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FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

CONSULTATION ON DERMAL SENSITIZATION

ISSUES FOR EXPOSURES TO PESTICIDES

May 5, 2004

[8:35 a.m.]

Holiday Inn Rosslyn at Key Bridge
1900 North Fort Myer Drive
Arlington, Virginia 22209

PARTICIPANTS

FIFRA SAP Session Chair

Steven Heeringa, Ph.D.

Designated Federal Official

Mr. Paul Lewis

FIFRA Scientific Advisory Panel Members

Stuart Handwerger, M.D.

Gary Isom, Ph.D.

Mary Anna Thrall, D.V.M.

FQPA Science Review Board Members

Paul Bailey, Ph.D.

Gary Burleson, Ph.D.

Ih Chu, Ph.D.

Iain Foulds, F.R.C.P.

A. Wallace Hayes, Ph.D., DABT, FATS, FIBiol., FACFE, ERT

Abigail Jacobs, Ph.D.

Jean Meade, D.V.M., Ph.D.

Torkil Menne, M.D.

Nancy Monteiro-Riviere, Ph.D., DABFE, DABFM

Richard Pleus, Ph.D.

Paul Siegel, Ph.D., MSPH

EPA OFFICIALS

Joseph J. Merenda, Jr. (OSCP)

Jim Jones (OPP)

Timothy McMahon, Ph.D. (OPP)

Jonathan Chen, Ph.D. (OPP)

P R O C E E D I N G S

DR. HEERINGA: Good morning and welcome to the second day of our session of the FIFRA Scientific Advisory Panel on the topic of a Consultation on Dermal Sensitization Issues for Exposures to Pesticides.

I'm Steve Heeringa. I'll be chairing this meeting again today. I'm a biostatistician and a senior research scientist at the Institute for Social Research at the University of Michigan. My specialization is not in toxicology or dermal sensitization but in design and analysis of population-based studies.

I'd like to have the other members of the Panel introduce themselves again this morning. And I'll begin to my left with Dr. Handwerger.

DR. HANDWERGER: I'm Stewart Handwerger. I'm a molecular and developmental

endocrinologist in the departments of pediatric and cell biology at the University of Cincinnati.

DR. THRALL: Good morning. I'm Mary Anna Thrall. I'm a veterinary pathologist at Colorado State University.

DR. ISOM: I'm Gary Isom, a toxicologists for Purdue University with the area of interest in neurotoxicology and specifically molecular mechanisms of neurodegeneration.

DR. PLEUS: Good morning. I'm Rick Pleus. I'm director of Intertox. I'm a toxicologists and pharmacologist from Seattle, Washington.

DR. HAYES: I'm Wally Hayes, a toxicologist at Harvard School of Public Health.

DR. MENNE: I'm Torkil Menne. I'm from Copenhagen. I'm a dermatologist. My main interest is allergic contact dermatitis.

DR. FOULDS: I'm Iain Foulds, a dermatologist in Birmingham in the United Kingdom. I run a contact dermatitis clinic there.

DR. MONTEIRO-RIVIERE: I'm Nancy Monteiro-Riviere from North Carolina State University. I'm a Professor of Investigative Dermatology and Toxicology. My area is dermal absorption of metal toxicity.

DR. SIEGEL: My name is Paul Siegel. I'm from the National Institute for Occupational Safety and Health. I'm a team leader for bioorganic chemistry. And my main area of research is hypersensitivity diseases.

DR. CHU: Good morning. I am Ih Chu from Health Canada. I'm a toxicologist. My research interest is in systemic toxicology and pharmacology. I'm currently a section head of systemic toxicology and pharmacokinetics.

DR. BURLESON: Good morning. My

name is Gary Burleson, immunotoxicologist from Raleigh, North Carolina. I am president of BRT, Burleson Research Technology. It's a contract research laboratory.

DR. JACOBS: I'm Abbey Jacobs. I'm a pharmacologist/toxicologist with the Center for Drug Evaluation and Research, FDA.

DR. BAILEY: I'm Paul Bailey. ExxonMobile. I'm a toxicologist. Research interests are in the area of dermatotoxicology.

DR. MEADE: Good morning. I'm Jean Meade. I'm from the National Institute for Occupational Safety and Health. And I'm the team leader for the agriculture and immunotoxicology group.

DR. HEERINGA: Thank you very much, Panel.

At this point, I'd like to outline the schedule for today. Many of you have the agenda in front of you and will be following

that particular order.

I wanted to mention a few minor changes. We're going to continue with public discussions this morning to wrap that up and give the public a chance to provide their comments and information.

At the conclusion of the public comment period, we'll have a period of general question and discussion. It will give a chance for the EPA to follow up. We'll have an initial little follow-up today. But then, also, there will be this question and answer period at the end of the public comment period.

At that point in time, I think we'll also have a little more of an extended discussion with the EPA staff on the issue of uncertainty factors. That was requested by the Panel.

Following that, we would like to take a early lunch. And that has been

requested by Panel members. So I expect that our lunch break will begin sometime around 11:30. We'll take an hour for lunch and then return to address the specific charge questions that have been put before the Panel. That's the anticipated schedule for today.

We've scheduled these meetings for three days. Whether we complete today or not, will depend on the progress of the discussion this afternoon. I see no hurry if we need the time to completely flesh out these issues and provide our response to the EPA questions. I will anticipate we will end today. And if need be, I may go to 5 or 5:30 if that would provide adequate closure on the proceedings.

At this point in time, I would like our Designated Federal Official, Mr. Paul Lewis, if he has any administrative comments to add

MR. LEWIS: Thank you, Dr. Heeringa, and thank you Panel members and members of the

public for coming to our second day of the FIFRA Scientific Advisory Panel.

I just want to remind everyone that this meeting of the FIFRA Scientific Advisory Panel operates under the guidance of the Federal Advisory Committee Act. So this is an open meeting. All materials of this meeting are available in our docket. In addition, our meeting minutes will be published approximately six to eight weeks after this meeting. It will be available both in the public docket and available on our the web site.

Thank you.

DR. HEERINGA: Thank you, Paul.

At this point in time, Mr. Jim Jones, the Director of the Office of Pesticide Programs, is here again today. Welcome back. Would you like to make a few additional remarks at this point?

MR. JONES: Thank you, Dr. Heeringa.

I would just like to remark that I thought we had a very good opening presentation yesterday from both the Agency and public commenters. I want to thank them all for their hard work there. I thought that the Panel was very engaged. And I look forward to this afternoon in particular where we're going to get into a bit more of your reaction to the questions that we have asked the Panel.

And I think we have the right people here, both from the risk management and the risk assessment side of house of EPA to help to frame the issues to the extent that the Panel feels necessary to give us the appropriate feedback.

Thanks very much.

DR. HEERINGA: Thank you very much, Mr. Jones.

At this point in time before we turn to the public comments, the agenda does

include an item for Dr. McMahon or Dr. Chen, if you have issues from yesterday for clarification.

DR. MCMAHON: Thank you, Dr. Heeringa.

I just have one issue that I wanted to clarify regarding the March 2004 USEPA Publication on Examination of Risk Assessment Principles and Practices.

I just wanted to clarify that this document states quite clearly up front that this does not establish new Agency policy or guidance or amend any existing Agency policy or guidance.

DR. HEERINGA: Thank you very much for that clarification.

At this point in time, I would like to return to the sequence of public comments that we've had that we began yesterday morning, early afternoon. And at this point, I'd like to ask Dr. Joel Barnhart, who is

representing Elementis Chromium, if he would be willing to come forward and make his presentation. Dr. Barnhart.

