AEROSOLS

Minutes

Report

Data

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Memorandum

To: CIR Expert Panel and Liaisons
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Subject: Inhalation Toxicity and Aerosols – Precedents
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At the September meeting, the Panel engaged in extensive discussions of the approach and presentation of their safety assessments of ingredients in cosmetic products that may be incidentally inhaled during use. Dr. Helga Rothe, Senior Scientist at the Procter and Gamble Darmstadt Innovation Center, described some of the inhalation exposure assessment modeling and measurement approaches used by industry, and detailed the particle-size distributions that can be expected from the use of some cosmetic spray products, especially pump and propellant hair and antiperspirant sprays. In addition, she briefly described some of the methods industry uses to ensure that cosmetic powders agglomerate, which minimizes potential exposures to respirable particles during product use.

The Panel discussed inhalation exposure issues throughout the meeting, including during the discussions of individual ingredients (i.e., alkyl PG sulfosuccinates, decyl glucosides, ethylhexylglycerin, pentaerythritol tetrates, and silylates). The relevant transcripts of the September meeting were excerpted, compiled, and presented in the attached minutes. The transcript excerpts from the discussions of individual ingredients were italicized and indented in the minutes to distinguish them from the transcript of Dr. Rothe’s presentation and excerpts from aerosols-specific discussions that occurred outside of the ingredient-specific discussions.

Over the course of the September meeting, the Panel clarified its overall approach to evaluating potential inhalation exposures to ingredients in products that may be aerosolized, especially when there are no useful inhalation toxicity studies for the ingredients. In addition, the Panel hammered out several templates or patterns for presenting the inhalation exposure issues and findings of the Panel, particularly in the Cosmetic Use and Discussion sections of safety assessments.

The background section of the Aerosols Precedents document has been extensively revised and elaborated to convey the Panel’s robust discussions during the September meeting. The document also presents the templates developed based on those discussions.

The Panel should review this latest draft of the Aerosols Precedents document to ensure that it addresses all of the pertinent issues clearly, completely, and accurately, based on the available information and the current state of the art. The task at this meeting is to finalize this document, so that it can be posted on the CIR website and linked to specific ingredient safety assessments when appropriate.
Introductory Session - 26 September 2011

Dr. ANDERSEN: … We've started over the last two or three meetings looking at both our boilerplate, our precedent setting, and we've devoted an awful lot of energy to focusing on the question of potential exposure to aerosol. And we're going to continue that discussion today. Hopefully, we'll make some ongoing progress.

I think it's important to notice that this is -- the whole topic has been fraught with a significant level of uncertainty. When we receive information that an ingredient is used in an aerosol, what we're really saying is potentially used in an aerosol because the category in which it's listed may include aerosol but whether or not it's actually used in an aerosol requires some more information. And the council through its surveys and the information that Carol has provided often is able to clarify that.

And we know at that point that it is either used in an aerosol or not used in an aerosol. But we don't always get the clarification. So we are stuck discussing aerosol without really knowing whether or not the particular chemical is used in a product that's going to be sprayed or not sprayed.

And then at the last meeting as we talked about silylates the question of particle size came up in the context of powders. And that added another layer of discussion, no pun intended. And I think it's an ongoing discussion but we have the benefit of some effort that's been taken. And I refer for the panel members.

We didn't include this in the -- in what was put online for the general public because we're not allowed to send out publications to everyone in the universe but all the panel members got the mini review published in Tox Letters on Special Aspect of Cosmetic Spray Safety Evaluations: Principles on Inhalation Risk Assessment. And I'm very happy that we have this morning with us Dr. Helga Rothe, and she's going to talk about inhalation exposure assessments. And we'll know more at the end of this than we knew at the beginning.

Dr. Rothe. We're connected so I think we're all set to go.

Dr. ROTHE: Can you hear me? I'll try to stay here. So good morning, everybody. I would like to thank you, the expert panel, to give me the opportunity to talk to you today about the Special Aspect of Cosmetic Spray Safety Evaluation.

The cosmetic industry over the past years has developed prediction models for the best estimate of inhalation exposure assessment by combining simulated computer modeling as well as actual measurements from each product and with market experience. This impact is driven by the toxicological profile of each individual ingredient, and I would like to talk today about -- oops, sorry that I included the agenda -- about typical products and ingredients, general considerations for exposure assessment, impact of particle size, and exposure assessment methods. And here I will focus on modeling, as well as measurements with a few examples. I was also asked to talk about, or more or less start a discussion about, special aspects of powders in decorative cosmetics. And here I would like to introduce some strategies, how industry is preventing airborne particles.

So when we think about cosmetic products which are sprayed, we all know that they are a combination and composed out of active ingredients, how we call them. These are the polymers in the hairsprays or the antiperspirant active in the [APDO; Antiperspirant/Deodorant]…, but also a lot of solvents like ethanol, water, oils, or whatever, and also some fine fragrances or perfumes to mask the smell of the product.

We have to distinguish between two main product types. These are aerosol and the trigger pump sprays. In the aerosol, we have additionally the propellant gas phase and this is packed in a pressure resistant can. Both of the different product types, the aerosol and the trigger pump sprays, are equipped with a product-specific pump unit and nozzle and this will generate the airborne fractions.

So the term "aerosol" is also used sometimes for other products, like mousses and other two-chamber systems. But when the nozzle is very, very different here, so what will come out of the can is not an aerosol-borne particle or droplet; it's really more a compact thing so there is no airborne fraction from that.
So when we do an exposure assessment, first of all, you all know the target of such a spray product is not to generate something in the air; it's really to target the scalp or the skin or the hair. So therefore, for the risk assessment here for this portion, we have to assess it similarly to the conventional cosmetics. But we do have the airborne fraction; so therefore, additional exposure of the emulation has to be taken into account.

As you all know, the respiratory tract can serve as a portal of entry for systemic exposure, like the vapors or gases, but also as a target organ. And here we have especially particles and fibers.

So what are the specific considerations for safety assessments of sprays? So as I said, we have from the (inaudible) spray …products and additional inhalation exposure, we have to assess the deposited portion on the scalp in the same way as we do it usually for cosmetics. For the total systemic exposure, it's important to know that we have to sum here the portion which is coming from the deposition to the skin but also from the inhalation route. And it's important to know that the appropriate inhalation toxicity assessment is depending on the knowledge of the quantity and composition of the ingredients as well as from the exposure pattern of the finer products.

So that means what about the particle size distribution here? So when we look to the construction of the respiratory tract, we divided in three main regions. That's a nasopharyngeal region, the tracheobronchial region, and the pulmonary region. The construction looks like a tree and you have the brighter lumen in the tracheobronchial region and the smaller ones in the pulmonary region. But that also explains why the particle size by itself dictates how deep a particle is going into the lung. So what we know is that in the nasopharyngeal region we have particles which are larger, 50 micron, which can deposit there by impaction or diffusion. In the tracheobronchial area we have deposition of particles between 10-50 microns, and this is by impaction, sedimentation, or by diffusion. The clearance effect here is the sneezing, blowing, and the coughing, but also via the mucous (inaudible) [mucociliary elevator]. In contrast to that we have in the pulmonary region also what we call the respirable fraction. That means particles below 10 microns can go there, but the clearance effect here is very different. So we have on one side the (inaudible) that it goes into the intestinal area but we have also the phagocytosis by macrophages which is limited. Therefore, we have here -- and I will come to that later -- what we call the overload effect by the lung or the deep lung.

So, as I said, the impact of the particle size -- so particle size is very important. The particle size distribution is an important parameter of central relevance in the exposure assessment for the spray products. The particle size distribution depends on a number of factors. It's not only the formula compositions, so that means how much solvent you have. Which is your solvent? Is it more evaporating? Less evaporating? Is it more oils? It's also the pump unit by itself, so it's also driven by the technical equipment of the pump unit and the spray, which is individually. So that means every time when we see a reformulation of the given spray product, we generate a new particle size distribution pattern if we see a modification of active ingredients, solvents, or propellant, but also when we have a change in the can size or in the pump unit, that means the nozzle, which will generate the airborne fractions.

So one important aspect on the respirable particles is that we have particles that are hardly soluble ingredients and these are mainly the polymers we have in the hairsprays. These are non-absorbable and therefore, we might get local effects, especially the fraction below 10 microns will deposit in the deeper lung. Because we have the limited clearance effect by the macrophages here, it will come to a chronic or might come to a chronic inflammation here.

So what we have in Europe in several countries and also under REACH is a threshold which is taking this into account and this threshold is at the moment with one microgram per cubic centimeter and this is coming from the occupational use for dust and so therefore it's not a daily dose exposure, it's the exposure for eight hours, five times per week, and compared to a cosmetic spray product it's independent -- if it is an [APDO] or hairspray or whatever, this is a very conservative one.

So how do we do an exposure assessment?

We have the French methods here. First of all, very simple is that you model it. You can do a simple model, what we call the one box model. This is assuming that the whole formulation is sprayed in a specific volume. More complex models are what we call the two box models. Here we assume that you have an initial phase the formulation sprayed in a very small cloud around your face or your body and then in a longer phase you have the
exposure or the distribution of the formulation in a whole room so that therefore, it's a first box and the second box. And we have a lot of models around which are publicly available.

First of all, the ConsExpo model and then we have also the IKW model which we published earlier this model and which is a very simple one and you can use it by using a calculator by yourself. Very easy to do. The ConsExpo model has a lot of other factors in like air velocity, air exchange rate in the room, etcetera. And you can use it as a refinement as well when the IKW doesn't work. You can do also some measurements and here we have to distinguish between different methods. And it really depends on what you would like to do and then you decide which methods you are using.

So first of all, we have the point of expulsion. That's an acute exposure. So that's a laser diffraction element. You can simulate the consumer exposure by... time of flight spectrometers, and this you can do for intended and forcible use scenarios and you detect the amount of the particle size distribution and concentration of the product in the breathing zone. And you can do an ambient sampling by cascade impaction to measure the residual air quality. So one example for the modeling. The key advantage here is that it is conservative as long as you use conservative defaults here, and these are published at different places. So when you think about the amounts (inaudible), you will find there are a lot of studies out about how much of the product is really used per usage and also the frequency, and you will find also the defaults about room size, etcetera, in the literature. So one example is a consumer applies the product. It might be an [APDO] product or it might be also hairspray in a small bathroom of cubic meters as instructed. The aerosol will distribute into the initial two minutes first application around the consumer's head -- whoops, sorry. This goes one way -- around the consumer's head in a cloud of one to two cubic meters. The consumer will stay there for a total of 20 minutes, so the remaining 18 minutes, and during this time you have the distribution in this larger room. So the total amount of spray product will distribute homogeneously in the entire room, bathroom, and 25 percent of the inhaled ingredients will be exhaled. And this number was published by the European Commission in 1998.

So when we think about the particle size which is then inhaled, we use for these assumptions here the measurement by the point of expulsion. That means the real particle size distribution pattern which comes out of the can at a distance of about 10 to 20 centimeters. You see here the numbers for pump spray and an aerosol spray, and what you can see here, the red line is the 10 micrometers and the 100 micrometers is the green line.

And the mean distribution of a pump spray is larger -- it depends really from product to product. It's always in the range between 60 and 80 [µm] I would say in the mean. The aerosol spray is a little bit smaller. It depends also again from product to product and for the hairsprays it's usually around 30, 40, 50, 25 [µm], something in this range.

But the important point here is the particle size, which is below 10 microns. And you can see for the pump spray it's really below one percent. It's really extremely small but you still see some of it. For an aerosol spray it's also very, very small. It's usually in the range of two percent, one percent, two and a half percent. It's always small but I would say never above five percent. So nothing I have ever seen is above five percent but I wouldn't exclude that there is sometimes something.

So another option is the simulated use studies to do a measurement in the breathing zone. So the key is always how much is really in the breathing zone. So the model has really taken this into account by just saying how much of the formulation in which volume or cloud this -- sorry -- the formulation is distributed and then you have the breathing concentration, but you can also ... simulate ... this [using] a measurement device in the breathing area. You spray it in use conditions. That means you use realistic amounts for the product and you measure it in the breathing zone. And you do it usually for 10 minutes or until it goes below the limit of detection. And usually you are using here the time of flight spectrometer.

The output you get here is the respirable dose and the inhalable dose, but as I said at the beginning, all the different kinds of measurements, the different methods, have advantages and disadvantages and have their limitations here. So you see here the outcome of such a study and don't get confused here. The scale on the X-axis is going only to 20 microns, so it's not really the whole distribution pattern. So when you remember what I showed you at the beginning, the distribution pattern which was going up to 150 microns, you see here only the very, very small portion which is below 20 microns. So that's important to note.
And also, when you look at the Y-axis, so you have here an [APDO] aerosol on the left hand side and a pump hairspray on the right hand side, but the scale is more than one magnitude of order lower for the pump spray. So but what you can measure here is not the percentage of mass volume, so the particle size distribution. What you measure here is really the particle number or the particle mass in... [µg/m³]. And what you can see here is that the particle number by itself is extremely low in all -- in both cases. And depending on the chemical you are looking to, then the particle mass is showing a peak.

So the output of the simulated use studies is that you have to correct to emulate human breathing conditions. You can do it by 10 liters per minute for a resting rate, which is a number published by the EPA. You can also use 20 liters per minute, which is the EPA number and relates to light exercises.

The data output is the aerosol concentration in the breathing zone, the particle size, particle mass, (inaudible) discharge rate, and inhalable and respirable dose. And as I said for the inhalable dose, it's just the fraction below 10 microns. It's not the whole spectrum; that's important to know. And it's also important to know that it is not comparable to the point of expulsion because you don't see the mass volume here.

So a very important finding is also when you compare the real time measurements with the models that when you look to the drop out with time in the breathing zone, you will see here -- do you see the cursor? So you have here the portion of the total exposure on the Y-axis, the time in minutes on the X-axis, and you see the dropout is by 35 percent in the first minute and it's starting with 60 percent in the second minute, and that's an example from the [APDO]. So that really tells you when we use the modeling with two minutes for the initial phase, that this is a very conservative number. What this also shows you is that you have drop-off of 90 percent after six minutes and 95 percent after eight minutes.

So when we model something and we use 18 minutes for the remaining time and we use the distribution in the room, this is again very conservative because we can demonstrate here by these measurements in the breathing zone that we have a drop-off of 95 percent of everything within eight minutes and it's going below the limit of detection in most cases within 10 minutes.

Dr. BELSITO: On that slide can you define what you mean by inhalable and respirable? Respirable less than 10 microns and inhalable, greater?

Dr. ROTHE: Yeah, that's 10 to 20. So that's only 10 to 20 because we don't measure the huge portion which is, I would say, 98 percent. This is not detectible by this method so that is one of the limitations.

Dr. BELSITO: So you're seeing no difference between particles less than 10 microns and those between 10 and 20?

Dr. ROTHE: Right. So, and when we go back here you could see that it is going up for the aerosol and for the pump hairsprays you have the peak around 10. And then it's going up and then it's going up again later, what you have seen on the other side before where I showed the complete pattern.

So to summarize that, beyond the situation of the application site safety assessment for cosmetic products requires consideration of potential exposure to the inhaled portions of the products. Qualitative and quantitative exposure assessment is key for importance of this part of the evaluation. The particle size distribution in liquid or particulate aerosol will determine penetration depth of the material into the respiratory tract. The local effects of inert particles smaller than 10 micrometers by deposition in the deeper lung. Particle size distribution is product specific.

As I said, it's not only the composition of the formulation; it's also the technical equipment of the pump unit. And you can do an exposure assessment by modeling (inaudible) assumptions or by these real-time measurements which also have some limitations.

So... I was asked also to give... an introduction to the discussion you will have here with PCPC members about special aspects of powders and decorative cosmetics. I will focus here only a very few strategies or on very few things, that means on strategies, how we prevent airborne particles in powders.
So, first of all, this is driven by the ingredients in the powder formulations. So we have what we call the de-dusting effects. That means we use binding material to agglomerate particles. So when you look how we generate powder formulations, so you have a mill and a blender and you put first your dry ingredients in, you mix it, and then you spray oils or the melted (inaudible), you mix it, and then you get an agglomeration of small dry ingredients. We also have hydroscopic ingredients in and this will increase the particle size through absorption of water. So the production of the powder formulation as I said before is very important and is also controlling more or less the particle size. That's on the mill conditions. And it's also by mixing the dry and the wax oil phase you get a relative high cohesivity.

I can speak here only for P&G. I don't know what the exact numbers are for the other companies here but we usually have a cohesivity between 60- Of cohesivity on a scale of 100. And we need this to ensure that the pressed powder survives the shipping, otherwise they will break into pieces. And the loose powders, like for eye shadows have to stick to the applicator, otherwise they would fall down.

Measuring the particle size from final products is a little bit more difficult and mostly does not reflect the actual size of the powders under use conditions because you always have to disperse the powder in a solvent or you disperse it with pressure and then the agglomerated particles would break. There are also some methods out and under development that you do it by photography, but honestly, I'm not familiar how good these really reflect the actual particle size. What you can really see is the particle shape but this is nothing P&G has a lot of experience with.

So it's mainly really driven by the cohesivity. Thank you.

Dr. BERGFELD: Any questions? Will you be available to the teams today?

Dr. ROTHE: I have to leave in one hour.

Dr. MARKS: So considering the safety of these products, you've shown us it's much more complex than just the particle size since with pumps [and] aerosols it depends on the technical aspects of how you deliver it and with powders on solvent… Do you have any ideas in which we could word our safety assessment to take this in effect? If we said just to be non-respirable, that isn't quite enough, I don't think, but have you thought about that?

Dr. ROTHE: I cannot talk about how you do it here in the U.S. because I come from Europe and therefore I am more in the discussion with the SCCS. So what we are doing is really that we measure all the time the particle size, especially for the hairsprays so we have it under control. And as I said during my talk we really do with every change where we think it's a real change to the composition of the formulation, we measure it again to keep it controlled at just extremely low and then we do the safety assessment as I said by these different approaches.

Dr. MARKS: So if we said it was formulated in a way that's not respirable, that would take care of particle size but then how would you deal with the mechanics of the delivery system?

Dr. ANSELL: Well, we've given some thought to some boilerplate which would reflect that, suggesting language perhaps along the line of potential for in-use exposure to respirable particles is minimized to reflect that what we're interested in is not the abstract particles but rather the human safety through actual exposure.

Dr. MARKS: You've interpreted where I was going, Jay, quite well.

Dr. BOYER: And just a quick question. You mentioned -- your talk was focused basically on hairsprays, at least the first part of your talk. Can you tell us a little bit more about other types of sprays -- deodorant sprays in particular -- where it seems that the particle sizes generated seem to be lower, particularly in the propellant sprays, propellant deodorant sprays. Can you tell the panel -- give them a good idea of what the difference is between -- comparing hairsprays to deodorant sprays, for example?
Dr. ROTHE: So we do not do a real difference here in the risk assessment. So we always measure the particle size, and you have seen there also one example for the real-time measurement. That means a portion below 20 micron. And you have seen there also that the number is extremely low. It's one order of magnitude higher regarding the number of particles, but it's still extremely low.

Dr. BOYER: Okay. So for the deodorant products, the fraction -- respirable fraction is still a very, very small fraction of the entire particle size distribution?

Dr. ROTHE: Yes. Yes. Because also the distance to the face is much larger. And you spray it not in the direction to your face. You spray it below it. So it is just a very small portion which is really reaching the breathing zone.

Dr. BELSITO: One of the issues that we were discussing at the last meeting was that you could have various chemicals that are put into aerosolized forms that would in that form not be respirable but would get down, say, into the tracheobronchial tree and then release a gas or something that then moves down into the alveoli. Your comments on that? Does that happen? Is it realistic that we should be thinking along those lines, or would something like that not be probable?

Dr. ROTHE: There was a publication from earlier this year. It was -- the last author was from RIFM, Dr. Singal, and they published the example of formaldehyde and they modeled that. And what they could show is that because it's a reactive compound it's reacting very fast with the tissue. So it's very unlikely that it goes really deep into the lungs. And you also have to take into account when you look to the small, let's call it channels, so I would assume when you inhale something that every particle gets a higher speed and then the density is increasing. So therefore, I would also assume that some of the particles would again agglomerate in the lung. I think it's difficult to test but that is what I would assume just from the physical behavior of the particles because they tend to agglomerate when the density is high enough.

Dr. BOYER: Also, based on what I've read, particles below about 40 microns or so, whatever is volatile, even water in those particles will tend to evaporate very, very quickly within a fraction of a second. So that whatever is volatile in those particles as they come off of the nozzle is likely to evaporate before any of those particles are inhaled or respired.

