  $5$  to  $<15$ , or  $>15$  years). Hauptmann et al (2004) updated the cohort through 1994, reporting a 35-year median follow-up duration.<sup>33</sup>

Hauptmann et al (2004) found 9 deaths from nasopharyngeal cancer (NPC) in this cohort, including 7 who were classified as “ever exposed” and 2 as “never exposed” to formaldehyde.<sup>33</sup> These authors assumed a 15-year lag for NPC, used Poisson regression modeling and an internal referent group (ie, either the unexposed or low- exposed group) to estimate the relative risks (RRs) for NPC, and regression analysis to evaluate dose-response trends, for each exposure metric (Table 4-2<sup>1</sup>). The highest RRs were 4.14 for  $\geq 5.5$  ppm-years cumulative exposure and 4.18 for  $\geq 15$  years exposure duration, although confidence limits were not provided. Statistically significant dose-response trends were apparent for both peak exposure ( $p < 0.001$ ) and cumulative exposure ( $p = 0.025$ ).

Marsh and coworkers evaluated the NCI data in a series of reports, focusing on Plant #1 (Wallingford, CT), a plastics-manufacturing plant where 5 of the 9 NPC cases evaluated by Hauptmann et al (2004) were found.<sup>35-38</sup>

Marsh et al (2002) conducted both a cohort and a nested case-control analysis of 7,328 workers employed in Plant #1 from 1941 to 1984, and independently evaluated the exposure assessment.<sup>35</sup> They counted 7 NPC cases 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. They reported that several formaldehyde exposure metrics were associated with NPC for Plant #1, including “ever exposed” (standardized mortality ratio [SMR] = 6.03; 95% confidence interval [CI]: 2.42-2.42), exposure duration  $\geq 10$  years (SMR = 12.46; 95% CI: 1.51-45.02), and cumulative exposure  $\geq 0.22$  ppm-years (SMR = 7.51; 95% CI: 1.55-21.93) (Table 4-2<sup>1</sup>). These 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.

In a more current analysis, Marsh and Youk (2005) found that 6 of 10 NPC deaths (ie, identified specifically as NPC) in the NCI cohort were associated specifically with employment at Plant #1, the remaining four cases distributed among four of the other nine plants studied.<sup>38</sup> They reported a regional rate-based SMR of 10.32 (95% CI: 3.79-22.47) for formaldehyde-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. They found that the statistically significant peak exposure-response relationship in the NCI cohort was driven by excess NPC risk associated with the highest peak exposure category ( $\geq 4$  ppm) at Plant #1. In this study, none of the exposure-response relationships for any of the four exposure metrics were statistically significant for plants #2 through #10, combined. They concluded that the suggestion by Hauptmann and colleagues<sup>33</sup> of a causal relationship between formaldehyde exposure and NPC mortality is based entirely on anomalous findings at Plant #1.

More recently, Marsh and coworkers provided additional data from their nested case-control study, based on 7 NPC cases in the Plant #1 cohort.<sup>36</sup> They reported a SMR of 4.43 (95% CI: 1.78-9.13; 7 deaths) for the exposed workers.

However, they discovered that 5 of the 7 NPC cases also held silver-smithing and other jobs related to silver or brass or other metal work, and that this work was relatively rare in the remaining study population (OR = 7.31, 95% CI:1.08-82.1). They 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.

Marsh and collaborators conducted additional re-analyses of the NCI cohort data, focusing on peak exposure and NPC mortality, demonstrating critical weaknesses in the model used in the Hauptmann et al (2004) study, including instability problems related to the data from Plant #1.<sup>37</sup>

Most recently, Marsh et al (2010) reviewed the recent finding reported by Beane Freeman et al (2009) that Hauptmann and coworkers missed 1,006 death certificates of the NCI cohort, with proportionally greater numbers of missing deaths in the un-exposed and low-exposed groups used as internal referents in the Hauptmann et al (2003) study.<sup>33,39-41</sup> Marsh et al (2010) noted that NCI has not provided corrected estimates for solid cancer deaths, including NPC deaths, for this cohort. They state that many of the recent meta-analyses, reviews, and regulatory evaluations of the potential carcinogenicity of formaldehyde to humans should be revised to address this critical error in the crucial reports of Hauptmann and coworkers.<sup>33,39</sup>

Other cohort studies reported no association between occupational formaldehyde exposure and NPC mortalities. For example, Coggon et al (2003) found 1 NPC case among 14,014 male British industrial workers, including 3,991 workers exposed to >2 ppm (RR = 0.5; 95% CI: 0.07-3.55; 2 cases expected),<sup>42</sup> and Pinkerton et al (2004) found 0 cases among 11,039 textile workers (82% female) (RR = 0; 95% CI: 0-3.00; 1 case expected)<sup>43</sup> (see Bosetti et al, 2008).<sup>44</sup> Further, a recent case-control study examining the potential association between formaldehyde exposure and myeloid leukemia in 6,808 deceased embalmers and funeral directors found 4 cases of NPC, only two of which had “ever embalmed” (OR = 0.1; 95% CI: 0.01-1.2).<sup>45</sup> Exposure estimates (based on 6 different metrics) for these 2 cases were indistinguishable from controls.

### *Nasopharyngeal cancers – mode of action*

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.

The subchronic or chronic inhalation of formaldehyde at high concentrations (eg,  $\geq 6$  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.

For example, Monticello and colleagues exposed F344 rats via inhalation for 1, 4, 9 and 42 days (short-term) or 13, 26, 52 and 78 weeks (long-term) to 0, 0.7, 2.0, 6.0, 10.0, and 15.0 ppm formaldehyde.<sup>46-48</sup> They reported statistically significant increases in nasal cell proliferation only at  $\geq 6.0$  ppm (short-term) and  $\geq 10.0$  ppm (long-term) in these studies. Conolly and coworkers 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.<sup>49-51</sup> 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. Subramaniam and Crump and their colleagues disputed this interpretation, because of the considerable uncertainty and variability in the data.<sup>52,53</sup> However, recent evidence from pharmacokinetic analysis and gene expression profiling in male F344/CrlBR rats indicate 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.<sup>54</sup>

Lu and co-workers developed a highly sensitive nano-ultra performance liquid chromatography-electrospray ionization-tandem mass spectrometry-selection reaction monitoring (nano-UPLC-ESI-TMS-SRM) method with an on-column detection limit  $\sim 20$  amol N<sup>2</sup>-CH<sub>3</sub>-dG.<sup>55</sup> They exposed male Fischer rats via inhalation to 0.7, 2, 5.8, 9.1, or 15.2 ppm [<sup>13</sup>CD<sub>2</sub>]-formaldehyde in a nose-only chamber for 6 hours, and used the nano-UPLC-ESI-TMS-SRM method to measure both endogenous and exogenous adducts (as N<sup>6</sup>-HOCH<sub>2</sub>-dG and N<sup>2</sup>-HOCH<sub>2</sub>-dG, respectively) in

the nasal musosa. They found that the formation of endogenous adducts did not change in a dose-related manner (eg,  $3.41 \pm 0.46$  and  $6.09 \pm 3.03$  adducts/ $10^7$  dG at 9.1 ppm and 2.0 ppm, respectively). However, the formation of exogenous adducts was highly non-linear, increasing 286-fold with a 21.7-fold increase in the exposure concentration (ie, from  $0.039 \pm 0.0019$  to  $11.15 \pm 3.01$  adducts/ $10^7$  dG at 0.7 ppm and 15.2 ppm, respectively). About 1% and 3% of the total number of adducts (endogenous plus exogenous) were exogenous adducts at 0.7 ppm and 2 ppm, respectively.

Moeller et al (2011) exposed cynomolgus macaques to 1.9 or 6.1 ppm [ $^{13}\text{CD}_2$ ]-formaldehyde, 6 hrs/day, for 2 days.<sup>56</sup> Using the nano-UPLC-ESI-TMS-SRM method, they detected endogenous ( $2.50 \pm 0.40$  and  $2.05 \pm 0.54$  adducts/ $10^7$  dG at 1.9 ppm and 6.1 ppm, respectively) and exogenous ( $0.26 \pm 0.04$  and  $0.41 \pm 0.05$  adducts/ $10^7$  dG at 1.9 ppm and 6.1 ppm, respectively) adducts in the nasal tissues at both exposure concentrations. Swenberg et al (2011) noted that, generally, the monkeys exposed to 6.1 ppm [ $^{13}\text{CD}_2$ ]-formaldehyde exhibited greater numbers of endogenous adducts ( $2.05 \pm 0.54$  adducts/ $10^7$  dG) and lower numbers of exogenous adducts ( $0.41 \pm 0.05$  adducts/ $10^7$  dG) in nasal tissues, compared with rats exposed to 5.8 ppm ( $5.51 \pm 1.06$  endogenous and  $1.04 \pm 0.24$  exogenous adducts/ $10^7$  dG, respectively), indicating that the percentage of exogenous adducts would be lower in primates than in rats at equivalent exposure concentrations.<sup>57</sup>

Meng et al (2010) exposed F-344 rats via inhalation to 0, 0.7, 2, 6, 10 or 15 ppm, 6h/day for 13 weeks.<sup>58</sup> They then used allele-specific competitive blocker-polymerase chain reaction (ACB-PCR) to examine the nasal epithelial tissues for the presence of a K-Ras mutation and a p53 mutation previously detected in the squamous cell carcinomas produced by chronic formaldehyde exposure in a two-year bioassay.<sup>59</sup> They also measured BrdU incorporation to monitor the proliferation of nasal mucosal cells in the rats. Meng and coworkers found that the 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.<sup>58</sup> However, BrdU incorporation increased with dose and was statistically significantly elevated in the rats exposed to either 10 ppm or 15 ppm formaldehyde. These results support the view that CICP plays a pivotal role in the formation of NPCs in rats and, thus, formaldehyde-induced carcinogenicity is largely a threshold effect.

The NRC agreed 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.<sup>2</sup> The NRC concluded that two primary modes of action contribute to formaldehyde-induced carcinogenicity in nasal tissues, including mutagenicity and CICP. A mutagenic mode of action is generally the reason for adopting the default low-dose linear extrapolation methods in a quantitative cancer risk assessment. However, the NRC noted that formaldehyde is endogenous, that nasal tumors are rare in both rats and humans, and that no increases in tumor frequency are observed in animal studies at formaldehyde concentrations that do not also cause cytotoxicity. Further, the animal studies reveal a substantial nonlinearity in dose-response relationships among formaldehyde uptake, cytotoxicity, cell proliferation, and tumor formation. Thus, the NRC recommended that the quantitative assessment of the risks of formaldehyde-induced NPCs incorporate the nonlinear phenomenon of CICP, as well as the mutagenicity of formaldehyde.

### *Lymphohematopoietic cancers - epidemiological studies*

Hauptmann et al (2009) conducted a case-control study of lymphohematopoietic (LHP) and brain-cancer mortalities in funeral industry workers among the "professional" workers previously studied by Hayes, Walrath and their coworkers.<sup>45,60,61</sup> They examined the death certificates (1960 to 1986) of 6,808 embalmers and funeral directors finding 168 deaths attributable to LHP cancers, including 99 lymphoid and 48 non-lymphoid cancers. The non-lymphoid cancers included 34 cases of myeloid leukemia. Cases were matched to control subjects (n=265) randomly selected from cohort members who died of other causes. They interviewed the next of kin and coworkers of the subjects to determine the funeral-home practices (eg, ventilation and spill frequency) and work histories (eg, frequency and duration of embalming conducted for jobs  $\geq 5$  years). This information was used to estimate formaldehyde exposures for each subject. Exposure metrics included lifetime 8-hour TWA (ppm), peak (ppm), cumulative (ppm-hours), and average intensity while embalming (ppm). Other exposure-related parameters estimated included "ever embalming," duration working in jobs involving embalming, and number of embalming conducted.

Hauptmann et al (2009) reported statistically significant increases in risks of LHP cancers of non-lymphoid origin for several of the exposure metrics, including the highest levels of exposure for cumulative, TWA, and peak exposures, as well as for subjects who embalmed for >20 years (OR = 3.5; 95% CI: 1.1-10.9; p=0.46).<sup>45</sup> For myeloid leukemia, in particular, strong, statistically significant associations were found for exposure duration (eg, OR = 13.6; 95% CI: 1.6–119.7 for >34 years), number of embalming performed (eg, OR = 2.7; 95% CI: 1.4–112.8 for >3,068 embalming), and cumulative exposure (eg, OR = 13.2; 95% CI: 1.5–115.4 for >9,253 ppm-hours) (Table 4-7<sup>1</sup>). In addition, they found a statistically-significant dose-response relationship between myeloid leukemia deaths and both exposure duration (p=0.02) and peak exposure (p=0.036). However, the mean estimated 8 hour TWA (0.2 ppm) and peak (8.6 ppm) exposures for the subjects that died of myeloid leukemia deaths were indistinguishable from those of the control subjects.

Hauptmann et al (2009) noted that there was only one case of myeloid leukemia in the reference group of non-embalmers.<sup>45</sup> Thus, they compared the subjects who performed <500 embalming, which included 5 cases of myeloid leukemia, to the subjects with >34 years embalming (OR = 3.9; 95% CI: 1.2 -12.5; p=.024) and subjects with more than 9,253 ppm-hours cumulative exposure (OR = 3.1; 95% CI: 1.0 - 9.6; p=0.047).

Several methodological issues have been identified for the Hauptmann et al (2009) study.<sup>62</sup> For example:

- (1) Myeloid leukemia cases among the study subjects were 50% more likely than controls to have begun employment in the funeral industry before 1942. This suggests that they belonged primarily to an older and earlier population than the controls and likely explains why they performed more embalming.
- (2) The single myeloid leukemia case in the control group yielded large, unstable confidence intervals in the Hauptmann et al (2009) study.<sup>45</sup> The ORs were substantially reduced when the referent group included both the controls and the subjects performing <500 embalming.
- (3) The myeloid leukemia cases and controls had nearly identical mean estimated average, 8-hour TWA, and peak exposures. The cases had higher estimated number of embalming 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.

Several reports evaluated the LHP cancer mortality risks associated with formaldehyde exposures for the 25,619 workers from 10 U.S. production plants in the National Cancer Institute (NCI) cohort study.<sup>32,39,63</sup> The occupational histories of workers first employed before 1966 were obtained from company records, and formaldehyde exposures were estimated for each job category in each plant, based on job titles, associated tasks, and monitoring data.<sup>32,34</sup> Beane Freeman et al (2009) updated this cohort mortality study with follow-up through 2004, reporting a 42-year median follow-up duration<sup>41</sup>.

They discovered, and included, 1,006 death certificates that Hauptmann et al (2003) had missed for this cohort.<sup>39,41</sup> Proportionally greater numbers of missing deaths were among the un-exposed and low-exposed groups used as internal referents in the Hauptmann et al (2003) paper.

Beane-Freeman (2009) defined exposure categories for each of four exposure metrics, including highest peak exposure (0, >0 to <2.0, 2.0 to <4.0, or  $\geq$  4.0 ppm), peak exposure frequency (short-term exposures exceeding 8-hour TWA, hourly, daily, weekly, or monthly), average intensity of exposure (0, 0.1 to ,0.5, 0.5 to <1.0, or  $\geq$ 1.0 ppm), and cumulative exposure (0, >0 to 1.5, 1.5 to <5.5, or  $\geq$ 5.5 ppm-years).<sup>41</sup>

These authors found 319 deaths from all LHP cancers (from a total of 13,951 deaths), including 286 “exposed” and 33 “non-exposed” cases.<sup>41</sup> Based on U.S. mortality rates, neither of these groups showed statistically significant elevations in SMRs estimated for all LHP cancer (Table 4-7<sup>1</sup>), all leukemia, lymphatic leukemia, myeloid leukemia, Hodgkin’s lymphoma, Non-Hodgkin’s lymphoma, or multiple myeloma.

Beane-Freeman (2009) assumed a 2-year lag for LHP cancers, after finding that assuming lag intervals from 2 to 25 years, by person-time, had little effect on RR estimates.<sup>41</sup> They used Poisson regression modeling and an internal referent group (ie, low-exposed group) to estimate the RRs for LHP mortalities in exposed workers, and either regression analysis or category ranks, as appropriate, to evaluate dose-response trends (Table 4-7<sup>1</sup>).

Beane Freeman and colleagues reported statistically significant elevations in RRs for all LHP cancers (RR = 1.37; 95% CI: 1.03-1.81) and Hodgkin's lymphoma (RR = 3.96; 95% CI: 1.31-12.02) for workers with peak exposures  $\geq 4$  ppm, compared to  $>0$  to 2.0 ppm (Table 4-7<sup>1</sup>). In addition, they found statistically significant dose-response trends for peak exposure and all LHP (p=0.02), all leukemia (p=0.012) and Hodgkin's lymphoma deaths (p=0.01), as well as for average exposure and Hodgkin's lymphoma deaths (p=0.05 excluding "never-exposed" workers; p=0.03 including them). However, the RR for Hodgkin's lymphoma in workers with the highest average exposure ( $\geq 1$  ppm; RR = 2.48; 95% CI: 0.84-7.32) was lower than for workers with lower average exposure (0.5 to  $<1$  ppm; RR = 3.62; 95% CI: 1.41-9.31).