While we take a moment here to set up Dr. Barnhart's presentation, maybe I can mention: If any of the other public commenters have presentations that they either have on a CD or DVD or a diskette, if they would like to bring that up. Or if you're going to bring your own laptop, I guess we'll make the transition when you're ready to speak.

I'll take this opportunity to -- we've tried to keep you abreast of items that have been added to the docket for these procedures. Dr. Menne yesterday afternoon distributed to the Panel a series of papers that he is a co-author on, recent work that they've done in your laboratories and clinics and Copenhagen. And those will be added to the docket as well.

We've also been joined this morning by Mr. Joseph Merenda who is the Director of the Office of Science Coordination and Policy at EPA. Good morning, Joe. I don't know if you wanted to say anything to the group at this point.

DR. MERENDA: Only just to express my appreciation for the very thorough discussion yesterday and look forward to further discussion today. I think the Panel is really digging into the issue.

DR. BARNHART: Good morning, everyone. I'm sorry for the delay. If I had known I was the first one to speak this morning, I would have spent a little more time getting ready, I think.

I'm speaking here as a technical person and not as toxicologist necessarily or as a physician. Let me get started here.

As I've said, I appreciate the opportunity to make this presentation. There

were a couple questions yesterday about the experience that people in industry have had in dealing with these chemicals. That's one of the things I'm going to be speaking to.

Certainly, if there's any experience that other members of the Panel or the audience are aware of that I don't cover or don't seem to have right, I would be more than happy to hear about it either here during the panel meeting or afterwards.

My background, and I have it listed on the slides. I'll continue on. I have listed my background there. Not all the speakers have done that. Most of them you know well. I'm sure you don't know me. I have, throughout my working career, been concerned with issues involving safety and health, my own health in particular.

Since I've worked in a variety of areas that offer a degree of hazard throughout my working career, I have been interested in

these issues. For the past 20 years, a little over 20 years, I've been working in the chromium chemicals production industry, and that's what I'm going to talk about in particular here.

I thought I'd start out -- Jonathan Chen did a good job yesterday of talking about chromium and some of the aspects of chromium. But that's really what my specialty is, in chromium and chromium chemistry.

Chromium, as you some of you may know, the word is derived from the Greek work chromo meaning color; and the different forms of chromium cover most of the colors of the rainbow.

It's the 17th more or less most abundant element, depending on whether you're talking about the crust of the earth or the surface soils or whatever. And as an element, it's as a picture; it's a hard silvery metal.

As Jonathan mentioned, the three

principal oxidation states are metallic, or zero oxidation state, the trivalent, and the hexavalent. And the hexavalent is the one that we're most concerned with. The trivalent is the form that is ubiquitous in nature. Nearly all the chromium existing in nature exists as the +3 oxidation state. There have been just very rare reports of either chromium metal or the hexavalent state in nature.

The trivalent state is the state that the ore is in that we receive when we convert it to other forms. The trivalent state is the state that's in nutritional supplements and various other multivitamins and is the essential nutrient that was mentioned yesterday.

We make chromium chemicals. And the major uses of chromium chemicals into the markets we sell are in the preservation of other materials, in natural materials in particular, such as leather, wood, iron. So

that's why it's found usually in fairly small amounts in a wide variety of materials because it acts more or less as a preservative.

If we look at the chromium industry in general, about 85 percent of the chromium mined as ore is used in the manufacture of stainless steel and specialty steels. Approximately 7 percent is used in refractories and in foundry grades. And that's a trivalent use.

About 8 percent goes into chromium chemicals. A little under 1 percent of the total chromium ends up being in wood-treatment chemicals.

Elementis Chromium, who I work for, is the largest manufacturer of hexavalent chemicals in the world. We're about twice as large as the second largest. We have more than 70 years experience in handling hexavalent chromium chemicals. And in the extraction of chromium from the ore in the

chemicals, it all goes through the hexavalent state. That's the way we separate it from the ore.

We fundamentally believe that a major factor in the fact that Elementis is now the largest chromium chemical producer, where 20 years ago it was third or fourth or maybe fifth on the list, is that we have been very conscious of health and environmental effects of hexavalent chromium and have taken that into account in the operation of our plants and in our interactions with customers and uses for these chemicals.

This is a photograph of one of our largest plants, and it's in Northern England. It's been in operation since 1927 producing chromium chemicals.

The second largest plant we have, and the second largest plant in the world, is a plant in Castle Hayne, North Carolina, just outside of Wilmington. They've been

manufacturing chromium chemicals since 1971.

In Corpus Christi, where I work, we have made chromium chemicals there since 1961. We have the largest chromate production kiln. And that's what we use to convert the ore to a hexavalent form. But due to market conditions, it's shut down at the moment. But it's still in place.

Typically, in our facilities, dermal exposures occur from very dilute solutions to up to our most concentrated solutions which are about 70 percent sodium chromium dihydrate or about 20 percent hexavalent chromium. So some of the solutions are very concentrated. The typical solutions that people come in contact with in our plants is between a pH of 4 and 10.

Our employees are closely monitored, especially for skin effects, because hexavalent chromium is an irritant for sure. And we've had discussions for the last day,

and we'll have more, on its other dermal effects.

In the plants over the last 20 years, usually there's been at least a monthly check of the employees especially their noses, hands, external skin, by a health care professional. Usually in the Corpus Christi plant, but usually in all three of the plants, it's by an occupational physician. Sometimes it's by an occupational nurse.

The most sensitive part of the body in our experience to hexavalent chromium, at least when it's present in a dust form, is nasal irritation. So that's one of the things that we monitor for on a frequent basis. We haven't had any significant nasal sores or certainly no perforations in a number of years. But that's something that we want to make sure we do prevent.

Up until about 15 years ago, chromium sores and other irritation-type

effects were common in the workers working in this industry. In some of the plants, because of the types of gloves available and the permeability of the gloves, people actually choose not to wear gloves in working with these chemicals because the gloves would get either saturated with sodium chromate or sodium dichromate or it would get inside the gloves and they would be then in contact, their skin would then be in contact with solutions, some of them very concentrated, for long periods of time. And we felt that that was significant with respect to the formation of chrom sores.

As gloves improved, as they were made more flexible so people could use them in doing their tasks, as we automated tasks where people didn't have to do so many manual things, as we put a lot more emphasis on people's hygiene practices and preventing these things, the last 15 years or so we

haven't seen any of these.

During the whole period that I've been in the industry at the three sites that are now Elementis Chromium sites, I haven't heard of any diagnosis for allergic contact dermatitis from the people that were working in these facilities. Now, no doubt, it could have occurred in earlier years where the contacts were even higher. But that's been our experience in our production facilities.

We also don't have any evidence of Cr(VI) causing sensitization in our employees or in contractors that we have come in and do jobs, removing refractories, removing equipment, and so forth, where they have opportunities for exposure to the hexavalent chromium compounds.

Certainly that's true for our three facilities. For facilities throughout the rest of the world, I can't say. And I would certainly be interested in hearing any

information that anyone else has on other chromium chemical facilities.

Also in my experience, I have an opportunity to talk to customers about their use of hexavalent chromium chemicals. I represent the company on several different health safety and environment committees and groups concerned about health effects of chromium chemicals.

The Chrome Coalition is a U.S.-based group that has about 15 companies and trade associations in it. The International Chromium Development Association is based in Paris, France; and it has 70 to 75 members in it, international members.

I have a lot of opportunities to talk to people. Some of them more open than others. But I'd like to pass along that experience that I've had anyhow. And, again, others that have contact with people in other areas may have other experiences.