Dr. ROTHE: Yep.

Dr. ANDERSEN: I think there is an opportunity for an ongoing panel discussion of the aerosol boilerplate at this point in time if you're interested. Otherwise, you have several ingredient reports on the agenda for which the question of use in aerosol products is relevant and you can discuss it ad nauseam at that point. But there's an ongoing opportunity now if there are other issues. Jay, I think I captured the language that you said, but if you could repeat it to make sure I got it right as a potential alternative to how we might describe this.

Dr. ANSELL: Yeah. The example I used was trying to capture the idea that... it's not the particles that sold. It's not the particles as they appear in the can, but what we're really concerned about is the human exposure. And so the language that I was proposing is safe when used, etcetera, when the potential for in-use exposure to respirable particles is minimized. That's perhaps a starting point.

Dr. BERGFELD: Would James care to make comment now?

Dr. MARKS: Yeah, I'd like to ask one more question. It would appear from your presentation, the endpoint of non-respirable is really not scientifically correct. It's really to, as you said, minimize and presumably if there was a concern, a margin of safety would be generated. But to say that if a particle -- you showed the tail off and it was maybe a one percent exposure to the alveoli with pump and aerosol two to three percent. Just saying non-respirable wouldn't be scientifically correct. Am I interpreting that correct?

Dr. ANSELL: Well, that's what... this language was trying to capture. And it's kind of modeled on when we talk about incidentals. Is that what we -- we never say zero. That the incidentals have to be reduced to zero. We use language like minimized consistent with GMPs. I didn't see how to work GMPs into this language but that is the idea -- is that industry recognizes that these are aerosols. The potential for respirable fraction is there but that it's
controlled through the selection of solvents' formulations, cans, the little spray nozzles, all of that goes into determining what the potential for human exposure is, and as we've heard in today's talk, industry is aware of that, monitors that, and tries to reduce that potential to minimize the respirable fractions.

Dr. BERGFELD: Could I ask a question? In the past we have eliminated or eliminated the need to have aerosol testing or inhalation testing if the particle size was appropriate. It sounds to me that we would have to incorporate other testing in animals. For instance, lung biopsies to see what has occurred. There must be -- we cannot just dismiss it on particle size. What is –

Dr. ANDERSEN: I think, if I get the thrust of what Dr. Rothe presented this morning, it's embodied in those distribution profiles that you saw in which for pumps it's very unlikely that there's anything less than 10, not that much less than 20. For aerosol it's a bit more problematic because the tail is pretty continuous but it's a small portion. Now the focus of the rest of her presentation was on that small portion. So we're already small. Now it's going to get even smaller in terms of what's going to get where. And I think there's no question that that is dependent on formulation. And if we don't acknowledge that we're missing the boat. It's dependent on the physical characteristics. If it's an aerosol, what's the can pressure, what's the nozzle diameter and shape? So there's lots of factors that are going to influence it. What we've been doing is simply asserting that there aren't going to be anything -- any particles less than 10, so no mas. We've basically given our blessing to that whole category. And what's on the table now is, I think, a bit more reasonable look at it.

Yeah, you can produce particles that are going to get into the front end of the respiratory system and maybe even all the way down, but the goal, which is attainable, is minimizing the end-use exposure to such particles. I think that shifts the monkey from us simply asserting that there's no problem to a responsibility on the part of industry to look at each formulation, match the formulation with the pressure with the nozzle to minimize exposure to respirable particles. And the use circumstances are a little different for deodorants versus hairsprays. We can acknowledge all of that. And I think we're painting for the scientific community a very accurate picture of our understanding of the whole thing.

Dr. BERGFELD: Don.

Dr. BELSITO: I would agree that...we're painting a clear picture of our understanding of particle size and the fact that some things may be respirable and clearance rates over time of those things that are less than 10 and 10-20. But I guess even if we say that in-use exposure to respirable particles is minimized, they're potentially respirable and we have absolutely no inhalation toxicity. How do we know that minimal exposure doesn't pose a risk? ...before we were told there's no exposure. There's a difference between zero and minimal, and so that creates really issues, at least in my mind, as to if we have no inhalation toxicity at all and there's going to be minimal exposure, how can you ask me as a dermatologist in particular to sign off and say, that's fine… if I had minimal exposure to a bullet wound in my aorta I'd be dead.

Dr. LIEBLER: So that was a very helpful talk. Thank you. And I have a question. One of the things that you said is that you had never -- if I remember correctly, when you were talking about the distributions for aerosol particles below about 10 microns, I think you said something like seldom ever see more than five percent in this part of the distribution tale. So this actually comes right from Don's question. We're probably going to find ourselves in some cases, in situations where we need to have some type of number that provides sort of an upper limit of the amount of the particle size distribution that will be respirable or that will be able to penetrate the lung parenchyma. Are there other sources that we could cite that represent a relatively broad range of aerosol -- hairsprays, deodorants, sunscreens, whatever -- that would provide us some numbers to use as reference for this? ...and that's one question. And second, how much variability is there in your experience in this distribution tail for aerosolized particles?

Dr. ROTHE: So I think there was no reference out there because industry is not collecting the numbers to publish it so far. So maybe this is something we should think about. The number of five percent is just my experience from the hairsprays. Insofar as I know that for [APDO]s it's not very different but it might be different. So, well, maybe we should really collect the numbers.

What you can do is you run it through the models and then do kind of a back calculation to come back with a number which is really acceptable but that really also depends on the tox profile of the ingredients, which makes it
more complicated. And that's the main reason why industry is doing the risk assessment for each of the products and we are measuring the particle size all the time for each individual product.

Dr. SHANK: I almost say this reluctantly but every time we talk about aerosol on the panel we seem to have comfort if the particle size is large and it just deposits in the nasal sinuses. I would like to remind the panel that the evidence is increasing that particles that lodge in the nasal sinus can be transported by the olfactory nerve directly into the brain. Most of this work has been done with particles that contain metals -- aluminum, iron, thallium, other compounds -- but it's now been shown in humans. The Japanese have just published a couple of studies where particles that lodge in the nasal sinuses are transported along the olfactory nerve directly into the brain. So I don't think we have to mention this in every report but we shouldn't have total comfort in the fact that if it's in the nasal sinuses it doesn't matter. Sorry to bring that up.

Dr. ANSELL: Well, we're aware of those papers and they tend to be very small particles at very high concentrations instilled. And I don't think we're arguing that the safety need not be assessed. I think what we've been talking about is whether inhalation is a relevant route of exposure and to what extent we need to pull that out. I think if we find that there's a significant -- if it is a relevant route of exposure, then we would need to assess the impact on the lung. And I think what we're arguing in these data is that based on the practice, industry practice, inhalation to insoluble particles is not a significant route of exposure in comparison to the topical route.

Dr. LIEBLER: So big particles are nothing to sneeze at? (Laughter)

Dr. ANSELL: Au contraire. That's exactly what we do, is we sneeze them.

Dr. BERGFELD: I wonder, Jay, if you would elucidate when you say relative. I heard, one, soluble versus insoluble. Would there be another definition?

Dr. ANSELL: We were talking about gases.

Dr. BERGFELD: And gases?

Dr. ANSELL: …the… issue of volatiles is entirely different than particles. Particles are…physical states. They settle… the exposure is very time limited because they do settle. One of the problems we often have is you go into a salon and you have this odor associated with it so the presumption is that there's high exposure. But it's not being exposed to the particles, it's the fragrances. And so when we talk about the concern about deposition in the lung and then the gases being off gas, I think the amount that would come from that route of exposure versus the fact that they're volatilized and will be consistently distributed through the room is a whole different model. Fortunately, we have the REXPAM Panel to worry about fragrances. I think the same issue is with deodorants. Deodorants by definition, at least in the U.S., do not contain the antiperspirant particles, the polymers, that they are fragranced materials. And so we need to be very, very precise in the questions we ask because water soluble lipophilic gases or either respiratory rate dependent in terms of exposure, insoluble particles are distributed based on the rate of circulation.

And all of these need to be integrated into the assessment. But the question we asked was I think much narrower which is the inhalation exposure to particulates when used in aerosol like hairsprays a significant route of exposure? And we say because of the particle size it isn't. In fact, most of it would be deposited and then swallowed, so oral studies would be far more relevant to their assessment than lung effects.

Dr. BERGFELD: Well, I think that the teams are going to have to wrestle with this today as to what they want to do. Hopefully, some resolution can be made but maybe not. This is a big subject and may entail a lot of study and added studies to what we've been looking at. Rachel?

Ms. WEINTRAUB: I just had a question to Jay. I mean, your previous statement rested on the assumption that fragrances' particle size is sort of insignificant. I mean, I'm not sure. I just sort of drew this distinction. Are you saying that because something is a fragrance its particle size is so small it's not a concern? Or were you more saying that fragrances fall under the jurisdiction of another body? Because in terms of your example of a salon and the
fragrances, you seem to imply, and maybe I'm just misunderstanding which is why I'd like a clarification, that the fragrances and the odor wouldn't be a route of potential exposure.

Dr. ANSELL: No, I think what I was trying to say was that when one looks at the potential for exposure, the modeling of particles -- solid, insoluble particles -- is really very, very different than vapors, gases, smoke, the whole spectrum of things that we see, fogs. All of those will impact the deposition. And so I think when we -- the common sense approach, which is often misleading, is that if we can smell it there must be particle exposure. No, there's not particle exposure; there's exposure to the part you're smelling. And that they're different assessments, not that one can be ignored or were not.

Dr. BERGFELD: Don.

Dr. BELSITO: I guess I would agree with you that the bulk of exposure to any given chemical we're looking at will be on the scan or will be oral compared to what will actually reach the alveoli. However, if the toxic endpoint is the alveoli, what actually reaches the alveoli may be… critical because what gets absorbed or what doesn't get absorbed through the skin or absorbed through the GI tract is going to be less. So the… greatest exposure could be the inhaled exposure to the end organ of concern. That's… in the absence of having any data on inhalation, at least for me, how do I know that that end organ is or is not a concern?

Dr. HILL: And I think what's troubling me at the moment and we need to think about it is because we review ingredients and not formulations, when we're talking about alveolar exposure and if we're talking about a 2.5 percent of a particle distribution and we may have the toxicology impacted by the presence of other things besides the ingredient we're considering, that's an issue that we do talk about in some things but I think we need to consider maybe more greatly than we have in the past if we know that maybe 2.5 percent of the particles -- I said particles -- perhaps 2.5 percent of droplets could get into the alveoli and potentially expose us there.

Dr. ANSELL: …I certainly agree with Wilma. I think that the issue of inhalation toxicity and the assessment of the safety of products which can be inhaled is going to require more than a couple minutes around the table. As informative as Dr. Rothe’s presentation was, there’s a whole lot of history that goes into this. And I would argue that we do know quite a bit about the behavior of particles, insoluble particles in the lung, and what are the drivers of toxicity? And the concern about particle overload and the issues of transport alone from inhalation into the brain. There's a lot of stuff out there and we would not argue that they're not worth assessing.

But I think we've gone way beyond the question that we were trying to address, which is do we get exposed? Is there a significant potential for exposure? And we continue to argue that inhalation is not a significant -- not that it doesn't occur, not that we don't need to look at it, but… we could throw in ocular exposure and conduct extensive assessments along those lines. So I think it's something we need to continue to talk about over a series of meetings.

Dr. BERGFELD: Don.

Dr. BELSITO: Well, …I think we usually do look at ocular, I guess my point is up until this meeting my assumption, what I was led to believe was that we had no concern because there was virtually no exposure. And now I'm being told, well, we really have no concern because there's minimal exposure but, oh, there is exposure. So I sit on this panel and my name goes out on these documents and I'm a dermatologist. I don't know about Tom and Ron and Kurt and Paul and Dan, I'm not comfortable signing off on that. So if my other colleagues aren't, then I think we probably need on the panel someone with a good degree of respiratory expertise because we're going to be struggling with this every time. …literally for almost every ingredient there's going to be some inhalation exposure. And while as a dermatologist I can say, yeah, chemical X, we only have sensitization data to two percent, but it's been around for 100 years and I've never seen anything happen. I'm comfortable doing that. That's my area of expertise. I'm not comfortable signing off on anything that's potentially respirable, and I don't know about my colleagues.

Dr. LIEBELER: So I think the fundamental difference as a result of our discussion today is we used to think of particle sizes as being a number and we could make a yes-no decision based on the number. And now we realize that particle sizes are distributions and there's essentially with each device there's a probability that a certain percentage of the product and the ingredients will reach the lung -- either the upper airways or the parenchyma and
produce potential toxic effects. So I think that's going to be a case by case consideration, depending on the toxicology of the compounds and we will never be able to really have a real handle on the distributions and all the products because as Ron said earlier, we really talking about ingredients as opposed to the products, but we have to anticipate the likely exposures in a product as it would be encountered.

I think... I would agree that having some respiratory tox expertise on the panel would be valuable and barring that, at least in the near term, I would recommend that we consider perhaps inviting a speaker or two in the next meeting or two to talk with us about aspects of respiratory toxicology that we think might be important to our decision process.

Dr. BERGFELD: That's a good idea. I'd like to add as a dermatologist that we're very much aware that mucosal membranes absorb everything faster. And it isn't a closed system, the respiratory system. If it's absorbed, it can be absorbed and taken anywhere. So Alan?

Dr. ANDERSEN: Message received. The transition that I think we're seeing is from the aerosol boilerplate being a decision-making process. It is maybe better relegated to an informational thing to acknowledge that distribution is what we're seeing as opposed to a sharp cutoff. It's certainly information that can and should be part of any safety assessment that involves the ingredient in a product that's aerosolized or sprayed or yada yada yada. But the thought process for safety determination can -- must go a bit farther than that. I think that's a good bit of progress.

The boilerplate has some limited functions here, and what you do in terms of the conclusion about safety is going to be a case by case determination. Inhalation toxicity data could be hugely valuable in making those decisions. In many cases we have those data so that it may not be as much of a leap as we might think. But where we don't it deserves some careful consideration.

Dr. BELSITO: Just one last, I guess, question to our speaker because it's going to come up later in our determinations, we had gone insufficient on a silylate because under certain shear forces it had particle sizes of less than 10 microns, which would be respirable and it was creating granulomas in mice. So we have a toxicologic endpoint but it's been argued that the silylate particles will agglomerate quite quickly, that those shear forces that cause those particles to be less than 10 micrometers is not something you would see in a cosmetic product. Are you knowledgeable about the silylates and is that a reasonable argument in your -- from your understanding?

Dr. ROTHE: No, I'm not familiar with that but I think as soon as you can derive a no effect level or a no effect concentration you have a threshold and then you need to know how much is really in the breathing zone. What is the particle size, distribution, and concentration in the breathing zone?

Dr. BELSITO: So you would need those numbers before you would be able to come up with some level of comfort as to safety?

Dr. ROTHE: That is what Industry is doing at the moment.

Dr. BELSITO: Thank you.

Dr. ANDERSEN: I think that ends the discussion with respect to inhalation exposure. The aerosol discussion. Dr. Rothe, thank you.

**Excerpts from Dr. Marks’ Breakout Session - 26 September 2011**

**From the Silylates Discussion**

Dr. MARKS: ...We’ll move on to the silylates... So, in June, the Panel issued a tentative safety assessment that concluded these ingredients are "safe as used" in leave-on and rinse-off products. But there is "insufficient data to support the safety of ingredients in products that might be inhaled." And then there was a suggestion that maybe we change that last to "when formulated to be non-respirable." So we put we could remove the "insufficient," just as long as we put "when formulated to be non-respirable." So -- comments? Do you like the conclusion as it reads now? Do you want to...put the onus, as we've done in
the past with some ingredients -- just as we just did earlier today, "formulated to be non-irritating"? Do we use the same reasoning to say "formulated to be non-respirable"?

Dr. BERGFELD: Well, what does that mean? ...nothing gets into the nasal passage at all? Or it doesn't get into the pulmonary?

Dr. MARKS: Carol.

Dr. EISENMANN: Well, have you looked at the additional data that's in this report? Because there are a couple of other studies that identify, I know, effect level of I think it's 10. So, to me, there's enough inhalation, that really the conclusion should be -- however you worded the conclusion for the silica report. Because this is really not that much different from silica. The amorphous silica, the other half of the information that's in this report. It was provided in the supplement. Lillian highlighted the additional studies in here that will need to be added to this report.

Ms. BECKER: The Wave 2 information.

Dr. SHANK: And that was on silica? Or one of these ingredients.

Dr. EISENMANN: It's on these ingredients. There's more information in this report on these ingredients that has yet to be put into the report.

Dr. MARKS: Was this the memorandum, Lillian, from you, dated September 16, 2011?

Ms. BECKER: Yes.

Dr. MARKS: So it starts out, "Subject: Wave 2 Data for the Draft Final Safety Assessment of Silylates."

Ms. BECKER: Yes.

Dr. MARKS: So the average particle... size is 5 to 15 µm. So it's below 10.

Ms. BECKER: Yes. But there's other information, saying that, especially from SASSI, that the particles aggregate and are larger ... and that for the testing that they've had ... to shear the particles down smaller to get them into the lungs of the test animals, and that they are not the sizes that are actually used in the cosmetics...

Dr. MARKS: ...SASSI's August 31, 2011, letter... says, “Based on information that has been made available, we consider as not relevant the studies referenced by the expert panel in forming their conclusion that 'inhalation data show that the particles do reach the lungs in rats and induce granuloma formation.’ There is also necrosis or atrophy of the olfactory epithelium observed. This... brings back what you said this morning, Ron, about absorption by the olfactory nerve in the upper respiratory tract. "There are currently no data available on which to base a finding of safe for use in products which may be inhaled”...

Dr. SHANK: Well, I agree with the conclusion "not safe if they're inhaled." It's just how do we state that? And I was waiting until we'd resolved the aerosol issue, which we certainly have not. So -- what we're going to do with that statement here is quite a problem. What do we mean by "not inhaled"? Are you going to give a particle size? And actually, I really objected, just relying on particle size, because what's really important is aerodynamic diameter, which is more than particle size. Harder, much harder to... –

Dr. BERGFELD: (Inaudible) distribution?

Dr. SHANK: That's the particle size, the shape, how it flows through air at various densities and temperatures. It's complex -- and usually not measured except by very high-powered inhalation toxicology facilities. So if it gets into the respiratory system, adverse health effects can occur. So right now, I would
have to say it shouldn’t be used in products that can be aerosolized. Or we have to come up with a boilerplate to handle aerosol. Because this is a problem repeating over and over. Yeah, repeating over and over again. Sorry.

Dr. BERGFELD: So, can I ask you a question? Then your comment on this morning’s presentation by Proctor and Gamble, that deal with size and distribution and vehicle -- you’re differing because they didn’t take up aerodynamics.

Dr. SHANK: Right. Most studies do not. They measure particle size. That’s a relatively simple measurement. But when you look at the distribution within the entire respiratory system — and from the mouth to the alveolus, it’s aerodynamic diameter, which the inhalation toxicologists use.

Dr. BOYER: Yes. And, actually, it is aerodynamic diameter that she was talking about this morning. So if she’s talking about particle size distributions, and median particle sizes... that is the aerodynamic diameter that they were measuring and reporting.

Dr. SHANK: ...what I saw on her slides were micrometers... And that could be just particle size, not necessarily –

Dr. BOYER: Well, actually, the aerodynamic diameter is expressed in microns -- micrometers. But it does take into account the other parameters that you’ve mentioned, including the density... So it’s basically reporting the effective size of the particle, based on a unit density. And it’s the settling -- it’s related to the settling velocity that an ideal particle would exhibit.

Dr. SHANK: Okay. Thank you. I didn't understand she was really talking about effective... dynamic diameter.

Dr. BOYER: Yes, I think it was understood that she was talking about aerodynamic diameter.

Dr. BERGFELD: By whom? (Laughter.)

Dr. BOYER: By her.

Dr. SHANK: Jim returns just in time. The presentation on aerosol -- particles, et cetera -- when the speaker talked about particle size, what, in fact, her data was aerodynamic diameter, which is the better measure. So if I've criticized that, I withdraw that, because I did not understand that. We're still left with the problem, what do we mean by "inhaled," respired. “And until we can decide that, I would have to say, for this particular group of compounds, not safe in products that can be aerosolized –

Dr. SLAGA: Yeah.

Dr. SHANK: -- or we have to come up with a way to handle this. Because it is coming up all the time.