No statistically significant associations or trends were found among the LHP cancers and the other exposure metrics examined in this study, including both frequency of peak exposure and cumulative exposure.<sup>41</sup>

Other recent cohort studies have reported no association between occupational formaldehyde exposure and LHP cancer mortalities. For example, Coggon et al (2003) found 31 leukemia deaths among 14,014 male British industrial workers, including 3,991 workers exposed to  $>2$  ppm (RR = 0.91; 95% CI: 0.64-1.29; 34 cases expected),<sup>42</sup> and Pinkerton et al (2004) found 59 cases among 11,039 textile workers (82% female) (RR = 1.09; 95% CI: 0.73-1.63; 61 cases expected)<sup>43</sup> (see Bosetti et al, 2008).<sup>44</sup>

### *Lymphohematopoietic cancers – meta-analyses*

An early meta-analysis examined 18 epidemiology studies that reported leukemia rates in professional or industrial workers exposed to formaldehyde (up to 3.5 ppm).<sup>64</sup> These authors used fixed-effects models to evaluate both cohort and case-control studies. They found no association between leukemia and formaldehyde exposure across all of the studies (RR = 1.1; 95% CI: 1.0-1.2), across all cohort studies (RR = 1.0; 95% CI: 0.9-1.2), or across all case-control studies (RR = 2.4; 95% CI: 0.9-6.5). They reported a slightly elevated risk of leukemia among embalmers (RR = 1.6; 95% CI: 1.2-6.0) and pathologists/anatomists (RR = 1.4; 95% CI 1.0-1.9), but none for industrial workers, even those with the highest reported exposures (RR = 0.9; 95% CI: 0.8-1.0).

More recently, Bosetti et al (2008) evaluated cohort studies using either a fixed-effect or a random-effect model, depending on the heterogeneity among the cohorts.<sup>44</sup> Using the fixed-effect model, they found a "modestly elevated" pooled RR for LHP cancers in professionals (ie, embalmers, anatomists and pathologists) (RR = 1.31; 95% CI: 1.16-1.47; 8 studies), but not for industrial workers (RR = 0.85; 95% CI: 0.74-0.96; 4 studies). They reported similar results for leukemia.

Zhang et al (2009) reviewed many of the same studies that were included in the Bosetti et al (2008) meta-analysis.<sup>44,65</sup> However, they attempted to increase the statistical power of the 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 also preferentially selected results for myeloid leukemia from studies that specifically addressed myeloid leukemia. These authors did not stratify the data to distinguish low-exposure (eg, embalmers, pathologists, anatomists) from high-exposure (eg, formaldehyde production) industries.<sup>44,66</sup> See Bachand et al, 2010, for discussion.<sup>67</sup> Zhang et al (2009) used a fixed-effect or random-effect model, depending on the heterogeneity among the cohorts.<sup>65</sup> Using the fixed-effect model, they calculated summary RRs (professional and industrial workers) for all LHP cancer (RR = 1.25; 95% CI: 1.09-1.43; 19 studies), all leukemias (RR = 1.54; 95% CI: 1.18-2.00; p<0.001; 15 studies), and myeloid leukemia (RR = 1.90; 95% CI: 1.31-2.76; p=0.001; 6 studies). They also reported summary RRs for Hodgkin lymphoma (RR = 1.23; 95% CI: 0.67-2.29; 8 studies), non-Hodgkin's lymphoma (RR = 1.08; 95% CI: 0.86-1.35; 11 studies) and multiple myeloma (RR = 1.31; 95% CI: 1.02-1.67; 9 studies).

Schwilk et al (2010) updated Zhang et al (2009) to include the Hauptmann et al (2009) and Beane Freeman et al (2009) cohort studies.<sup>41,45,65,68</sup> They reported that formaldehyde was associated with increased risks of leukemia (RR = 1.53; 95% CI: 1.11-2.21; p=0.005) and myeloid leukemia (RR = 2.47; 95% CI: 1.42-2.47; p=0.001), using methods similar to Zhang et al (2009).

Bachand et al (2010) conducted a meta-analysis that evaluated all cohort, case-control, and proportional mortality ratio (PMR) studies published through May 2009.<sup>67</sup> This study incorporated NCI cohort data updated to address the missing 1,006 death certificates reported by Beane Freeman and coworkers.<sup>41</sup>

In their summary risk estimates for leukemia, Bachand et al (2010) found no statistically significant increase in the cohort (RR = 1.05; 95% CI: 0.93-1.20; 15 studies) or case-control studies (odds ratio [OR] = 0.99; 95% CI: 0.71 - 1.37; 2 studies).<sup>67</sup> Further, they reported no statistically significant increase in the summary leukemia RRs for embalmers and other professionals/technical workers (RR = 1.28; 95% CI: 0.98-1.66; 7 studies) or for industrial workers (RR = 0.99; 95% CI: 0.86-1.15; 8 studies), or in the overall RR for myeloid leukemia (RR = 1.09; 95% CI: 0.84-1.40; 3 studies) calculated from the cohort studies.

Although Bachand et al (2010) found that their summary 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.<sup>65-67</sup>

### *Lymphohematopoietic cancers – mode of action*

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.<sup>9</sup> Further, formaldehyde is a highly reactive, rapidly metabolized chemical yielding short-lived DPCs and DNA-adducts that are amenable to rapid reversal and repair.<sup>69,70</sup> 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.<sup>9,71,72</sup> 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 three proposed modes of action by which formaldehyde exposure may cause leukemia include:<sup>73</sup>

- 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.<sup>1</sup>

In a preliminary study, Zhang et al (2010) measured complete blood counts and peripheral stem/progenitor cells in 43 Chinese formaldehyde-exposed workers from two factories (one producing and the other using formaldehyde-melamine resins) and 51 frequency-matched controls from three other workplaces in the same region.<sup>73</sup> All participants wore diffusion samplers for a full shift for up to 3 working days over a three-week period to monitor formaldehyde exposures, and the factory workers wore organic vapor monitors at least twice to be analyzed for benzene and other organic solvents. The median (10<sup>th</sup>-90<sup>th</sup> percentile) formaldehyde exposure concentrations were 1.28 (0.63-2.51) ppm for the factory workers and 0.026 (0.0085-0.026) ppm for the controls.

Zhang et al (2010) reported statistically significant decreases in mean ( $\pm$  SD) WBC count ( $5,422 \pm 1,529$  vs.  $6,269 \pm 1,422$  cells/ $\mu$ l;  $p=0.0016$ ) and lymphocyte count ( $p=0.00002$ ) in the subjects compared with the controls.<sup>73</sup> Similarly, statistically significant decreases in granulocyte, platelet, and RBC counts, and increase in RBC mean corpuscular volume (MCV) were found. No occupational co-exposures to benzene or other hemotoxic or genotoxic solvents were detected in this study.

In addition, Zhang et al (2010) conducted in vitro colony-forming unit – granulocytes, macrophages (CFU-GM) – assays on blood samples, from all 94 participants, cultured for 14 days.<sup>73</sup> They reported a 20% decrease in progenitor cell colony formation in the blood samples from factory workers, compared to controls, but this result was not statistically significant.

Next, Zhang et al (2010) cultured mononuclear cells from a male volunteer of Chinese origin for 14 days after adding 0, 100, 150, or 200  $\mu\text{mol/l}$  formaldehyde/methylene glycol to the culture medium on the first day.<sup>73</sup> They found statistically significant, dose-related decreases in the number of colonies formed per plated cells.

Finally, Zhang et al (2010) analyzed metaphase spreads of the cultured CFU-GM cells from 12 of the highest exposed workers and 10 matched controls, using fluorescence in situ hybridization (FISH).<sup>73</sup> They found statistically significant increases in the frequencies of both chromosome 7 monosomy ( $\sim 2$ -fold;  $p=0.0039$ ) and chromosome 8 trisomy ( $\sim 4$ -fold;  $p=0.04$ ) in the cells from the workers, compared with the controls. The authors indicate that both of these aneuploidies are common findings in individuals with myeloid leukemia, myelodysplastic syndromes, or benzene exposure.

In a letter to the editor, Speit et al (2010)<sup>74</sup> indicate numerous problems in the Zhang et al (2010)<sup>73</sup> study and questioned the reliability of the results. For example, they note that:

- All of the blood counts in the exposed workers were within the reference range.
- 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.
- The most frequent chromosome aberrations associated with myeloid leukemia are translocations, but Zhang et al (2010)<sup>73</sup> investigated neither translocations nor aneuploidies other than monosomy 7 and trisomy 8.
- Formaldehyde is mutagenic predominantly by a clastogenic, not an aneugenic mode of action.<sup>75-77</sup>
- Formaldehyde has been shown to damage several cell types directly exposed in vitro, an effect therefore not unique to myeloid progenitor cells.

Lu et al (2010) exposed male Fischer rats via inhalation to 10 ppm [ $^{13}\text{CD}_2$ ]-formaldehyde in a nose-only chamber, 6 hours/day for either 1 or 5 days.<sup>78</sup> They added vaporized [ $^{13}\text{CD}_2$ ]-formaldehyde to the air by thermally depolymerizing [ $^{13}\text{CD}_2$ ]-paraformaldehyde. From each rat, they collected epithelial tissue samples from the right and left sides of the nose and the nasal septum, 3-5 ml of blood by cardiac puncture for lymphocyte isolation, and bone marrow from both femurs by saline extrusion. They also collected whole organs, including the spleen, thymus, lung and liver. Next, these authors isolated DNA from each tissue sample, including  $\sim 30$ -50  $\mu\text{g}$  DNA from nasal tissue, 60-100  $\mu\text{g}$  DNA from WBCs, and 200  $\mu\text{g}$  from the other tissues, and hydrolyzed the DNA samples with DNaseI to analyze for both formaldehyde-DNA adducts and DDCs. These authors measured the formaldehyde-adducts ( $\text{N}^2$ -HOCH<sub>2</sub>-dG and  $\text{N}^6$ -HOCH<sub>2</sub>-dG) in the DNA samples as  $\text{N}^2$ -CH<sub>3</sub>-dG and  $\text{N}^6$ -CH<sub>3</sub>-dG, after reduction with NaCNBH<sub>3</sub>. DDCs were measured as dG-CH<sub>2</sub>-dG. They developed liquid chromatography-electrospray ionization-tandem mass spectrometry-selection reaction monitoring (LC-ESI-TMS-SRM) methods to quantify both the formaldehyde adducts (on-column detection limits  $\sim 240$  amol and  $\sim 75$  amol for  $\text{N}^2$ -CH<sub>3</sub>-dG and  $\text{N}^6$ -CH<sub>3</sub>-dG, respectively) and DNA-DNA crosslinks (on-column detection limits  $\sim 60$  amol dG-CH<sub>2</sub>-dG). These analytical methods clearly differentiated the endogenous ( $\text{N}^2$ -CH<sub>3</sub>-dG and dG-CH<sub>2</sub>-dG) from the exogenous ( $\text{N}^2$ - $^{13}\text{CD}_3$ -dG and dG- $^{13}\text{CD}_2$ -dG) products.

Using these methods, Lu et al (2010) found exogenous products exclusively in the nasal tissues after 1 day (mean  $\pm$  SD =  $1.28 \pm 0.49$  monoadducts/ $10^7$  dG; 0.14 DDCs/ $10^7$  dG) or 5 days (eg, mean  $\pm$  SD =  $2.43 \pm 0.78$  monoadducts/ $10^7$  dG;  $0.26 \pm 0.07$  DDCs/ $10^7$  dG) of exposure.<sup>78</sup> No exogenous products were detected in the DNA hydrolysates from any other tissue, even though, for example, the analytical method can detect  $\sim 3$   $\text{N}^2$ - $^{13}\text{CD}_3$ -dG adducts/ $10^9$  dG. This detection limit is  $\sim 30$  times less than the endogenous  $\text{N}^2$ -CH<sub>3</sub>-dG adducts/ $10^9$  dG measured in WBCs.

In contrast, endogenous products were found in all of the tissues examined, including blood (eg,  $1.10 \pm 0.28$  monoadducts/ $10^7$ dG,  $3.66 \pm 0.78$  monoadducts/ $10^7$ dA, and  $0.10 \pm 0.07$  crosslinks/ $10^7$ dG for 5-day exposure) and bone marrow (eg,  $1.17 \pm 0.35$  monoadducts/ $10^7$ dG,  $2.99 \pm 0.08$  monoadducts/ $10^7$ dA, and  $0.11 \pm 0.03$  crosslinks/ $10^7$ dG for 5-day exposure).<sup>78</sup> The levels of endogenous products were comparable across all tissues examined.

Lu et al (2010) concluded that 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.<sup>78</sup> In addition, their results support the conclusion that genotoxic effects of formaldehyde/methylene glycol are not plausible at sites distant from the portal of entry. Likewise, the results demonstrate the implausibility of 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.

Subsequently, Lu and co-workers developed a highly sensitive nano-UPLC-ESI-TMS-SRM method with an on-column detection limit  $\sim 20$  amol  $N^2$ -CH<sub>3</sub>-dG.<sup>55</sup> They exposed male Fischer rats via inhalation to 0.7, 2, 5.8, 9.1, or 15.2 ppm [<sup>13</sup>CD<sub>2</sub>]-formaldehyde in a nose-only chamber for 6 hours, and used the new method to measure endogenous and exogenous dG adducts in nasal mucosa and bone marrow. They found measurable numbers of endogenous adducts in both the nasal mucosa (eg,  $4.24 \pm 0.92$  adducts/ $10^7$  dG at 15.2 ppm) and bone marrow (eg,  $\sim 15$  adducts/ $10^7$  dG in at 15.2 ppm), and exogenous adducts in the nasal mucosa (eg,  $11.15 \pm 3.01$  adducts/ $10^7$  dG at 15.2 ppm), but did not detect exogenous adducts in the bone marrow after exposure to up to 15.2 ppm [<sup>13</sup>CD<sub>2</sub>]-formaldehyde. Similarly, Moeller et al (2011) exposed cynomolgus macaques to 1.9 or 6.1 ppm [<sup>13</sup>CD<sub>2</sub>]-formaldehyde, 6 hrs/day, for 2 consecutive days (whole body).<sup>56</sup> Using the nano-UPLC-ESI-TMS-SRM method, they detected endogenous and exogenous adducts (eg,  $2.05 \pm 0.54$  and  $0.41 \pm 0.05$  adducts/ $10^7$  dG, respectively, at 6.1 ppm) in the nasal tissues of both exposure groups, but only endogenous adducts (eg,  $12.4 \pm 3.6$  adducts/ $10^7$  dG at 6.1 ppm) in the bone marrow.

The NRC noted that little is known about the potential modes of action by which formaldehyde might cause LHP cancers, other than mutagenicity.<sup>2</sup> 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.

## IARC cancer risk evaluations

IARC (2006)<sup>5</sup> concluded that there was *sufficient* epidemiological evidence that formaldehyde causes NPC in humans and *strong but not sufficient* evidence for a causal association between leukemia and occupational exposure to formaldehyde. They also elevated their evaluation of formaldehyde from probably carcinogenic to humans (Group 2A) to carcinogenic to humans (Group 1).

In 2009, IARC<sup>79</sup> updated their evaluation to conclude that there is *sufficient* evidence for a causal association between leukemia, particularly myeloid leukemia, and occupational exposure to formaldehyde.<sup>73,79</sup> 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, reported by Hauptmann et al (2009).<sup>45</sup>
- The levels of chromosome 7 monosomy and chromosome 8 trisomy in myeloid progenitor cells and hematological changes in formaldehyde exposed workers reported by Zhang et al (2010).<sup>73</sup>

The IARC Working Group was almost evenly split on the prevailing view that the evidence was sufficient for formaldehyde causing leukemia in humans (IARC, 2009)<sup>79</sup>.

## Reproductive and Developmental Toxicity

### *Non-Human*

Özen et al (2005) exposed male Wistar rats (6/group) by inhalation in a whole-body exposure chamber to 0, 5, or 10 ppm formaldehyde, 8 hours/day, 5 days/week for 91 days.<sup>80</sup> They used a chemi-luminescent enzyme immunoassay to measure serum testosterone concentrations, stained testicular tissues with Hematoxylin-Eosine (H-E) for histopathological examination, and immunohistochemical staining to estimate heat-shock protein 70 (Hsp70) levels in the tissues. The authors reported that the rats exposed to 5 or 10 ppm exhibited unsteady breathing, excessive licking, frequent sneezing, and hemorrhage of nasal mucosa, attributable to formaldehyde-induced irritation. They found statistically significant decreases ( $p < 0.0001$ ) in serum testosterone concentrations in the rats exposed to 5 ppm ( $244.01 \pm 23.86$  ng/dl) or 10 ppm ( $141.30 \pm 23.86$  ng/dl) formaldehyde, compared with controls ( $406.54 \pm 16.82$  ng/dl) (Table 4-62<sup>1</sup>). Similarly, seminiferous tubule diameters were reduced ( $p < 0.001$ ) in rats exposed to 5 ppm ( $236.17 \pm 13.09$   $\mu$ m) or 10 ppm ( $233.24 \pm 10.13$   $\mu$ m) formaldehyde, compared with controls ( $259.22 \pm 16.18$   $\mu$ m). In addition, Hsp70 levels were increased in the spermatogonia (+1 to +2), spermatocytes (+4 to +5), and spermatids (+4 to +5) of the treated rats (5 ppm or 10 ppm), compared with controls (0 to +2).