Metal finishing is another one. Chrome plating is the biggest metal finishing operation involving people. OSHA estimates that there are over 200,000 workers in that industry that are exposed annually to hexavalent chromium. In talking to the people in that industry -- and in the last few weeks I've called around and talked to people again to make sure there was nothing I missed -- they say that they were concerned about hexavalent chrome irritant effects. They were concerned about nickel allergic dermatitis.

But hexavalent chromium allergic dermatitis has not been a major concern in recent years. As was reported yesterday, you can get reports from 30, 40 years ago that there was at least some problem there.

Wood treating, which is probably most appropriate for what we're considering here, hexavalent chromium irritant effects are concern there because they do deal with

chromic acid. It is the main hexavalent chromium compound that is used as a raw material.

The treating solutions, actually the chromic acid, is converted to a higher pH solution and it is more of an -- form. But I could find no reports and in talking to people in the industry could -- I didn't have any reports of diagnosed, at least, hexavalent chromium allergic dermatitis.

And in looking at the Bureau of Labor and Statistics data, they don't show any occupational-related allergic contact dermatitis from wood-treatment plants for that period of '93 to 2002.

We do talk to other customers. They are concerned about Cr(VI) irritation effects; Cr(VI) exposure in the air. We have developed low dusting grades of chromium acid to reduce the amount of dust in the air and exposures from that. But they don't mention allergic

contact dermatitis.

Another piece of information, OSHA is currently working, developing a workplace exposure rule for hexavalent chrome mainly concerned with inhalation but also about other exposures. In that, while they do mention the possibility of dermatitis in a variety of exposures, the one they concentrate on and that is the cement industry.

On the next slide is what NIOSH has said about the cement industry. And this is wet cement exposure in particular. And I think the wet is important. And in our own chemical plants, minimizing people's exposure to wet hexavalent chrome solutions for extended periods of time is one of the things that we do. And we believe that that's important.

The NIOSH statement here is, "In the United States, all cement contains chromium. Allergic sensitivity to dichromate is often

associated with cement dermatitis. In such cases, the primary irritant action is of alkali plus the abrasive and hygroscopic properties of cement precede and favor sensitization by chromium salts."

To me, they're expressing a sequence of events there. And pH in these cements is typically 12 to 12 and a half which is very alkaline.

To kind of summarize industrial experience from at least our experience and the experience of the people I have direct contact with and our customers, we have numerous exposures to dermal exposure to hexavalent chromium and don't see sensitization or allergic contact dermatitis as a major problem.

I, myself, when I'm not here in Washington, D.C., spend a lot of time in the plant and commission much of the equipment that we use in out plants. And I have

frequent dermal exposure to hexavalent chromium. So I'm concerned about it. But I'm just one person. But looking at our entire work force, they've had similar experience.

In relevance to the proceedings here, the EPA charged the SAP is to advise on strengths and weaknesses of proposed quantitative approach. And I would like to say -- and it was said yesterday and probably better than I can say -- that normal quantitative risk assessment methodology that is designed to assess risk of cancer, birth defects, and mutagenic affects, this has certainly justified highly conservative assumptions. Those are serious. Allergic contact dermatitis is serious, but it's fundamentally different from those effects certainly in my view.

Residual levels the hexavalent chrome on the surface of ACC-treated wood are anticipated to be much lower than exposure

levels in patch tests. Now, there was discussion yesterday on how relevant that is. I learned a lot yesterday. I might have said some of the things in my presentation differently if I had had all the instruction I had yesterday before I prepared it. But to me, this was meaningful. I understood that the patches were expected to be nonirritating and nonsensitizing to essentially everyone.

The surface of treated wood, the pH around five and a half is similar to skin pH. So I wouldn't expect corrosive effects associated with the chemical environment that hexavalent chromium might be in on the surface of wood. And the surface of wood is not like cement-type exposure because it's not abrasive.

My take on what I've presented in my experience is that the size of the uncertainty factors that are needed to compare various type of tests, including patch tests, in the

patch test, the exposure to 24 to 48 hours under occluded conditions is different as was noted yesterday from typical environmental exposures. And I would say that that should have an impact on what uncertainty factors are considered.

In LLNA test, again, I learned more about it yesterday. But to me the use of DMSO seems like something that's very appropriate when you're looking for what things sensitize and to make sure you get a positive response when you should get a positive response. How pertinent it is to develop quantitative risk assessment on is not clear to me. But that is not my area of expertise.

I guess my plea to the Panel is, in determining how conservative to be, to consider the endpoints in question, to take into account this is a reversible condition. And I think it's important to the Panel, to all of us as citizens and as consumers, that

we recognize that the preservation of wood structures is an important need for society. There's a limit on the number of forest.

There are structural safety questions. I think it is important, and I would hope that the outcome of these deliberations and the deliberations by the EPA based on what's determined by this Panel is that the use of this particular group of wood-treatment chemicals containing chromium is not overly restricted because I do believe it is valuable.

Thank you.

DR. HEERINGA: Thank you very much, Dr. Barnhart.

Are there any questions from the Panel to Dr. Barnhart? Yes, Dr. Menne.

DR. MENNE: I have two questions. One question is that you're seeing some irritation in the workers, skin irritation. And I presume this must be on the hands or

somewhere else. I'd like to know, since you exclude contact allergy, how have you done this? Is that by clinical impression? Or have people really been patch-tested, or how is this carried out?

DR. BARNHART: That's a good question. And to my knowledge, our physicians have not chosen to patch test any of the people. The people that do show irritation are not routinely removed from the exposures they have. If they do have some sort of irritation, and it's extremely rare nowadays at least to appear to be occupational related. Sometimes somebody will get poison ivy or some other thing.

The procedure we take is to make sure that the part of the skin that appears to be irritated from whatever, maybe it's a scratch from a pet or maybe it's poison ivy or maybe it's something that was developed in the workplace, is covered and protected in a way

that it won't be exposed to solutions containing hexavalent chromium the next day at work or that day at work.

DR. MENNE: But not patch-tested.

DR. BARNHART: As far as I know. And when this question came up, I was very curious about it, and I asked. And our physician, well, no, they haven't seen the need for it. So I don't know of any. I think that we've had a change in physicians over the 25 or 30 years a couple of times, and there may have been some in the past. But I could not find any records.

DR. MENNE: My second question is concerning the ulcerations in the nasal septum. That used to be a good indication of inhalation of chromate. At least in the nickel industry where they have similar problems, not with the nasal sores but with the nasal cancers, they similarly don't see allergic contact dermatitis. And that can, of

course, be improvement of industrial hygiene. But they also speculate with the inhalation in the factories of chromate lead to immunological tolerance so that the population we have in the factories is actually very different from the population you have among the consumers because they are immunologically tolerant because of chromate inhalation.

Can you comment on that?

DR. BARNHART: That's a very interesting point. I wasn't really aware of that until fairly recently that that was an idea, and it is intriguing. One thing I would say is, that in our factories, there's a wide range of exposures. Some of the people that are, say, packing chromic acid which is a dry solid material. It's called "chromic acid." It's really the anhydrous form of chromic acid is chromium trioxide that can be dusty. Those people are the people that have the most opportunity for this type of nasal irritation

because of the dust in the air.

Some of the other people like people working in the laboratories or people working in other parts of the plant generating power or something where they have occasional exposure to hexavalent chrome but don't have frequent inhalation-type exposures, their experiences as far as dermal effects in at least allergic contact dermatitis all seems the same.

And since this is kind of a wide range of inhalation-type exposures, I would think that that was at least significant in considering that. They all couldn't have become desensitized, I don't think.