Dr. EISENMANN: So you don't think this can be an overload problem? Because... these studies were really using high concentrations. ...one of them is like 35 mg/m3. And... like the respirable dust TLV is 5. And there's another monkey study in here of one of those compounds at 10 that didn't show any effects. So -- I just think this is likely an overload problem, rather than anything else.

Dr. SHANK: I understand that. The problem is we don't know what the consumer is being exposed to in these pumps, and –

Dr. EISENMANN: Well, if you remember the data from her, ... in general, ... it was very low, in terms of milligrams per meter-cubed. And then this is a small percentage of what would be in the product.

Dr. SHANK: The distribution went low -- down to 5 percent below 10 µm.
Dr. EISENMANN: But even then –

Dr. SHANK: Percent of what?

Dr. EISENMANN: -- the slides that focused on the level that's below 20, those were fairly low concentrations also.

Dr. BOYER: Yes. I think the likelihood of overload, as she expressed it, is very, very small. It's negligible, at least in terms of the use of spray products, in a human...

Dr. BERGFELD: You're agreeing it's overload, though? That the interpretation is correct? It's overload in the study?

Dr. BOYER: In an animal study it's overload that they largely describe.

Dr. MARKS: So, translating that -- Ivan, instead of "overload." you would say the dose exposed to these animals was much greater than would be in the present use and exposure in cosmetics.

Dr. BOYER: Absolutely. The dose of respirable particles was much, much greater in those studies. And you get –

Dr. MARKS: But I guess there, we don't have a NOEL, do we? So you'd say, okay, a high dose you get granulomas, but at what doses don't you get a granuloma. Isn't that –

Dr. BOYER: At high dose and at -- well, again, it's high dose of respirable particles. So it's that –

Dr. EISENMANN: Although there's not a lot of details, there are two additional studies that are not in here yet, that are at lower doses, that show a NOEL. One's a monkey study. But it's not a lot of details. But it's in there.

Dr. MARKS: So that, to me, that would be very reassuring.

Dr. EISENMANN: So, ...I'd be fine if you want to wait until you actually get a chance to look more carefully at the information. So if you haven't had time, that's appropriate, too. And I also -- if you wanted to read this study, this is the study where -- the, where the granulomas were. They compare it to quartz. I think it's... an interesting, useful study to look at. And you might want to actually read it. They do several different types of silica quartz, one of the surface-treated, and then a couple of the silica that you've already –

Dr. MARKS: So were these studies sent out in Wave 2, or are these new studies?

Dr. EISENMANN: Part of this document was sent out in Wave 2.

Ms. BECKER: I just handed the copy to Dr. Slaga that I brought with me. But the summaries were all sent to you in Wave 2.

Dr. MARKS: This boilerplate is the last agenda item on my list. So I don't know if we want to try and finish with this ingredient, or try and arrive at some conclusion with a boilerplate? Because can we -- Ron, do we need to change, since we even are questioning what does "inhaled" mean, it seems like the conclusion is going to have to be changed anyway in this, since we say that there's insufficient data to support the safety of these ingredients and products that might be inhaled. So we have some uncertainty what we mean by "inhaled." And then you're talking about we do have a NOEL, if it does reach the alveoli, that it doesn't cause toxic effects. Am I interpreting your comments correctly, Carol?

Dr. EISENMANN: That's how I see it, yes.
Dr. BOYER: And there is a fairly precise definition of what it means to be “inhaled.” Any particle under about 100 µm or so is considered “inhaled,” and that just means it's going to get into the upper respiratory tract. When you're below 10 µm or so, that's when you're talking about “respirable” particles.

Dr. MARKS: And that's what I think we've generally used as a cutoff, in terms of its inhalation safety.

Dr. BOYER: Right.

Dr. MARKS: Whereas actually this morning's presentation, it's not only -- as Ron said, the aerodynamics of these particles, but it's also the device it's put in. So how do you want to proceed? Shall we handle this ingredient? And then, Ivan, you’re here. Can you stay with us? We have two other ingredients before we get to the boilerplate. Or shall we again go out of order and do the boilerplate right after the ingredient? Lillian, do you have a comment?

Ms. BECKER: I'm thinking do it at the same time.

Dr. SHANK: Okay, the use -- it says it's used "in powders." What kind of "powders"? The presentation we had today was basically hair sprays. Okay? What I'm having difficulty with is extrapolating from the presentation on hair sprays to all aerosol powders and sprays, airborne things. I got a feeling that there was quite a bit of variation between products and dispensers. And to use the hair spray data to extrapolate to what it says in here, just "powders", is causing me some concern.

Dr. BOYER: And actually, toward the end of her presentation, she did discuss powders, and gave several reasons why she didn't think that powders would generally be of concern with respect to particle sizes. They're basically formulated to be applied to the skin. They typically agglomerate, so they form fairly large particles in product. They're applied directly to the skin...

Dr. SHANK: ...then I think we need those data in the report...

Dr. MARKS: So, let's get back to silylates. How do you want to proceed? Do you like that conclusion? Or do we need to change it? And if we change it, obviously then it's going to be a re-revised tentative safety assessment.

Dr. SHANK: Well, there are two conclusions. So, it's not final, anyway. We have a choice of two conclusions here, do we not? Isn't that this report?

Dr. MARKS: No, it said concluded "safe in leave-on and rinse-off." But there is "insufficient data to support the safety of the ingredients in products that might be inhaled." And that's what we've been talking about, is the potential of inhaling it, or aerosol powders, or sprays.

Dr. SHANK: ...and then there's an alternate conclusion, too...

Ms. BECKER: -- the alternate conclusion is what we proposed after we got more information. The first one, not in italics, is what you all decided at the last Panel meeting. And if you stick with that, we're going final. If you want to change it or adjust it as the italics one, the one we're suggesting, then it's coming back in December.

Dr. MARKS: Yes, that's -- thank you, Lillian, that's the point I was making... because it would be a revised conclusion. Therefore it would have to be a revised tentative. Do you like the alternative conclusion better?

Dr. SHANK: Not anymore. I did. But I think that the non-italicized conclusion, the one we came up with last time, is more appropriate.

Dr. MARKS: And, Ivan, when we use the word "inhaled," is that generally known? We could obviously put what that means in the discussion, or the summary, so that we could define what "inhaled" is, if anybody had issues about that.
Dr. BOYER: That's well defined in inhalation toxicology.

Dr. MARKS: Right. That's what I figured.

Dr. BOYER: "Inhaled" versus "respired."

Dr. MARKS: So, do you like the conclusion as it is? Cross out the alternate? I agree... we talked about the alternate conclusion emphasizes particle size, which is only part of it, and would be really misleading, I think, to the reader... So, so far, we don't have to re-revise. Ron Hill, you wanted to say something.

Dr. HILL: Well, I think you addressed -- because I was going to make a comment about that potential alternative conclusion, which was the particle size as supplied to formulators are not respirable. In practicality, that's impossible, I think.

Dr. MARKS: Yes. Okay.

Dr. HILL: It's what fraction is respirable of the total that's there.

Dr. MARKS: So can we move forward with a final safety assessment with the silylates, with the conclusion as stated on Panel Book page 33? And the main thing there is, of course, the inhalation -- that we have an "insufficient data." Ron, Tom, Ron? Move forward with that conclusion?

Dr. LORETZ: Just one quick comment? So what data, then, are you looking for?

Dr. MARKS: I think it's probably that NOEL effect...

Dr. SHANK: Oh, in our discussion we ask for a 13- week inhalation toxicity study. Now you say these are available. Actually, carcinogenicity studies -- yes? ...

Dr. SHANK: Inhalation carcinogenicity studies?

Dr. EISENMANN: There's a one-year monkey study.

Dr. SHANK: Okay. But the other --

Dr. EISENMANN: And I think there's a rat study that might be long-term... she provided it and highlighted it. It would be nice if we would take a little --

Dr. SHANK: Well, I looked at the PDF that came in Wave 2... That's only half of the problem. The other half of the problem is what is the consumer exposed to?

Dr. EISENMANN: Well --

Dr. SHANK: And I don't think we have a handle on that.

Dr. EISENMANN: Well, but -- yeah, it's going to be very low... this is an overload effect. So overload, generally -- so they're putting so much more that the lungs cannot remove the particles.

Dr. SHANK: That's not a proven mechanism.

Dr. EISENMANN: We'll have to provide some more information on that, then.

Dr. MARKS: I don't hear compelling evidence for the team to not issue the final safety assessment, with this conclusion. Is that correct? Tom? Ron?
Dr. SLAGA: Yes.

Dr. SHANK: But we'll have to come up with what is insufficient.

Dr. MARKS: And you summarize that.

Dr. SHANK: Well, we have the studies that came in Wave 2. That's half of the problem -- a very important part. We still have a problem of what is "inhaled" or "respired."

Dr. HILL: Would there be a way to word it such that the maximum respirable...load was somehow specified? I'm not suggesting we do that tomorrow, I'm just -- if we're talking about an overload, that means it's what amounts to a threshold effect.

Dr. SHANK: If you have a no-effect-level after a year, in the monkey, inhalation, you could use that as your standard, if you will, for respirable products. I'm still concerned, is what is actually being delivered to the consumer.

Dr. HILL: Yes, and I think then maybe we'd be in a situation where you build in a margin of safety and make some conservative estimates based on -- but again,... now we're down to products again, as opposed to ingredients. That's the problem. And I don't see the way out -- easily.

Dr. MARKS: ...Well, this should make, probably, for an interesting discussion tomorrow. I will go ahead and certainly propose our team's conclusion, which is the one in the book. And then, in terms of the identification in the discussion, what is insufficient, and that is what is inhaled or respired by the consumer...

Dr. BERGFELD: Could I just ask a question? Ron, define for me "inhaled" versus "respiratory"?

Dr. SHANK: "Inhaled" focuses on the entire respiratory tract, so that includes what is deposited in the nasal sinus, the nasal pharynx. "Respirable" is deeper lung –

Dr. BERGFELD: Okay.

Dr. SHANK: -- below the trachea.

Dr. BERGFELD: Thank you...

**From the Pentaerythritol Esters Discussion**

Dr. BERGFELD: Could I ask a question about the inhalation? It says it's used in aerosol. And we have stated in our discussion that toxicity is not available in aerosol. But particle size are not respirable. Are we going to attack that? Do we say "inhaled"?

Ms. WEINTRAUB: Doesn't it also say "typically"?

Dr. BERGFELD: What's that?

Ms. WEINTRAUB: Doesn't it also say "typically," in the discussion? And that.. bothered me. It's an unusual word for us, I think, in a discussion.

Dr. SHANK: Well, the aerosol boilerplate has to go in the conclusion. So that means it's going to have to go out -- it's going to go out again anyway.

Dr. BERGFELD: What is "the aerosol boilerplate"? I'm not sure I know what it is today.

Dr. MARKS: Well, we're going to find out -- maybe.
Dr. BERGFELD: But that sentence would change.

Dr. MARKS: Yes. I think, Lillian, when this -- this probably shouldn't go immediately out as revised until we are sure we know what the boilerplate is. That's how I would handle it. Because you raise a good question, Rachel. And so that's important. That's how I would handle it. We're going to send it out as a revised, anyway, because we removed one of the ingredients from the conclusion that was sent out for comment. And before it would be sent out again, let's make sure of two things: we have the use and concentration, Carol, that you said you were going to give us. And then the second thing is the inhaled/respiratory boilerplate. Yep. Any other comments? Do you think that's going to -- and then we'll change the wording appropriately at that point. Because we know from this morning's presentation, just particle size may not be totally -- obviously, if it's huge, I don't care what they put it in, you probably can't get it down into the alveoli. But we will deal with that on the revised --

Dr. SHANK: How about rather than concentrating on particle size, a whole other take, and just say if it's used in aerosolized products, it should not cause irritation to the nasal pharynx or lung?

Dr. SLAGA: I actually would like --

Dr. MARKS: Write that down, Ron. Because we're going to get to the boilerplate shortly. So please write that down... Or remember it ... so tomorrow I'm going to move that we issue a revised safety assessment, and the reason is because that one of the ingredients which was sent out was deleted, or removed. But we also want to await the use concentration and the inhalation boilerplate.

**Aerosol Inhalation Boilerplate Discussion**

Dr. MARKS: …I think the last is the aerosol inhalation boilerplate… yes, we talked about it with the silylates. And then we decided to defer. So the boilerplate is in Buff Book -- no, do we have our boilerplate?

Dr. BERGFELD: No, we don't…

Dr. ANDERSEN: It was inserted into the book…

Dr. MARKS: …"Inhalation Toxicity and Aerosol-Precedents," dated September 1st… So one potential was, "Safe when formulated to be non-respirable"

Dr. ANDERSEN: Well, that sounded like a great idea when we were putting all of this together. But I'm not sure, after this morning's presentation, that it's reasonable to say "when formulated to be non-respirable." The data that -- how they're presented show a distribution with tails. And the tail goes into the respirable region. Now, is most of it higher than 10 microns? Yeah. But if that tail, let's say, for aerosol, is 5 percent of the total, … 5 percent is not chopped liver. It's enough that were the chemical to be of toxicologic concern for the lungs, would we problematic. So, in a sense, the answer to the question may not be resolved. And I think the package that Ivan put together had already hinted at this. That now that you start to see that particle size is below 10 microns is not impossible, and maybe not even rare, but regularly occurring. And the only question is at what percentage.

Now, you're asking a different question. Is what we know about the toxicity of this chemical, coupled with a low exposure to the lungs -- no question about that, this isn't all getting in -- does that make it okay? And in the case in which there are no inhalation tox data, what is the Panel's comfort level, and how do we express that? And I think… there's a lot of material that we have put together, but my take on the, if you will, the nervousness, and the reason that Ivan has been pushing to get this back on the table, is that our hand-waving that none of this is going to get in the lungs just ain't so.

And now that we're there, where do we go? And I'm not sure I have infinite wisdom to suggest. But I think that our previous comfort level of ensuring everybody on earth that cosmetic aerosol aren't inhaled isn't any longer a good approach. And I don't know that putting the monkey on the industry's back solves anything, either. I think we still
have a need to look at Chemical X and think, "What are we concerned about"? And if the absence of inhalation tox data bothers us, then we probably better ask for it.

Dr. SLAGA: Well, that deals with going down to the lung. But I think we always forget that nasal, pharyngeal and other parts of the respiratory tract are important, too. And… if there's any irritation, or any long-term problems, you develop some bad effects from it. …Well, formaldehyde.

Dr. SHANK: I would like to suggest considering a different approach, where we don't have inhalation toxicity data for an ingredient, use a phrase such as, "Use in products formulated to be non-irritating to the respiratory tract." If there is a specific toxic effect that we're interested in, then we would ask for the toxicity data, the inhalation toxicity data. But if it's a more general problem, with no toxicity data, what do we do? I would suggest using the very sensitive indicator in the respiratory tract, irritation, and just say, "When formulated to be non-irritating to the respiratory tract." That gets rid of all of this particle size difficulty.

Dr. ANDERSEN: But it acknowledges, in a sense, that the amount that is going to come in is not huge… even if particle size is subtracted, a spray directed at the foot is going to have a smaller chance of being inhaled than a spray directed at the hair. And deodorants directed at underarms are somewhere in between. So the acceptance that not all of what's sprayed is going to go in, and where there are inhalation tox data, we use them. Where there aren't we go in this direction. This is kind of the biological version of my non-respirable language.

Dr. HILL: Let me ask the hypothetical question, then. You're proposing that irritation would be the sentry. Let's suppose we had a compound that was solid in formulation, and there were at least a modest number of particles -- let's say 2 percent of the distribution -- that could be truly respirable. In other words, they're making it down into alveoli. And then they dissolve there. And then they're biotransformed by P-450s that are enriched in lungs and nowhere else in the body, of which there are some. How are we going to capture, if we use irritation as the sentry, that that could occur?

Dr. SHANK: You ask for inhalation toxicology data on that individual ingredient.

Dr. HILL: Because we'd have information from that ingredient that that would be a concern.

Dr. SHANK: That's right.

Dr. HILL: But how would we know it was a concern, hypothetically, if it was something that was occurring because of biotransformation of enzymes that are there in the human lungs and nowhere else? In other words, by it being bioactivated by metabolism, that we aren't picking up in other studies. I think we would pick them up, probably, in our standard mutagenesis profile. I'm just –

Dr. BOYER: Well, a similar point, respirable particles, as we said, are going to end up in the alveoli. They're more likely, much more likely, to be absorbed there. The residence time in the alveoli is going to be much longer than it would be if the particle was trapped in the mucociliary escalator. So if you're concerned about potential systemic toxicity, that would be also a consideration.

Dr. HILL: I'm talking not about systemic toxicity, I'm talking about toxicities expressed in the cells of the lungs… And the alveoli.

Dr. MARKS: I guess, Ron, then you would be to the point where you would have to have every ingredient have an inhalation testing. Because there's no way, what we're trying -- obviously, what we're crafting with this, is if there's no alerts from the chemical structure, and no metabolites that you're concerned about, then presumably we're not going to be worrying if it's non-irritable. So I would probably handle it that way. Ron Shank, I wonder whether I might put one more caveat in here, after what we heard this morning -- "Formulated and delivered in a way to be non-irritating to the respiratory tract." Because she emphasized, this morning, that the delivery methodology was quite important also, besides the formulation.

Dr. SHANK: Excellent. Definitely add that.
Dr. MARKS: Any other comments?

Dr. BERGFELD: I think we shouldn't forget the particle size. But I love this.

Dr. MARKS: Well, that would be -- obviously, in the boilerplate, we're going to have robust discussion of all this background information, I would think. And then we always refer to -- we could do just the same as the hair-dye epidemiology, as we use our boilerplate. And then we have a link to what the full discussion would be. That's probably how I would suggest handling it. I don't think we want to have a full discussion on every ingredient that we just went -- that we go through.

Dr. ANDERSEN: Well, I think part of my wish-list -- although I don't know that it's possible to provide it -- is that all uncertainty about use of Chemical X in products be eliminated. So if it's in the category of deodorant, that you actually know whether it's a spray or not. Right now, the VCRP doesn't give us those data. And the Council survey often elicits that information. And that's great. But I don't think I can expect that we're going to know every single time. Or if it's in a suntan preparation, whether that's one of the new spray ones or not.

So I think there are always going to be gaps. We can strive to gather as much information as possible. We've seen hair color sprays a couple of times in reports in this thing. And I'm not sure we really know what to expect from hair color sprays, compared to the two data sets that Dr. Rothe showed us this morning. And I think I'd like to. But we don't right now have those data.

And as we move to the future, it would be nice to have a better characterization of those particle sizes, so that we would actually have a better handle on thinking through what are we going to rely on for that particular aerosol exposure.

Dr. BERGFELD: Can that come in the chemical composition description that we get in table form? Particle size could be added to that?

Dr. ANDERSEN: Right now, I don't think there is a source. And Linda and Carol can jump in to help -- but I don't think there is a Dr. Duke that you can go to to find out what the particle sizes are for each and every spray product that's on the market. I think there's limited --

Dr. BERGFELD: Well, that would include talcs? A lot of products could emanate some kind of particle. There is a report in the medical literature about women who have applied lotions to their skin who, on autopsy, show lotion in their lung. So particle size could be a very interesting notation on all ingredients…

Dr. ANDERSEN: I think that -- well, I have to leave that to Carol and Linda to think about. I don't think we find any such data when we're searching for information. There are data available for categories of things that we know are sprayed, like aerosol that we saw the data presented today. Or pump sprays. We have information there. But those are generic, in a sense of this is a category. And you start changing the nozzle, you change the pressure of the aerosol, and as we heard this morning, things can change. So I think that would have to be in what we would ask suppliers, or formulators, to actually provide. I don't think you can expect it to be anywhere.

Dr. MARKS: And I guess, to me, what I heard this morning, even particle size, it's just a direction. So besides in the aerosol and the pump has a significant impact of how much is delivered, she stated in the powders it's the solvent and the pressure in which the powder is delivered that can also affect how much is respirable. So, I think the statement "formulated and delivered" covers both the formulation, in terms of, say, size, solvents, et cetera, and the way it's delivered would cover the physical aspects of the pump, the aerosol, or whatever the pressured delivery device is.

Dr. ANDERSEN: Our discussion, when it focuses on particle size, is talking droplet technology. When we go to describe a particle of a silylate, it ain't a sphere. And I'm not sure that any of that information directly applies. So we have separate problems ahead of us as we try to talk about the places that particles get that aren't droplets.