Zhou et al (2006) exposed adult male Sprague-Dawley rats (10/group) by inhalation to 8 ppm formaldehyde 12 hours/day for 2 weeks in a chamber (presumably whole-body exposure).<sup>81</sup> Vitamin E (30 mg/kg/day) was administered by gavage to one of the groups during formaldehyde exposure. The control group consisted of rats that were not exposed to formaldehyde and received only the physiological saline vehicle by gavage during the exposure period. These authors did not report the overt toxic effects of the formaldehyde exposures. However, they reported a statistically significant ( $p < 0.05$ ) reduction in testicular weight in the formaldehyde-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 formaldehyde exposed rats. These authors found statistically significant ( $p < 0.05$ ) reductions in epididymal sperm count, percentage of motile sperm, activities of testicular SOD and glutathione peroxidase (GSH-Px), and GSH levels, and elevations in MDA levels in the formaldehyde exposed rats, compared with controls. All of these effects were markedly reduced in formaldehyde exposed rats that were also treated with Vitamin E.

Golalipour et al (2007) exposed Wistar rats (6-7 weeks old, 7/group) to 1.5 ppm formaldehyde (mean of measured concentrations), 4 hours/day 4 days/week, 2 hours/day 4 days/week, or 4 hours/day 2 days/week, by inhalation for 18 weeks in a "dissection room" (presumably whole-body exposure).<sup>82</sup> Control rats were not exposed to formaldehyde. Testes were fixed, embedded, sectioned at 4  $\mu$ m, and stained with H-E. They measured the diameter and height of 20 seminiferous tubules/testis morphometrically. They reported statistically significant reductions in both parameters in the exposed rats, compared with controls (Table 4-63<sup>1</sup>). Further, they found severe reductions in the number of germ cells in the seminiferous tubules and evidence of arrested spermatogenesis after exposure 4 hours/day 4 days/week, decrease in the number of germ cells and increased thickness of the tubule basement membrane after exposure 2 hours/day 4 days/week, and disruption in the arrangement of Sertoli and germinal cells, with increased spacing between germ cells, after exposure for 4 hours/day 2 days/week. These authors did not report the overt toxic effects of the formaldehyde exposures.

Xing et al (2007) exposed male mice (12/group, strain not specified) to 0, 16.9, 33.8, or 67.6 ppm formaldehyde via inhalation 2 hours/day, 6 days/week for 13 weeks.<sup>83</sup> They then evaluated the reproductive capacity of the males, using a dominant-lethal protocol with untreated females, and examined sperm morphology. The English abstract of this Chinese paper does not detail the exposure method or report the overt toxic effects of the exposures. However, these abstract indicates that there was a statistically significant increase in the sperm aberration rate ( $p < 0.05$ ) and decrease in mean live fetuses/litter ( $p < 0.01$ ) after exposure to 67.6 ppm formaldehyde (Table 4-64<sup>1</sup>). Resorption rates were statistically significantly elevated ( $p < 0.05$ ) for all groups of formaldehyde rats.

Aslan et al (2006) and Sarsilmaz et al (2007) exposed neonatal male Wistar rats (10/group) to 0, 6, or 12 ppm formaldehyde whole-body in a glass chamber, 6 hours/day, 5 days/week for 30 days.<sup>84,85</sup> After exposure, 5 rats/group were euthanized for neuropathological examination on PND30 or PND90. These authors did not report the overt toxic effects of the formaldehyde exposures. However, they reported lower numbers of both granular cells

in the hippocampal dentate gyrus<sup>84</sup> and pyramidal cells in the cornu ammonis of the hippocampus<sup>85</sup> at PND90, compared to PND30, in rats exposed to 12 ppm formaldehyde.

Kum et al (2007) exposed female Sprague-Dawley rats (6 dams/group) and their offspring, in a whole-body exposure chamber, to 0 or 6 ppm formaldehyde 8 hours/day for 6 weeks, starting on gestation day 1 (GD1), post-natal day 1 (PND1), or at 4 weeks of age. In another group, exposure was initiated during adulthood.<sup>86</sup> These authors did not report the overt toxic effects of the formaldehyde exposures. However, the found statistically significant decreased mean body and liver weights in the offspring ( $p < 0.01$ ) when exposure began on GD1. For example, mean body weights were  $20.83 \pm 1.38$  g ( $p < 0.001$ ) and  $58.17$  g ( $p < 0.001$ ) in the exposed rats on GD1 and PND1, respectively, compared with  $30.33 \pm 0.67$  g on GD1 and  $67.33 \pm 1.73$  g on PND1 for controls. However, liver weight was increased when exposure began at 4 weeks of age  $3.83 \pm 0.22$  g ( $p < 0.01$ ), compared with controls ( $3.25 \pm 0.11$ ). The authors also reported a statistically significant increase in liver catalase (CAT) activity and malondialdehyde (MDA) concentration, decrease in liver glutathione (GSH) concentration, and decrease in liver superoxide dismutase (SOD) activity in the offspring when exposure began on GD1, PND1, or at 4 weeks of age. No other significant differences in these parameters were observed among the exposed rats compared with controls.

### *Human*

Taskinen et al (1994) conducted a case-control study of spontaneous abortions in women occupationally exposed to formalin and other chemicals used in hospital laboratories in Finland.<sup>87</sup> They identified subjects from the payrolls of state-employed laboratory workers, the laboratory workers' union, and a register of workers occupationally exposed to carcinogens. They selected 208 women who had a single spontaneous abortion, and 329 controls who had delivered a baby without malformations, during 1973–1986. These authors used mailed questionnaires (82.4% response rate) to obtain health status, medication, contraception, pregnancy history, and exposure-related information from the subjects. Industrial hygienists developed an exposure index for each subject, based on their descriptions of work assignments, solvent use, and fume-hood use.

Taskinen et al (1994)<sup>87</sup> noted that another study (cited as Heikkilä et al, 1991) reported a mean formaldehyde concentration of 0.45 ppm (range: 0.01-7 ppm) in similar Finnish pathology/histology laboratories and that the highest exposures occurred during emptying sample containers, washing dishes, and preparing formaldehyde solutions.

Taskinen et al (1994) reported a statistically significant association between exposure to formalin/formaldehyde 3-5 days/week and increased incidence of spontaneous abortion (OR = 3.5; 95% CI: 1.1–11.2), 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.<sup>87</sup> Exposures to toluene (OR = 4.7; 95% CI: 1.4–15.9) and xylene (OR = 3.1; 95% CI: 1.3–7.5) were also significantly associated with the elevated incidence of spontaneous abortions.

Taskinen et al (1994) also reported no association between formalin exposure and congenital malformations in 36 laboratory workers compared with 105 controls registered in the Finnish Register of Congenital Malformations.<sup>87</sup>

Taskinen et al (1999) conducted a retrospective cohort study of fertility in women occupationally exposed to formaldehyde and other chemicals in the woodworking industry in Finland.<sup>88</sup> They recruited subjects from the woodworkers' union and other wood-processing businesses, and linked them to the Finnish national register of births. These authors identified 1,094 women who were born between 1946 and 1975, had a live birth at age 20–40 years during 1985–1995, worked in the wood processing industry for at least 1 month, and were first employed in the wood processing industry beginning at least 6 months before the index pregnancy (ie, the first pregnancy that fulfilled the other criteria). They used mailed questionnaires (64% response rate) to obtain personal, pregnancy, and exposure-related information. The final sample included 602 women, after other exclusions (eg, based on history of infertility, unknown time-to-pregnancy, or contraceptive failure). Industrial hygienists estimated the mean daily exposure during the time-to-pregnancy period for each subject, based on the proportion of the workday during which exposure occurred and either concentrations measured at the subject's factory in the early 1990s or concentrations reported for similar industries.

The subjects were divided into three categories, based on the TWA exposure estimates: low (0.1 to 3.9 ppm), medium (4.0 to 12.9 ppm), and high (13.0 to 63 ppm).<sup>88</sup> The authors calculated fecundability density ratios (FDRs) for each exposure category, by dividing the average pregnancy incidence density of the exposed women by that of 367 employed, unexposed women. They adjusted the FDRs for employment, smoking, alcohol consumption, parity, and menstrual irregularity.

Taskinen et al (1999) reported a statistically significant decrease in the FDR for the formaldehyde exposed women in the high exposure group (OR = 0.64; 95% CI: 0.43–0.92;  $p=0.02$ ), and in the women in the high exposed group who did not wear gloves ( $n=17$ ; OR = 0.51; 95% CI: 0.28–0.92).<sup>88</sup> The reduced FDR among women in the high exposed group who wore gloves was not statistically significant ( $n=22$ ; OR = 0.79; 95% CI: 0.47–1.23).

Taskinen et al (1999) also reported associations between formaldehyde exposure and spontaneous abortion 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.<sup>88</sup> The 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 formaldehyde exposure in women in the high exposure category (OR = 4.5; 95% CI: 1.0–20.0).

In an earlier case-control study, John et al (1994) investigated spontaneous abortions during 1983–1988 in cosmetologists, compared with controls who delivered a live infant during the same period.<sup>89</sup> The subjects were identified from the 1988 North Carolina cosmetology license registry. They gathered information using mailed questionnaires (72.5% response rate). Among the full-time cosmetologists who qualified for the study, 61 cases of spontaneous abortion were selected for comparison to 315 controls.

Johns et al (1994) reported a crude OR of 2.0 (95% CI: 1.1–3.8) for use of formaldehyde-based disinfectants.<sup>89</sup> The OR was 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).

Collins and coworkers<sup>90</sup> conducted a meta-analysis of epidemiological studies that examined the potential association between spontaneous abortions and formaldehyde exposure, including John et al (1994)<sup>89</sup> and Taskinen (1999).<sup>88</sup> They reported a meta-RR of 1.4 (95% CI: 0.9–2.1). However, they noted no increased risk of spontaneous abortion in formaldehyde workers after adjusting this estimate for reporting and publication biases (meta-RR = 0.7; 95% CI: 0.5–1.0).

### *Mechanism*

The NRC noted that a small number of epidemiological studies suggest an association between occupational exposure to formaldehyde and adverse reproductive outcomes in women.<sup>2</sup> 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. 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.<sup>80,85</sup> There are no multigenerational tests for reproductive function.<sup>1</sup> The NRC agreed that 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.

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**Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde**

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May 20, 2011

Alan Andersen, PhD  
Director, Cosmetic Ingredient Review  
1101 17th St., N.W., Ste. 412  
Washington, D.C. 20036-4702

Dear Dr. Andersen:

The Professional Keratin Smoothing Council (PKSC) is a beauty industry association that represents manufacturers of professional-use only keratin hair smoothing products across the country. The members of the PKSC represent a select few members of the industry producing these products. The principles that bring the members of the PKSC together include corporate responsibility, utmost care and concern for the safety of salon professionals and consumers, and a commitment to producing the most effective products with the lowest level of active ingredients necessary to achieve desired smoothing results.

The PKSC is responding to your recent call for additional information as part of the CIR's ongoing review of methylene glycol and other potential formaldehyde releasers that are sometimes used in cosmetic products. We understand this review was triggered by an FDA letter asking the CIR to express its opinions about the safe use of methylene glycol, as well as to review previously published opinions on formaldehyde.

The PKSC believes that when the CIR takes a critical look at the science, as well as the testing results, and examines the many issues with respect to the testing methodologies and nomenclature and reviews the air monitoring data they will come to the conclusion that keratin smoothing products are safe for use in salons. Specifically, the products produced by PKSC members have been repeatedly demonstrated to be safe for use as directed. All relevant, properly conducted analysis of these products definitively demonstrate that any emissions from the products as properly used are below actionable limits established by relevant regulatory agencies. Additionally any short-term spikes that may lead to symptoms of ear, nose and/or throat irritation can be eliminated if the products are used in accordance with manufacturers' directions and salons' use of ventilation appropriate for the performance of such procedures.

The PKSC is primarily concerned for professional stylists and wants them to have all of the information needed to ensure they are offering safe services in a safe work environment. That is why the PKSC recommends strong warning language on keratin

smoothing products. These are necessary to protect stylists and will provide them with the proper warnings needed to work safely. Some example for consideration would be;

- Minimize the formation of irritating vapors by proper product application and always use proper, appropriate and necessary ventilation to ensure that there is no sensory irritation, such as to the eye, nose and throat.
- Sensory irritation is a warning sign of poor ventilation which could indicate that services should not be performed.
- CAUTION: Upon heating this product releases a low level of formaldehyde gas that may irritate the eyes, nose and throat.
- Safe handling requires use of proper ventilation that is capable of eliminating early warning symptoms when services are performed in accordance with manufacturer's directions.

Critically, our members have consistently provided clear safe use instructions and training for salon professionals, and fair and accurate information to consumers, demonstrating these safety factors. They are fully committed to continuing focusing on these important areas. Unfortunately, as often happens in the open marketplace, inaccurate information has been disseminated that has muddled the picture of the safety and low risks associated with PKSC members' products. We are providing this information to the CIR to aid in the creation of a clear, science-based and responsibly developed record, to clarify the marketplace information and ensure fair treatment of our members by regulatory agencies. The lack of accurate information has been regrettable and largely caused by analytical test methods that distort products in a manner that would not be repeated in the salon environment, resulting in the reporting of exaggerated levels of formaldehyde. Complicating the problem further is the chemically inaccurate nomenclature used in existing state and federal regulations. These regulations and related guidance and/or standards often incorrectly refer to formalin, methylene glycol, paraformaldehyde, trioxane, timonacic acid and a wide range of cosmetic preservatives and other substances as "formaldehyde" simply because under certain specific circumstances they may release varying amounts, albeit very low, of "formaldehyde" gas.

It is confusing and scientifically inaccurate to allow these misconceptions to continue. Our hopes are that the CIR will address and correct the record by restoring proper scientific understanding and nomenclature to finally resolve public misunderstanding and the lack of clarity in regulatory responses. For more than 100 years, the generic term "formaldehyde" has been misused by manufacturers, consumers, governments and the media to describe a wide range of dissimilar cosmetic products that vary greatly in their chemical composition and properties as well as their potential to become

available in the environment, thus presenting health risks. This myth began when Ferdinand Blum bubbled formaldehyde gas through water and mistakenly assumed that a large portion of the gas merely dissolved, when in fact formaldehyde's supposed solubility in water is actually due to the formation of a different compound- methylene glycol (CAS#463-57-0). Although Blum's work is considered a major achievement in histopathology, it also created the basis for a chemical misunderstanding that plagues medical and scientific research to this day.<sup>1</sup>

We urge you to correct these historical errors to ensure that proper and accurate scientific nomenclature is used during your analysis and in your conclusions, while recognizing that these regularly misused terms are found throughout medical/scientific literature and even within existing government regulations, guidelines and/or standards. Universally, cosmetic manufacturers are required to use proper ingredient names on packaging, but this was not possible for keratin smoothing products until late 2008 when the International Nomenclature of Cosmetic Ingredients (INCI) Dictionary Committee assigned the name methylene glycol with the monograph ID 23672. Until then, the only INCI name available was "formaldehyde", which erroneously suggested to consumers that the products contain the same gaseous formaldehyde which is classified as a human carcinogen by the International Agency for Research on Cancer (IARC). However, methylene glycol is an entirely different substance and contains only traces of dissolved formaldehyde (as "free formaldehyde"). This has resulted in wide spread confusion in the cosmetic industry and led to the creation of a large body of confusing scientific information, much of which ignores the fact that formalin contains 59% methylene glycol and between 5-15% methanol, even though it is also erroneously reported as "liquid formaldehyde" or simply "formaldehyde".