DR. MENNE: Thank you.

DR. HEERINGA: Any other questions for Dr. Barnhart?

DR. FOULDS: If I could just make a sort of a clinical observation along similar lines. I've always been interested in people

working with sensitizers who have high levels of exposure. And a number of years ago, I investigated a plant which produced phosphorus sequisulfide which used to be a potent sensitizer in non-safety matches. And normally people who are allergic to this will react to this at parts per million.

In this plant, people were paddling around in the actual chemical with 100 percent exposure. I tested 20 people there. Some of them complained of sore eyes. And not one of them had a positive patch test with that sort of high levels of exposure.

This may be a similar situation to chromium that there may be some sort of induction of immunological tolerance. Or it may be that people who get problems are weeded out and disappear off into other industries. It's just an observation.

DR. BARNHART: I think that's a good observation. If I could respond to that.

As far as people weeding out, I feel confident that anyone that developed a sensitization would have -- we would know about because they would have developed a rash and come to the doctor. And if they did and eventually found that they could not work in our environment would leave, but we would know about that.

And in our facilities, people tend to work for many years. When I first came to the Corpus Christi facility, I think the average experience level was 18 or 19 years. So these people are not just people that come in for a few days and leave, and then we don't know what's happened to them in many cases.

Now contractors are different, and there could be some contractors that came in, did a job for two or three days, left, and developed something subsequent to that that we didn't find out about. But I think that that's not a frequent occurrence.

DR. HEERINGA: Thank you very much, Dr. Barnhart.

DR. BARNHART: Thank you for the opportunity. I'm sorry about the delay in getting started.

DR. HEERINGA: No problem. We've all been there.

At this point in time, I'd like to invite our next public presenter, Dr. Warren Stickle, who's speaking on behalf of the Chemical Producers and Distributors Association.

DR. STICKLE: Mr. Chairman, members of the Scientific Advisory Panel, EPA officials, and guests, my name is Warren Stickle. I'm president of the Chemical Producers and Distributors Association. I'm really very pleased to be here today and appreciate the opportunity to comment on EPA's examination of quantitative risk assessment in the context of dermal sensitization issues for

exposure to pesticides.

By way of background, CPA is a voluntary, nonprofit organization of about 90 companies engaged in the formulation, manufacture, distribution, and sale of about $6 billion of generic products used on food, feed, and fiber crops, and in the care of lawns, gardens, and turf. Many of our members are involved in the development and sale of adjuvants and innerts used to increase the efficacy and the efficiency of crop protection formulations as well as a variety of cover-based pesticide products. As such, EPA's rules, regulations, and guidelines affect our members companies significantly.

While CPDA understands that a driving force behind this Science Advisory Panel meeting is in part a focus on chromium, the potential impact for this discussion and possible mode of addressing chromium would extend far beyond chromium and address dermal

sensitization efforts from the complete range of chemicals our members produce, manufacture, distribute.

First, CPDA is not clear that there is in fact a health or environmental concern at issue. We ask of you as the expert Panel examine whether in fact there is a problem that is both real and widespread and about which EPA needs to be concerned. In this context, we urge you to consider whether in fact there is a pattern of allergic contact dermatitis associated with pesticide use and whether any such pattern suggests that the frequency of allergic contact dermatitis is on the rise. If there is no such pattern, CPDA questions what problem in fact EPA is trying to fix.

While the utility of a new tool that allows refined risk assessment is really welcome information, it's not clear EPA has a problem to which it needs to apply such a

tool. Simply stated, our concern is that the burdens that the potential quantitative risk assessment concerns raise are not in fact commensurate with whatever adverse effects may result from dermal skin sensitization to pesticide products.

While CPDA supports research into potential dermal risks, if you're going to develop a quantitative risk assessment methodology, it's really important to develop the methods and the tools that are scientifically proven and based on good science and clinical statistics; and that if you're going to apply this hypothesis, that you apply it across the board to not just one example but to all pesticides and all chemicals.

CPDA is also concerned about extending the potential impact of the quantitative risk assessment for dermal exposure on trade, small businesses, and the

already sizeable regulatory burden on our members companies, many of which are small companies. Our members produce and distribute many, many end-use products. And CPDA is concerned that the imposition of a new, overly conservative quantitative risk assessment approach to assessing the risk of generating a reversible skin rash in a hypersensitive population may limit the sale of these end-use products.

For this reason, we really ask that the Agency step back from the process and consider what the problem is that it intends to address if in fact there is really a problem here. If there is a dermal exposure issue screaming for attention out there, CPDA is not aware that any products its member companies are producing or distributing are the source of any such problem.

As an example, we note that the CCA-treated wood recently banned by EPA for

residential use because of the arsenic in the formulation was studied thoroughly by EPA and by two separate Scientific Advisory Panels. And in no instance was it determined that the use of CCA, which contains hexavalent chromium, was creating a health problem associated with hexavalent-chromium-induced allergic contact dermatitis. In fact, it's our understanding that there have been no complaints of allergic contact dermatitis from the handling or use of CCA-treated wood.

CPDA is concerned that EPA is becoming increasingly distracted from the other regulatory initiatives that are really very high, I think, in need of attention to our knowledge, sound science and real-life information. And we've heard a lot of important testimony over the last day that basically talks about the 60,000 human tests that have been done.

The fact that there's very little

occupational exposure, and all of these things where the use of the product leading to a documented health or environmental hazard. These are questions that are being raised. And we suggest that EPA's resources might better be used in some other areas. In essence, EPA has so many other things on its plate that we're really suggesting that they really don't have the luxury of expending resources to refine a tool to fix something that perhaps is not broken.

While CPDA is not adverse to the concept of a new risk assessment model and associated tools that go along with it, we are also concerned about the liberal use of overly exaggerated uncertainty factors that have the potential unfairly to remove safe and effective member-company products from the market place and the piling on of one conservative assumption on top of another conservative assumption frequently leads to

exaggerated estimates of nonexistent risk.

I'd also like to bring to your attention EPA's concerns that, when you're looking at and reviewing a dermal sensitization and where that has arisen in the context of a specific pending ME2 product application, and that in this process, EPA has attempted to impose some new and unprecedented policies and criteria for approving the ME2 registration application.

CPDA's interest in this general issue of whether EPA is really changing underlying rules, positions, rationale for the registration decisions affecting registration of ME2 products.

First, if you allow me to point out that in the context of the dermal sensitization, it's my understanding that EPA and the Office of Pesticide Programs has never identified dermal irritation as a health effect upon which EPA has assessed the

underlying registered ability of the particular pesticide. If dermal effects are to be assessed by EPA in considering the registration of one pesticide, they really ought to be applied to other pesticides and perhaps to all pesticides.

We're looking at a situation where in fact many, many pesticides could be implicated in such a review, and many of them could be unregistered or removed from the market place. In this case, what we would see is perhaps an unnecessary elimination of many products and the creation of a new de facto standard for the registration of pesticides.

Second, if EPA seeks to change it's policies or to newly mint criteria for approval or evaluation of applications inconsistent with past precedence in a manner that has a binding effect on all potential registrants, then we would respectfully submit that EPA has not followed appropriate

procedures and requirements in developing such requirements.

To our knowledge, EPA has never articulated or even hinted at establishing new requirements or new policies in this area; nor has it explained why any such changes would be necessary. To do so now and apply a change to pending registrations or policies would be contrary to EPA's much publicized commitment to due process, to fair play, to transparency that was most recently suggested in late 2003 in its paper entitled, "OPP Procedural Guidance for the Development, Modification, and Implementation of Policy Guidance Documents." I believe that's the so-called policy and policy statement.