Dr. BOYER: And on that note, I think we need to be careful that when we're talking about particle sizes that we're actually -- we mean aerodynamic diameter…
**Excerpts from Dr. Belsito’s Breakout Session - 26 September 2011 Panel Meeting**

**From the Ethylhexylglycerin Discussion**

Dr. BELSITO: Anything else on the priority list? ...So next on our list is ethylhexylglycerin, Green Book, AKA alkyl glyceryl ethers. And I guess before we start this, the question is did we need to go to the respiratory boilerplate or -- because this has hairspray and other spray uses. And if you look on page 12 of the Panel Book, or page 6 of this report, the last paragraph of acute oral toxicity we actually have a risk characterization for aerosolized for ethylhexylglycerin, and it seemed to be okay at 0.6 percent. So we could perhaps get around the respiratory discussion for this ingredient by saying safe as used in products that could be inhaled at levels of 0.6 percent or lower.

But if we want to go safe as used, I think then we need to probably first do a respiratory discussion. So, I throw that out for comments from my teammates. Because other than the fact that it's a penetration enhancer, I didn't make much of the chimyl alcohol effects on UV-induced tanning. If anything, it was a sunscreen. Big deal. So, ...the rest of the uses, short of the aerosolized uses, are safe as used as far as I'm concerned. But how do we deal with the aerosol? Limit it to 0.6? Or have the aerosol boilerplate discussion now?

Dr. SNYDER: I anticipate that the aerosol boilerplate discussion is probably going to reside somewhere along the lines of it's going to be the total data set, and what kind of things do we need to make us comfortable for safety. And I think this type of information is stuff that certainly makes me feel comfortable without having inhalation data or other specific data. We should have some information regarding the potential effects -- the potential for inhalation.

Dr. KLAASSEN: The whole topic of ventilation is, I think, definitely chemical by chemical... the one issue is, is there going to be significant more chemical getting into the systemic circulation if there's also inhalation? So that's one question. The other question, is it likely that this chemical has both respiratory toxicity -- that is, does it produce toxicity to the lung and respiratory tract? And so I think... for each chemical as we go through the books we need to... look at these two things. And so it's really not anything all that different or unique.

I think as far as the increase in the amount... of the chemical that's going to be absorbed is probably going to be relatively small if we're talking about 1 to 5 percent at maximum getting down to the alveoli to be absorbed. I think a more significant question is how many of these chemicals are probably toxic to the respiratory system. And we have... from the other routes of administration we can get a clue to the overall toxicity. And we got to just look at each chemical one by one by one, and I don't think we can make any general statement that's -- like we thought we could do before.

Dr. LIEBLER: So I completely agree with everything you just said, Curt. I think you laid out the right issues to consider. The overall toxicology by multiple doses, are there red flags that would make us worry about toxicity? I do think the extra absorption by respiratory route is probably going to be minimal, except in perhaps certain unique cases. And then the question is, as a respiratory toxicity specifically or reason to suspect that, or any evidence in the animal data or non-human data. And if we don't have something like that to go on and we have a reason to have a concern or red flag, then I think we can flag it for insufficient. In this case where we have this risk characterization, I don't know if that's the same thing as a risk assessment. But it would suggest to me that at least up to 0.6 percent we're okay with this one.

Dr. BELSITO: So, do we limit it to 0.6 percent? Or, ...if you go to the tables -- so we have in an underarm deodorant, which we just learned if it were a spray could have even smaller respirable particles, it's up to 2 percent into the inhalation sprays, which I assume represents that underarm deodorant, 2 percent.

Dr. LIEBLER: Right.

Dr. BELSITO: So if we say safe as used, we're saying it's safe as used up to 2 percent in a hairspray, and
then we have that data. And the other thing with that data is, all they have...[is] an acute inhalation
toxicity. And so I don't really understand how they did that risk characterization.

Mr. JOHNSON: Dr. Belsito, also I'd like to call the team's attention to CIR Panel Book page 65, whereby there is a request to delete that risk characterization from the report. The last page of the -- yeah.

Dr. BELSITO: So, they -- we're being asked to risk characterization as an acute mortality study should never be considered sufficient to assess repeated consumer exposures. That was my point. I don't understand how they calculated risk assessment from an acute exposure... my point is that someone please tell me that they are absolutely comfortable making these assessments on respiratory effects on drugs that I have no understanding of....this is not my area of expertise and my name is on these reports. And I'm very uncomfortable signing off on things that we now know can reach the alveoli, and will probably be -- 95 percent will be cleared and however many minutes we're shown today, but they get down there. And we have no data on what happens when they get down there... So if we don't have that expertise, then we need the data. ...I don't know what you guys do...

Dr. LIEBLER: We have no data. In this case we really have -- the only data we have are -- looks like a relatively high exposure to ethylhexylglycerin... And then below it is the short paragraph that refers to the risk characterization. Other than that, we really have no data.

Dr. BELSITO: ... you guys know I'm a dermatologist... if it's metal toxicity, ... I know -- Curt knows everything in the world about metal toxicity. I'm not sure what his knowledge is on lung toxicity of every chemical that we're going to be seeing. So... that's what makes me uncomfortable after hearing this data this morning.

Dr. LIEBLER: As toxicologists, I think probably I could speak for Curt as well, we are familiar with certain classes of chemicals that have a tendency to produce lung toxicity. This is -- does not appear to be one of them. It doesn't ring a bell with me in that respect. That's not to say that we have data.

Dr. BELSITO: No, but you have knowledge.

Dr. LIEBLER: Yeah.

Dr. BELSITO: That's what I'm asking. I'm asking that, ...up until now.... as you feel out your panel members you get to know what their expertise is. I've never had to feel you out for your expertise in respiratory issues because it was always sort of a non-issue because we assumed they weren't respirable. So, I'm... relying on you guys...when it comes to respiratory toxicities.

Dr. ANSELL: Let me note that it's not clear that that underarm deodorant is actually an aerosol.

Dr. BELSITO: No, it's not clear.

Dr. ANSELL: Yeah. And that's one of the problems we have with some of the new reports. But look at the doses in those acute studies ... they were taken up to nuisance dust levels ... they're whopping grade doses. So..., while a risk assessment based on a single study is not relevant ...we should get some sense of the difference between the potential exposure 0.6 or at ... a fraction of a percent which may be respirable, and doses which were artificially designed to be wholly respirable at concentrations up to 5 milligrams per liter. Not micrograms, but milligrams.

Dr. LIEBLER: Right. So, I would say these data aren't relevant to our consideration.

Dr. ANSELL: Right. And all they should --

Dr. LIEBLER: That's why I say we have no data.

Dr. ANSELL: Well, all we saw was irritation.
Dr. LIEBLER: Right.

Dr. ANSELL: At these enormously high levels. So, ...they weren't full clinical workups, but acute data, acute studies don't really get to that. ...I think the acute irritation which was observed can be linked to the concentrations and there was no other systemic toxicity seen in any of the oral studies where there was systemic exposure. So while there isn't a full workup, I think... we can address many of Curt's key points.

Dr. SNYDER: From my perspective... I looked at the total data set... if it's a relatively low toxicity, both oral and other route and the total data set, I don't even get a certain comfort level of whether or not I can suspect there will be any -- certainly inhalation and systemic exposure or effects. But the bigger issue becomes regarding whether it be localized inhalation. But again, as Dan already stated, that there are only a handful of chemicals that are known to have direct localized effects on the respiratory system. And so knowing that knowledge we have, and if we're suspicious or suspect, I think we would then raise a flag or raise an issue.

...so I have a certain comfort level based on the systemic toxicity and what's happening. And... I think that for whatever reason, the particle sizes indicated now shouldn't be the driving factor in determining exclusively toxicity, but it is a factor -- one of the factors. And so if we do have particle size data and we do have concentration of use data in formulations, I think we take the total body set of data together to reach a reasonable conclusion.

Dr. LIEBLER: Well said. I agree with that completely. And for that reason, I was safe as used on these.

Dr. BELSITO: Okay.

Dr. KLAASSEN: I would, too.

Dr. BELSITO: Good, ...So, safe as used

**From the Alky PG Sulfosuccinates Discussion**

Dr. BELSITO: ...so what are we doing with respiratory here? ...

Dr. ANDERSEN: Do we actually know that it's used in aerosols?

Dr. KLAASSEN: I don't think so.

Dr. LIEBLER: Two percent in incidental inhalation sprays, table 3. That's for both -- well, trisodium succinate just went away, but trisodium laureth sulfosuccinate –

Dr. BELSITO: Is used in hair color sprays... And effects on the lungs that may be induced by aerosolized products... and we go on to particle diameters which we learned today are not true. So, we need to change that. So, the third paragraph on Panel Book page 9 is the issue. Then, since we don't have the discussion, it'll need to be carried out into the discussion as well...

Dr. LIEBLER: This gets to my question after the presentations this morning about how variable are the distribution of particle sizes, and it sounds like there's some variability but what I was trying to get at is, will it be consistently true that 5 percent or less of the particles are under 10 microns?

Dr. ANDERSEN: Yes.

Dr. LIEBLER: If that's consistently true, then we don't need to completely change our approach to this, but we need to recalibrate our statement because essentially what we're saying is, in practice, aerosols should have at least 99 percent of their particle diameters of a 10 to 110 micron range. So, the reality is, aerosols have approximately percent of their particle diameters in the -- or, yeah, percent, in that range, instead of
99 percent.

Dr. ANDERSEN: And the word "should" is almost misleading there. It sounds like we're instructing that that's to be the case when, in fact, what we're trying to say is there data that say --

Dr. LIEBLER: So, you could --

Dr. ANDERSEN: -- 95 percent?

Dr. LIEBLER: -- delete "should" and practice aerosols have at least -- and that's why I asked about what we could cite.

Dr. KLAASSEN: Yeah, and we could say -- well, according -- well, (inaudible) [she] said from her experience...

Dr. ANDERSEN: Two to 3 is normal, never over 5 percent, in her experience, was what we had today.

Dr. KLAASSEN: But she said she didn't have a manuscript that she could cite.

Dr. LIEBLER: Right. Yeah.

Dr. SNYDER: But she said the pump spray is less than 1 percent, for aerosol sprays 1 to 2 percent.

Dr. KLAASSEN: Yeah, but it could go up, maybe as high as 5, she said, once. That was the worst number she gave.

Dr. SNYDER: Was for hairspray, then she qualified it.

Dr. BOYER: And I think -- that's specific for hairspray, and there is some --

Dr. BELSITO: No, it was underarm deodorant sprays --

Dr. BOYER: Deodorants --

Dr. BELSITO: -- were the ones that were more likely to have the smaller --

Dr. BOYER: -- the smaller particles, right.

Dr. BELSITO: Right.

Dr. KLAASSEN: Why is that?

Dr. BOYER: Well, actually we've got a document that describes the modeling approach, the mathematic modeling approach that our speaker this morning was talking about, and the Germans did some studies, it was fairly limited, but they chose three hairsprays, they chose three deodorant sprays, and they did the particle measurements, particle size measurements, and they characterized the distributions and they used those values as actually fairly conservative estimates of those particle size distributions as defaults in their modeling. And when you do that, the hairsprays pretty much are -- a very large fraction, she said 95 percent, probably more like 99 percent, are above 10 microns.

Dr. KLAASSEN: Right.

Dr. BOYER: But for the deodorants look at that default distribution and the median is right at 10 microns. So, if you believe that, without knowing just how conservative they're being in generating those distributions, then you could have as much as 50 percent of the deodorant spray down below that size particle.
Dr. LIEBLER: But Ivan, you said that they only looked at a few products?

Dr. BOYER: They only looked at a very few.

Dr. LIEBLER: So, I think if we had -- we don't know if that observation for the underarm spray particle distribution is more of a chance finding... it could always be a chance finding.

Dr. BELSITO: Could be, but -- it certainly makes sense... if you look at what is in a hairspray, ...it's going to be copolymers and acrylates and plasticizers. If you look at what is going to be in a deodorant, not an antiperspirant, which is also more common in Europe. Americans tend to use deodorants -- or antiperspirants, Europeans use deodorants. Deodorants have no antiperspirant, they have deodorant, they have fragrances. So, basically, you're dealing with a hydro alcoholic product that's going to be a much finer mist than a polymer acrylate (inaudible) copolymers.

Dr. LIEBLER: So, I agree, Don. Your interpretation is a very reasonable interpretation if indeed that observation holds true across underarm deodorants, and if it's a chance finding with one can or something, then it's plausible, perfectly reasonable, logical, and wrong.

And so I guess what I'm saying is, I think it would be great to have some data, and I don't know if somebody can just pay for buying about 100 cans of different products, doing a standard analysis of particle distribution, and then having a data set that would be much more plausible that we could base boilerplate estimates with much higher degree of confidence. And I don't know if there's a way to generate a data set like that, but it would be quite relevant to us because we would be able to -- for numbers from something like that with confidence, particularly if there is a difference in the type of product -- if there really is a difference in the type of product, I think we should be able to point it out with confidence, because then every time we have an underarm deodorant that's the issue, it's going to shift our thinking a little bit relative to a hairspray.

And I think we need to know if there's a real difference or if there isn't a real difference.

Dr. KLAASSEN: It was my impression from what she said today that probably the industry could get that data for us relatively easily.

Dr. LIEBLER: The data may exist.

Dr. KLAASSEN: ...she said it wasn't available, but she thought she could... she was very positive in what she said... if you have the right equipment, this is not a big deal.

Dr. SNYDER: Can we default back to our original thinking even though maybe it was somewhat flawed in the data, but the philosophy was still good, so could we say that -- something along the lines of particle size distribution measurements should not exceed 1 percent for particles less than 10 microns, or something? ...

Dr. BELSITO: ...just to go back to my starting issue is, what you guys were telling me was that there's only a limited dataset of chemicals that you would be concerned about causing toxicity if they got down to the alveoli. So if that's true, does it really matter whether those that you have no concern about get down there at 1 percent or 5 percent? She also showed us data that when things got down there, whether they were respirable, i.e., less than 10 microns or inhalable, which in her data was, I guess 10 to 20, right? She did that short end on the inhalables. They all got eliminated, what, down to 95 percent of what got down there within 8 hours. So, if you're not concerned at 1 percent, are you concerned at 5 percent?

Dr. KATZ: It was minutes.

Dr. BELSITO: Minutes. ...if we're going without data based upon your experience that they're not issues, does it matter whether it's 1 percent or 5 percent if 95 percent of it is out of there in 8 minutes?
Dr. KLAASSEN: I don't think it changes my conclusion unless there's a specific toxicology associated with the compound, and I think what we could do with this language here, is simply say in practice aerosols have at least 95 percent of their particle -- or have 95 to 99 percent of their particle diameter is in the 10 to 110 range. So, change "aerosols should have at least 99 percent" to "aerosols have 95 to 99 percent." That's based on the data we received this morning.

Dr. BELSITO: So, get rid of "in practice" --

Dr. KLAASSEN: You could say "in practice," that's okay. "In practice aerosols have," so remove "should."

Dr. BELSITO: "95 to 99 percent of their particles," and the mean particle diameter is --

Dr. KLAASSEN: And I don't know if that number is --

Dr. LIEBLER: I don't think that's necessary.

Dr. BELSITO: ...right. Period. "Therefore most aerosol particles are deposited and not respirable," and then where do we go from there?

Dr. LIEBLER: And that's still true.

Dr. BELSITO: Right.

Dr. LIEBLER: Well, that's still true and then I think the question -- unless there's some reason, either some data that suggests that there's some pulmonary toxicology or if there's some... literature data suggesting there's some pulmonary toxicology, then I think we're talking about a relatively very small amount of the compound that's going in the lung with no reason to suspect a problem.

Dr. BELSITO: But then how do we finesse that in the absence of any data?

Dr. LIEBLER: So, we're really not doing anything different than we've already done, but we're actually thinking about it more.

Dr. BELSITO: No, we are doing something different because before we said nothing's getting in.

Dr. LIEBLER: But that's not -- that's what we thought, but that's not what it said. We said up to 1 percent is getting in. That's what it literally says, ...99 percent of their particle diameter is in the 10 to 110. That means the other percent is below and that could get in. We never really thought about it that way, but that's literally what we were saying.

Dr. BELSITO: Yeah, I guess that's what we're saying. Dan, but it's not what I was thinking.

Dr. KLAASSEN: Yeah, and I think that that's true. What we said and what we thought we were saying wasn't necessarily the same. We used to think 1 percent was nothing, now we're --

Dr. LIEBLER: Let's forget about it.

Dr. KLAASSEN: Yeah, forget about it. Now we are.

Dr. ANDERSEN: It depends on the chemical.

Dr. KLAASSEN: Yeah, I think it does --

Dr. ANDERSEN: What we said might actually be nothing.
Dr. ANSELL: Well, it's not 1 percent exactly. It's 1 percent of...

Dr. ANSELL: -- [the] dose for 8 minutes as opposed to most of the inhalation standards, which are based on 8-hour exposures 5 days a week, so, ...it's again what I was trying to say this morning. I think evaluating the toxicology is entirely appropriate, but we have to evaluate it within the dose and these are --

Dr. ANDERSEN: Well, neither Jay nor I are good people to answer the question, how long do you spray a color spray. And I really don't have a clue as to what the answer to that is, but I don't think it's eight minutes...

Dr. ANSELL: The breathing zone goes to zero in eight minutes...

Dr. ANDERSEN: There is a link that I don't want to let you off the hook on, though, the Lubrizol material safety datasheet, which is disodium lauryl succinate flags respiratory irritation...

Dr. ANSELL: For the material itself... If that's aerosolized.

Dr. ANDERSEN: So, ...I don't know how you factor that into this thinking, but it's there and we ought to at least say why that's not an issue.

Dr. BELSITO: ...well, I don't have a problem with what we just did for the cosmetic section, ... that, ...95 to 99 percent of their particle diameter, therefore, most aerosol particles are deposited -- where I'm going to have issues are in the discussion when we say that there are aerosol uses and we have 0 toxicology and we've now said that, ...1 to 5 percent of the product itself is respirable. So, then, what do we say? The expert panel was not aware of any toxicology... any respiratory toxicology concerns? ...we could then formulate reports without any data and say, well, the dermatologist wasn't concerned, we weren't concerned, there's absolutely no data, but no one was concerned, so it's safe as used.

Dr. ANSELL: Well, it's not really no data. We've got carcinogenicity, we've got mutagenicity, we've got systemic toxicity. The lung effects can be direct irritation. We have some titration in terms of the irritation potential of these materials. There is a concern, I suppose, about direct effect on the lung tissue that might be unique from --

Dr. BELSITO: Well, I'm thinking of things like acetyl. Who would have thought that popcorn butter would create... the significant fibrosing alveolitis that it does? So, ...that doesn't have carcinogenicity, it doesn't have a lot of other issues to it, it has a pulmonary issue... when heated in microwave popcorn and you have all these workers who can't breathe anymore because of it, supposedly... Diacetyl, I'm sorry, but you know what I was talking about. So, that's my concern that... it may have all of this other safety data, but it may have a significant effect on the lung.

Dr. LIEBLER: So,... if you decide you're going to look at it that way and there's this little red flag in the MSDS on the Lubrizol and it says it could be respiratory and you don't have any other data then you say it's sufficient for respiratory and you need a study, because right now we don't have that, but we do have the dermal irritation which is modest +/- depending on the preparation. You have the ocular irritation, which is only in... high concentrations, so that suggests that unless there's some unique mechanism that happens in the lung, modest exposure is not going to be toxic to the lung or even irritating to the lung. But that's my hunch based on these other datasets.

...If you want to have a procedure for dealing with this, if there are no lung data and there's a flag in the datasheet or some other -- some other mention of it, but there's not enough data to allow us to determine, then you say insufficient.

Dr. ANDERSEN: This is the perfect stage to do just that. So, first time you looked at this, there's no reason you can't make that determination and see what data might be available.

Dr. ANSELL: Well, what would be the data which would be responsive? Certainly not testing the material
as sold. To what concentration or what... an installation of a dilute material and then -- I'm not sure what experiment would -- particularly putting the non-animal overlay into it.

Dr. BELSITO: Well, ...if the company has in their MSDS sheets that it could be irritating, perhaps they have some data to show at what levels it irritates and perhaps they have data that shows nonirritating levels. ...I just don't know.

Dr. ANDERSEN: The MSDS did say that the company concluded that there was no inhalation toxicity issue. So, what's the basis for that part of the determination?

Dr. LIEBLER: So, let's get it --

Dr. ANDERSEN: They told us it could be irritating, but that it wasn't an inhalation toxicant.

Dr. LIEBLER: Yeah, I agree.