### **Common Problems with Analytical Testing Methods**

Methylene glycol is normally stable in cosmetic products but can be destabilized by elevated temperatures and/or extreme pH shifts. Unfortunately, the most widely accepted and commonly used analytical tests for "free formaldehyde" are destructive and therefore prone to significantly over reporting the actual levels of formaldehyde that are available under normal usage conditions. For instance, common HPLC methods significantly shift the products pH (acidic) and employ elevated temperatures as part of the analytical procedure which leads to rapid, atypical degradation of susceptible cosmetic ingredients. This is only one of several problematic issues related to "formaldehyde", test methods that are reviewed by Tallon.<sup>2</sup>

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<sup>1</sup> Fox, C.H., Johnston, F.B., Whiting, J., Roller, P.P., Formaldehyde Fixation, Journal of Histochemistry and Cytochemistry, Vol., 33, No.,8, pg. 845-853, 1985

<sup>2</sup> Tallon, M., Merianos, J.J., Subramanian, S., Non-Destructive Method for Determining the Actual Concentration of Free Formaldehyde in Personal Care Formulations Containing Formaldehyde Donors, SOFW-Journal, 135, 5, pg 22-32, 2009.

In other words, the test results are a consequence of unusual (for these types of products); analytical conditions that would NOT normally occur under typical use conditions. These test methods cause other ingredients, besides methylene glycol, to be erroneously measured and reported as "free formaldehyde", as discussed below.

Although keratin smoothing products are heated, the pH of these products remains relatively constant and therefore limits the amount of formaldehyde that will form. As a table presented later in this document will show results indicate, methylene glycol doesn't necessarily create formaldehyde, even when heated to 425°F (218°C) in the presence of water (liquid or vapour). Actually, a full conversion would be surprisingly difficult to achieve, due chiefly to the stability of methylene glycol, as previously demonstrated.

Equilibrium calculations indicate that the majority of methylene glycol remains unaffected and does not re-equilibrate to create formaldehyde. These observations match results from actual, properly conducted, salon testing, as shown later in this report in Table 3-5. Unfortunately, the most commonly accepted analytical test methods for "free formaldehyde" all require the use of a destructive combination of high heat and acidic pH changes which work to degrade susceptible ingredients in cosmetic products and thereby force the release of far more formaldehyde than would be released during normal and proper use conditions. These methods do not provide the public with useful information. The professional training received by licensed cosmetologists, additional manufacturers' product safety training, safe use instructions and cautions and product MSDSs are far better tools.

The erroneous information generated by HPLC testing will never be able to approximate or replace the results obtained via active air monitoring, yet it seems that regulators have been largely content with HPLC data and have done little salon testing. The high numbers that have been reported for formaldehyde supposedly "found" in keratin smoothing products, reported to be as high as 12%, are clearly not supported by the results of salon air monitoring, which reveals an entirely different picture.

In other words, cosmetic products would never be subjected to such harsh conditions in normal use. Chemical trapping agents such as DNPH subject these products to highly acidic conditions, increasing formaldehyde production and subsequent binding to the generated formaldehyde which forces an equilibrium shift that results in the creation of additional formaldehyde that in turn, binds with additional DNPH, etc., etc. This process repeats itself until all susceptible ingredients are exhaustively decomposed. Furthermore, these results are then deceptively and improperly reported as "free formaldehyde", suggesting this is formaldehyde that is available to cause human exposure, when in fact an overwhelming portion of this was methylene glycol and would have remained as such. This creates a situation which generates misleading analytical findings. Since these methods do not measure the amount of formaldehyde that

actually exists in the product, these methods are NOT a true measure of potential exposure. The reporting of these results unfairly suggests to the general public that the results obtained from high heat and acidic pH test conditions are replicated in the salon environment. This is demonstrably not the case.

It is unwarranted to ignore the science and not take into consideration the well-established equilibrium characteristics of these substances to determine the actual level of formaldehyde and methylene glycol in the product. These two substances, can and should be reported and monitored separately and NOT considered to be 100% interchangeable and synonymous. They should be reported and considered as individual and unique chemical substances.

The PKSC understands that regulatory bodies such as OSHA change slowly. Out-dated paradigms prevent change. One example is the regulation which requires OSHA to consider methylene glycol to be the same substance as formaldehyde, even though they are chemically, physically, and toxicologically different. OSHA is forced by improper or outdated regulations into making this incorrect assumption. The PKSC urges the CIR to address these chemical misconceptions in a clear and concise fashion. The PKSC strongly recommends that the CIR establish separate limits for formaldehyde and methylene glycol, just as they are listed separately as different ingredients in the INCI dictionary. Existing HPLC data would be more useful if the scientifically accepted equilibrium constant were applied to the resultant data so that "free formaldehyde" and methylene glycol could be reported separately. These data would also provide more accurate evaluation of actual use conditions and would therefore create a more proper evaluation model for distinguishing between the different formulations of hair smoothing products. As indicated, the formulations used by PKSC members result in exposures well below actionable levels. Other products not meeting these levels should be subject to appropriate regulatory scrutiny.

## Other Methodologies

<sup>13</sup>C-NMR spectroscopy does not suffer from these drawbacks and has been successfully used to non-destructively measure methylene glycol in water-containing cosmetic products in real-time.<sup>2</sup> These methods directly measure methylene glycol concentration and rely upon use of the equilibrium constant to calculate the actual amount of formaldehyde that might be present. <sup>13</sup>C-NMR has been used by several members of the PKSC to accurately measure methylene glycol concentrations for numerous products as shown in Table 1. These are <sup>13</sup>C-NMR results for several typical keratin smoothing products sold in the USA. Each test indicates that free formaldehyde (FFA) concentrations are all below 10 ppm and methylene glycol concentrations are below 2.25%, the ranges the PKSC believes are safe for salon services, if properly and correctly performed.

**Table 1\*. 13C-NMR Results for Several US Sold and Distributed Keratin Smoothing Products**

Company	Product	Total MG (Wt %)	Total FFA (Wt %)
M&M International	Brazilian Keratin Treatment (BKT) Testing performed by Intertek-ASG	2.23	0.0009
M&M International	Brazilian Keratin Treatment (BKT) Testing performed by Process-NMR	1.05	0.00042
M&M International	Chocolate Extreme De-Frizzing Treatment Testing performed by Process-NMR	0.80	0.00032
M&M International	Advanced Brazilian Keratin Treatment Testing performed by Process-NMR	0.72	0.00029
Keratin Complex	Natural Keratin Smoothing Treatment Testing performed by Process-NMR	2.22	0.0009
Keratin Complex	Natural Keratin Smoothing Treatment-Blonde Hair Testing performed by Process-NMR	1.71	0.0008
Cadiveu International	Brazil Cacau Testing performed by Process-NMR	2.6	0.00104
Cadiveu International	Acai Berry Testing performed by Process-NMR	1.213	0.00048

\* Original reports are included with this submission.

Interestingly, Intertek ASG/Germany repeated the 13C-NMR on the same product (M&M Brazilian Keratin Treatment) tested by Process-NMR/Connecticut, USA. Both reported very similar results showing formaldehyde exists only at around 0.0009-0.00042%, respectively; trace amounts for a cosmetic product by any measure. It is important to note that Intertek/Germany also performed the official EU HPLC test method (DNPH and heat) as previously described. The identical sample now reportedly contains between 1.4-1.9% formaldehyde. Intertek then used this same data, as recommended by the PKSC, and applied the equilibrium constant to HPLC results to report 15 ppm free formaldehyde, rather than 2.2%. This same product tested via HPLC in two separate laboratories produced even greater discrepancies of 0.81% and 2.2% free formaldehyde. Obviously, 0.00042% to 2.2% formaldehyde reported for the same products is highly indicative of the problem faced by all cosmetic manufacturers that utilize compounds which may be erroneously reported as containing or emitting formaldehyde. Table 2 shows the 13C-NMR results from these two separate laboratories

and a comparison with HPLC data both with and without the equilibrium constant being properly applied.

**Table 2\*. Comparisons of results obtained by testing the identical product in different laboratories using various methods**

Testing Company	Dissolved FFA (13C-NMR) Real-time	Dissolved FFA (HPLC) $K_h$ used	Dissolved "FFA" (HPLC) EU Method
Intertek-ASG	0.0009%	0.0015%	1.4-1.9%
Process-NMR	0.00042%	–	–
Advanced Chemical Sensors	–	–	0.81%
S&N Labs	–	–	2.2%
Eurofins GmbH	–	–	2.3%
Health Canada	–	–	1.8%

\* Original reports are included with this submission.

The equilibrium constant could easily be applied to this data to calculate the correct value for free formaldehyde, but some interpret the existing regulations in such a way as to prevent the use of the scientifically correct equilibrium constant. When properly applied, the equilibrium constant allows correct reporting for "free formaldehyde" (FFA). For these and many other reasons, the PKSC believes it is more accurate, informative and provides for better regulation if formaldehyde and methylene glycol are reported separately. The PKSC opinion is that the CIR should recommend that cosmetic products not exceed 2.6% methylene glycol or 0.0020% free (dissolved) formaldehyde that exists in real-time; within the product and that the free formaldehyde value should be reported separately and not included with methylene glycol.

It is important to note, that a measured value of 0.0009% or 9 ppm found in the product does NOT indicate that this small amount is sufficient to appreciably raise existing levels of formaldehyde in salon air. Although not likely, but even it were possible to instantly release all dissolved free formaldehyde into the container, this would rapidly dilute in the salon air since the percent volume is so low (0.0009%). If release this tiny amount

would have practically no measureable effect on the average levels of formaldehyde in salon air and could NOT be equated to 9 ppm exposure via inhalation, which would exceed all regulatory limits, even the OSHA 15 minute STEL of 2.0 ppm.

OSHA has chosen to ignore the clear scientific distinction between formaldehyde and methylene glycol. As a result, OSHA regulations ignore the well established physical and chemical differences by continuing to propagate the erroneous interpretation that methylene glycol is a synonym for formaldehyde when each has its own separate and distinct CAS number.

A similar situation exists for another keratin smoothing ingredient, timonacic acid, used by Keratin Complex in their keratin smoothing formulations. This ingredient is stable and will not easily degrade when heated and therefore creates very little exposure to formaldehyde when keratin smoothing services are performed as shown in a later section. Analysis via <sup>13</sup>C-NMR (Table 1) confirms that formaldehyde concentrations are 0.0009%, equilibrium data provided by Kallen<sup>18</sup> confirms that a solution containing 2.5% timonacic acid should contain only 0.005% formaldehyde as a trace contaminant (not a measure of what may be emitted), yet a very different result is found when such solutions are tested via traditional, standard HPLC methodologies used by regulatory agencies in the US, Canada, EU and Australia.

Kallen shows that the stability of timonacic acid is highly pH dependant. Acidifying the product to a lower pH causes timonacic acid to degrade and can yield erroneous results.

HPLC methods commonly employ derivatizing agents such as 2, 4-dinitrophenylhydrazine (DNPH) will acidify the product causing the timonacic acid to decompose to yield results that report erroneously high values for formaldehyde. This has been shown by others, as well.<sup>3, 4, 5</sup>

An expert report issued by Professor David Brynn Hibbert, School of Chemical Sciences, University of New South Wales pertaining to the applicability of the very widely used EPA HPLC methodologies for measuring formaldehyde concluded, "... USEPA methods TO-5 and TO-11A are not appropriate for the analysis of formaldehyde in a product that contains timonacic acid, such as Keratin Smoothing Therapy, because (1) the methods are explicitly for measurements of formaldehyde gas in ambient air, and (2) the method of analysis requires the combination of formaldehyde with a chemical that will also react with timonacic acid to give an identical product. Therefore in solutions containing

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<sup>3</sup> Pesek, J.J., Frost, J.H., Decomposition of Thiazolidines in Acidic and Basic Solutions, Spectroscopic evidence for Schiff Base Intermediates, Tetrahedron, Vol. 31, pg. 907-13, 1975

<sup>4</sup> Butvun, P., et al., Solubility, Stability and Dissociation Constants of (2RS,4R)-2-Substituted Thiazolidine-4-carboxylic Acids in Aqueous Solutions, Chem. Papers, 53, pg 315-22, 1999

<sup>5</sup> Doughty, A., Review and Comment on the Report Number M110364 Prepared by Leader Consulting, Chemica , 2011

timonacic acid there will be a result, apparently for formaldehyde, that arises not from formaldehyde but from timonacic acid".<sup>6,7</sup>

Therefore, HPLC measurements are not appropriate for predicting actual salon exposure levels, yet HPLC testing such as this has become the sole basis for making safety determination in many countries, including the EU, Canada and Australia. HPLC measurements lead to artificially elevated test results pertaining to the reactive ingredients in hair smoothing products, and needlessly alarm the public. Consumer information regarding potential health and safety exposures should be properly developed based on science and appropriate testing methods. The present instance of concern over hair smoothing products should follow along this well-established model. To achieve this outcome, the PKSC asks the CIR to set specific and separate safe use limits for both formaldehyde and methylene glycol and clarify to which substance these limits apply, as well as to comment on the measurements used to meet CIR recommendations.

## Air Monitoring Studies and Results

Oregon OSHA has collected air samples which a portion of the data in Table 3 is based, from seven salons in the northwest part of the US using active air monitoring methods. The full details of the study are included with this report.<sup>8</sup> Table 3 is an overview of these results, as reported by Oregon OSHA. The manufacturer of the product tested is not a member of the PKSC, but results are public and the PKSC believes them to be informative since they represent the likely "worst case scenario" in terms of methylene glycol content of the product and potential for salon exposure. Even then, the results obtained are low. This product reportedly contains 8.68% "formaldehyde" according to Oregon OSHA and 8.4% according to Health Canada. The PKSC believes these reported values are likely exaggerated since product testing was done via HPLC using DNPH and elevated temperatures. The PKSC suggests that the actual value is closer to 3-4% methylene glycol. Table 3 also lists similar results collected by Tennessee OSHA, but for one salon.<sup>9</sup>

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<sup>6</sup> Hibbert, D.B., Expert Opinion, School of Chemical Sciences, University of New South Wales, April 2011

<sup>7</sup> Hibbert, D.B., Expert Opinion Supplementary Report, School of Chemical Sciences, University of New South Wales, May 2011

<sup>8</sup> Oregon OSHA and CROET at Oregon Health & Sciences University, "Keratin-Based" Hair Smoothing Products and the Presence of Formaldehyde, Oct. 29, 2010

<sup>9</sup> Letter from Tennessee OSHA Area Supervisor, March 4, 2011

**Table 3.\* Results Reported by Oregon OSHA (Case 1-7) and Tennessee OSHA**

Location/Sample Id	8 hour TWA Time Weighted Average in ppm	STEL
Case 1	0.331	No STEL reported
Case 2	0.075	No STEL reported
Case 3	0.035	15 min. STEL reported as " <i>below the limits of quantification.</i> "
Case 4	0.051	No STEL reported
Case 5	0.006	No STEL reported
Case 6	0.006	0.176 ppm (15 min.)
Case 7	0.050	0.471 ppm (15 min)
Diva Color Studio/ Sample 1	0.10	
Diva Color Studio/ Sample 2	0.10	
Diva Color Studio/ Sample 3		1.07 ppm (15 min)
Diva Color Studio/ Sample 4		0.62 ppm (15 min)
Diva Color Studio/ Sample 5		0.46 ppm (15 min)
Diva Color Studio/ Sample 6		0.34 ppm (15 min)
Diva Color Studio/ Sample 7		0.30 ppm (15 min)

The 8 hour TWAs are all well below the OSHA Action limit of 0.5 ppm (8 hour TWA) and in all but one case, well below the ACGIH's 0.1 ppm (PEL). The STEL ever exceeded either. These values are in-line with those reported to us by member companies, as shown below. All testing was performed using standard active air monitoring methods and proper analytical techniques. Copies of the original reports have been supplied.

**Table 4.\*\* Air Monitoring Results Reported by PKSC Members**

Salon ID	Breathing Zone Tested	8 hour TWA** ppm	STEL ppm
Salon 1	Client	0.0327	
Salon 1	Client	0.0031	
Salon 1	Stylist	0.0035	.0217 (15 min)
Salon 2	Client	0.065	
Salon 2	Client	0.065	
Salon 2	Stylist	0.097	
Salon 2	Client	0.0464	
Salon 2	Stylist	0.057	
Salon 3	Stylist	0.120	
Salon 3	Client	0.097	
Salon 4	Stylist		1.67 (15 min)
Salon 4	Stylist		1.71 (15 min)
Salon 4	Stylist		1.23 (15 min)
Salon 4	Stylist		0.76 (15 min)
Salon 4	Stylist		1.63 (15 min)
Salon 4	Stylist		1.67 (15 min)
Salon 4	Stylist		1.21 (15 min)
Salon 3	Stylist	0.18*	
Salon 3	Stylist	0.18*	
Salon 3	Stylist	0.18*	
Salon 3	Stylist	0.28	
Salon 3	Client	0.24	

\* Three stylists wore passive dosimeter lapel badges.  
\*\* Original reports are included.  
\*\*\* Actual values obtained, not adjusted to exclude background.

These air monitoring results indicate that exposures are generally surprisingly low, but for short-term spikes above 0.3 ppm. These brief spikes can lead to the most common reported symptoms; sensory irritation of the eyes, nose or throat. The PKSC believes these brief spikes are best addressed through safety education, cautionary statements, and use of proper and appropriate ventilation.