In this document, EPA renewed its commitment to increase public participation in the development, modification, and implementation of OPP policy guidance documents. And we think that's an important

step in that direction. But to establish sweeping new FIFRA policies in this context that we're talking about would be inconsistent with what I believe the policy on policy statement is all about.

I want to thank you very much for the opportunity to be here and to speak on behalf of the generic pesticides industry. And I look forward to working with the Scientific Advisory Panel as it comes to grip with these issues. Thank you very much.

DR. HEERINGA: Thank you very much, Dr. Stickle. Are there any questions from the Panel to Dr. Stickle's presentation? Thank you very much.

DR. STICKLE: Thank you.

DR. HEERINGA: At this point, I would like to invite our next public commenter, Dr. Jane Vergnes, who is with the ISP Corporation but here on behalf of the ACC Biocides Panel.

DR. VERGNES: First, I'd like to thank you for the opportunity to present these comments on behalf of the American Chemistry Council Biocides Pane. I am Jane Vergnes. I'm a manager of toxicology at International Specialty Products. And I've been in that capacity for about two and a half years.

I was trained at the University of Pittsburgh Graduate School of Public Health, so I do come from a public health background. And I have gone from being a study director of studies that are conducted under various test guidelines to the risk assessment end.

Right now I have placed several studies using the LLNA procedure, so I do have, not direct experience hands-on with the assay, but have had experiences running the assay and using the data as well as experience in the risk assessment and science policy areas.

I've also had occasions where I've

been on the telephone with clinical dermatologists or with workers in the workplace who have had issues with allergic contact dermatitis. So I'm also familiar with the human practical day-to-day side of that.

Basically, the Biocide Panel's comments are oriented toward technical and risk assessment issues and not specifically about Cr(VI). But we are concerned about this process being a paradigm for how dermal sensitization risk assessment will be done in the future. And I'll keep my comments brief.

The Biocides Panel would like to commend EPA for its efforts to advance the science of human health risk assessment with regard to the dermal sensitization endpoint. The Agency's interest in developing risk-oriented, weight-of-evidence approach that considers sensitization thresholds, area doses, and exposure conditions are welcomed by the Panel as important in development of a

sound scientific approach.

But we have several process concerns about the consultation as well as scientific concerns about the methods that EPA is proposing to use for quantitation of the potential risk to humans of determine sensitization subsequent to pesticides exposure. And, first, I'll talk a little bit about the process concerns.

Given the impact that this consultation may have on methodologies that will be used by the Agency to evaluate many pesticides, the Biocides Panel would have welcomed the opportunity to present more detailed comments to the SAP. That wasn't feasible within the time frame that was provided for public comment.

Second, while the Panel recognizes that the members of the SAP are highly qualified experts in their fields, we feel that the consultation process would have been

better served if one or more of the scientists involved in the laboratory effort to validate the localized lymph node assay and to explore the feasibility of the sensitization reference dose methodology could have been included among the Panel members. And we are concerned about the lack of this specific technical expertise at this point in the development of this assay.

And, again, we think that the Panel would have been strengthen by the presence of a U.S.-based clinical dermatologist who has the U.S. workplace exposure context in their experience.

We have three principal technical concerns. The first is the use of the LLNA data as a basis for quantitative human health risk assessment for this dermal sensitization endpoint. Some concerns about the use of the minimum elicitation threshold concept; and, of course, we're concerned about the basis for

the uncertainty factors and how those will be determined.

The Agency noted in a December 2001 SAP report that the LLNA, "is applicable to test chemicals for the potential to elicit allergic contact dermatitis." And this is a hazard characterization endpoint. And we should also note that the assay as it was validated was validated for that purpose.

The Biocides Panel agrees that the LLNA, when properly conducted and interpreted using the total weight of evidence approach, is a useful method for predicting the potential for allergic contact dermatitis in humans. As the Agency has noted, the assay is objective, evaluates dose response, and has been validated very well and offers animal welfare advantages.

However, although the assay has been subject to extensive interlaboratory validation studies and is a standard assay

with an approved OECE protocol, industrial experience with the assay as a hazard characterization tool is still limited. Given that data bases for assay validation are heavily weighted in agents that are likely to be positive in the assay and the relatively short history of experience with this assay outside of the laboratories that were involved in the validation effort, it would be prudent to gain more experience with the technique before making it a critical element in a regulatory quantitative risk assessment process.

We've heard anecdotal reports about test articles that are false positives in the assay. They're beginning to surface more frequently but haven't reached the peer-review literature yet. Other biological phenomena unrelated to induction of an allergic response but capable of causing radiolabled thymidine incorporation in the auricular lymph node are

not always well understood among the personnel conducting the LLNA in the contract laboratory environment.

Choice of vehicle for the assay and of the dose range is intended to maximize exposure in order to identify potential hazards. However, such test conditions may provide information that does not reflect potential human exposure conditions either qualitatively or quantitatively and, therefore, limits the utility of the data for risk assessment because the exposures are too different.

Until more is known about the predictivity of the LLNA under real-word conditions, what types of test articles are likely to elicit false positive results, greater availability of tools to discriminate true sensitizer from irritants, it's not sound scientific practice to expand the use of the data generated of by assay in to quantitative

human health risk assessment.

Furthermore, the assay was developed as a relatively quick screening tool that would identify potential hazards while reducing the number of animals and the potential of stress to animals. It is focusing only on the induction phase of the response. And it was designed sort of to function as other short-term tests. It's kind of like the ones we used to identify genotoxic hazards. The use of LLNA for quantitative human health risk assessment would be similar to using results of genotoxicity tests to perform quantitive human health risk assessments for the cancer endpoint.

The Agency's pointed out that a number of investigators are exploring the use of this assay to rank relative potency of sensitizers. And we would like to emphasize that this is still a research activity and that the types of data of suitable quality to

establish relative potency are different from those needed to perform quantitative estimates of potential health risks to populations.

The Biocides Panel also questions the relevance of extrapolating MET data developed in a few sensitized individuals to human populations. We're not likely to have sufficient information to address issues such as how much quantitative variability exists among sensitized individuals with respect to other elicitation doses.

After the comments that were made yesterday, we can see that there is more information out there. But still from the point of view of looking at population, are we really going to have a large enough population to look at in this assay to get a good idea of variability?

Presumably use of a sensitize subpopulation would obviate the need for some uncertainty factor. However, without the

information addressing variability among sensitized individuals or what proportion of an exposed population becomes sensitized, the appropriateness of using these data for population risk assessment is questionable. And where no such data exists, we question whether it's appropriate to perform studies in sensitized individuals to generate the data.

We certainly don't want to limit the use of high-quality data based on human experience when they're available and were generated under widely accepted ethical standards.

The third point of technical concern to the Panel is the use of default uncertainty factors. It looks like uncertainty factors of up to 10,000-fold might be applied assuming a worse case factor of 10 for each of the areas of uncertainty in the risk assessment: One for interspecies variability and susceptibility, a second for interindividual

variations, a third for vehicle or product matrix effects, and a fourth for exposure considerations.

The Panel would like to note that this aspect of risk assessment methodology has not been developed for the dermal sensitization endpoint since strong quantitative data haven't really been available. And the application of uncertainty factors in the manner proposed by the Agency could lead to unnecessarily conservative estimates of sensitization thresholds. This is an area where further research and discussion are needed before quantitative risk assessments are performed.