Dr. BELSITO: ...it's a green document, so we're going out -- I guess since it's green we don't even say safe as used when formulated not to be irritating, we just say --

Dr. ANDERSEN: No, it's an insufficient --

Dr. BELSITO: We just say insufficient for inhalation toxicity.

Dr. ANDERSEN: Or further clarification of just what the inhalation effects are that were reported, MSDS. Certainly inhalation toxicity data would resolve the issue, which may or may not be available.

Dr. ANSELL: Well, because we're not talking about the material as potentially irritating. Irritation is clearly concentration dependent, and so what data would clear that up in terms of the incipient concern that there's some pathology occurring deep in the lung? ...I'm not sure that we have enough irritation data here to start talking about drawing non-irritating thresholds ... we know it's mucus membrane issues.

Dr. KLAASSEN: I think we're saying that they... apparently have some information on irritation in the lung. Let's see it and maybe that will clear it up for us or help us to feel more confident about it. I think that's all we're asking right now. We're not necessarily asking for an experiment...

Dr. LIEBLER: So, if they came back and told us that they observed that exposure to the concentrated product produced irritation in whatever it was... but they further described why they said that at lower concentrations there's no irritation, if they just described that in more detail I'd be fine with that. If they happened to have an animal study in which they exposed rats to... nose only, low concentration of the product, that would even be better, but I think we would take either. It would be more informative than where we are now, which is -- we just start scratching our heads.

Dr. BELSITO: ...if you look at... the Lubrizol document... you look at respiratory protection, they say, "Use NIOSH MSHA approved (inaudible) with a combination organic (inaudible) high-efficiency (inaudible) if recommended exposure limits are exceeded"...Which means they have recommended exposure limits.

Dr. SNYDER: It says here, "If material is misted or if vapors are generated from heating, exposure may cause irritation of the mucus membranes and upper respiratory effect based on data from components for some of the material"... So, we have data ... components of this or --

Dr. BELSITO: Similar material. So, there's data out there. All we're asking at this point is if Lubrizol could provide us with the data that allowed them to make the statements in their material safety data sheet. Is that what I'm hearing?...

Dr. BELSITO: ...so insufficient, we need further clarification of the inhalation effects, more specifically if
Lubrizol could provide us with their inhalation data that resulted in the statements they made in their material safety data sheets.

Dr. BELSITO: ...so... we're going insufficient for additional inhalation effects, specifically asking the Lubrizol company how they came up with their inhalation statements about irritation and safety and what kind of inhalation data they have. And then depending upon that, there may be other data requests...

Dr. SNYDER: I wouldn't limit it to Lubrizol, I'd just say any additional inhalation data --

From the Pentaerythritol Esters Discussion

Dr. BELSITO: ...under Cosmetic Use, used in hairsprays and could be inhaled. The average particle size of aerosols from aerosols in hairsprays, what did we do for the sulfosuccinates? ...let's do a boilerplate here.

So, we said, “Particle diameters of 60 to 80 microns and greater than 80 microns have been reported for anhydrous hairsprays and pump hairsprays respectively. In practice, aerosols have 95 to 99 percent of their particle diameter in the 10 to 110 micron range. Therefore, most aerosol products are deposited in the nasopharyngeal region and are not respirable.” So, that's our boilerplate under cosmetics.

But we haven't developed a boilerplate for the discussion and this has gone out as safe as used. So, on the discussion page we said... "Some products in which these ingredients are used may be aerosols and the potential for inhalation of pentaerythrityl tetraisostearate compounds exist. Inhalation toxicity data are not available for these ingredients and they're not respirable," which is not true, so.

Dr. ANSELL: Well, ...there's a fair amount of inhalation data in the toxicokinetic section. Inhalation exposure to rats of pentaerythritol dust up to 11 kilograms per cubic meter, which would exceed the nuisance dust standard, cause no effects, rats, dogs, pigs, inhaling dust up to 8 grams per cubic meter... for 90 days, NOAEL....

Ms. BECKER: And you do have the one study under the genotoxicity in vivo with the C5-9 acids for -- on page 4 or 4/30, on the very bottom.

Dr. BELSITO: So, the inhalation -- there were no inhalation studies discovered for pentaerythritol --

Dr. LIEBLER: It's under Toxicokinetics...

Dr. BELSITO: That's pentaerythritol, not pentaerythrityl tetraisos. Now, we could argue that there's data on what we assume would be the major metabolite if that's how you want to do it. And whether there is data on the other components of the esters we're looking at, I honestly don't know.

Coconut, isostearic, oleic, lauric, myristic, and stearic acids are the free fatty acids that would result from. Previous safety, determined that these fatty acids are in the present practices of cosmetic use. We know that benzoic acid, ...we said was okay in inhalation. I don't know, did we deal with inhalation for the others? It starts to create a vicious cycle, too. If we dealt with inhalation by saying they weren't being inhaled.

Ms. BECKER: And you do have the one study under the genotoxicity in vivo with the C5-9 acids for -- on page 4 or 4/30, on the very bottom.

Dr. BELSITO: So, they weren't cytotoxic. But again, doesn't mean that it doesn't have respiratory toxicity.

Ms. BECKER: Mm-hmm. That's what we have.

Dr. BELSITO: I know what we have, ... I'm not in a position to make the comments. These are not my areas of expertise as to whether there is reason to believe we don't need data or we do need data.

Dr. LIEBLER: These have minimal irritation, they have no oral toxicity, they have no genotoxicity, they have no repro. If you look at the structure, there is nothing that I would regard as a structure alert or a
lung specific toxin or a metabolizable to a reactive intermediate lung type toxin... And the only difference between our emerging interpretation and our old interpretation is that we've gone from "can't possibly get into the lung" to "a little bit might get into the lung."

Dr. KLAASSEN: And I think it'd be interesting to look at this on Panel Book 30, this reference 31... where rats were exposed to aerosolized pentaerythritol C5 esters at 0.5 milligram per liter for 6 hours per day, 5 days per week for 2 weeks and... I would suspect if these animals were having some problems, it would have been noted, which would give me even more confidence, but I don't think I would even need that.

Dr. BELSITO: ...but it's good support data --

Dr. KLAASSEN: Exactly.

Dr. BELSITO: If the panel could say that... it noted the relative absence of inhalation toxicity, however, pentaerythritol was negative and in a genotoxicity assay animals were exposed to for without any reported pulmonary effects. And then at least there's some, now, basis for our rationale rather than simply saying, oh, the panel just decided that there shouldn't be any -- that there are no structural alerts, when we don't even have... then run a structural alert data.

...I guess where I become sensitized is with the diacetyl thing... this just happened, what, five, six years ago? ... the fibrosing alveolitis and would you have predicted diacetyl from a structural alert? ...Somehow it snuck up on us.

Dr. LIEBLER: Yeah, ...it's the exception that proves the rule and the rule is that most of these are fine and then there's the unanticipated exception that we learn things from... I think here we've got a way forward. We've got essentially a lot of data streams that suggest that there's really nothing happening with these. We've got this reference 31, which is an EPA data summary, unpublished data submitted to the High Production Volume Information System. So that may be accessible, I don't know.

Dr. BELSITO: ...in this case I'm comfortable because we have some respiratory data, you guys are telling me that it's fine, and I think all of that needs to be brought into the discussion so slight change in... the way we do the boilerplate under the cosmetic use section to mimic what we did for sulfosuccinates, and probably just in the discussion getting rid of that third paragraph and saying, "Some products in which these ingredients are used may be aerosols and the potential for inhalation exists. The panel noted that inhalation toxicity data are not available for these ingredients, however," and get rid of the particle size issue.

Say, "However, pentaerythritol was studied," and comment on that, "and furthermore, in a genotoxicity study, mice were exposed to," yadda, yadda, yadda, "without any reported pulmonary effects. Therefore, overall, given the low potential for respirable particles, the panel was not concerned," or something to that effect.

Dr. LIEBLER: Agree. This is just case by case, one at a time.

Dr. ANDERSEN: Just, Jay, if you could make a note, there was -- I think all of that hangs together, as we went through it, there's one little nagging piece of information for the use in what we think are for sure sprays. It looks like the concentration is 1 percent or less, low concentration, low amount inhaled, all in the right direction, but there's a figure of 36 percent under deodorants, and if we knew that that was not a spray, that would be real helpful. Given that these are viscosity increasing agents, at 36 percent, chances are, it ain't a spray.

Dr. ANSELL: ...it looks like you skipped a line.

Dr. ANSELL: Dermal. Inhalation powders, dermal. It's not the deodorant. It's not reported.

Dr. ANDERSEN: ...I read that wrong --
Dr. ANSELL: Pentaerythrityl tetraisostearate -- for all the reasons you just cited...

Ms. BECKER: Yeah, deodorant looks like it tops out at ... percent... 0.1...

Dr. LIEBLER: Number 36 is under... Dermal inhalation powder to dermal.

Dr. ANDERSEN: ...just -- I don't know where that inhalation is coming from.

Dr. SNYDER: Well, inhalation powder, dermal contact (inaudible).

Dr. ANDERSEN: Yeah, just in our new structure, I don't remember what that's likely to mean. And that bothers me that I don't know what that means.

Dr. SNYDER: So, in our use category should we be a little more specific when we talk about aerosolize issues.

Dr. ANDERSEN: Well, we're serving a couple of masters, one is condense the hell out of it so that it provides only the useful information, but now I'm looking at this and I'm confused and that makes it un-useful.

Dr. LIEBLER: So, we may have to tweak these table formats a little bit... just to help us deal with the inhalation issue.

Dr. ANDERSEN: ...Because whether it's deodorant or not, you've got a 36 percent in a category that we've labeled inhalation... And I can't explain what that is, but --

Dr. ANSELL: Don't somewhere you actually put in a footnote? Is one listed? You have no idea whether it's actually inhaled or not.

Dr. BELSITO: Well, ...if we put a footnote that we don't know if it's actually inhaled, ...and it's 36 percent, which is not negligible, ...I think we need to put something in our discussion as to why we thought inhaling 5 percent of 36 percent is okay.

Dr. ANSELL: No. But I don't think the conclusion is with the 36 percent. I think we just drop the line, but we do later -- we've added this new use category called deodorant and everyone's thinking that that's a spray product, but an underarm deodorant --

Dr. ANDERSEN: It ain't necessarily so.

Dr. ANSELL: -- isn't necessarily --

Dr. BELSITO: Right. So, that's our point. I think... what Dan said before is we need to tweak the system, and when we do deodorants, particularly since that was singled out to us as having one of the higher levels of less than 10 micron particles, it should be aerosolized and roll-on or non-aerosolized, however you want -- whatever term you want to use, so that we know --

Dr. LIEBLER: Spray/non-spray...

Dr. SNYDER: It just comes down to our data needs and what we're doing to make an interpretation... We now understand that our interpretation of aerosolized and respirable particle size distribution is different now, so we just need a different dataset to --

Dr. BELSITO: Right, and overall this new format is wonderful, it allows you to more quickly assess where the high concentrations are, how they're being used as opposed to the long list we had before, particularly when we're dealing with big families. I think what we realize today is that from a respiratory standpoint,
that we need -- everyone understands a hairspray is a spray... it may be a pump, it may be an aerosol, but deodorants are a different category and they need to be split out.

Dr. ANDERSEN: And this is late in the process. If this were a green document you would have had a sheet someplace that showed the raw data from the VCRP, and be able to go back and track and try to figure out just what does that mean.

Dr. ANSELL: Does the VCRP allow that? The use category deodorant? Does it break it down farther, aerosol versus non-aerosol.

Ms. BECKER: No.

Dr. ANSELL: I don't think so...

Ms. BECKER: But if you've got your book from the last meeting with you, it should have the data in it from their survey.

Dr. ANDERSEN: The council's survey?

Ms. BECKER: Yeah... The raw data from the original -- that would have been included in the last meeting's book...

Dr. ANDERSEN: If -- I'm looking at the rows right now, the deodorant says not reported... So, they're not going to find much useful looking at the data... So, we have some changing in the discussion to point to the pieces that we do have and not rely on the absolute that nobody's going to inhale this stuff because of the particle size... That's not trivial, but it's the least of the arguments to be made at this point.

Dr. BELSITO: Right, but for pentaerythrityl tetralaurate, we have deodorant, underarm 0.1...

Dr. ANDERSEN: Which fits into the argument that low concentration, low portion of the particles that get respired, all consistent with needing a real red flag on the toxicity side to be of concern and there's an absence. In fact, all of the places that have been looked at, there were no (inaudible) to be found. So, it hangs together in that fashion. That's... what we've got.

Dr. BELSITO: Right. Plus, as you point out, ...if we're looking for other arguments in the discussion,... these are viscosity increasing agents, so you're not going to put high concentrations in something that's going to have small particle and be respired, you're going to put those higher concentrations on a roll-on that you want to be viscous and adhere to the underarms.

Dr. ANDERSEN: That's what would make sense to me. It's -- is there reason to negate all of that and push for a more comprehensive inhalation toxicity assessment on this? Right now that assessment is incomplete. We have some signals. From what everybody said, it sounds like those signals are all enough to make the decision.

Dr. BELSITO: Right. ...unless my panel mates are concerned, I think we can go to the discussion and say, ...there was no direct inhalation toxicity for these,...the best information we have for use in a probable spray deodorant is 0.1 percent, pentaerythritol was negative. We've looked at many of the other component acids to these esters and they've been fine. We have a genotox study, which, while it didn't look at inhalation, was negative for genotox and doesn't appear to say that there were any lung issues. And finally, this is a viscosity-increasing agent, it's not going to be used in high amounts in fine sprays. So, overall, given all of that, we had no concern about the lack of data.

Ms. BECKER: ...And just to make sure on the pentaerythrityl tetrahexanoate for incidental inhalation sprays, it does go up to 50...

Dr. BELSITO: I'm assuming those are foot sprays are the incidental inhalation sprays... do we even know...
that they're sprays? What's in that category?

Ms. BECKER: Things that may be sprays or we know are sprays, that includes perfumes, which may or may not be a spray, foot powders and sprays, which may or may not be a spray. We added suntan -- the indoor tanning that now are in sprays...

Dr. LIEBLER: Can somebody restate the conundrum here? I'm getting lost on our string of conundrum.

Dr. BELSITO: The conundrum is that we have no definitive tox data. We've already gone out as a safe as used and we now either have to retract that conclusion and say safe as used but insufficient for inhalation, or we need to come up with a new discussion, because right now in our discussion we say, "Inhalation toxicity data are not available, however, the particle size are not respirable"...

Dr. BELSITO: Now, we've now changed that to say, "Up to 5 percent of the particle size is respirable," so what we have in our discussion is no longer correct or pertinent. So we need to create a new discussion as to why, if up to 5 percent of these particles are respirable, we are not concerned about any of the data. What Lillian is saying is that while under deodorant the highest level underarm we have is 0.1. Right above it it says incidental inhalation powders, we have a level of 0.06 to 50 for pentaerythrityl tetraurate.

Dr. KLAASSEN: I think we need to look to see what those large numbers really are.

Dr. BELSITO: So, are you saying table it?

Dr. KLAASSEN: I think so.

Dr. LIEBLER: I agree. ... we don't really have enough information to make a decision about these things because... we've essentially forced ourselves to totally reexamine the inhalation issues because we've gone from no way any of it gets into the lung to some of it -- small amount of it may get into the lung and then we have to have respiratory tox or a good argument based on the -- all the other data, and then we have a number like this that's big that looks like it may be respirable or it may be inhalation relevant... We may need more data if these turn out to be true, and... the fact that we've changed our approach to handling inhalation is going to impact some of these things that were near final, and that's just life in the big city.

Dr. BELSITO: Let me bring up another point. Impact things that are near final, what about all the other things we've done in the past five years where we haven't worried about inhalation because we said they weren't inhaled?

Dr. KLAASSEN: Well, you have to go with the knowledge you have of the day.

Dr. LIEBLER: Yeah, and I do think our approach... to inhalation -- I have just a gut feeling that we are lurching based on a very small number and a relatively small distinction. Now, you might feel the distinction between none in the lung and a small amount in the lung is actually a big distinction. It could be for the right compound. I admit that, but in most cases it's probably going to be a very small distinction and I think we need to figure out how we want to deal with that as a panel and that might have to be a discussion with the entire group.

...in the case of these compounds based on all the other data available, I'm not particularly concerned. That big number, it's hard for me to imagine there's 50 percent weight of this compound in something that's actually going to be inhaled, but -- and it's not possible to really tell very well by looking at the use tables as they're currently configured.

Dr. KLAASSEN: I exactly second that. I see it exactly the same way. I'm okay until I see this 36 and 50 percent, ...my guess... is that this 36 and 50 percent isn't real in inhalation.

Dr. BELSITO: Right. It's probably real, but they're not probably products that would be used around the respiratory zone.
Dr. KLAASSEN: Right. So, we just need to find out what that is. If it is, then we -- one step at a time.

Dr. ANDERSEN: And just to make sure that we clarify, it's easy to misalign the row that says, "Inhalation powders dermal."

Dr. KLAASSEN: Right.

Dr. ANDERSEN: I don't know what that is at this point in time, but what Lil flagged was above that, "Incidental inhalation sprays," and there's a 50 percent figure for tetraethylhexanoate, and that we were thinking was a spray. To be honest with you, I don't think we know that...

Dr. KLAASSEN: So, all of those where it suggests that we have inhalation at 36 and 50 percent, we got to find out if that's --

Dr. SNYDER: What's real?

Dr. KLAASSEN: -- what really is it? Is it spray on your foot or spray in your hair? ...

Dr. SNYDER: Don, to your point about the last five years reports and the interpretation of inhalation data based upon particle size distribution, I can say from my standpoint that I've always looked at total dataset. ...even in the absence of inhalation data or looked at inhalation data present or not present in the full assessment of toxicity, and so I'm extremely confident that even in that misinterpretation of the particle size that we likely haven't missed anything. And so I just think that we're clarifying better and we're moving forward in a better mindset and scientific approach to the inhalation data. I don't think -- but like I said earlier, I don't think what we're going to do is going to be all that much different than we did previously. It's just going to be a little tighter and it's going to be a little bit more confidence in that dataset. So I just want to make that statement just because somebody made a statement about particle size distribution, I completely ignored all that other toxicity profiling.

Dr. LIEBLER: ... I think the net effect of this particle distribution issue is that it's going to simply make us take a closer look at the inhalation tox data as opposed to simply getting a number and then turning off that neuron and not even thinking about it anymore... I don't think it's going to change what we've done in the last five years. I think it's going to change how carefully we look at inhalation going forward. And it's going to really mean that we need... [to] tweak our data requirements for description of the levels in the products.

Dr. SNYDER: And in the same line we want to make sure that we're not going to be requesting inhalation studies in animals going against the decreased use of animal usage when it's not appropriately justified based upon other parameters...

Dr. KLAASSEN: And you remember 10 years ago we weren't putting much attention to teratogenicity, et cetera, and now are, so, ...what we look at does evolve with time...

Dr. BELSITO: ...what we want now in all reports are when we get things like deodorant we want aerosolized/non-aerosolized or spray/non-spray. That is -- are there any other categories -- foot? ...

Ms. BECKER: Perfumes...

Dr. BELSITO: ...increasingly most perfumes are being put in atomizers simply because in many cases oxidation is what creates the allergenic compounds of the fragrance, so they're put into a spray simply so oxygen can't get into the container. I suppose --

Dr. ANSELL: Fragrances fall outside the scope --

Dr. BELSITO: Right, plus they're outside the scope, right. So, no, I think the big issue is going to be
deodorants, because hairsprays obviously are going to be sprays. I guess the -- so, when you do dermal contact deodorant underarm, we need to have aerosol/non-aerosol.

I guess the other question, ...as we look at this, since we really want to be specific, incidental inhalation sprays would be... all hairsprays or -- and foot sprays?

Ms. BECKER: And anything else that could come in a spray like suntan lotion and sun block now.

Dr. BELSITO: ...well, I guess what we'd want to know, really, would be hair and sunscreen? Those would be the two that would be in the respirable zone? I can't think of anything else... a foot spray.

Dr. KATZ: It could be.

Dr. BELSITO: What?

Dr. KATZ: It could be.

Dr. ANSELL: It's all just a matter of dose.

Dr. KATZ: Yeah, ...and where a person is when they're using the application. And one could make the argument for hairspray as well (inaudible).

Dr. BELSITO: It's further away.

Dr. KATZ: It's further away, but even still, if you were applying it to someone else and you may still be able to (inaudible)....

Dr. BELSITO: I guess when there's an aerosol use, specifically information we could get as to what products it's used in would be best... Otherwise --

Dr. ANDERSEN: Nice to know what's going on.