The use of timonacic acid in a keratin smoothing product demonstrates the problems created when regulations are not properly written and/or inappropriate test methods are required, e.g. HPLC. Air monitoring performed by a highly respected independent environmental laboratory (Exponent/Oakland, CA.) during the performance of a typical keratin smoothing procedure using products containing timonacic acid shows that only

small traces of formaldehyde are detected. Exponent performed an exposure assessment during a typical keratin smoothing treatment and reported the following;<sup>10</sup>

**Table 5.\* Air Monitoring Results Reported by Exponent**

Sample ID	Sample description	Duration (min)	Volume (L)	Raw Concentration ( $\mu\text{g}/\text{m}^3$ )	Adjusted Concentration ( $\mu\text{g}/\text{m}^3$ )
S-1	Personal sample - stylist	142	27	322	292
S-2	Personal sample - stylist	130	26	263	233
			<b>Average stylist 262</b>		
M-1	Personal sample - model	141	27	209	179
M-2	Personal sample - model	142	27	225	195
			<b>Average model 187</b>		
A-1	Area sample - station	95	62	331	301
A-2	Area sample - window/station	139	31	268	238

\* Original reports are included with this submission.

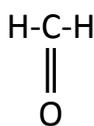
Using these data, Exponent concluded in their report that if the higher of the stylist's two personal exposure readings (322  $\mu\text{g}/\text{m}^3$  for 142 min.) is equivalent to 117  $\mu\text{g}/\text{m}^3$  8 hour time weighted average (TWA), that is well below the OSHA action limit (0.5 ppm or 615  $\mu\text{g}/\text{m}^3$ ). Exponent concluded that at no time did exposures exceed the American Conference of Government Industrial Hygienist (ACGIH) recommended Threshold Limit Values (TVL) of 0.3 ppm (369  $\mu\text{g}/\text{m}^3$ ).

Exponent further calculated that the lifetime average daily dose for the both the stylist and model would, 262 and 187  $\mu\text{g}/\text{m}^3$ , respectively for the 2.3 hour procedure. Assuming the client would repeat this procedure twice per year and a stylist would repeat the procedure once per week, for 8.9 years (median occupational tenure for cosmetologists), then the resulting estimated inhalation dose is approximately 10  $\mu\text{g}/\text{day}$  for the stylist and 1.1  $\mu\text{g}/\text{day}$  for the model, well below California's Proposition 65 warning threshold of 40  $\mu\text{g}/\text{day}$ .<sup>10</sup>

<sup>10</sup> Exponent Project: 1008216.001, Formaldehyde Exposure Assessment of Keratin Hair Smoothing Treatment Product, 2011

## Structure and Reactivity

Formaldehyde gas (CAS#50-00-0) must be protected from combining with other substances and owes its fleeting existence to the absence of water, since formaldehyde is anhydrous and will rapidly react with many substances other than water. Formaldehyde is an anhydrous, highly reactive gas that is commercially available and must be stabilized to prevent it from reacting to create other substances. Formaldehyde is inherently unstable and therefore does not readily build up in nature. Formaldehyde does not accumulate in the environment because it is broken down within a few hours by sunlight or by bacteria present in soil or water. Neither does formaldehyde accumulate in the body, as humans metabolize formaldehyde quickly.<sup>11,12, 13, 14</sup>



Formaldehyde

CAS 50-00-0

EINECS 200-001-8



Methylene Glycol

CAS 463-57-0

EINECS 207-339-5

Methylene glycol is highly soluble in water and highly stable. It is the chief constituent of formalin, the common name for commercially available solutions of the reaction product of formaldehyde with water to produce primarily methylene glycol with methanol as a stabilizing agent to prevent polymerization to high molecular weight polymers with lengths than can vary.



Polymethylene Glycols

Varying Molecular Weight

<sup>11</sup> American Chemistry Council, Formaldehydefacts.org, 5/17/11

<sup>12</sup> EPA office of Air Quality National-Scale Air Toxics Assessment SAB Review Draft Table 4-8, 2001

<sup>13</sup> Formaldehyde and Other Aldehydes, Committee on Aldehydes Board on Toxicology and Environmental Health Hazards, Assembly of Life Sciences, National Research Council, pg. 10, 1981

<sup>14</sup> Kim, L. Collins, L.B., et al., Distribution of DNA Adducts Caused by Inhaled Formaldehyde is Consistent with Induction of Nasal Carcinoma but not Leukemia, ToxSci Advance Access, Toxicological Sciences, Society of Toxicology, 2010

In their 1984 opinion, the CIR correctly stated that formaldehyde is safe up to 0.2% measured as free formaldehyde. The 1984 opinion went on to say, "In aqueous solution, the dominant form of the formaldehyde is methylene glycol." So, the term methylene glycol is not new and is definitely not just an attempt to fool consumers, but instead the correct and preferred terminology which should always be used.

It is deceptive (and improperly alarmist for consumers) to suggest that just because a substance can produce formaldehyde, doesn't mean that material is the same as formaldehyde. When wood and many plant materials are burned they release formaldehyde as a combustion by-product. However, these materials are never marketed as containing formaldehyde, and are not required by regulation to be sold as containing formaldehyde. The responsible and legally appropriate labeling practices of PKSC members have followed this approach.

### Equilibrium Chemistry

The rapid reaction which produces methylene glycol (also referred to as methanediol in biological systems) is highly irreversible and is only likely to be significantly disrupted by extreme temperature and/or pH changes. This equilibrium in an aqueous solution is highly stable and unlikely to create significant quantities of formaldehyde. Such solutions are often mischaracterized as a "formaldehyde generators", when in fact, the opposite is closer to the truth and any trivial amounts of formaldehyde that may be present are readily and quickly removed in the presence of moisture and even humidity found in the air, e.g. it is converted back to methylene glycol.



$$\text{Equilibrium Constant } K_h = \frac{(\text{Methylene Glycol})}{(\text{Formaldehyde})(\text{Water})}$$

In several scientific articles published between 2000 and 2003, Winkleman, et al.<sup>15,16</sup> established an equilibrium constant;  $K_h$  which, assuming water is always present, this calculation may be used to determine that 37% formalin is made by mixing 37% formaldehyde gas (by weight) into water and that the formaldehyde does not dissolve;

<sup>15</sup> Winkleman, J.G.M., Voorwinde, O.K, et. al., Kinetics and Chemical Equilibrium of the Hydration of Formaldehyde, Chemical Engineering Science, 57, pg. 4067-76, 2002.

<sup>16</sup> Winkleman, J.G.M, A.A.C.M. Beenackers, Correlations for the Density and Viscosity of Aqueous Formaldehyde, Ind. Eng. Chem. Res., 39 pg. 556-562

instead almost completely reacts with water to form 59.2% methylene glycol with only 0.0466% formaldehyde (25°C) or 466 ppm dissolved formaldehyde remaining in solution.

## Vapor/Gas Phase Calculations

The previously cited scientific work performed by Winkleman can be used to predict the temperature at which complete conversion of methylene glycol to formaldehyde occurs. Using the equilibrium constant to make this estimation it is seen that complete conversion is theoretically calculated to occur at 775°F (413°C), far in excess of any temperatures likely to be achieved in a salon setting and greatly exceeding the melting point of hair. Not surprisingly so, industrial processes for complete dehydrogenation of methylene glycol to formaldehyde use specialized, silver-based catalysts and temperatures of 1200°F (650°C).

Winkleman's research may also be useful in developing estimates of the ratio of methylene glycol to formaldehyde which can exist within the high humidity vapor generated when a keratin smoothing product is heated by a salon flat iron, as shown in Table 6. Although salon flat irons often claim to achieve temperatures as high as 450°F (232°C), in reality they are much cooler during actual use. Based on measurements made by our membership, a typical flat iron's temperature is expected to normally fluctuate at a range between 400-425°F (204-218°C). Therefore, as shown in the table below, it is likely that only 9-12% of the available methylene glycol applied to the hair will ever be dehydrated to form formaldehyde at temperatures expected for keratin smoothing services. This is largely the reason why air monitoring studies record relatively low levels of formaldehyde in salon air, as will be shown. See Table 6.

At any prevailing temperatures or air flow conditions achievable in the typical salon environment, methylene glycol will always largely dominate over the release of free formaldehyde, even in the vapor generated by the flat iron. These calculations show how difficult it is to convert methylene glycol into formaldehyde. Formaldehyde does NOT simply "bubble out" of solution, as seen when carbon dioxide escapes from an open soda can, and it is clearly erroneous to suggest otherwise. Also, upon cooling in the presence of water vapor, available formaldehyde will rapidly react to form methylene glycol. Whenever water molecules are available, they will continually drive the equilibrium reaction toward formation of the more thermodynamically stable methylene glycol. This same effect seen in salons is also found in nature and is the reason formaldehyde levels do not continually concentrate in the atmosphere, just as atmospheric concentration is limited and highly affected by ambient humidity,<sup>11,12,13</sup> the levels in salons will behave accordingly.

As previously discussed, even upon heating to high temperatures, methylene glycol strongly resists conversion to formaldehyde as a result of the equilibrium strongly

favoring methylene glycol rather than formaldehyde. A similar dynamic equilibrium will exist in the vapor phase, since the vapors created when the product is heated are chiefly water vapor. Using the equilibrium constant, the ratio of methylene glycol to formaldehyde can be calculated for a wide range of temperatures, some of which are listed in Table 6 below. It is important to note that the work on which these calculations are based was performed at temperatures between 68-140°F (19-60°C).<sup>16</sup> Even so, the PKSC believes these extrapolations represent a close approximation and are the best available model for examining the methylene glycol : formaldehyde ratio within the steam/vapor created by heating with a flat iron.

It is clear that formaldehyde hydration reactions will occur rapidly in the gas phase as has been shown to be the fate of environmental formaldehyde gas.<sup>2,3,4,5</sup> The evidence indicates that the lifetime of formaldehyde in aqueous media may be somewhat greater than that of the gas-phase species, because the hydrated form of formaldehyde, which dominates in these conditions, does not absorb sunlight appreciably.<sup>4</sup> Additionally, it is also expected that as the vapor phase quickly cools, the equilibrium ratio will alter just as quickly to favor formation of methylene glycol. Therefore, it is highly unlikely that methylene glycol is constantly being converted to formaldehyde gas or that it will serve as a so-called constant source or "reservoir" for formaldehyde gas formation, under typical conditions expected in the salon during use of keratin smoothing products. This behavior is simply assumed by some regulators and has not been demonstrated to actually occur. Consequently, it is incorrect to simply assume that measuring methylene glycol in a cosmetic product is a valid measurement of consumer exposure to formaldehyde, especially for keratin smoothing products. The PKSC is currently investigating analytical methods for directly measuring these ratios in real-time and expects the results will closely match our calculations and conclusions. We hope to have this data within the next several months.

There is no evidence to suggest that formaldehyde would be predominant over methylene glycol at any normal temperatures reached in a salon. Nor is there any evidence to show that the extreme analytical conditions used to decompose ingredients in cosmetics is a realistic measure of potential exposure during product use; yet this is what is being considered "evidence" by OSHA, Health Canada and others. This is being done to avoid facing the facts that actual measurements of formaldehyde created in salons during the performance of keratin smoothing services is much lower than regulators expected, based on incorrect or inappropriate test methods, while exposures are generally within limits considered safe. Utterback et al., reasoned that short- and intermediate-length oligomers of formaldehyde must be involved in the gas phase equilibrium formation of the long-chain polymers from the monomer. It is important to note, that they determined that the vapor phase species in equilibrium with a formalin solution were shown to be, "Within the accuracy of measurement, all the formaldehyde equivalents in the vapor phase in equilibrium with the formalin solution were in the form of methal, methylene glycol, and three oligomeric poly (oxymethylene) glycol

monomethyl ethers containing one, two, and three formaldehyde units."<sup>17</sup> These other species were also found to be in equilibrium with formaldehyde gas in the vapor phase.

Table 6 demonstrates that it is misleading and incorrect to report methylene glycol as free formaldehyde or to assume that methylene glycol is likely to convert into 100% formaldehyde. Table 6 shows the calculated ratios of formaldehyde to methylene glycol at various temperatures ranging from room temperature to what is expected when a flat iron is used. Significantly, these equilibrium conditions, and their suppressing effects on the release of formaldehyde from products when properly used, are borne out by the actual test data arising from PKSC member companies' products, as shown later in this report.

**Table 6. Relationships between temperature and methylene glycol: formaldehyde ratios calculated using the equilibrium constant**

Temperature	Ratio of Methylene Glycol : Formaldehyde
68 <sup>0</sup> F (20 <sup>0</sup> C)	99.94 : 0.060
75 <sup>0</sup> F (24 <sup>0</sup> C)	99.92 : 0.08
125 <sup>0</sup> F (52 <sup>0</sup> C)	99.78 : 0.22
200 <sup>0</sup> F (93 <sup>0</sup> C)	99.18 : 0.82
300 <sup>0</sup> F (149 <sup>0</sup> C)	96.77 : 3.23
350 <sup>0</sup> F (176 <sup>0</sup> C)	94.48 : 5.52
400 <sup>0</sup> F (204 <sup>0</sup> C)	90.97 : 9.03
425 <sup>0</sup> F (218 <sup>0</sup> C)	88.69 : 11.31

<sup>17</sup> Utterback, D.F., Gold A., Millington, D.S., Quantitative Analysis of Formaldehyde Condensates in the Vapor State, Formaldehyde: Analytical Chemistry and Toxicology, Advances in Chemistry, Vol. 210, pg 57-65, 1985

## Methylene Glycol and Hair

Methylene glycol is a well-known tissue fixative that cross-links keratin protein as shown in the diagram below.<sup>18</sup> Methylene glycol is the reactive ingredient in many keratin smoothing products. Methylene glycol's action on the hair's keratin is demonstrated by the several main reaction mechanisms presented below in which the "R" group represents bulk surface proteins on the hair to which cross-linking occurs. These mechanisms (Diagram 1) show that methylene glycol is an effective keratin cross-linker and that formaldehyde is not required, and definitely NOT an "ingredient". The effectiveness of keratin smoothing products does not depend on the formation of formaldehyde, which is chemically inevitable (but at levels far below safe exposure limits and established regulatory limits). Instead, the desired cosmetic outcome results from energy delivered by heat, which greatly accelerates the chemical reactions shown below, so keratin smoothing treatments can be delivered in a reasonably short time frame of less than two hours. Also, very low levels of resulting formaldehyde, which are well below established exposure limits, are easily managed in the professional salon setting if proper ventilation is used, as required by manufacturers' directions.

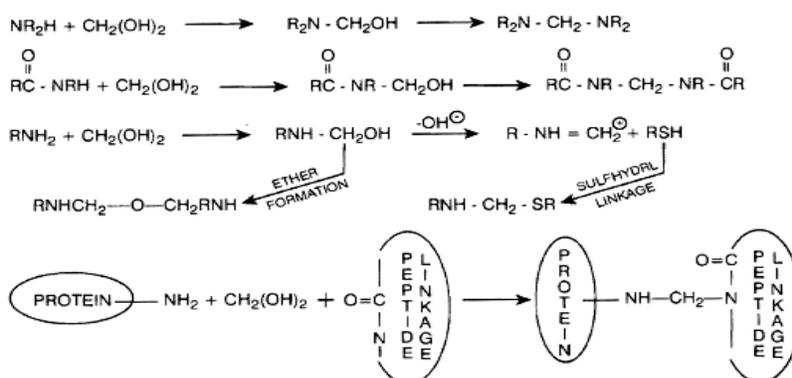


Diagram 1: Methylene glycol reaction mechanisms

<sup>18</sup> Bedino, J.H., Expanding Encyclopedia of Mortuary Practices, No. 649, pg. 2619-20, 2003

## Other Mischaracterized Keratin Smoothing Ingredients

Timonacic acid is another example of a keratin smoothing ingredient that has been mischaracterized as "formaldehyde". See Diagram 2. Timonacic acid (Thiazolidine-4-carboxylic acid) is a stable reaction product of cysteine and formaldehyde as shown below,<sup>19</sup> that has been widely used in keratin smoothing formulations.