Just to summarize, the Panel favors a weight-of-evidence approach that includes all data relevant to the dermal sensitization endpoint. We encourage a broader scientific discussion of quantitative risk assessment methodologies that may be applicable to the

dermal sensitization endpoint. Further study of the LLNA and any other approaches that may provide quantitative data should be encouraged.

Experts currently engaged in research into the feasibility of using the LLNA in human health risk assessment should be brought together to validate this new proposed use of the assay data. The expertise of dermatologists, research scientists, risk assessors, and other appropriate scientists should be engaged to study, review, and recommend appropriate methods for conducting dermal sensitization risk assessment and consider the current state of the science.

And the Biocides Panel would welcome the opportunity to work with the antimicrobials division in the development of sound scientific approaches to dermal sensitization risk assessment.

DR. HEERINGA: Thank you, Dr.

Vergnes.

Just for the record, I'll make a note. The agenda shows your representation of the ACC Biocides Panel. Is that correct?

DR. VERGNES: The American Chemistry Council.

DR. HEERINGA: Okay. So it is ACC.

DR. VERGNES: Right.

DR. HEERINGA: Thank you very much. Are there any questions for Dr. Vergnes at this point?

DR. HAYES: Is it possible to get a copy of her statement?

DR. VERGNES: We have it.

DR. HEERINGA: We do have it in the packet. If you don't have it, it was distributed, I believe, yesterday, Dr. Hayes.

DR. HAYES: Thank you.

DR. HEERINGA: Any other questions from the Panel? Thank you very much.

DR. VERGNES: May I make just one

other comment that's not in my prepared statement?

DR. HEERINGA: Absolutely.

DR. VERGNES: In going back and looking at the LLNA data -- and, again, this is an assay where unfortunately I'm engaged in a research program because I have a compound that happens to be, we believe, a false negative in the assay -- it's a compound that has been widely used in humans, so there has been human exposure, extensive human exposure, for many years without any reports of adverse effects.

It came out as a strong dose response positive in the assay, and we don't know why. Again, the material doesn't have evidence of it being a strong irritant. But it has brought to my attention that, as this assay is transferred from the laboratories that are very experienced with it to laboratories that were not involved in this

validation process, that there is a lot that other users don't know about the assay yet that are important in developing the assay and interpreting the data.

And as I was going back through the ICVAAM, both the full property report and the peer-review publication of their report, a couple of things that came to my attention were that, of the 209 chemicals that were tested, there were several materials that are known genotoxins that are positive in standard assays for genotoxicity and some of which are carcinogens.

They include substances such benzopyrene, ethyl methane sulfonate, I believe ethyl nitrosaluria, and a few others. And these compounds were positive in the LLNA assay. We don't have any data as to whether or not these materials are sensitizer. But one of the points that this brings home is that there are other phenomena that may be

occurring upon exposure in this assay where you're looking at incorporation of either tritiated label thymidine or some other analog. That may not reflect a sensitization response. It may not reflect initiation.

DR. HEERINGA: Any questions from the Panel in response to this last? Yes, Dr. Burleson.

DR. BURLESON: Well, I think what I hear you saying is a resounding endorsement of the local lymph node assay. And it seems that you have experience with it. It seems to me that the negatives that you're bringing forth, for example, of laboratories performing this test when they're not qualified, I would think that has happened in every area of toxicology; and we know that is a problem. But I don't think that is a reason to disband this.

It seems to me that your comment that the one false negative was a surprise. And I think there are more false positives

than there are false negatives. And I think that's good if you want to have one or the other. So I do think we need more trained laboratories to use this tool. It's an excellent tool. And if I read the documents correctly, it's only to be used as a starting point for QRA not as a established method for QRA.

If we don't take the training wheels off, we're never going to ride the bicycle. You know, I think it's an excellent starting point.

DR. VERGNES: I don't mean to imply that the laboratory that I've had my unfortunate experience with was unqualified. What I'm saying is that, in the development of any assay, as the assay moves into more general use, there is going to be a period where communication of knowledge and experience and improvement of technical expertise, there is going to be a period where

we learn a lot more about the assay than was learned in the initial stages even when you had a very well conducted validation assay.

And, again, the validation assay was conducted from the point of view of a yes/no type of approach, sensitizer or not a hazard classification not from the point of view of quantitation or ranking or anything else. Those approaches are still experimental. They haven't been through validation.

So I don't mean to imply that the individuals that are conducting or that conducted the assay for me were inexperienced. They were experienced. It's just that, again, I think that this is something we have to recognize about where we are in the development of this assay.

And that if we go back to other assays that have been brought into general use, we will find parallels with those; that only after they were in broad use did we find

out about some of the things that could confound the results, some of the things that need to be considered in interpreting whether a positive result in the assay means you have a sensitizer.

DR. HEERINGA: Any other questions? Thank you very much, Dr. Vergnes.

We have one more scheduled public commenter. And that is Mr. Richard Wiles who is speaking on behalf of the Environmental Working Group.

MR. WILES: Thank you. I'm here to make some general comments about Cr(VI.) I'm not any kind of an expert on dermal sensitization or this bioassay. And I think one of the reasons environmental groups haven't been here is that we really don't have a lot of information on what we think is the main issue here, which is the risk that Cr(VI) might pose to workers and the public by dermal routes or oral routes if it becomes the

replacement for CCA. So I'll keep this really short. And, hopefully, I won't get kicked out.

We worked hard, along with the EPA staff and some portion of the wood-treatment industry, to achieve the phase out of CCA, the arsenic-based wood preservative. We considered it a major step forward, one that some sectors of the wood-treatment-industry seem willing to accept. In fact, some portions of the wood-treatment industry embraced the transition to safer alternatives and are not planning to use ACC.

But then along comes ACC. And I got to tell you, our first reaction was, you got to be kidding me. Cr(VI), a known human carcinogen by inhalation, is the safe alternative to arsenic. But anyway, here we are with Cr(VI) as a safe alternative. So don't worry, we're told, the chromium is all fixed in the wood and transformed to Cr(III).

Which we know in fact does occur, but the question is how fast.

And the answer we get from the Agency -- and I think that's the answer that's an honest answer -- is that they don't know. Those data aren't in yet. So dermal sensitization, cancer risk, environmental fate, we, the public, really have no data at all that is relevant to the actual end use of this material on the wood as it enters commerce and the risks that will occur dermally in terms of cancer or any environmental issues.

Obviously, there's lots of peer-reviewed literature on dermal sensitization. But there's not much known about how this pesticide is going to behave and the risks it's going to present when it's actually used in commerce. So all I can do is raise the issues that we hope the EPA will consider and that you might consider as well

because this may be the last SAP Panel that reviews any aspect of this pesticides use.

But before I do that, let me remind you why ACC has not been on the market for 50 years. Why has the chromium-based pesticide not been on the market for about 50 years in any significant degree? Because it doesn't work. The chromium has no pesticidal value at all.

It's in there to fix the copper basically in the compound. But in the end, in fact, it's not even recommended or may not be used. It may be allowed, but it isn't used for any ground-contact uses because it has no insecticidal value at all. That's what the arsenic did in the prior formulation.

So in and of itself, the chromium is basically all risk and no benefit. In our view, that doesn't pass the basic test in the pesticide law, even FIFRA, which is a pure risk-benefit balancing statute. So the

proposal in our view is to put a dermal sensitizer and an known human carcinogen that doesn't even work as an insecticide into wood products to which thousand of workers and millions of people will be exposed.

Even as -- and this is the ultimate irony to us -- major players in the wood-treatment industry, pesticides companies stand poised to utilize far safer alternative products. They'll probably be edged out of the market place, though, if ACC is registered.