Dr. BELSITO: Right. ...So, we're tabling it...

From the Silylates Discussion

Dr. BELSITO: ...so basically, we've got quite a wave 2 on these. And the bottom line to this wave was that our concern about the small respirable size of these particles under certain shear forces was not really reasonable and that these were done to do lung studies and that the particles are going to aggregate in formulation and they're not going to be respirable. Well, that was the argument until this morning, so, again, not my area of expertise. It makes me very happy to say that. So, Dan, Curt, and Paul, where are you on these?

Dr. LIEBLER: Well, actually, I liked the alternate conclusion that was suggested, which is listed on the bottom of Panel Book page 33, report page 12. That was before the discussion this morning. I'm not sure the discussion this morning really changes that. It really depends on the particle sizes in these silylates. I think the information provided to us in wave 2 suggests that these particle sizes are considerably larger than what we were worried about. Is that your interpretation, fellows?

Dr. BELSITO: That was mine, but I'm not an expert. ...basically what they were saying is they sheared these things to make them respirable and the studies they did and that's now how they would be in the real world, in the cosmetic world that we're talking about. So, ...what I would do here is I would add that comment that we got from SASSI exactly about how they got particles about micron size by shearing it, and it's not a production method that would be used in cosmetic formulations and that the particle size in cosmetic formulations would be, again, using the data that SASSI had given us.
Dr. LIEBLER: Correct.

Dr. BELSITO: So, where you say inhalation data shows that the particles do reach the lungs in rats and induce granuloma formulation when these preparations are prepared at whatever shear force to create... however, in cosmetic formulations, these issues are irrelevant.

Dr. LIEBLER: Right. Basically, ...the SASSI document explains that to do the rat inhalation study there's a requirement that the particles be within a certain size range and it's a very small size range, 1 to 4 microns, which is really irrelevant to the ingredients as supplied for use in cosmetics.

Dr. ANDERSEN: Arguably a giant self-fulfilling prophesy.

Dr. LIEBLER: Yeah,...you make it so that you can do an inhalation study in a rat, but you make the compound different enough that the results are not applicable.

Dr. KLAASSEN: Do we have good data, what the size is in cosmetic products?

Dr. BELSITO: Well, SASSI gave us a whole bunch of data and then they --

Dr. KLAASSEN: Well, they say here in the Panel Book 46 that most of the particles are greater than 125 and none are less than 90.

Dr. BELSITO: That's pretty good.

Dr. KLAASSEN: ...that's good. The question is ...do we have some kind of hard data or we just take their word for it? It's not that I doubt them for saying this. In fact, that gets us off the hook.

Dr. BELSITO: We actually -- what they're quoting there is our report.

Ms. BECKER: Right, reference --

Dr. BELSITO: Page two of our report.

Dr. KLAASSEN: ...but you don't think that they're... supporting that statement when they kind of repeat it that way?

Dr. BELSITO: No, I think what they're saying is you're... not being consistent here, ...what they've told us is that the only study in which we see granuloma formation in the lungs is an artificial study where they've sheared these particles to the point where they'd be respirable.

Dr. KLAASSEN: Right.

Dr. BELSITO: And that isn't the way the material is prepared for cosmetic use, number one, and under situations of cosmetic use, in fact you would expect the particles to actually aggregate so the actual size would be larger than the individual size of any given particle. That's what I took home from reading this.

Dr. ANDERSEN: I think in the supplemental material that you have provided the August 31st letter from SASSI also gets into the question of the fundamental particle size, which they acknowledge is an average of 20 microns, but that it is uniformly aggregated in chains or clusters and then the aggregates are further agglomerated, so -- and then there's a citation --

Dr. ANSELL: Two citations.

Dr. ANDERSEN: -- that show that -- to demonstrate that nothing is below 100 microns.

Dr. BELSITO: Right. The ECETOC [JACC report No. 51, 2006] and the Gray and Muranko, right...
Dr. ANSELL: The exposure is 36 milligrams per cubic meter 6 hours a day, 5 days a week versus 8 minutes occasionally. And the effects noted are well documented. They have nothing to do with the chemicals, but they have to do with any large -- well, any insoluble particle which is inhaled at... whopping great doses.

Dr. KLAASSEN: This can be -- as long as they have those two references, we're okay.

Dr. BELSITO: So, our conclusion would be... first of all in the discussion you have to point out that the granuloma occurred under situations that are not relevant to the cosmetic product, that as used the cosmetic product actually aggregates and the average size is, and reference those two references we just discussed, that's discussion. And then our conclusion is that they're safe as used. I'm not even sure that we need to add when particle size is supplied to the (inaudible) are not respirable because we've dealt with that in the discussion, that our understanding is that they are not respirable.

Dr. SNYDER: That works for me.

Dr. LIEBLER: Yeah, I agree.

Dr. SNYDER: I just think you need to go back beyond the discussion a little bit more study details in regards to those studies and... how the ingredient or the compound was handled. That doesn't appear (inaudible) the first time in the discussion, so just capture some more of those study details, please.

Dr. ANDERSEN: But you really have to work at making these things get into (inaudible) [the lungs].

SPEAKER: Well, that's the problem with all inhalation studies.

Dr. ANSELL: They have to be artificially manipulated otherwise they aren't inhalation studies, then they're dermal studies.

Dr. ANDERSEN: That's the problem with making a medical device that produces stuff that can be inhaled, it's not easy. So, revised tentative conclusion –

From the Decyl Glucoside Discussion

Dr. BELSITO: ...Respiration issue, what do we have here? We have sprays, 0.8, 0.5, 0.6. Deodorants, 0.6, not reporting. Sprays, the highest sprays, looks like is going to be 8 percent for lauryl glucoside. Is that right?

Ms. FIUME: It looks like it fits it.

Dr. BELSITO: So, under the cosmetic use section, we're going with the boilerplate that we developed for whatever that compound we developed it for. So, a few of the ingredients are reported to be used on page 3, Panel Book 26. Spray or powder forms, it's not known if any product containing these ingredients are actually sprays or powders. "Particle size of aerosol hairsprays and pumps," that needs to be changed. What is the compound that we did the boilerplate for?

Dr. LIEBLER: I think alkyl PEG sulfosuccinates, right?

Dr. BELSITO: I think. Yes, so, it was, in practice, aerosols have 95 to 99 percent of their particle diameters and the 10 to 110 µm range or micron range... Therefore, most aerosol products are deposited in a nasopharyngeal region and are not respirable. So, get rid of the particle size of aerosol hairsprays and pump hairsprays and use that language from the sulfosuccinate report. And then that leaves us with a discussion, which hasn't been formulated yet, so, how do we deal with 8 percent? Is that what I said? ... Lauryl glucoside in a spray.... That may be used in a spray. We're not sure.
Dr. ANDERSEN: The 8 percent is definitely a spray… It was a hair color spray. The other uses that are in the potential spray category, we just have… The deodorants, the suntan products, we don’t have a clue whether they’re in sprays… Zero inhalation tox data…

Dr. ANSELL: We have ocular data showing material is not irritating, the decyl. We have no concern about systemic toxicity. Non-genotoxic, repro.

Dr. ANDERSEN: Really, the only hanging piece of information are those case studies. Patch-testing with decyl glucoside in patients who had reactions to a bunch of products was positive for decyl glucoside at 0.5 to 10 percent… But in terms of the leave-on uses, you’ve got sensitization testing… More than adequate for the leave-on. Although, the question is inhalation… So, everything else that Jay went through is not positive.

Dr. ANSELL: But it all goes to the inhalation assessment.

Dr. ANDERSEN: I agree. Yes, again, the only thing that there’s any… a flag of those case reports, everything else is just (inaudible).

Dr. BELSITO: Well, we have no inhalation data…

Dr. LIEBLER: This is another one of those ones where I think all the available data suggests to me that there’s no reason to worry about inhalation except that we don’t have an explicit inhalation study.

Dr. BELSITO: …so, how do we craft a boilerplate for this and all of the other ingredients that are going to fall under the same thing? … Where there are reported uses that could result inhalation, where we have no data that gives us concern for anything else, but we have no inhalation tox data. How do we draft that? Do we say the expert panel waved its magic wand and…

Dr. LIEBLER: I think it's systemic toxicity because, …as Curt pointed out earlier, there are two ways in which an inhaled compound can be important. One is it's a gateway to systemic and the other is, is in lung target organ toxicity. So, first of all, from the systemic point of view, there's not going to be enough absorption to the lungs to contribute to systemic toxicity, particularly given the systemic toxicities. So, absorption to the lung, a systemic toxicity due to absorption, due to an inhalation is unlikely to be significant. So, that's the first part.

And then the second part is, even though despite an absence of inhalation toxicity data, a lack of systemic toxicity, a lack of ocular toxicity, and minimal --

Dr. ANSELL: Exposure, minimal exposure.

Dr. SNYDER: This is where… we need to have our foundation of information based on particle size distribution of the category whether it's pump spray, whether it's a deodorant, or whether it's a aerosolated spray so we know that we're talking less than 1 percent or 1 to 2 percent or what it is, the comfort level of potential doesn't mean it is, but I can’t --

Dr. BELSITO: Five percent of 8 percent --

Dr. ANSELL: Or (inaudible). I don't see that it's fundamentally different than what we do with a 90-day oral study and lack of dermal irritation and molecular weight all kind of aggregating to convince us that... we're not concerned. The inhalation route has different issues, it doesn’t…. first (inaudible) [pass] metabolism, the route of absorption, but I think when we look at the data and we say very short exposures to low concentrations absent irritation, absent systemic issues, I would not argue that we have no inhalation data. We have a lot of data which you relied upon to make a reasonable assessment.

Dr. LIEBLER: Well, we have the other types that I just mentioned that, together with the very brief and small inhalation exposure, could lead the panel to conclude that the risk of lung toxicity, inhalation toxicity
is not significant.

Dr. SNYDER: Not biologically condemning. Toxicology.

Dr. LIEBLER: So, we have this recurring situation, as Don just pointed out, where we have a compound and we have an ingredient that has really minimal toxicities, maybe some irritation on skin on some individuals, and that depends on the formulation and so forth. We have no inhalation tox data, but there's a potential for some inhalation of the compound. So, that's what we need a boilerplate for. And... I'd be happy to try and draft some tentative language to work on that. I don't think we have time to talk about that before we're done today, but, tomorrow, I don't know if we're going to have time in the agenda to get into that.

Dr. BELSITO: Well, I think... we really need to... This is going out as a final.

Ms. FIUME: It'll be tentative.

Dr. BELSITO: Tentative, right, but... we need a fairly good boilerplate for our discussion because it's going to be happening over and over again, and something that maybe we can cross out or add in, but what are all the points that we, as a panel, want to consider when we have inhalation exposures and there is no inhalation toxicities?

So, it would... be nice if we could find for those inhalation exposures what the relevant particle size would be. That would be nice. Certainly, breaking out inhalation exposures into deodorant and deodorant exposures into aerosol, non-aerosol would be nice. General absence of other toxicologic endpoints is what I hear Dan saying. Low concentration of use always helps, but then what's low? Define "low"...

Dr. KLAASSEN: Another very important one is when the chemical was given orally or what have you, it didn't produce a lung toxicity... the target organ is not liver entry.

SPEAKER: Lung.

Dr. KLAASSEN: It's not lung entry.

Dr. LIEBLER: Yes, right. Yes, many classic lung toxins that are activated, certain furans, naphthalene, regardless of the route of administration, it goes to the lung and causes toxicity there...

Dr. BELSITO: But I hate to beat... a dead horse, but microwave popcorn eaters did not have a problem with fibrosing alveolitis. So, the diacetyl, when it was ingested, did not create problems in the lungs.

Dr. KLAASSEN: Well, it's probably the dose.

Ms. WEINTRAUB: Sometimes, you get different kinds of funny reactions that occur in the lungs when something needs to come out.

Dr. KLAASSEN: Oh, yes, like pouring gas... that's different, but what you're doing is producing hydrochloric acid. Most of the things that produce lung entry from inhalation are either extremely reactive, like ozone, or chlorine gas, or you have the compounds that really are systemically toxic to the lungs, which they get into the lung through the blood or either way. For example, some of the herbicides, and some of the cells in the lung metabolize the compound to a toxic compound with the naphthalene, et cetera, and that's what causes the toxicity... It'd be interesting to look at the data on the diacetyl, what really has been done in laboratory animals...

Dr. BELSITO: It's on allergic reaction, isn't it? It's a immunologic reaction specific to the lung that results in fibrosing alveolitis.

Dr. KLAASSEN: ...I don't know if anybody knows the mechanism... a compound like that, you might
imagine acetylating proteins... to form some immunogen that then triggers an immune response that leads to this, but I don't know if there's enough mechanistic information...

Dr. ANDERSEN: Coming back though to the profile that Dan was trying to describe, I think while,...this one, you may not have complete information, but let's say that we did recognize the importance of having more detailed information on particle size, here, we have a particular kind of product, a hair color spray, and I'd like to know what that distribution is. And if we knew that, that would probably inform a discussion, but let's then just say, for example, that it is in the 3 percent of the particle size is a respirable. Then going down the path that Dan went through, we would argue that that can't be a significant route of systemic exposure because it's just too low a percentage, and that chemical would then be absorbed through the lungs. So, systemic exposure isn't the issue for that product.

Now, let's look at the other question. What about the lung tissue itself? And if we then look through what's in there and there's low demonstrated systemic toxicity, which is true for most, and I put the caveat of well, there's also as part of that they looked at the lungs and nothing was wrong, low reproductive, low geno tox, low ocular, and if you go down through the mantra of systems that were tested, and there's an absence of toxicant responses, then we can infer that lung tissue is also not going to be damaged, and that route, as best I can tell, is the way to tie it together. Yes, it's an inference. You'd like to have the actual data showing that whatever is inhaled didn't do anything, but --

Dr. ANSELL: Well, no, I think that's fine and we'd be happy to try to find additional data, but we keep talking about 3 or 5 percent, and as if this is 3 or 5 percent applied dermally or 3 or 5 percent in (inaudible). No, it's 3 to 5 percent of interior aerosolized to a few grams per cubic meter that are inspired for minutes, and if we start doing that with a respiration rate of 0.02 cubic meters per minute, all of a sudden, we're getting into background levels.

Dr. ANDERSEN: Well, I think that, arguably, could be added to this mantra as a way of saying where's the beef?

Dr. ANSELL: Yes.

Dr. ANDERSEN: Yes, we haven't written that yet. That's what I think people --

Dr. ANSELL: I also think if you start looking at inhalation data, it's going to be very complicated because you don't do an inhalation study where the animal isn't being exposed to respirable --

Dr. BELSITO: ...so, the boilerplate in the cosmetic use section will definitely be changed. I think we're happy with that. We're going to go with the safest use conclusion for this.

We're going to ask the CIR staff and the scientific committee of the PCPC and maybe include Dan, since he already volunteered to do this, but no one is going to do it tonight, to talk back and forth over the next however many days, 30 days or 90 days before all of these issues come back to us in December, and come up with some type of boilerplate that we're going to deal with these chemicals when we have inhalation data.

Dr. ANDERSEN: ...I'm not uncomfortable with putting a first version of that discussion in a tentative document that we will issue.

Dr. BELSITO: Sure.

Dr. ANDERSEN: I think I can get pretty complete... And then you guys can polish it...

Dr. SNYDER: One last comment. So, there's two footnotes here, and which I think we should try to eliminate it so that includes some (inaudible) for which it is not known whether or not [the concentrations] reported in a product [are in] spray [products], same thing with deodorants. We need to know that because I think that when we end up with those large percentages in a category that we don't know whether
or not that truly is inhalation, could provide inhalation exposure. That's one of the more refined data we need from this use table.

Dr. BELSITO: Well, I think that's what we've been saying all along.

Dr. SNYDER: Yes.

Dr. BELSITO: Those product categories, we'd like it split out into aerosol, non-aerosol.

Dr. SNYDER: Well, it's got to pump spray, whatever, yes.

Dr. ANSELL: Well, let's take it back home, take it back home and talk about this. It's quite possibly what we're really talking about, difference between 1 and 50 is a microgram.

Dr. BELSITO: So, but wait a minute, let's just go back to Paul's point for a second. So, you would like it split three ways, aerosol, non-vaporized or whatever.

Dr. LIEBLER: Non-spray.

Dr. BELSITO: Non-spray, pump, aerosol non-spray. You would like all three categories?

Dr. SNYDER: Well, that's because of the data that we presented this morning. In the pump spray --

Dr. BELSITO: Less likely, right.

Dr. SNYDER: -- less likely, and then the aerosol spray is 1 to 2, but then we heard the deodorant is even different again because it had a greater proportion of the particles that could review less. So, I think that we have to be careful. We want to make sure we are asking specifically what we want from the standpoint of --

Dr. BELSITO: ...so, what you would like would be non-aerosol, aerosol pump, aerosol spray?

Dr. SNYDER: Correct...

Main Session
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Dr. BERGFELD: …We had a very interesting presentation because we've been interested in inhalation and respiratory particles yesterday by Dr. Helga Rothe as I think she pronounces her name from Procter & Gamble. We had a long discussion on what we're going to do about inhalable particles or substances and this will probably ongoing for quite a time…

Dr. BERGFELD: …Moving on the next ingredient, Dr. Belsito, the silylates.

Dr. BELSITO: In June we looked at this and we issued a tentative safety assessment for the silylates group of four ingredients and our conclusion was safe in the present practice of use and concentration, leave-on and rinse-offs, but insufficient data for use in products that might be inhaled. The issue there was granuloma formation and some inhalation toxicity studies where these particles were sheared down to dimensions of less than 10 microns that were respirable in order to do the inhalation toxicity studies.

However, under the practices of use these are not sheared to those levels and that was very nicely pointed to us as was the fact that under use conditions these particles usually agglomerate and end up with much larger particle sizes that would not be respirable. Based on that information which of course would need to go into the discussion of the granuloma formations were because of artificial shearing and the agglomeration of these particles in real life we felt that we could conclude that silica silylate, silica
dimethyl silylate, trimethylsiloxysilicate and trifluoropropyl dimethyl trimethylsiloxysilicate are safe in the practices of use and concentration described in the safety assessment.

Dr. BERGFELD: That's a motion?

Dr. BELSITO: That's a motion.

Dr. BERGFELD: Is there discussion or second?

Dr. SHANK: There's nothing in your conclusion regarding inhalation and respiration.

Dr. BELSITO: Nothing in our conclusion regarding inhalation or respiration, no...

Dr. BERGFELD: Do you want to make a comment, Ron?

Dr. SHANK: I think there should be.

Dr. BERGFELD: Would you comment on what it should be?

Dr. SHANK: We have to decide on what the boilerplate is going to be for airborne materials and I think we came up with a pretty good one. Dr. Marks can read it.

Dr. MARKS: What we had as the boilerplate would read when formulated or -- formulated and delivered to be nonirritating to the respiratory tract.

Dr. BELSITO: When formulated and delivered to be nonirritating to the respiratory tract, is the formation of lung cancer a nonirritating phenomenon so that if something were delivered to the respiratory tract that didn't irritate it but created cancer, that would be okay?

Dr. SLAGA: Lung cancer is irritation. Chronic irritation has a very strong relationship to lung cancer.

Dr. SNYDER: Probably more important is allergic reactions and so I don't think the irritation would also be a prelude to allergic reactions.

Dr. ANSELL: And I'm not sure for a carcinogenic material we would get to the point where we had to add the safety boilerplate.

Dr. BELSITO: Irritation does not seem to be the right end point. Do we want respirable, less than 10 microns?

Dr. ANSELL: Inflammation?

Dr. BELSITO: I don't know, but irritation to me doesn't seem to –

Dr. SLAGA: Isn't that a very sensitive biological response by the respiratory tract?

Dr. BELSITO: I'm a dermatologist. I'm not a pulmonologist. I don't know. But the proper term that just seems to me as a dermatologist you could formulate something to be not irritating but it could be highly sensitizing.

Dr. MARKS: Certainly to me that seems like if it's a carcinogen it's fairly infrequent that we deal with agents where we're worrying about an anaphylactic reaction. We could certainly include sensitizing and irritating if you would do that.

What we heard yesterday morning clearly shows that just using particle size is not going to be enough, that the way it's delivered whether it's a pump or aerosol and we know that below 10 microns there is still come
delivery even though there's a small amount. Then with powders we heard it was solvent that had an impact also. So that's why we phrased it in a way which we thought would address the issues in a broader way and not just on particle size. That's why we used formulated and delivered. The biologic end point is irritating. If you feel strongly we should put sensitizing in there, that's fine.