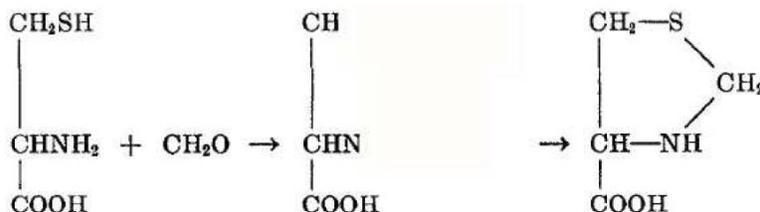


Diagram 2: Formation of Timonacic Acid

The role of timonacic acid as a keratin smoothing ingredient is shown in the reaction mechanism shown in Diagram 3.<sup>20</sup>

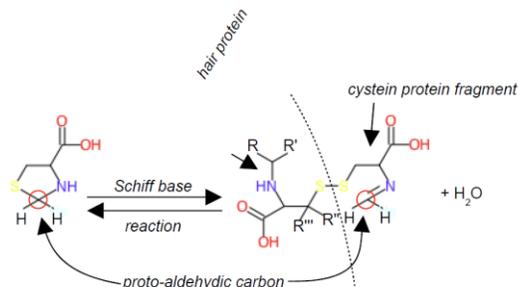


Diagram 3: Formation of Timonacic Acid

<sup>19</sup> Kallen, R.G., Equilibria for the Reaction of Cysteine and Derivatives with Formaldehyde and Protons, *Journal of the American Chemical Society*, 93:23, pg. 6227-35, 1971

<sup>20</sup> Ballantini, D.C.V, Behavior of the Keratin Complex Smoothing Therapy by Coppola, Role of Timonacic Acid (Thiazolidine-4-carboxylic acid) in Formaldehyde Detections during Analysis,

It is important to note that formaldehyde is not the reactant and therefore should NOT be considered an ingredient in keratin smoothing products using timonacic acid in their formulations. Even so, this ingredient is tested via the same methods used to test methylene glycol, which leads to an artifactual excess and unrealistic release of free formaldehyde. The stability of timonacic acid is disrupted by the acidic conditions of HPLC test methods. This analytical environment and the conditions to which this product was subjected caused a pH driven decomposition of timonacic acid to release formaldehyde, at levels that far exceed normal conditions found in the product or during use.

## **New Information Concerning the Toxicology of Formaldehyde**

During their March, 2011 meeting the CIR panel expressed interest in the National Academy of Sciences/National Research Council (NRC) soon to be completed review of the U.S. EPA Integrated Risk Information System (IRIS) assessment of formaldehyde (EPA 2011), which is the data the EPA/IRIS assessment used to reach its most recent conclusions concerning formaldehyde toxicology. The NRC panel was highly critical of most the of EPA's study selection for assessing key health endpoints, its unwarranted dismissal of certain studies, and lack of transparency in how studies were selected.

Appendix A is a review of the criticisms offered by the NAS/NRC panel which calls into question some of the conclusions reached by the IARC and NTP since all rely on the same data as the basis for their respective conclusions. This information is important for the CIR to consider and may lead to changes in their final report, especially in relation to non-cancer effects including sensory irritation, asthma, and reproductive/developmental effects. See Appendix A for this discussion and additional information.

## **Importance of the Keratin Smoothing Category**

**While members of the PKSC consider safety as not only their principal concern, but their obligation to salon professionals and consumers, they also have a professional obligation to the professional salon industry as a whole to present means by which salons and licensed professionals can achieve success and provide excellent service to their clients.** During the approximately 5 year span since the introduction of the keratin smoothing category, it is fair to estimate that via PKSC members' distribution alone, 50,000 or more salons are safely providing these services to hundreds of thousands of consumers with no adverse reactions and while achieving the desired results. The addition of the keratin smoothing category to the economic landscape of the professional salon industry has served to grow salon revenues, and in many cases allowed numerous businesses to survive these difficult times. As salon professionals we

take our responsibility to ensure the safety of our products very seriously and hope that the CIR will be open minded to considering all of the data provided herein resulting in a critically important positive impact on the industry.

## Key Recommendations

The PKSC believes that the data definitively demonstrates that keratin smoothing products can be used safely. The formulations and safe use instructions, consumer disclosures, and safety training provided by PKSC members ensure this outcome. However, inaccurate information, inappropriate test methods and confusing nomenclature has created inaccurate information which is now reaching the public. This in turn has led some consumers and regulators to incorrectly assume these services are unsafe because keratin smoothing products can be irritating to the eyes, nose and throat if proper procedures aren't followed and/or appropriate ventilation is not used. A vigorous program to educate stylists and salons about the need and importance of proper ventilation has been a consistent element of the business practices of PKSC members that we will be building on over the coming months.

We ask the CIR to recommend that keratin smoothing products be restricted to use by trained and licensed professionals who undergo additional training on proper use and safe handling, to include training about understanding and properly using an MSDS, ventilation and safe handling. The PKSC suggests that in the CIR recommendations, proper ventilation is addressed. Proper ventilation is needed to ensure stylists aren't experiencing irritation of the eyes, ears, nose and throat.

These early indicators warn of the increased potential for overexposure and would adequately warn a trained and licensed cosmetologist that the ventilation in use was probably inadequate for the task at hand. The PKSC believes that proper formulation, training, and disclosures, in concert with proper ventilation, are the keys to safe application of our members' products, for both salon professionals and consumers. In each of the cases presented above, the salons were using a wide range of ventilation solutions. Some were successful and some solutions were inadequate and need improvement. The PKSC understands there are many steps to improving salon air quality and in many cases, proper ventilation is not well understood or observed in salons. Even so, these services are in high demand, so stylists are seeking ventilation systems that eliminate the most common symptoms of irritation. The PKSC believes the data shows these symptoms are triggered by occasional, uncontrolled short-term spikes up to and sometimes exceeding 0.3 ppm. These brief spikes are what lead to reports of headaches and other acute irritation symptoms, but this is easily controlled though the use of safer practices and improvements in mechanical ventilation and even supplemented with local exhaust ventilation systems and high capacity room air

cleaners, such as systems sold by one of our member companies Aerovex Systems, Inc.<sup>21</sup>

This company, as well as others tests, develops and sells ventilation systems for salons. Aerovex has specifically developed a "local source capture" ventilation system (Image 1) designed for use with professional keratin smoothing products in the salon setting. These types of systems are adjuncts to existing salon ventilation and can effectively lower exposures by capturing the vapours at the source and removing them from salon air. PKSC is working to develop an educational program aimed at stylists, salon owners, students, educators and salon distributors to help them better understand the importance of using proper salon ventilation for the many services performed in salons, including keratin smoothing. Ventilation in salons has been historically over looked by both salon owners and regulators alike. The PKSC believes that some salons don't pay proper attention to air quality and ventilation and this is largely responsible for the short-term spikes above 0.3 ppm that increase the potential for the most common symptoms previously described.



Image 1. This local source capture ventilation system is one of many types of ventilation systems used in salons to control vapors, mists and dusts. Photo Courtesy: Aerovex Systems, Inc.

The PKSC has reached out to salon ventilation companies and experts. One of our goal is to raise awareness of these issues and encourage the development of salon ventilation systems that will help maintain high air quality in salons. Presently, some salons rely solely on open door or fans and do not properly maintain their mechanical exhaust systems, which will have a great effect on salon air quality. Our membership has found that salons that 1.) practice proper ventilation and 2.) follow proper application procedures to avoid using excessive amounts of smoothing treatment products in the hair, result in little to no eye, nose, and throat or skin irritation. Our members have

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<sup>21</sup> Aerovex Systems, Inc., [www.AerovexSystems.com](http://www.AerovexSystems.com).

been providing these safe use instructions to salons continually throughout the marketing and sales of their products.

We believe that all salons are required to and should use proper ventilation as appropriate for each salon environment with consideration to the various services the salon and/or stylist choose to perform. Studies show that 10-20% of the general population may be susceptible to the irritating effects of formaldehyde at low concentrations. In laboratory investigations, under controlled conditions, responses have been recorded at formaldehyde concentrations as low as 0.01 ppm when formaldehyde was present in combination with other air pollutants.<sup>22</sup> Ventilation and safe practices are capable of lowering exposures to safe and acceptable levels and will prevent clients and stylists from experiencing these unusual signs of irritation or excessive exposure. Salons not able to provide proper and appropriate ventilation as described, should not offer these services until they resolve the conditions/issues preventing them from having the level of ventilation necessary to control potentially irritating vapours and dusts created during the performance of their services, e.g. hair lightening and coloring, permanent waving or Japanese thermal straightening, etc.

The PKSC also suggests that the CIR recommend cautionary labelling language that warns stylists that they must work in a manner that minimizes formation and inhalation of irritating vapours and also that any sensory irritation is a warning sign of poor ventilation. By way of example; "CAUTION: Upon heating this product releases a low level of formaldehyde gas which may irritate the eyes, nose and throat. Safe handling requires use of proper ventilation that is capable of eliminating early warning symptoms when services are performed in accordance with manufacturer's directions."

Finally, it is important to note that formaldehyde has not been reclassified under the EU Cosmetic Directive and many so-called "formaldehyde-containing" products continue to be permitted under the laws and regulations of Canada, the EU and many other countries. Confusion exists largely because many different substances are lumped under that term "formaldehyde" and great attempts are made to avoid recognizing these other substances or ingredients by using confusing "code" terms such as "free formaldehyde" or "hydrated formaldehyde" or "unhydrated formaldehyde", "unhydrated free formaldehyde", "bound formaldehyde", "unbound formaldehyde" all just to avoid using the proper chemical names.

For these reasons, the Professional Keratin Smoothing Council is requesting that the CIR take this opportunity to lead the way and insist on the use of chemically accurate terminology and proper nomenclature by the cosmetic industry. If the CIR determines to take this approach, which is consistent with sound regulatory practices and public

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<sup>22</sup> Formaldehyde and Other Aldehydes, Committee on Aldehydes Board on Toxicology and Environmental Health Hazards, Assembly of Life Sciences, National Research Council, pg. 13, 1981

safety, it will set the foundation for proper regulatory action and appropriate public education and response.

It is obvious that safe levels exist for formaldehyde exposure as demonstrated by a 1997 law suit related to California Proposition 65 in which it was erroneously claimed that exposure to formaldehyde in nail salons exceeded the "safe harbor" levels established by the State. Those making erroneous claims that certain nail product vapors contained harmful levels of formaldehyde attempted to rely upon theoretical projections, calculations and very limited testing. However, when a multi-year study was performed in the winter and summer in salons at three different geographical locations, the results provided evidence for a completely different conclusion. Mr. Edward Weil, California Deputy Attorney General, stated in an April 2000 letter that, "*...the evidence is clear that exposures to consumers and salon customers from nail polish to... formaldehyde do not pose a sufficient risk to require a warning, even under the strict standards imposed by Proposition 65*". An overview of this important study was published in the Journal of Inhalation Toxicology.<sup>23</sup> This shows that as long as proper ventilation and other safe handling practices are followed, working with keratin smoothing products is safe for stylists and clients alike.

Over reporting levels of formaldehyde harms and does not increase safety for the consumer, creates confusion in the marketplace, needlessly alarms politicians and provides fodder for those who regularly distort the facts in order to deceive the public into believing that cosmetics products are unsafe. Due to long standing confusion over terms such as formaldehyde, formalin and methylene glycol, some groups have taken advantage of the misinformation and used it to provoke unwarranted fear and needless concern by misleading the public into believing they are being harmed by exposure to levels of formaldehyde they claim are hundreds or thousands of times higher than the facts support.

This misinformation is being wrongly used to magnify the perceived threat and creates a false perception of hair smoothing products. These groups incorrectly suggest that manufacturers are intentionally using large concentrations of "formaldehyde" as a cosmetic ingredient and pointing to this as evidence that cosmetic manufacturers intentionally add this "carcinogen" as an ingredient. The PKSC believes and hopes that the CIR agrees that it is in the best interest of the consumer to address and correct these misconceptions resulting from departures from established safe product testing protocols and scientific methods.

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<sup>23</sup> McNary, J.E, Jackson, E.M., Inhalation Exposure to Formaldehyde and Toluene in the Same Occupational and Consumer Setting." Journal of Inhalation Toxicology, 19, pg. 573-576, 2007.

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## Summary of Key Recommendations

- Keratin smoothing products should be restricted to use by trained and licensed professionals who are required to undergo additional training on proper use and safe handling, e.g. undergo additional training on ventilation, proper product use and safe handling and understanding of MSDSs.
- CIR should make a recommendation that proper ventilation is necessary to ensure stylists/clients do not experience irritation of the eyes, ears, nose and throat.
- Rely on air monitoring results to evaluate safety of these products as used in salons.
- Rely on <sup>13</sup>C NMR data as the best methodology for measuring methylene glycol and free formaldehyde or other ingredients that are known to release low levels of "formaldehyde".
- Recommend the use of proper nomenclature for methylene glycol, formaldehyde and the wide variety of ingredients that may release varying amounts of "formaldehyde" gas.
- Recommend that methylene glycol and formaldehyde NOT be considered to be 100% interchangeable and synonymous, recommend specific safe levels for both, and clarify to which substance these limits apply, as well as to comment on the measurements used to meet CIR recommendations, e.g. use of equilibrium constant with HPLC data.
- Recommend cautionary labelling language that warns stylists that they must work in a manner that minimizes formation and inhalation of irritating vapours and also that any sensory irritation is a warning sign of poor ventilation, e.g. "CAUTION: Upon heating this product releases low levels of formaldehyde gas which may irritate the eyes, nose, throat and lungs. Safe handling requires use of proper ventilation that is capable of eliminating these symptoms when services are performed in accordance with manufacturer's directions."

Respectfully Yours,

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## Appendix A

Recently Developed Information Related to the Toxicology of Formaldehyde for CIR Consideration.

A panel convened by the National Academy of Sciences/National Research Council (NAS/NRC 2011) recently completed its review of the U.S. EPA Integrated Risk Information System (IRIS) assessment of formaldehyde (EPA 2011). The data relied upon in the EPA/IRIS assessment to reach conclusions about potential formaldehyde carcinogenicity are the same data relied upon by IARC (2009) and the U.S. National Toxicology Program (NTP 2010) to reach their almost identical conclusions. Consequently, the NAS/NRC critique of these data, as used in the EPA/IRIS assessment, can be considered as applying equally to the conclusions of IARC and NTP as well. The criticisms of the NRC panel are sufficiently strong that they call into question the conclusions of IARC and NTP that formaldehyde could be considered to be a known human carcinogen. Virtually all aspects of the EPA/IRIS assessment including conclusions on cancer endpoints (e.g., lymphohematopoietic malignancies), selection of studies for establishing non-cancer reference concentrations (i.e., RfCs) as well the entire data evaluation process were criticized by the NRC panel. Because of the implications of the NAS/NRC conclusions as they pertain to the overarching issues of the likelihood of formaldehyde-induced cancer and non-cancer effects, it is incumbent that the CIR make note of this in a revised version of the "Tentative Amended Report." This should include an acknowledgement of the following points as they pertain to leukemia, nasopharyngeal cancer (NPC) and certain non-cancer effects including sensory irritation, asthma and reproductive/developmental effects.

### Leukemia and Related Hematopoietic Cancers

The NRC committee concluded that the EPA's claims that formaldehyde causes leukemia, myeloid leukemia or related hematopoietic cancers were not supported in the IRIS assessment noting that *"As a result, the conclusions appear to be based on a subjective view of all the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies of the epidemiologic data, the weak animal data, and the lack of mechanistic data."* Particularly with respect to the epidemiology data, the NRC panel concluded that they were limited by *"...uncertainties of exposure assessment, possible confounding by other pollutants, and reliance on mortality data rather than incidence data...."* (NRC 2011, p. 83)

The lack of mechanistic data that might explain how formaldehyde could induce leukemia is highlighted by findings in both rats and non-human primates (Lu et al. 2010, Moeller et al. 2010, Swenberg et al. 2011) unequivocally demonstrating that inhaled formaldehyde-DNA adducts are undetectable in potential target organ sites distal to the

nasal epithelium, particularly white blood cells and bone marrow. With respect to the issue of systemic delivery of inhaled formaldehyde to distant sites, the NRC panel found that *"...the more contemporary work performed by Lu et al. (2010) that examined formaldehyde-induced DNA adducts and DDX cross-links provided no direct evidence of systemic availability of inhaled formaldehyde. The Lu et al. 2010 study used <sup>13</sup>CD<sub>2</sub>-labeled formaldehyde and showed that <sup>13</sup>CD<sub>2</sub>-formaldehyde-DNA adducts and DDX were confined to the nasal cavity of exposed F344 rats, even though they examined much more DNA isolated from bone marrow, lymphocytes, and other tissues at distant sites for the adducts."* It should be pointed out that while the EPA/IRIS formaldehyde assessment cited the results of Lu et al. (2010) for the finding of exogenous formaldehyde-DNA adducts in the nasal epithelium, it omitted the far more important finding of no detectable exogenous formaldehyde-DNA adducts at any sites distal to the nose.

The above findings call into question how inhaled formaldehyde, which doesn't enter the systemic circulation to change normal endogenous levels (Heck et al. 1985 Casanova et al. 1988), would be capable of inducing leukemia. This is particularly the case since chemical leukemogenesis is a well studied phenomenon with an absolute requirement of systemic delivery to the bone marrow as an obligatory event (Golden et al. 2006, Pyatt et al. 2008). Given the uncertainties and deficiencies in the epidemiology and mechanistic data in conjunction with the conclusions of the NRC panel pertaining to a causal association between formaldehyde inhalation and leukemia it appears premature to accept the EPA/IRIS inhalation cancer unit risks for leukemia without appropriate caveats.