So the scenario plays out like this as far as we can determine. Putting ACC on the market will expose workers to a major dermal sensitizer and a hell of a lot more of a carcinogens, Cr(VI), than they're being exposed to now. Not a problem we're told.

Then they ship it to Home Depo, Lowes, mom and pop hardware stores, where presumably the Cr(VI) is not completely fixed

yet and there's a large dermal contact. Not to worry. It's a negligible risk. We don't have the data yet, but don't worry.

Then we sell it to contractors and homeowners, and presumably the Cr(VI) is not completely fixed either; or maybe it is. It might be, but we don't know. Then these people saw and sand and hammer and build stuff and create a lot of dust with Cr(VI) that's inhaled which is our real concern.

What is the risk to carpenters who day in and day out saw and build with this material? We don't know? Nobody does. But we know it would be a lot riskier than working with the alternative, ACQ, which is what many players in the pesticides industry would like to get on the market.

And for people that work at EPA to have me here saying anything good about anybody in the pesticide industry just has to tell us how concerned we are about Cr(VI) or

just how amazed we are that we're dealing with Cr(VI) as a safe alternative product.

So what's the exposure to Cr(VI) or Cr(III) on the desk or the playset with the kids crawling all over it that we just built after we bought it from Home Depot. Oops, sorry. We don't know that either. And then let's clean that deck with a bleaching compound which makes more Cr(VI). Is that a problem? How long until the Cr(VI) refixes? Well, we're not sure. But we're going to get back to you on that one as soon as possible.

And then there's the fact that Cr(VI) doesn't work anyway as a pesticide, so the deck won't last very long. So we'll have to tear it down when there will be more dermal sensitization, sawdust inhalation. And then we'll ship it to a landfill where the Cr(VI) will leach into the ground water, unless, of course, the companies get an exemption from hazardous waste requirements as the arsenic

guys did.

So to us, obviously, these are not the kind of probable comments that you've been receiving on the methodology related to the dermal sensitization test. We think dermal sensitization is an issue. It should be looked at.

The real issues here are the broader issues of the cancer risk from the Cr(VI) to the workers who make this pesticide, the workers who inject this pesticide, the workers who sell the pesticide, the workers who work with the pesticide, and the homeowners that may or may not be exposed to Cr(VI) when the deck is in place after it is built with this pesticide.

We think we can do a lot better than ACC as a newly registered pesticide in the year 2004. We know we can. And we hope that we do.

Thank you.

DR. HEERINGA: Thank you very much, Mr. Wiles. Are there any questions from the Panel first? Thank you very much for your comments.

At this point in time before we move on, this is the period of public comments. And there's been a tremendous amount of information, scientific, experiential, exposure presented in the last six to eight hours of our session. And I would like, in fact, to give one more chance. And I would hope people would be to the point and concise in their comments, either for the EPA or for prior public commenters, to offer points of clarification or rejoinder at this point.

I'll begin with the EPA. Dr McMahon or Dr. Chen?

DR. CHEN: I'd like to make some kind of clarification. For CCA-treated products, we do see different kinds of instance related to dermal effects. And most

of those are more like newly treated decks or a person working on the CCA-treated wood. And the reasons that we didn't really pinpoint that as chromium-related because we know arsenic also has some kind of dermal irritation effect.

So at this moment, we don't have any instance related to ACC. Because at this moment, it's not really registered yet. And so this is something I'd like to point out.

And for the CCA risk assessment, at this moment because we don't have the method to really to assess the dermal-related effect. And for the wipe studies that we have for the CCA, basically those are for decks that are already put there for a while. So we don't -- so at that time the Cr(III) is a primary one that's being detected. So this is the reason that we didn't really look into the effect for the CCA risk assessment.

So it's not really said that we're

not concerned about this. And I think this is the primary reason we bring this issue to this Panel.

DR. HEERINGA: Thank you, Dr. Chen. Is there any other public comment at this point? Yes, Dr. Morgan.

MR. MORGAN: Thank you. Dennis Morgan with Forrest Products Research. A couple of rebuttals or comments with the last public speaker.

The Environmental Working Group may not be aware of the data that is out there. But the EPA has requested some of the cancer studies that were discussed and some of the worker-exposure studies. And, Dr. Chen, I believe you asked me yesterday about some sawdust issues.

While there's no with dermal sensitization which was going on, we have some studies on the inhalation exposure to people cutting wood, freshly treated wood, within one

week of treatment, an hour a day for a period of time. So those issues weren't brought up yesterday because they weren't specific to dermal sensitization.

In the discussion of the wipe study and that fact that we have not submitted data to the EPA, we've been in discussion with the EPA on the protocol for that. But from a registrant's point of view, until you know what the goal is, what the level is you have to be at to be at a safe standard, doing studies and, say, you're floating around out here without knowing where the goal post is, that's not a wise use of resources or money.

You know, we have a certain belief where the dermal sensitization, the hexavalent chrome point is safe for leaving the plant. We do know that once it leaves the plant, the reaction continues. In warm summer-like conditions -- you saw some data from Dr. Cooper that says it happens very fast.

It's not like it -- this product is somewhat unusual in the fact that, depending upon the time of year and when it gets into service, the time from Cr(VI) and Cr(III) in the amount on the surface changes depending upon the weather conditions. These are all part of the exposure factors that we think goes into the risk assessment in discussing on some of these uncertainty factors.

I think the issue that I didn't make clear yesterday, Dr. Meade did a decent job of bringing me to a point. I'd like to reemphasize it. That is we do think that the LLNA is a tool. And it has a lot of possibilities. And I think it is a fairly well-validated tool for Cr(VI). I'm not comfortable in speaking to other chemicals as to whether it's well-validated.

But what we're concerned about and what we tried to point out with the patch test, and with the Ryan test where they did it

in water, wasn't the application to the LLNA. It's where the uncertainty factors fit into the use of the LLNA data in reaching a regulatory endpoint and how other test data or other human experience should be added or reviewed when discussing uncertainty factors on the input.

Our concern is you have a chance, and then it becomes a mathematic odds rate formula in going forward without any reference to any other experiences. And that's what we were trying to put forward.

Thank you.

DR. HEERINGA: Thank you very much, Dr. Morgan.

Any additional contributions to this public comment? Yes, Dr. McMahon.

DR. MCMAHON: Thank you. Regarding the presentation by Dr. Stickle, I just wanted to clarify that. He may not be aware.

We have considered dermal irritation

previously as a health endpoint when considering the registration of a particular pesticide product. I'm certainly not at liberty to discuss confidential matters related to the pesticide product.

But I just wanted to let you know that the matter has come before us previously, and we have dealt with the issue regarding dermal irritation at least in the registration of a pesticide product. So the issue for us does go back a few years.

And also keep in mind here, and I think we all know this, that while we do have a specific issue before the Panel regarding chromium, we do have a number of significant science questions in general to the Panel related to dermal sensitization. Those are also important to us, scientific methodologies outside of regulations or policies which we're not here to discuss. So I just wanted to clarify that. Thank you.

DR. HEERINGA: Thank you very much, Dr. McMahon.

Seeing no additional interest from the public, I'd like to draw the period for public comment to a close. We're at just shy of 10:10. I would recommend that we take a 15-minute break and return here at 10:25 at which point we will have a period of general discussion. And I think a review by the EPA of its approach of considering uncertainty factors or available approaches in considering uncertainty factors in risk assessment.

See you back here at 10:25.

[Break taken at 10:12 a.m.

Session resumed at 10:30 a.m.]

DR. HEERINGA: Let's begin again.