Dr. BERGFELD: Ron Shank, do you want to respond again?

Dr. SHANK: Saying formulated and delivered without irritation or sensitization is fine.

Dr. BERGFELD: Paul? Dan? Curt?

Dr. SNYDER: The only question is whether or not the irritation or sensitization are too specific terms, but I can't come up with anything better.

Dr. BERGFELD: Alan, do you have something?

Dr. KLAASSEN: I think for now this might be appropriate, but I think for many of these compounds there are other things that give us confidence that it's not a major problem in the lung and those definitely should be added as well including the dose. A dose that gets to the alveoli is still extremely small and from what we heard yesterday at the extreme of up to 5 percent. So there are other things that should be added into our discussion or wherever it goes that gives us confidence that this compound is most likely not going to cause problems and not just irritation.

Dr. BERGFELD: So you're suggesting that we always put into the discussion some kind of phrase or paragraph regarding why we have said what we have said about inhalation.

Dr. BELSITO: There are several aspects of the change in all of the boilerplates that we've been using. We discussed this also extensively. The first changes in the cosmetic use section when we mention that it's used as an aerosol, previously we had said in practice aerosols should have at least 99 percent of their particle diameters in the 10- to 110-micron range and the mean particle diameter of the typical aerosol spray has been reported to be approximately 38 microns.

So we thought that based on what we heard yesterday the standard boilerplate for an aerosol in the cosmetics section would be in practice aerosols have 95 to 99 percent because we heard they could have as much as 5 percent of their particles less than 10 microns, so that have 95 to 99 percent of their particle diameters in the 10- to 110-micron range, period. Therefore most aerosol particles would pause in the nasopharyngeal region and not respirable. That was sort of standard boilerplate in the cosmetic use section.

We thought that in terms of if there's absence of inhalation toxicity data then it really is going to be case by case. Dan and Curt felt very strongly that there are a limited number of compounds that are known to be respiratory toxicants and obviously if we're dealing with those, that would be one issue.

But the other side of the equation would be would inhalation increase the body burden? If it would and then you had significant negative oral tox, et cetera, that we would say that the body of evidence looking at the oral toxicity and the dermal toxicity that the exposure to the lungs would or would not contribute to this and finesse it that way, that it would be very difficult to come up with a boilerplate that would cover inhalation but we have to look at the full range of all other toxicities that we had and that would be our boilerplate, what other tox data do we have, and that's why we didn't need the inhalation.

In the case of the silylates, the bottom line is based on the new we have, they're not respirable so that's why we took that out. Here we have information that the granuloma formation that we're seeing was because these particles were artificially sheared down to 10 microns and forced down the lungs of these animals. That's not what happens. What happens as they showed is with these aggregates, first of all they're nonrespirable to begin with and then they aggregate to further larger size which is why we felt we did not need to put the caveat on the conclusion.
Dr. BERGFELD: Thank you. Ron Hill?

Dr. HILL: I'm not sure we have data that says that that aggregation that you're talking about occurs with every silylate, and when you say nonrespirable, I think that's impossible to achieve because you will have some cut, some fraction of particles no matter what that are going to be in that respirable range. In the case of the issues that were identified in that inhalation study, yes, all the data now suggests that it was an overload situation and so what you'd want is some way of ensuring that the load of respirable particles be it 0.5 percent of what's present or even 0.1, and in clearly in this case that's almost certainly the case, but we don't control the manufacture, we don't control whether somebody makes a substandard aerosol generator, we don't control any of that.

So I think the statements that need to be there need to somehow ensure that if any of that were to happen that would be beyond the conditions under which we've established for safe use. So having something about, what did we say, formulation delivery, to ensure that we don't overload. Like I say, the chances seem remote, but I don't think we know in every silylate that these agglomeration -- I've worked with agglomeration and I did agglomeration research for a year or two so I know what that's about. I'm not sure that we can ensure that every silylate that conforms to this category now and in the future that that's in fact true. So if we have some statement in there that says formulated and delivered in such a way that we, effectively what we need to say in this, don't overload the lungs to the point where these kinds of problems could occur, we're good.

Dr. ANDERSEN: A couple of comments. One is that this is the first time in quite a while that we've really focused on particles that aren't aerosols so that these are not the nice round aerodynamically pleasing predictable in terms of the data that we heard yesterday. These are asymmetric, these are aggregating, these are agglomerating so that while we may want to bank on that conceptually, it's just different than what we heard about yesterday. That said, the folks from SASSI who have provided the input are extremely confident that their particles would meet the language that Jim suggested, that when formulated and delivered they would be nonirritating to the respiratory tract from their perspective because there won't be significant exposure, but they're comfortable that that's not an impediment to manufacturing these ingredients and supplying them to formulators. So I think because these are, I keep wanting to say powders and that's probably not the right word to use, but these are not aerosol particles from pump sprays or aerosol sprays that we're talking about. This is particles that are of a different sort and putting a little constraint on it I'm not sure hurts and the companies involved feel that that they can meet that.

Dr. BERGFELD: Don, it's ingredient, it's your conclusion and Jim has added something to this. Are you going to accept that?

Dr. BELSITO: Could you repeat?

Dr. MARKS: Instead of the insufficient we would change it to be when formulated and delivered to be in this case change slightly, no irritation and sensitization to the respiratory tract so that we cover irritation and sensitization and the respiratory tract is obviously upper and lower and middle so it covers all that and I think it addresses the sensitization issue although with this chemical that's not an issue.

Dr. BELSITO: So safe in the present practice of us and concentration described in the safety assessment when formulated and delivered to –

Dr. MARKS: To be no irritation and sensitization to the respiratory tract. That could be wordsmithed.

Dr. BERGFELD: Non?

Dr. MARKS: Non, yes.

Dr. BERGFELD: Nonirritating?
Dr. MARKS: You could say nonirritating and nonsensitizing. However you want to word it, that I think is an editorial portion of the conclusion.

Dr. BELSITO: Paul had a comment. When formulated and delivered in the final product? Do you want that added?

Dr. MARKS: Yes. That's good. Yes. Thank you, Paul. In the discussion I think we could handle it like the hair dye epidemiology that there is a brief paragraph with a link to this very robust discussion. Ivan are you the one who's authoring the aerosol boilerplate that it would go into a great deal of detail in terms of what was presented yesterday morning, et cetera?

Dr. BERGFELD: Jay, you wanted to speak?

Dr. ANSELL: Yes. I think as boilerplate that's fine, but the boilerplate needs to be applied within the context of this ingredient and there is extensive data showing it's not irritating or sensitizing including rather long-term inhalation data. So do we need the boilerplate specific to this report?

Dr. MARKS: I thought the reason we did was because we didn't have the inhalation toxicity, we have the theoretical the way it is, but am I incorrect that we actually have animal studies?

Dr. SNYDER: No, I agree. I think that it is part of our basis for our weight of evidence approach to the safety assessment.

Dr. BERGFELD: So you would continue to have it included? Is that what you're saying?

Dr. SNYDER: Included or reference to a document that talks about the different aerosolization and the different particle size distribution. All of that information that we've learned I think is important because I think that's all part of our knowledge that we're applying on a case-by-case basis to these ingredients.

Dr. BERGFELD: But as to the second part of the question, would you have the inhalation statement and the respiratory in the conclusion?

Dr. SNYDER: In the absence of inhalation data I would prefer it to be in.

Dr. BERGFELD: The question is there an absence.

Dr. MARKS: That's what I'm asking, in this particular do we have enough inhalation? That's what Jay's bringing up. Do we have enough inhalation toxicity to say we don't need this caveat? If we don't then we need to include it.

Dr. BERGFELD: Paul?

Dr. SNYDER: My opinion differs a little bit from Dr. Hill's opinion in that that was a very robust inhalation study in which they looked at a hydrophilic and hydrophobic situation. Despite the fact that they were sheared, the lesions were minimal related to the silylates and what few lesions there were, they were reversed. In an extreme overload those animals are treated for 6 hours, 5 days a week for 13 weeks. So I have pretty good confidence that these brief intense exposures of a minute or 2-minute duration would not likely result in any significant toxicologic effect on the lungs on a case-by-case basis. Again it might be different if you ask me on the next ingredient.

Dr. BERGFELD: Lillian?

Ms. BECKER: You also have the additional aerosol studies that we went to you in Wave 2, animal studies.

Dr. BELSITO: Then we have all the studies in Table 4.
Dr. BERGFELD: Tom, Ron, Ron, do you have any comment about the caveat to put in the conclusion, whether it should stay or not, whether it should just go into the discussion as a discussant point? Paul, do you want to comment on the animal studies in the second wave of information?

Dr. SNYDER: That was the study that I was referring to.

Dr. SHANK: We have inhalation data in the report which was not a trivial response. We can explain that but it’s still in the report. So I think it should be part of the conclusion. If you don’t, you have to make a very strong case or discussion of the inhalation data and why you’re not concerned about it.

Dr. BERGFELD: Ron Hill?

Dr. HILL: Again I say I agree that the studies came up clean but they were using materials that were current sources from current manufacturers and who’s to say 15 years from now somebody else doesn’t go into that business and come up with a product that ends up in a final product that could cause these kinds of problems? So we put in not only the information in the discussion but also something in the conclusion that forcefully brings to the attention of anybody who might be interested in doing that to check all this stuff out before they put something out on the market because we don’t have any control over they could be manufacturing in a way that will suddenly cause and problem and that would prevent it.

Dr. BERGFELD: Curt?

Dr. KLAASSEN: I agree it should be in but I think it should be in the discussion and not the conclusion.

Dr. HILL: I’d be okay with that.

Dr. BERGFELD: Tom and Ron, do you agree with that? Then Jim?

Dr. MARKS: I second the motion.

Dr. BERGFELD: You second it and you second it as stated by Don without the inclusion of the inhalation statement. Is that correct?

Dr. MARKS: That’s correct. And then we’ve already had a really robust discussion and we know that’s going to be included in the discussion.

Dr. BERGFELD: Yes, we have.

Dr. MARKS: Hopefully we’ve maybe hammered out our boilerplate which is still on the agenda for aerosols…

Dr. BERGFELD: Moving on to the next, the tetraesters, by Dr. Marks…

Dr. BELSITO: …We’re concerned that we didn’t have concentration of use data in aerosols particularly now that we know that we can no longer say that aerosols aren’t respirable. So we had said table it for concentration of data in the aerosols, and of course then to change our respiratory boilerplates. But I don’t have a problem with reissuing it as insufficient or formally dropping the cocoate and having it come back to us… I think that while we all appreciate the ease with which we can assess concentration ranges in leave-ons and in rise-offs and in mucus membranes, the issue becomes particularly with underarm deodorants since we heard that those tend to have the lowest particle size yesterday and also with anything that could be sprayed, what we would like to see in the future would be deodorants, aerosol, nonaerosol -- what were the words? Not aerosol.

Dr. SNYDER: Nonspray.

Dr. BELSITO: Spray, nonspray, and then under spray, pump aerosol. So if we could begin to get that
kind of information which would give us a little bit more specifics about, one, because a deodorant could be a roll-on. There is no respiratory component. Or it could be a spray or it could be -- use it to spray, not a pump, but hairs could be sprays or pumps. We now know that the mean diameter of a spray is smaller than the mean diameter of a pump. It would give us some idea of what kind of respiratory toxicity we're looking for, so we would like that change in future reports.

I think the other area for discussion that came up in our group and we may not want to go there now is what do we do with all these reports of the past 5 years where we just blew off the lack of inhalation toxicity because we assumed that they were not respirable based on the information we had yesterday? At some meeting do we need a list of those and a decision as to whether based upon our combined wisdom we need to go back and readress some or do we say that was done and that was done?

Dr. BERGFELD: I'd like to take the prerogative of the chair and say that we will make that an agenda item for a later meeting and discuss how we will handle that. In the meantime, Alan can get the list up for us.

Dr. ANDERSEN: Message received.

Dr. BERGFELD: Jay, did you want to make a comment on how you're going to be able to accommodate Dr. Belsito's requests?

Dr. ANSELL: I think what come up yesterday and during our meeting is that the potential for inhalation is going to require some significant discussion and I think that's appropriate. I do think that we came to the conclusion that we can address these through looking at systemic toxicity and irritation potential. But I also wanted to make a point which I have the microphone that yesterday's discussion was intended to focus on the potential for inhalation exposure, not that inhalation exposure should be ignored.

We did some back-of-the-envelope calculations overnight and I still think we end up coming to the conclusion that this is not a significant route of exposure, that based on the data we saw, based on average application/use rates, depending on the assumptions for the breathing zone in the room, we come up with exposures in the order of 50 nanograms to a microgram for percent used in the product. I think this is important and should be assessed, but I do think we need to keep the dose in these considerations.

To the specific request, I think I'll have to turn to Carol and see how we can address that and provide the type of data. Perhaps it would be valuable to look at it once and it might not be necessary then to go back and look at it every single time in every single product, but I don't think until we've had a chance to consult with the CSSC we could respond...

Dr. BERGFELD: Thank you. Alan?

Dr. ANDERSEN: I think in many of the discussions yesterday, a problem came into very specific focus and I want to at least acknowledge it. It's not easy gathering these use concentration data and getting the information on whether a chemical used in a deodorant is used in a spray or a stick or whatever. A very thorough job has been done to try and gather those data, but as we get more pushy about what it is we want to receive, I think appropriately so, it's just going to make it that much harder. I don't want to suggest that this is a wrong direction to go. I think maybe for CIR staff it has a message that maybe some more time needs to be provided in order to gather sufficiently accurate data to resolve some of these questions.

We're going to be increasingly sensitive to that issue and at the same time, Jay clearly appreciates that the panel is putting an additional burden to get more data, more characterization and we'll see if we can work together to give you what you need when you get a report. But getting a report that has missing information, that the survey is underway and you haven't got the data yet, doesn't accomplish a whole heck of a lot. We need to make sure that this process isn't moving too fast...

Dr. HILL: I'm not a toxicologist by training, but I've worked with toxicologists for some number of years now and as a medicinal chemist I'm heavily focused on biochemical pharmacology and increasingly
mechanistic toxicity. One of the fundamental tenets of toxicity is the dose is really the key piece of information upon which you base a decision of safe or unsafe. Lacking that information and the route of delivery, you’re trying to make a decision without adequate information. I wasn't around when the reporting became voluntary.

Dr. BERGFELD: Thank you for all your discussion and your questions... Going on to the next blue final which is the crosslinked acrylates. Dr. Marks?

Dr. BELSITO: Then we need to do what is the respiratory boilerplate for this one.

Dr. BERGFELD: Do you have a suggestion?

Dr. ANDERSEN: I think certainly as of now we are offering the blanket comfort that they're nonrespirable and that clearly needs to change.

Dr. BELSITO: Right.

Dr. ANDERSEN: We talked yesterday about what the full presentation of an argument on the safety of ingredients that are used in products that may be aerosolized. Jay expanded a short while ago on one aspect of that which is sprays enter a breathing zone, don't enter a breathing zone and there are issues of how much gets in that are independent of what's the particle size. A small percentage of particles can get in but there is not that much material. I guess you parlay those two pieces of information into an argument that it's unlikely that inhalation is going to be a significant route of exposure for systemic toxicity so I think that gets captured.

Then it’s a matter of looking at the individual chemicals to see what's the use concentration and that's another factor that deserves mentioning. If that's low, it's another factor in the right direction that there is no concern.

In the document if there are oral systemic repeated dose toxicity data that are say it's simply clean and in particular no evidence of lung damage, that's a further factor. If there is reproductive and developmental tox data that are negative, that's another factor, genotox, right down through while they're not inhalation toxicity end points, they add to that picture of what do we know about the particular ingredient.

Paul commented yesterday that over the long term those are all things that we've looked at every single time anyway. Now we would potentially be putting them into a way of capturing that for the reader now to see in the discussion.

So instead of that one lonesome little sentence that says don't worry about it, it becomes a more expanded and I think robust discussion, but it must be tailored to each individual ingredient. I'd like to think that there's a boilerplate but I think it's a way of presenting the data and if they're there, we include it, if they're not, we don't include it.

Dr. BERGFELD: What are you proposing for this ingredient?

Dr. ANDERSEN: I think for this ingredient that single sentence that says don't worry about inhalation because particles won't be inhaled gets replaced with a paragraph that goes through those factors.

Dr. BELSITO: The same with TA.

Dr. ANDERSEN: I think so.

Dr. BERGFELD: Is this going to come back to us to look at or is this going to be automatically placed and this sent out? What is the procedure here?

Dr. ANDERSEN: I think if the panel is comfortable with the pattern -- which one are we talking about?
Dr. BERGFELD: We're talking about crosslinked.

Dr. ANDERSEN: Alkyl acrylates. This is something that since I'd rather have this issued as a final, I think we can develop that discussion language and run it by the chair and the two team leaders and proceed.

Dr. BERGFELD: Is that acceptable?

Dr. MARKS: Alan, I would suggest since it's easy, the electrons, run it by all the panel members and not just the chair, just the team leaders.

Dr. ANDERSEN: Can do.

Dr. BERGFELD: We'll have an email signoff of the inhalation statement in the discussion. We've had a motion made and seconded to go forward with safe with some caveats here at the N-nitroso. I think that is in this one too. Yes.

Dr. HILL: So if the minutes could reflect that we're going to do that and then when we approve the minutes next time that will say we did it.

Dr. BERGFELD: Yes. The minutes on these are being taken as we speak. Can we move the question now or is there further discussion? Move the question. All those in favor then of this conclusion please raise your hands. Unanimous...

Dr. BERGFELD: Is there any other discussion? Seeing none, I call for the question. All those in favor raise your hands. Thank you. Unanimous. We have really done a lot of work here. Thank you so much everyone. I'd like to know if we have to discuss the aerosol precedent. We've been discussing it all morning.

Dr. ANDERSEN: I don't think any further discussion is needed. We have a couple of homework assignments clearly related to a couple of these documents and I think that will advance the discussion. I have no doubt that we'll be revisiting this at future meetings, but for now I think let's not waste our time.
COSMETIC INGREDIENT REVIEW

CIR Precedents

Aerosols

Draft Revision

12/2011

This document is a compilation of issues discussed by the CIR Expert Panel along with precedent language used in CIR Reports to articulate the Panel’s views. Standard formats for Tables used in Panel Reports are also addressed. This is intended to provide background on issues and serve as a reference explaining the reasoning behind previous Panel decisions.
Sprays/Powders  
Update 12/2011

Precedent language for specific report sections:

**Cosmetic Use Section**

[INGREDIENT(S) is OR are] used in [LIST TYPE(S) OF PRODUCT(S), e.g., cosmetic sprays, including hair, deodorant, foot, and other propellant and pump spray products], and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters in the 10 to 110 µm range [IF PRODUCT(S) MAY INCLUDE BOTH PROPELLANT AND PUMP SPRAYS, ADD: ,with propellant sprays yielding a greater fraction of droplets/particles below this range compared with pump sprays.1,2] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal region and would not be respirable to any appreciable level.3,4 [IF PRODUCT(S) MAY INCLUDE DEODORANT SPRAY(S), ADD: There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.5 However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.]

**Discussion**

For Tentative Reports for which the Expert Panel has requested available inhalation toxicity data

Because [this ingredient OR these ingredients OR some of these ingredients] can be used in products that may be sprayed, the Panel discussed the issue of potential inhalation toxicity. The Panel requested safety test data that may be available to evaluate this endpoint directly. In the absence of such data, the Panel will consider other data that may be pertinent, including data available to characterize the potential for [INGREDIENT(S)] to cause systemic toxicity, ocular or dermal irritation or sensitization, and other effects. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable level. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

For Tentative Reports for which the Expert Panel has not requested available inhalation toxicity data

Because [this ingredient OR these ingredients OR some of these ingredients] can be used in products that may be sprayed, the Panel discussed the issue of potential inhalation toxicity. In the absence of sufficient safety test data to evaluate this endpoint directly, the Panel considered other data that were available to characterize the potential for [INGREDIENT(S)] to cause [LIST TOXICITIES EVALUATED, e.g., systemic toxicity, ocular or dermal irritation or sensitization, and other effects]. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable level. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

For Final Reports and Re-Review Summaries

Because these ingredients can be used in products that may be aerosolized, including [SPECIFY PRODUCT TYPE(s), e.g., cosmetic powders and sprays], the Panel discussed the issue of
potential inhalation toxicity. [NOTE INHALATION TOXICITY DATA, e.g., The limited data available from inhalation studies, including an acute-exposure study and a chronic-exposure study, suggest little potential for pulmonary overload or other respiratory effects at relevant doses.]