Although EPA postulated a mutagenic mode of action for leukemia and other hematopoietic cancers, the evidence is very weak, particularly as it relates to low, environmental exposures, with the NRC committee observing that *"Although EPA postulated that formaldehyde could reach the bone marrow either as methanediol [methylene glycol] or as a by-product of non-enzymatic reactions with glutathione, numerous studies...have demonstrated that systemic delivery of formaldehyde is highly unlikely at concentrations below those which overwhelm metabolism according to sensitive and selective analytic methods that can differentiate endogenous from exogenous exposures."* Finally, the NCR panel noted, *"However, the mode of action for formaldehyde-induced Hodgkin's lymphoma and leukemia has not been clearly established. Moreover, the highly limited systemic delivery of formaldehyde draws into question the biologic feasibility of causality between formaldehyde exposure and the two cancers. Thus, substantial uncertainties in using Hodgkin's lymphoma and leukemia for consensus cancer risk estimation remain."*

## Nasopharyngeal Cancer (NPC)

The NRC panel agreed with the EPA/IRIS assessment that the combined weight of epidemiology findings, results of animal studies, and mechanistic data were supportive of a causal association between formaldehyde and NPC. The epidemiology finds are principally driven by a study by Hauptmann et al. (2004) which was reviewed extensively in the CIR. With respect to this study, the NRC panel noted that *“a serious concern has been raised about an unexplained under ascertainment of deaths in the Hauptmann et al. (2004) study (Marsh et al. 2010). In the update of findings on lymphatic and hematopoietic cancers in the NCI cohort, Beane-Freeman et al. (2009) noted that 1,006 deaths that had occurred before 1995 were missing from earlier analyses of the NCI cohort.....The effect of that under ascertainment of deaths and the additional follow-up period has important implications for analyses of the NCI cohort and NPC. Given the importance of the NCI study to the formaldehyde assessment, EPA should make an effort to update its assessment once the NCI study findings on NPC become available.”*

It is unknown why this study updating the NCI cohort, which has been completed for some time, has not been released by NCI. While the committee was *“not recommending that EPA wait until release of the update to complete its assessment,”* the potential problems with the NCI studies, in general, suggest otherwise. For example, in the Beane-Freeman et al. (2009) update of the Hauptmann et al. (2003) study on lymphohematopoietic malignancies, accounting for the “missed” deaths in the earlier study resulted in substantial changes in the SMRs based on various exposure metrics. In addition, the Beane-Freeman et al. (2009) update incorporated an additional more biologically plausible exposure metric than the controversial peak exposure as used in

both NCI studies. Using this metric, i.e., number of peaks  $\geq 4$  ppm, there were no statistically significant associations with leukemia mortality or any other lymphohematopoietic malignancies. This may have implications for the update of Hauptmann et al. (2004) study if a similar approach is used. Given the substantial changes in the conclusions from the 2003 and 2009 lymphohematopoietic studies, there is also a high probability that the significant findings concerning NPC may not be statistically significant in the updated study.

However, the NRC panel also took the position that there was likely a threshold for NPC effect based on their strong endorsement of the biologically based dose response (BBDR) model as developed by Conolly et al. (2004). In addition, the NRC panel was critical of EPA-sponsored papers (Crump et al. 2008, 2010, Subramaniam 2008) that sought to marginalize the BBDR model noting that *“some of the manipulations are extreme, may not be scientifically justified, and should not have been used as the basis of rejection of the use of the BBDR model in its assessment. Model manipulations that yield results that are implausible or inconsistent with available data should be rejected as a basis for judging the utility of the model.”*

Finally, the committee was supportive of the biologically based dose response (BBRD) model developed for risk assessment of formaldehyde induced nasal tumors and highly critical of EPA's development *"of alternative models that yielded the most extreme deviations from the Conolly et al. (2004) low-dose extrapolations"* which *"produced unrealistically high added risks for humans at concentrations that have been observed in the environment of occupationally exposed workers (100% incidence at concentrations a low as about 0.1-1 ppm). Thus, the committee recommends that manipulations of model parameters that yield results that are biologically implausible or inconsistent with the available data be discarded and not used as a basis for rejecting the overall model."* Instead the NRC panel suggested that EPA *"chose not to use the BBDR models developed by Conolly et al. (2003, 2004) on the basis of "...extreme alternative model scenarios"* and recommended that the results using this model *"be compared with those of the approach currently presented in the draft IRIS assessment, and that the strengths and weaknesses of each approach be discussed."* It appears obvious that the BBDR model (which is accepted and used by regulatory agencies around the world), now augmented with dose-response toxicogenomic data (Andersen et al. 2008, 2011) generated according to the recommendations of another NAS panel (2007) will be the only risk assessment approach that can be scientifically justified.

## Sensory Irritation

The NRC committee was critical of the EPA for not including the controlled human studies in the derivation of a reference concentration (RfC) for sensory irritation; *"EPA set aside the chamber and occupational studies too soon in the process."* It should be noted that these studies, the only ones that can demonstrate the 25-30% incidence of false positive reports of sensory irritation at formaldehyde concentrations of less than 1 ppm, have been endorsed and relied upon by regulatory and authoritative agencies from around the world including NAS (2007), Health Canada (2005), Germany (BfR 2006), Australia (NICNAS 2005), the European Union (SCOEL 2008), and WHO (2010). The NRC panel concluded that a key study selected and relied upon for development of the RfC (i.e., Ritchie and Lehnen 1987) should have been rejected as invalid (i.e., *EPA should not have used it*). Overall, for the studies relied upon for the sensory irritation RfC the NRC committee observed that *"...study details... and study weaknesses (such as the limitations of the exposure assessments performed in the residential and occupational epidemiologic studies) were not thoroughly presented or critically evaluated in a consistent manner by EPA."*

## Asthma

With respect to asthma, the NRC noted that *"In infants and children, wheezing illnesses that are the result of lower respiratory tract infections are often labeled as asthma, and in adults, the symptoms can overlap with those of other chronic diseases, such as chronic obstructive pulmonary disease. Thus, a critical review of the literature is essential to*

*ensure that what is being evaluated is asthma....this issue is not adequately addressed in the draft IRIS assessment.” Also noted was that “EPA advanced a study (Rumchev et al. 2002) [for derivation of the asthma RfC] that most likely suffers from misclassification of infection-associated wheezing in young children as asthma.”*

It should also be pointed out that previous NAS committees have addressed the formaldehyde/asthma issue. A comprehensive report by the NAS Institute of Medicine (IOM 2000) examined the evidence for associations between indoor biologic and chemical exposures and either the development or exacerbation of asthma. The report concluded that *“There is inadequate or insufficient evidence to determine whether or not an association exists between formaldehyde exposure and asthma development.”* More recently, another report (NAS/NRC 2007) summarized the available controlled clinical studies evaluating the irritant effects of formaldehyde in asthmatic and nonasthmatic

individuals, finding no differences in sensitivity between the two groups concluding that *“asthmatic individuals exposed to airborne formaldehyde at exposure concentrations at or below 3 ppm do not appear to be at greater risk of suffering airway dysfunction than non-asthmatic individuals.”* Finally, the NRC (2011) committee concluded that *“The ad hoc approach taken in the draft IRIS assessment may reflect inadequate guidance on asthma.”*

## **Reproductive and Developmental Toxicity**

As reviewed in the CIR “Tentative Amended Report” the study by Taskinen et al. (1999) was also selected by EPA/IRIS as the basis for derivation of the reproductive and developmental reference concentration (RfC). With respect to the Taskinen et al. (1999) study, the NRC panel noted that the EPA/IRIS assessment *“has minimal discussion of study strengths and weaknesses, and the discussion of bias is misleading or incomplete. Specifically, the discussion dismisses potential confounding by xylene exposure...”* This issue was discussed in the CIR review, particularly the disappearance of significant effects in women wearing gloves, since formaldehyde is not absorbed through the skin. The NRC committee also disagreed with the EPA’s overall conclusion that the totality of the epidemiologic evidence related to the reproductive and developmental effects of formaldehyde were supportive of *“a convincing relationship between occupational exposure to formaldehyde and adverse reproductive outcomes in women”* (EPA 2010, p. 4-85). Instead, the NRC committee, *“after assessing the literature, finds a suggestive pattern of association among a small number of studies rather than a convincing relationship.”* The lack of systemic delivery of formaldehyde to potential target sites distal to the nasal epithelium also calls into question how effects on reproduction or development might occur.

### Specific Comments and Suggestions Related to the CIR Tentative Amended Report

P. 12; under “Several methodological issues...” Suggest adding a final critical point to this list of methodological issues Another issue in the Hauptmann et al. (2009) study calls into question the rigor of their analysis and the likelihood that the reported results are correct. Because there was only one case of myeloid leukemia in the reference group of non-embalmers, risks for this condition were evaluated in a different comparison group consisting of individuals who performed less than 500 lifetime embalmings in order to include five additional cases of myeloid leukemia in the reference group for purposes of risk assessment. As stated by the authors, *“These represent more conservative but probably more reliable risk estimates for high-level exposure than those shown in Table 3.”* A simple inspection of the ORs for myeloid leukemia in Table 4 shows quite clearly that there is no significant trend even though the *p*trend values are reported as significant. However, in a footnote to Table 4 it is noted that *“Trend tests for LHPM of non-lymphoid origin and myeloid leukemia are the same as those presented in Table 3.”* In other words, none of the results presented in Table 4, which are described as *“more reliable risk estimates”* than those shown in Table 3 were actually tested for statistical significance. This substantial error calls into question the conclusions of this study.

This issue was the subject of a letter-to-the editor of the Journal of the National Cancer Institute (JNCI) by Cole et al. (2010) which noted that *“Surprisingly, the more reliable exposure–response analyses are not accompanied by their attendant P values. Even more perplexing is that they were accompanied by the P values obtained from the less reliable data.....We are left with a study that is described as positive for a formaldehyde–myeloid leukemia association among embalmers, but which provides little evidence of an overall excess of myeloid leukemia among them and whose most reliable data on exposure–response relationships were not tested for statistical significance.”* In their response, Hauptmann et al. (2010) failed to address the key issue raised by Cole et al. (2010) of transferring the same *P* values from Table 3 to Table 4 without actually testing the findings presented in Table 4 for statistical significance.

P. 14; under “Lymphohematopoietic cancers – mode of action; last sentence in 1<sup>st</sup> paragraph should read; ...there is no scientific evidence supporting....

P. 20; under US EPA Risk assessments- non cancer effects the second paragraph starting “U.S. EPA also noted a two-stage carcinogenesis assay... this paragraph has nothing to do with non-cancer effect and is irrelevant for cancer effects and should be deleted...it adds nothing to the discussion

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P. 20 under US EPA Risk Assessments – Carcinogenicity

As described in the CIR document, the EPA's IRIS assessment developed an upper bound  $10^{-6}$  unit risk of 0.008 ppb (i.e., 8 ppt). It is incumbent that this be put into perspective in the CIR document in order to demonstrate how out of touch this value is with respect to the real world. Since the upper level of exhaled formaldehyde in the breath is about 2 ppb, the EPA's value of 0.008 ppb poses a cancer risk  $>10^{-4}$  which falls outside of EPA's acceptable range of  $10^{-4}$ -  $10^{-6}$ . This value also implies that formaldehyde concentration in the air of pristine locations ( $\approx$  9 ppb), as well as those typically found in indoor air (20-100 ppb) would pose even greater risks of cancer. Finally, this value, if correct, would predict huge cancer risks from exposure to the OSHA formaldehyde standard of 0.75 ppm (i.e., 750 ppb or 750,000 ppt).

P. 21 last paragraph the sentence ending... "published studies of formaldehyde, given the chemistry of these two chemicals, actually determined the toxicity of both formaldehyde and methylene glycol" is incorrect. Methylene glycol is the hydrated form of formaldehyde found in all living systems, with every organ bathed in methylene glycol as a consequence of its presence in the blood. As such, it has no toxicity and studies conducted with gaseous formaldehyde are only relevant with respect to gaseous formaldehyde. In fact, several comprehensive studies in rats, monkeys and humans demonstrate that inhaled formaldehyde, even at concentrations of almost 15 ppm in monkeys for 4 weeks, do not change normal endogenous levels of formaldehyde (as methylene glycol). Consequently, this erroneous statement should be deleted.

P. 22, 1<sup>st</sup> paragraph; sentence starting "while debate is ongoing regarding the dose-response of the induction.... There is no more debate about this issue as the mode of action for formaldehyde induced nasal tumors is well understood, has been described in great detail and is now supported by dose-response toxicogenomic data collected according to the recommendations of another NAS (2007) committee (*Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment*). The strong endorsement of the BBDR model by the NRC committee coupled with its criticisms of the EPA for attempting to marginalize this model (with several appendixes in the IRIS formaldehyde assessment devoted solely to this goal), has substantial implications. The most important is the fact that with a clear threshold for the hypothetical induction of NPC, no conceivable environmental exposure would be associated with increased risk of this cancer.

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May 11, 2011

Please reply to:

c/o **Myra Y. Irizarry**

Manager - Government Affairs  
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Scottsdale, AZ 85254

Alan Andersen, PhD  
The Cosmetic Ingredient Review  
1101 17<sup>th</sup> Street, NW Suite 412  
Washington, DC 20036-4702

Dear Dr. Andersen:

On behalf of the Nail Manufacturers Council, a Council of the Professional Beauty Association, representing the manufacturers of professional nail products, we are making this submission as part of your ongoing review of formaldehyde in cosmetic products, primarily triggered by current actions being taken by Regulators against hair smoothing/hair straightening products. Nail hardeners have safely been used in the market for decades and now run the risk of being swept up in the furor surrounding hair smoothing/hair straightening products.

The nail care industry has an excellent record regarding the lack of sensitization with nail hardeners, no doubt due to the fact that there is essentially, for the reasons explained below, no formaldehyde in the product. In fact, a recent confidential survey submitted to COLIPA for consideration in the European Union's review of formaldehyde revealed that, of the leading five professional nail hardener brands, there was only one adverse health reaction reported—a complaint the product irritated the skin--over a three-year period in which more than 7.6 million units were sold.<sup>1</sup>

We are asking you to look to the science and to the use of accurate and proper scientific nomenclature when conducting your review. Regrettably, and likely because of the lack of a requirement to be chemically accurate in the past, loose language has been employed to colloquially refer to formaldehyde, formalin, methylene glycol etc. as "formaldehyde".

It is common practice in daily parlance to utilize a generic or common term to improperly refer to chemically different products. For example, "ice cream" is used to

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<sup>1</sup> Letter to David Steinberg from Lisa Halko dated May 5, 2008.

describe real ice cream as well as frozen yoghurt, ice milk, frozen desserts made with vegetable fats and so on. Dairy councils in many parts of the world are undertaking public awareness campaigns and government lobbying in an effort to educate consumers as to what "ice cream" truly is. So it is with the products in issue here. For decades "formaldehyde" has been a term of convenience misused by manufacturers, industry, consumers and governments alike to describe a multitude of products which are not the same, chemically or physically. Although it is proper for one chemical substance to have many names, it is not proper for many chemical substances to be referred to with a single name.

We urge you to correct historic inaccuracies and ensure that proper recognition is given to accurate nomenclature in your analysis and report. Unfortunately, imprecise and colloquial terminology is also present in some of the scientific evidence which you may be considering during your review.

Manufacturers of salon nail care products must use proper ingredient descriptions on labels throughout the world. Of specific relevance is that the hardening ingredient formerly referred to by some manufacturers as "formaldehyde" is now being changed to the more technically correct term Methylene Glycol.<sup>2</sup>

The International Nomenclature of Cosmetic Ingredients (INCI) Dictionary Committee assigned the name Methylene Glycol in 2008 in response to a petition with supporting documentation (see discussion below) to establish the more accurate term for the reacted chemical substance created from the reaction of water and Formaldehyde. The purpose in doing so was, and remains, to clarify what has become an increasingly confusing situation to consumers and others and to rectify the erroneous appellation conveniently, but incorrectly, used by many, including our own industry, for a substantial number of years. We welcome your comments and will supply any supporting material that you might need.

There are several recognized chemicals commonly, and confusingly, referred to as "Formaldehyde." Two are described below and Formalin is most often also similarly misnamed

- *Formaldehyde* - anhydrous gas CAS 50-00-0 EINECS 200-001-8
- *Methylene Glycol* CAS 463-57-0 EINECS 207-339-5

*Formalin* is a common name for commercial solutions of the reaction of formaldehyde with water to produce chiefly methylene glycol.

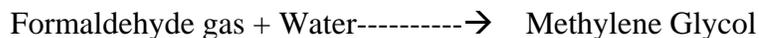
The anhydrous gas, Formaldehyde, reacts within nanoseconds and creates a highly irreversible equilibrium when it comes into contact with water to form Methylene Glycol. Significantly, the chemical structure, properties and safety characteristics for

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<sup>2</sup> The chemical commercially sold as "Formalin" is an aqueous solution of Methylene Glycol. Bedino, J.H., (2003). Expanding Encyclopedia of Mortuary Practices, 649, 2619

these two chemicals are very different. Moreover, the substances come from different chemical families, aldehydes and alcohols (specifically "glycols"), differ in physical and toxicological properties, as well as having been assigned different CAS and EINECS numbers.