[ADDRESS PARTICLE SIZES TESTED, e.g., Although particles appear to have reached the lungs in these animal studies, the sizes of the particles used were either clearly within the respirable range (ie, ≤10 µm) or were not reported. The Expert Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics.] The Panel considered other data available to characterize the potential for [INGREDIENT(S)] to cause [LIST PERTINENT TOXICITIES EVALUATED, e.g., systemic toxicity, irritation, sensitization], or other effects. [SUM UP PERTINENT TOXICOLOGY RESULTS, e.g., They noted the lack of systemic toxicity at high doses in several acute and subchronic oral exposure studies and one chronic oral exposure study, little or no irritation or sensitization in multiple tests of dermal and ocular exposure, the absence of genotoxicity in multiple Ames tests and a Chinese hamster ovary test, and lack of carcinogenicity in a lifetime oral exposure study.] [SUM UP PERTINANT PHYSICOCHEMICAL PROPERTIES, e.g., In addition, these ingredients are large macromolecules, insoluble in water, and chemically inert under physiological conditions or conditions of use, which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract.] Further, these ingredients are reportedly used at concentrations [MAXIMUM PERTINENT CONCENTRATION OF USE, e.g., ≤4%] in cosmetic products that may be aerosolized. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable level. [NOTE OTHER PERTINENT INFORMATION, e.g., Furthermore, several of these ingredients are used for viscosity increasing functions and would not be likely to make it to the lungs.] Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information indicates that inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

BACKGROUND

Inhalation safety is an important consideration for sprays and powders containing cosmetic ingredients. The inhalation safety of ingredients in such products depends, in part, on where the ingredients may contact tissues in the respiratory tract and whether they can cause local adverse effects in the respiratory tract tissues or systemic effects after absorption from the respiratory tract.4

The deposition and absorption of gases and vapors in the respiratory tract depend mainly on their water solubility and reactivity with the fluids or other components of the surfaces of the airways.6-8 For example, absorption of an insoluble, non-reactive gas is negligible. A moderately soluble or reactive gas will be deposited throughout the respiratory tract. A highly soluble or reactive gas will be rapidly deposited or absorbed almost entirely in the nose and upper airways.

Similarly, the deposition, absorption, clearance and, ultimately, the effects of ingredients in aerosols (liquid droplets or solid particles) in the respiratory tract depend on the solubility, reactivity, and toxicity of the ingredients. However, the size of the inhaled aerosol droplets/particles also plays an important role.4,7,9

The physical parameter most strongly associated with the deposition pattern of an aerosol in the respiratory tract is the aerodynamic equivalent diameter, \(d_{ae}\).10,11 The \(d_{ae}\) of a droplet/particle is defined as the diameter of a hypothetical, smooth sphere of unit density (1 g/cm³) that has the same gravitational settling velocity as the droplet/particle in calm air, regardless of its actual geometric size, shape and density.5

The droplets/particles of an aerosol can be divided into three mass fractions, based on the depth to which they will penetrate the respiratory tract. These fractions include the inhalable fraction (median \(d_{ae}\)
=100 µm), which can enter the nasopharyngeal region through the nose or mouth, the thoracic fraction (median dae =10 µm), which can pass through the larynx to enter the trachea, bronchi and bronchioles, and the respirable fraction (median dae =4 µm), which can enter the alveolar region of the lungs. In the nasopharyngeal and thoracic regions of the respiratory tract, mucus-secreting and ciliated cells form a protective mucociliary blanket that carries deposited droplets/particles to the throat. Thus, droplets/particles deposited in these regions can be sneezed or spit out or swallowed. In the pulmonary region, the clearance of inert, poorly soluble particles is mediated primarily by alveolar macrophages, and is slow and limited by comparison.

There is broad scientific consensus that the probability of penetration of droplets/particles with dae >10 µm into the pulmonary region is essentially zero. Thus, only droplets/particles with dae <10 µm are considered to be respirable. This is a conservative assumption because a dae of 5 µm is often reported in the scientific literature as the threshold below which droplets/particles can reach the alveoli. In addition, there is consensus that droplets/particles with dae >15 µm are deposited almost exclusively in the nasopharyngeal and thoracic regions of the respiratory tract, and that healthy people will clear particles with dae >7 µm from these regions within 24 hours through mucociliary action.

Particle size distributions are product specific. Numerous factors determine the initial size distribution of droplets or particles released from a spray product, including the product formulation (e.g., volatile or nonvolatile solvent), propellant, can size, type of spray mechanism (e.g., propellant or pump), nozzle characteristics, and differential pressure through the nozzle. After release to the air, the particle size distribution can change rapidly through aggregation, agglomeration, sedimentation, evaporation of volatile components, or hygroscopic absorption of water. For example, all of the water and other volatile solvents and propellants in droplets with dae <40 µm will evaporate within 1 second of release from a spray can, so that the remaining particles will contain non- or low-volatile constituents (e.g., polymers with little or no biological activity in hairs sprays). Accordingly, a wide spectrum of particle size distributions can be released from cosmetic sprays.

Aerosols are broadly defined as multiphase systems of particulate solids or liquids dispersed in air or other gases, including mists, fumes and dusts. Both pump sprays and propellant sprays (also called “aerosol sprays”) produce aerosols, but the aerosols from propellant sprays have larger fractions of respirable droplets/particles than aerosols from pump sprays. For example, the median dae of the airborne droplets/particles of pump hair sprays range from 60 µm to 80 µm. Typically, <1% of the airborne droplets/particles released from pump sprays are in the range considered to be respirable (i.e., dae <10 µm). In comparison, the median dae of the airborne droplets/particles of propellant hair sprays range from 25 µm to 50 µm. Usually, 1% to 2.5% but no more than 5% of the droplets/particles emitted from propellant hair sprays are within the respirable range.

Further, different types of propellant-spray products may yield substantially different particle size distributions. For example, conservative estimates indicate that propellant hair-spray aerosols have a median dae of 35 µm with a coefficient of variation of 0.3. Thus, the insoluble aerosol particles inhaled during hair-spray use will be deposited primarily in the nasopharyngeal region, where they can be trapped and cleared from the respiratory tract through mucociliary action. In contrast, analogous estimates indicate that deodorant-spray aerosols have a median dae of 10 µm with a coefficient of variation of 0.3, suggesting that half of these particles are within the range considered to be respirable.

These differences in droplet/particle size distributions between pump and propellant spray products and between hair spray and deodorant spray products are important considerations for evaluating the safety of cosmetics ingredients that may be respired during use. This is because they suggest that the margin of safety may be lower for propellant sprays compared to pump sprays, and for propellant hair sprays compared to propellant deodorant sprays. The inhalation of respirable droplets/particles from cosmetic products, including pump and propellant hair sprays and deodorant sprays, is likely to be very small, even negligible, compared with dermal contact and other exposure routes associated with the use of these products. Further, products like underarm deodorant and foot sprays are not usually sprayed in the direction of the face, so less of these products will likely be sprayed...
directly into the users breathing zone compared with hair sprays, for example. However, the limited evidence currently available does not provide adequate support for these assumptions.

Pulmonary overload is a condition in which the accumulation of any inert, poorly soluble particulate material in the lungs overwhelms the capacity of the alveolar macrophages to clear the material from the lungs. Chronic pulmonary overload can cause persistent inflammatory responses, fibrosis and tumors, although the mechanism(s) of overload-induced tumor formation is not completely understood. The European Union’s current threshold for protecting workers from pulmonary overload during occupational exposure to respirable dust particles is 1.5 mg/m³ 8-hour time-weighted average. In comparison, inhalation exposures to aerosols from cosmetic sprays will be much lower than this threshold, primarily because of the much shorter exposure duration associated with cosmetic spray use (i.e., only a few minutes).

The droplets/particles released from a propellant hair spray are distributed within a 1 to 2 m³ space in the breathing zone during the first 2 minutes after spraying, which expands to form an homogenous 10-m³ cloud (about the size of a bathroom) over the subsequent 18 minutes. Simulation studies revealed that all of the droplets/particles released from both pump sprays and propellant sprays settle quickly after spraying, including the respirable and inhalable fractions, which substantially reduces the overall potential for inhalation exposure. Specifically, about 35% of the airborne droplets/particles drop away from the breathing zone in the first minute, 60% in the second minute, 90% in six minutes, and 95% in eight minutes after spraying. The droplets/particles are likely to be undetectable in the breathing zone within 10 minutes after spraying.

Industry can ensure that inhalation exposures to cosmetic sprays and powders are minimized. For example, particle size distributions can be characterized and exposures estimated each time a significant change is made in the formulation or spray mechanisms of spray products to ensure that potential inhalation exposures are very low.

Similarly, industry can minimize airborne particles from cosmetic powder products by controlling the milling of the ingredients and adding binding materials, such as oils, waxes or hygroscopic ingredients, in the formulations. The binding materials foster the agglomeration of the ingredients and substantially increase their cohesivity. These measures increase the size of the particles in the product, as well as ensuring that pressed powder products are shipped and delivered intact, and loose powder products, such as eye shadows, stick to the applicators for example.

However, characterizing the particle size distributions released from finished powder products that are sprayed is difficult, because the size distributions in a product do not correlate well with the size distributions of the particles released from the product under use conditions. The primary reason for this that the particles agglomerated in the finished product break up in the solvents and under the pressures used to disperse them during use. Some photographic methods are being developed to characterize the actual sizes and shapes of the particles released from powder products during use. However, it is not clear whether these methods are amenable to characterizing the aerodynamic equivalent diameters of such particles.

The CIR Expert Panel noted that, in practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters in the 10 µm to 110 µm range. Thus, most aerosol droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal region of the respiratory tract and would not be respirable to any appreciable level. However, some of the droplets/particles are respirable, including up to 5% of the particle size distribution during the use of some products. Such information should be included in each safety assessment for which the ingredient(s) may be used in a pump or propellant spray. Information will continue to be sought from suppliers and formulators to specifically identify such spray uses.

The Panel recognized that aerosols from propellant sprays are distinct from aerosols from pump sprays. For each ingredient or ingredient group assessed, the Panel would like to know whether the current practices of use include propellant sprays, pump sprays, or both, when appropriate and the
information is available. Identifying the use of ingredients in deodorant spray products may be especially important, because they potentially release the largest amount of respirable droplets/particulates among the products evaluated. However, better information about particle size distributions and their variabilities (within and across product types) that can be reasonably expected, generally, from a broad range of products (e.g., hair, sunscreen, indoor suntanning, foot and deodorant sprays, and cosmetic powders) would substantially increase confidence in safety assessments of ingredients in products that may be aerosolized.

The Panel will continue to review all of the relevant inhalation toxicity, use, and other data to determine the safety of cosmetic ingredients. The Panel will evaluate the importance of the inhalation route for assessing the safety of an ingredient or group of ingredients, and evaluate data that may be available to estimate potential respiratory doses from aerosolized products. Factors to consider include whether or how much of the spray products enter the breathing zone, the likely droplet/particle size distributions in the breathing zone, and the exposure durations that can be expected during product use. The Panel agreed that, generally, inhalation exposure to ingredients in aerosolized cosmetic products is unlikely to be significant compared to the dermal or other exposure routes associated with the use of cosmetic products. However, this may not be true for an ingredient that has the potential to act as a potent systemic or local respiratory tract toxicant or to accumulate in the body.

The Panel noted that inhalation toxicity studies on test animals are often conducted using high concentrations of droplets/particles with size distributions well within the respirable range to ensure that the potential for pulmonary or systemic toxicity will be detected. However, the adverse effects reported in such studies may have little or no relevance for evaluating the inhalation safety of cosmetic ingredients. This is because, for example, the ingredients, as supplied to the cosmetic product manufacturers, have particle size distributions well above the range considered to be respirable. Further, the concentrations and durations of inhalation exposure to respirable droplets/particles from the use of cosmetic products will likely be much less than those used in the animal studies.

For example, the Panel noted studies that reported pulmonary granulomas in animals exposed to high concentrations of inhaled silylates sheared to form particles with aerodynamic equivalent diameters ranging from 1 to 4 µm, which is well within the range considered to be respirable. However, this ingredient, as supplied to formulators, has an average aerodynamic equivalent diameter of about 20 µm, and the ingredient aggregates and agglomerates to form clusters and chains with dae >125 µm and none <90 µm. Thus, the formation of granulomas in the animals was not considered to be relevant for evaluating the inhalation safety of this ingredient as used in cosmetic products.

If inhalation toxicity data are absent or provide an insufficient basis to support the safety of an ingredient used in products that may be aerosolized, the Panel will evaluate the sufficiency of other data that may be available on a case-by-case basis. Such data would include, for example, the potential for the ingredient to cause systemic toxicity, ocular or dermal irritation or sensitization, or other effects after repeated exposures. Other factors to consider include whether the ingredient belongs to a class of toxicants recognized to have the potential to cause lung injury after exposure via inhalation or other routes, possesses structural alerts based on known structure-activity relationships, or has a noteworthy potential to yield reactive intermediates or other metabolites of concern in the lungs.
References


SPECIAL ASPECTS OF COSMETIC SPRAY SAFETY EVALUATION

Dr. Helga Rothe

CIR Expert Panel
26th September 2011
Special Aspects of Powders in Decorative Cosmetics

- Strategies to prevent airborne particles
- Measurements
- Modeling
- Exposure assessment methods
- Impact of particle size
- General considerations for exposure assessments
- Typical products & ingredients

Safety Evaluation

Special Aspects of Cosmetic Spray
TYPICAL PRODUCTS & INGREDIENTS

- Typical Products
  - Aerosols*: 
    - Hairspray
    - Deo/AP aerosol
    - Oral sprays
  - Trigger / pump spray
    - Suncream
    - Moisturisers
    - Deodorants
    - Perfumes

- Typical Ingredients
  (across all product types)
  - Propellant (aerosols only)
  - Antiperspirant active
  - Oils/emollients
  - Ethanol
  - Water
  - Polymers
  - Fragrances

* Mousses as well as other 2 chamber systems are also classified as aerosols but their use is not associated with inhalation exposure so they are excluded from consideration in this context.
EXPOSURE ASSESSMENT

Portion of sprayed products deposited at target (skin/hair/scalp) is assessed similarly to conventional cosmetics

Additional Exposition via inhalation route

Respiratory tract can serve as

- portal of entry for systemic exposure
  - E.g. vapors or gases (e.g. benzyl alcohol etc.)
- or as target organ
  - E.g. particles or fibers (e.g. SiO2)
SAFETY ASSESSMENT OF SPRAYS

- Aerosolisation of products may lead to additional inhalation exposure

- Portion of sprayed products deposited at target (skin/hair/scalp) is assessed similarly to conventional cosmetics

- Potential local and systemic effects of inhaled portion have to be considered.

- For total systemic exposure, all relevant exposure routes (inc. dermal and respiratory tract absorption) are relevant for the final assessment

- Appropriate inhalation toxicity assessment is dependent on knowledge of quantity and composition of ingredients as well as the exposure pattern of the final product.
IMPACT OF PARTICLE SIZE

Particle size distribution in liquid or particulate aerosols will determine penetration depth of materials into the respiratory tract.

**Nasopharyngeal region**
Deposition – impaction, diffusion
Clearance – mucociliary, sneezing/blowing
Pathology – inflammation, cancer, ulceration
>50um particle
Highly reactive, water soluble gas

**Tracheobronchial region**
Deposition – impaction, sedimentation, diffusion
Clearance – mucociliary, coughing
Pathology – obstruction, irritation, cancer, ulceration
10-50um particle, 200um fiber, “inhalable”

**Pulmonary region (parenchyma)**
Deposition – sedimentation, diffusion
Clearance – phagocytosis, solubilization, interstitial
Pathology – inflammation, fibrosis, cancer, edema, emphysema
< 10um particle, 10-12um fiber
“respirable”, Less reactive/water soluble gas
Particle size distribution (spectrum) is an important parameter of essential relevance in exposure assessment for spray products. Particle size distribution is dependent on a number of factors such as product composition (formula) and technical features of the functional packaging (spray valve, propellant pressure).

Upon reformulation of a given spray product, particle size distribution may have to be re-assessed in case of substantial modifications of active ingredients, solvents or propellants; the same is true for modifications of packaging (spray head, can size, propellant pressure).
RESPIRABLE PARTICLES

Particles and or hardly soluble ingredients (e.g. polymers) → non absorbable → local effects

Deposition of particles < 10 µm diameter in deeper lung → Lung overload with inert particles (limited clearance)
EXPOSURE ASSESSMENT METHODS

- **Modelling**
  - Simple models (1-box model)
    - BAMA
  - More complex models (2-box model)
    - ConsExpo
    - IKW

- **Measurement**
  - Point of expulsion (e.g. Malvern Spraytech)
    - Acute exposure
  - Simulated consumer exposure (e.g. TSI Aerodynamic Particle Sizer)
    - Intended and forseeable use scenarios
  - Ambient sampling (e.g. cascade impaction)
    - Residual air quality
EXPOSURE ESTIMATION

Key advantages
Conservative (use conservative defaults), easily applicable

Example:
- The consumer applies the product in a small bathroom (10m³) as instructed.
- The aerosol will distribute during the initial 2 minutes post application around the consumer’s head in a cloud of 1-2 m³.
- The consumer will stay for a total of 20 minutes in the bathroom.
- The total amount of sprayed product will distribute homogeneously into the entire bathroom, 25 % of inhaled ingredients will be exhaled.
POINT OF EXPULSION

Pumpspray

Aerosolspray

From FEA Guide on Particle Size Measurement from aerosol products
SIMULATED USE STUDIES

- Measurement of the mass of non-volatile material that has the potential to be deposited in the bronchial, bronchiolar and alveolar regions of the human lung if inhaled under simulated use conditions (use and foreseeable misuse).
- Use of realistic amounts for product
- Measurement in breathing zone
- Measure from breathing zone for 10 mins (until LOD) including typical application using time-of-flight spectrometer (e.g. Aerodynamic Particle Sizer (APS))
- Output
  - Respirable Dose
  - Inhalable Dose

From FEA Guide on Particle Size Measurement from aerosol products
SIMULATED USE STUDY OUTPUT

Particle Size Distribution - AP Aerosol

Particle Size Distribution - Pump Hairspray

From FEA Guide on Particle Size Measurement from aerosol products
OUTPUT OF SIMULATED USE STUDIES

- Data is corrected to emulate human breathing conditions
  - 10 l per minute (Casarett & Doull, 2008; US Dept Labour, 2006)
    - Maximised resting rate of 20 breaths per minute
  - 20 l per minute (worst-case conditions – 2-fold correction)
    - Relates to light exercise

- Data output
  - Aerosol concentration
  - Particle size
  - Particle mass
  - Sample discharge rate
  - Inhalable and respirable dose (g/sec spray)

Casarett & Doull (2008) Toxicology: The Basic Science of Poisons
Breathing Zone Aerosol

Proportional drop out with time (example: use of ADPO)

- Inhalable
- Respirable

60%, 90%, 95%
SUMMARY

- Beyond the situation at the application site (i.e. topical effects), safety assessment for cosmetic spray products requires consideration of potential exposure to inhaled portions of the products.

- Qualitative and quantitative exposure assessment is of key importance for this part of the evaluation.

- Particle size distribution in liquid or particulate aerosols will determine penetration depth of materials into the respiratory tract.

- Local effects of inert particles < 10 μm by deposition in deep lung.

- Particle size distribution is product specific (control fraction < 10 μm).

- Exposure assessments can be done by modeling using worst case assumptions or real time measurements.
SPECIAL ASPECTS OF POWDERS IN DECORATIVE COSMETICS
STRATEGIES TO PREVENT AIRBORNE PARTICLES IN POWDERS

Ingredients in Powder Formulations

- Dedusting effects by
  - Use of “binding” material (adhesives) to agglomerate particles (dry material):
    - Unctuous material (e.g. oils, mineral oils, fatty alcohols, waxes)
  - Hygroscopic ingredients
    - Increasing particle size through adsorption of water
STRATEGIES TO PREVENT AIRBORNE PARTICLES IN POWDERS

Production of Powder Formulation

- Particle size depends on mill conditions in final production step (blender)

- Relative high Cohesivity
  - Usually 60 – 98% COH (scale 0-100)
  
  Needed to insure
  - Pressed powders to survive shipping etc.
  - Loose powders to stick to applicator

Measuring particle sizes from final product does not reflect actual size of powders under use conditions due to

- dispersing the powder in a solvent
- dispersing with pressure
Questions are guaranteed in life; Answers aren't.