The Formaldehyde nomenclature is used frequently, and incorrectly, for nail hardeners and other products, notwithstanding well-established published data<sup>3</sup> that demonstrate Formaldehyde, in the presence of water (even traces of moisture), is almost completely reacted to form Methylene Glycol, as expressed in the following:



$$\text{Equilibrium Constant } K_h = \frac{(\text{Methylene Glycol})}{(\text{Formaldehyde})(\text{Water})}$$

Prof. Winkelman<sup>4,5</sup> in 2002 established an equilibrium constant  $K_h$  using the rate of hydration and the rate of dehydration. Performing experiments to mimic conditions in industrial formaldehyde absorbers, Winkelman established an equilibrium constant  $K_h = \exp(3769/T - 5.494)$  in presence of water, which translates into 0.0787% unreacted formaldehyde at 25 deg. C.<sup>5</sup> At 50 deg. C, the unreacted formaldehyde is 0.2093%.

Commercial "formalin" is made by mixing 37% formaldehyde gas (by weight) with water. However, the equilibrium constant shows that the formaldehyde (mol. wt. 30) does not merely dissolve, but nearly all reacts with water to form methylene glycol (mol. wt. 48). A simple mass balance calculation shows that, after the reaction, the resulting solution is actually 59.2% by weight methylene glycol, and only 0.0466% formaldehyde at 25 deg. C ( $0.0787\% \times 59.2\% = 0.0466\%$ , or 466 ppm).

With these two pieces of information, we can correct the former, inaccurate, method of calculating formaldehyde levels in nail hardeners. Historically, the practice has been to simply multiply the formalin level by 37% and report that figure as "formaldehyde." To make a nail hardener nominally "1% formaldehyde" – a typical marketplace level – a formulator would add 2.703% formalin ( $2.703\% \times 37\% = 1\%$ ). But, mass balance shows that a product with 2.703% formalin, contains 1.60% methylene

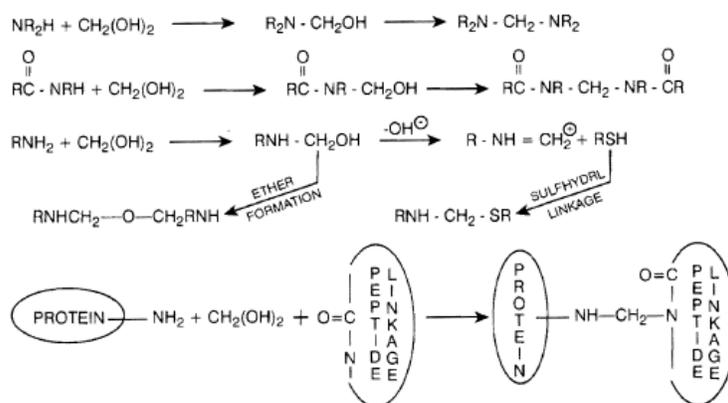
<sup>3</sup> Bieber, R. & Trumpler, G (1947). Angenaherte spektrographische Bestimmung der Hydratationsgleichgewichtskonstanten wässriger Formaldehydlosungen. *Helvetica Chimica Acta*, 30, 1860 – 1865; Iliceto, A. (1954). Sul sistema acqua-formaldeide. Nota VI. Equilibri della fase liquida e gassosa. *Gazzeta Chimica Italia*, 84, 536 – 522; Sutton, H.C. & Downes, T.M. (1972). Rate of Hydration of Formaldehyde in Aqueous Solution, *Journal of the Chemical Society, Chemical Communications*, 1 -2.

<sup>4</sup> Winkelman, J.G.M. & Beenackers, A.A..C.M. (2000). Correlations for the Density and Viscosity of Aqueous Formaldehyde Solutions, *Industrial Engineering Chemistry Research*, 39, 557 – 562.

<sup>5</sup> Winkelman, J.G.M., et al. (2002). Kinetics and Chemical Equilibrium of the Hydration of Formaldehyde, *Chemical Engineering Science*, 57, 4067 – 4076.

glycol ( $2.703\% \times 59.2\% = 1.60\%$ ), and from the equilibrium equation, we calculate that the 1.60% methylene glycol product actually contains only 12.6 ppm, or 0.00126% formaldehyde at 25 deg. C ( $0.0787\% \times 1.60\% = 0.00126\%$ ). **Summarizing, a nominally “1% formaldehyde” nail hardener is actually only 0.00126% (12.6 ppm) formaldehyde.** The traditional calculation yields a nearly 800-fold overstatement of the actual formaldehyde level.

Several mechanisms of methylene glycol fixation of surface nail protein are provided.<sup>6</sup> Methylene glycol is the reactive ingredient in nail hardeners as demonstrated by the reaction mechanisms shown below (R=nail surface proteins). These mechanisms explain why formalin is so effective at room temperature, even with levels of free formaldehyde existing in the ppm range. Free formaldehyde is unavoidable in formalin, in trace amounts only, according to Winkleman.



While we believe, and the data show, that nail hardeners are safe, the inaccurate nomenclature causes consumers and others to incorrectly believe that nail hardeners contain Formaldehyde and, therefore, present a risk to their health. We need only refer to IARC's controversial 2004 reclassification of Formaldehyde. While, wisely, Formaldehyde has not been reclassified under the EU Cosmetic Directive, or the Dangerous Substances Law by the European Chemicals Bureau, and, although nail hardeners containing so-called “Formaldehyde” continue to be permitted under EU law, controversy and confusion are still associated with the use of the term Formaldehyde on product labels.

For these reasons, the Nail Manufacturers Council requests that, in its deliberations and examinations, CIR take the opportunity to champion accurate terminology and the use of chemically accurate nomenclature by industry and governments. Consumers will follow.

We are working to eliminate nomenclature uses which perpetuate confusion, especially within our own industry. Old habits die hard!

<sup>6</sup> Bedino, J.H., (2003). Expanding Encyclopedia of Mortuary Practices, 649, 2620

As nail hardening products (nail strengthening products) do not have a history of causing adverse effects, are not heated and contain Methylene Glycol rather than formaldehyde, we submit that CIR conclude that no further restrictions need be placed on nail hardening products using Methylene Glycol as an ingredient within the ranges currently employed by the industry.

In about 1997, a law suit was commenced in California relating to Proposition 65 claiming exposure to formaldehyde and toluene in nail salons exceeded the “safe harbor” levels established by the State. To accumulate scientific data for the State and the Court to allow them to better address the issue of actual potential harm, Clayton Environmental Consultants, now part of Bureau Veritas, was commissioned to conduct a multi-year study of exposure. Rather than relying upon theoretical projections, this exposure was examined in actual nail salons in three geographical areas and spanning many seasons, at a cost of hundreds of thousands of dollars.

The result was reviewed by Jed Waldman, PhD, Chief of Indoor Air Quality Section of the California Department of Health Services, who was directly involved in the establishment of the testing protocols for toluene and formaldehyde, and he provided an Affidavit relating to these results as part of the Record in the litigation. The substance of the issue related to the manufacture and use of nail care products including base coats, color coats, top coats and nail strengtheners and whether health warnings were required for salon workers.

On behalf of the Attorney General of the State of California, Mr. Edward Weil, Deputy Attorney General, stated in a letter dated April 17, 2000<sup>7</sup> that “**the evidence is clear that exposures to consumers and salon customers from nail polish to toluene and formaldehyde do not pose a sufficient risk to require a warning, even under the strict standards imposed by Proposition 65**” (emphasis added). The summation of the study was published by McNary and Jackson in the peer reviewed journal *Inhalation Toxicology*, in 2007.<sup>8</sup>

Following the accumulation of scientific evidence and its presentation, a Judgment Pursuant to Stipulation was entered on or about August 4, 2000 finding that the ten subject nail manufacturing companies, based on their current formulations, were not under a duty to provide Proposition 65 warnings concerning formaldehyde to either salon employees or consumers.

To assist in better understanding the litigation relating to proposition 65, and its resolution, we are including the Clayton Study (complete with Appendices), the Waldman Affidavit, the California Attorney General’s letter (Weil letter) and the Judgment Pursuant to Stipulation on a CD along with copies of the other authorities relied upon in these submissions.

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<sup>7</sup> Letter on behalf of Bill Lockyer, Attorney General for the State of California, dated April 17, 2000, signed by Edward G. Weil, Deputy Attorney General

<sup>8</sup> J.E. McNary and E.M. Jackson. “Inhalation exposure to formaldehyde and toluene in the same occupational and consumer setting.” *Inhal Toxicol.* (2007); 19: 573–576

The following chart sets out the differences between Formaldehyde and Methylene Glycol:

<b>FORMALDEHYDE - anhydrous gas</b>	<b>METHYLENE GLYCOL - liquid</b>
CAS 50-00-0	CAS 463-57-0
EINECS 200-001-8	EINECS 207-339-5
Chemical Family – Aldehyde	Chemical Family - Alcohol (Glycol)
INCI Name – Formaldehyde	INCI Name – Methylene Glycol

We are copying the Personal Care Products Council in hopes they will correct the nomenclature found in their INCI Dictionary. Their monograph on Formaldehyde (id 1054) should be removed as this anhydrous gas is never used as a cosmetic ingredient. Methylene Glycol monograph id 23672 should be corrected to reflect the correct uses and other technical names such as methandiol (IUPAC) and formalin should be listed.

In hopes that it will assist you in your understanding of this very complex situation, we are attaching three Appendices: a Glossary; reproductions or excerpts from our citations and, as mentioned above, a CD containing the full text of the materials referred to in these submissions.

Please let us know if you have any questions or would like to discuss this matter further.

Very truly yours,




Eric S. Schwartz – [EricS@opi.com](mailto:EricS@opi.com)  
 Co-Chairs  
 Nail Manufacturers Council of the  
 Professional Beauty Association

Doug Schoon – [dschoon@cox.net](mailto:dschoon@cox.net)

Attachments:

- Appendix “A” - Glossary
- Appendix “B” - References
- Appendix “C” - Full text of References (CD format)

cc: John Bailey, PhD Personal Care Products Council, 1107 17<sup>th</sup> St. NW Suite 300, Washington, DC 20036-4702  
 Carol Eisenmann, PhD Personal Care Products Council. 1107 17<sup>th</sup> St. NW Suite 300, Washington, DC 20036-4702  
 NMC Members

## Appendix "A"

### **Formaldehyde (CAS 50-00-0/EINECS 200-001-8)**

Highly reactive anhydrous gas and simplest member of the aldehyde family of chemicals. Formaldehyde has a molecular formula of  $\text{CH}_2\text{O}$  and a molecular weight of  $30.01 \text{ g mol}^{-1}$ . Inherently unstable, but commercially available as an anhydrous gas.<sup>1</sup> INCI name "formaldehyde".

### **Methylene Glycol (CAS 463-57-0/EINECS 207-339-5)**

The simplest geminal diol (glycol) and a member of the alcohol family of chemicals (diol)<sup>2</sup>. Methylene glycol is a reaction product of formaldehyde and water, having a molecular formula of  $\text{CH}_2(\text{OH})_2$  and a molecular weight of  $48 \text{ g mol}^{-1}$ . Highly stable and commercially available as an aqueous solution stabilized with methanol to prevent polymerization. INCI name "methylene glycol" and IUPAC name of Methanediol.

### **Formalin (37%)**

A water-based solution typically containing 59% methylene glycol, 10% methanol and  $> 0.05\%$  free formaldehyde<sup>3</sup>. Formalin is made by reacting anhydrous formaldehyde gas with water to create the highly stable methylene glycol. Formalin is widely available as a stabilized aqueous solution. INCI name "formaldehyde".

### **Tosylamide/Formaldehyde Resin (TSFR)**

A high molecular weight polymer made from several reactants, including formaldehyde which is consumed in the reaction. Any leftover formaldehyde is hydrated to methylene glycol by the water molecules generated in the reaction. Hence the formaldehyde content of the resin is essentially nil.

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1. Scott Specialty Gases, 6141 Easton Rd., Plumsteadville, PA., 18949,

<http://www.scottecatalog.com/ScottGas.nsf/web/AppsFormaldehyde>

2. March, Jerry (1985), Advanced Organic Chemistry: Reaction, Mechanisms and Structure, 3rd ed., NY, Wiley, ISBN 0-471-85472-7

3. Winkelman J.G.M., et al. (2002) Kinetics and Chemical Equilibrium of the Hydration of Formaldehyde, Chemical Engineering Science **57**, 4067.

## Appendix “B”

### References cited:

2. Bedino, J.H., (2003). Expanding Encyclopedia of Mortuary Practices, 649, 2619  
The chemical commercially sold as “Formalin” is an aqueous solution of Methylene Glycol.
3. Winkelman, J.G.M. & Beenackers, A.A..C.M. (2000). Correlations for the Density and Viscosity of Aqueous Formaldehyde Solutions, Industrial Engineering Chemistry Research, 39, 557 – 562.  
Reviews the dehydration of methylene glycol to anhydrous formaldehyde gas using hydroxymethane sulphonate as the react to capture the formaldehyde. The work correlates with other publications at a temperature of 293°K ( 68°F, 20°C- room temperature)
4. Winkelman, J.G.M., et al. (2002). Kinetics and Chemical Equilibrium of the Hydration of Formaldehyde, Chemical Engineering Science, 57, 4067 – 4076.  
Reviews the kinetics and equilibrium of the reaction of water with formaldehyde gas from 20°C (68°F) to 60°C (140°F) at pH from 5 to 7.
5. Letter to David Steinberg from Lisa Halko dated May 5, 2008  
Reactions to nail hardeners as reported to the manufacturers and then sent to an independent law firm to comply results of actual safety reactions in the US.
6. Bedino, J.H., (2003). Expanding Encyclopedia of Mortuary Practices, 649, 2620
7. Letter on behalf of Bill Lockyer, Attorney General for the State of California, dated April 17, 2000, signed by Edward G. Weil, Deputy Attorney General
8. J.E. McNary and E.M. Jackson. “Inhalation exposure to formaldehyde and toluene in the same occupational and consumer setting.” Inhal Toxicol. (2007); 19: 573–576

# Greenberg Traurig

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May 5, 2008

VIA E-MAIL to davidpreserve@comcast.net

David C. Steinberg  
16 Mershon Lane  
Plainsboro, NJ 08536

Re: Formalin-Containing Nail-Care Products

Dear Mr. Steinberg:

This letter summarizes data collected from five U.S. companies whose businesses include making and selling nail-care products, such as nail hardeners, containing formalin (“formaldehyde”). At the request of the Nail Manufacturers Council of the Professional Beauty Association, data was collected confidentially from the five member businesses. To protect both competition and trade secrets, each company submitted its to Greenberg Traurig LLP only. No price or market data was collected from any company. Only aggregate data will be shared with member companies or disclosed to anyone else. Each company submitted only (1) a list of products containing formalin, (2) the units of each product sold in 2005, 2006, and 2007, (3) the milliliters of product in each unit, (4) the proportion of formalin in each product, and (5) the number of complaints received from consumers about adverse health reactions.

A total of 18 separate SKUs were reported, with a total of 7,640,225 units sold during the three calendar years 2005, 2006 and 2007. These units represent a total of 115,311,423 milliliters of formalin-containing product. Since the average consumer uses approximately 0.15 milliliters of product per application to 10 fingernails, this represents about 768 million potential applications. All submissions reflected formalin below 5%, as a 37% aqueous solution of formaldehyde. Only one company received one complaint from a consumer of any adverse health reaction –in this case, an accusation that the product irritated the skin. It is important to note that the particular product’s proportion of formalin was in the mid-range at just over 1%; products with more than twice the formalin received zero complaints.

We understand that COLIPA will present this report to the European Union’s Enterprise Directorate-General. I release this report to you for that sole purpose.

Yours truly,



Lisa L. Halko  
cc: Nail Manufacturers Council

- ALBANY
- AMSTERDAM
- ATLANTA
- BOCA RATON
- BOSTON
- BRUSSELS\*
- CHICAGO
- DALLAS
- DELAWARE
- DENVER
- FORT LAUDERDALE
- HOUSTON
- LAS VEGAS
- LONDON\*
- LOS ANGELES
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- WASHINGTON, D.C.
- WEST PALM BEACH
- ZURICH

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Expanding Encyclopedia of Mortuary Practices. Number 649, 2003. PP2614-2632  
Embalming Chemistry: Glutaraldehyde Versus Formaldehyde. James H. Bedino,

231. Angenaherte, spektrographische Bestimmung der Hydratation-gleichgewichtskonstanten  
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McNary JE, Jackson EM. Inhalation Exposure to Formaldehyde and Toluene in the Same Occupational  
and Consumer Setting. Inhalation Toxicology, 19:537-576, 2007.