Welcome back to the continuation of this meeting of the FIFRA Scientific Advisory Panel on the topic of the Consultation on Dermal Sensitization Issues for Exposure To Pesticides.

And I just want to mention that Dr. Jack Helsinger of the Antimicrobial Division, Office of Pesticide Programs, is also going to be joining us at the table here.

At this point, I mentioned earlier this morning, that members of the Panel were interested in hearing from the scientific staff at the EPA their thoughts on approaching uncertainty factors in the assessment of risk for dermal sensitization. And I think at this point, Dr. McMahon or Dr. Chen.

DR. MCMAHON: Dr. Chen is going to make one comment before I start.

DR. CHEN: This is Jonathan Chen. And the Agency has just made another kind of paper done by Thompson and Baresto as one of the background material.

DR. HEERINGA: Panel members have received that by the way.

DR. CHEN: Yeah. And, basically, in this paper it says for the chromium

sensitivity, dermal sensitivity is like kind of decreased from 1972 to 1996. However, there is a trend. It's like it's coming back. The incidence is increasing again. And so I just include this as one of the reference to the Panel members.

DR. MCMAHON: Okay. I'm going to, hopefully, provide some insight and clarity to the question of areas of uncertainty with respect to the dermal sensitization issue.

Yesterday in my presentation, I mentioned four areas that are considered, at least in the proposal of methodologies regarding scientific uncertainty, that being interspecies extrapolation such as results from animal tests to humans, obviously intraspecies variations within humans, product matrix effects, and exposure considerations.

Two of these, as I think we all know, the interspecies and intraspecies uncertainty factors, are traditional factors

used by EPA and other agencies when using the results of animal tests to make determinations of hazards and risk in humans. So the standard in that respect has usually been a factor of 100, a 10-fold factor for each of those two areas as a maximum unless there are other special circumstances. That can range, obviously, from 1 to 10.

With respect to dermal sensitization in this regard, we've seen that some proposals have suggested that the interspecies factor can be less than 10 based on the results of, for example, the LLNA data that seemed to correlate somewhat well with the human testing experience.

And with respect to intraspecies, we've also seen in one of our proposals that it could be less than 10 based on, for example, the use of sensitized populations that seem to show less variability in response.

I think two unique areas for us, that actually have been not published though, are with respect to the product matrix and the exposure. I would just mention that, with respect to Dr. Gerberick's publications and reviewed by Susan Felter, the product matrix with respect especially to cosmetics may need to be considered as we mentioned because of formulation that may alter the potency of any sensitizing chemicals that are in a formulation.

And exposure considerations, obviously, being repeated exposure or patterns of use for certain consumer products that also includes where the product may be applied or then integrity of the skin and environmental conditions of exposure. These were mainly considered previously in the area of consumer products. But we know also that we have pesticide formulations from active ingredients that may need to be considered in that respect

with product matrix.

Dr. Griem's approach also includes an interspecies and intraspecies uncertainty factor. And as you've seen in some of his proposals and in his public comment that these are not always a factor of 10 depending on sometimes the chemical of interest. In his proposal, the exposure is more of an issue with respect to the time issue or repeated exposure because, as he has mentioned, the repeated exposures that could result in a subclinical sensitization or the effect of repeated exposures at lower dose on induction of the allergic contact dermatitis. So he includes an uncertainty area for that.

Each one of these, obviously, is not set at a specific level but is sometimes dependent on the chemical and dependent on how that chemical is used.

I hope that perhaps provides... I'd be happy to answer any further questions on

those areas.

DR. HEERINGA: Any questions? Dr. Hayes.

DR. HAYES: Can I go back to the interspecies and intraspecies?

When these are used classically, you can account for the differences based on pharmacokinetics and pharmacodynamics. But that's only if you've got specific chemicals. And I think these people are just making arbitrary adjustments based on experience coming up with their number of 3 or the number of 8 or whatever.

And, traditionally, if you don't have the kinetic and dynamic data, 10 has been the default. And so I need some help in understanding why you guys are moving to a 3. I think that's the number that you moved to.

DR. MCMAHON: For the --

DR. HAYES: For the interspecies.

DR. MCMAHON: Interspecies. I

think, in our reading of the material, that was based on the fact that the animal data results for, I think it was, induction thresholds were not very dissimilar to the thresholds observed from the human studies. And that with respect to...

DR. HAYES: Again, in those studies, that was just an arbitrary number that the authors chose. They didn't give, if I remember correctly, a basis for choosing that number other than it's closer to humans.

DR. MCMAHON: Right. I don't believe there was a specific discussion of kinetics or dynamics. And I do think it can vary by chemical. Right. But, obviously, there's that general question that you raised. And then there's the question of the specific chemical that we're talking about and how much data do we have on that chemical.

DR. HAYES: Do we have the kinetic and dynamic data for Cr(VI), which I don't

think we do, by the dermal route?

DR. MCMAHON: I don't think we have it by the dermal route. I do have some data by the oral route.

DR. HEERINGA: Dr. Meade has a question.

DR. MEADE: Maybe just to add to that question. My understanding of the reduction in that is based on the development or the induction the sensitization being a dose per surface area phenomena as opposed to a mg/kg dose whereas the induction takes place in the skin. So penetration through the skin really will relate more to permeability coefficients of mouse versus human skins and concentrations of Langerhans cells in the skin, and that the human and the mouse are much more closely aligned than, say, pharmacokinetics for on orally ingested or injectable dose.

DR. HEERINGA: Any other questions

about in relation to the discussion on uncertainty factors from the Panel? Yes, Dr. Hayes again.

DR. HAYES: Can you explain a little bit more the matrix; and also, the exposure, how it differs from the exposure element in a risk assessment?

DR. MCMAHON: Okay. I'll see what I can do.

With respect to the matrix, and this is, I think, a general answer not really chemical specific so much. With regard to how the products may be formulated from active ingredients and components of that formulation has been suggested that some components may alter the potency of whatever may be considered sensitizers in there.

So, therefore, having an effect on potency, say, if it were to increase, that area of uncertainty would have to be dealt with if we didn't know for sure that the

chemical may cause a great effect but we suspect it may, applying a factor for how the sensitizer ends up in a product.

I think with respect to exposure --

DR. HAYES: Before you get off of that. If they could show that in the wood that it was tightly bound and didn't come out, you would give a smaller number to the matrix factor than if a tremendous number leached out it would be a higher number?

DR. CHEN: Well, I think at this moment we need more like clarity to kind of differentiate the Gerberick approach and the Griem's approach. And Gerberick's approach basically is more like a product-specific kind of approach. Because in many cases that deal with may be cosmetic or some other kind of -- it's product-specific. So they have concern that in some kind of product itself may contain some kind of like a dermal surfactant or some kind of irritant. It may increase the

penetration of that allergen going through the penetrated skin. So it can increase the possibility to initiate the allergic contact dermatitis.

So Gerberick's approach is more like a product-specific approach if we really, really look into the detail of this kind of approach. So for the same chemical may have different kind of endpoints or CCDS based on what kind of product it's in.

And Griem's approach is more like a traditional risk-assessment approach. So, basically, just interspecies variation, intraspecies variations, and repeated exposure variation. Because the approach, it was proposed based on the LLNA data. So he thinks the limited exposure may not be enough to initiate the direction. Maybe at the lower concentration, lower term more frequent exposure may increase a chance to initiate the reaction.

So Gerberick's approach does have the matrix effect. But in Griem's approach, they only have more like time, the frequency exposure kind of uncertainty factor.

And I discussed this issue with the researchers in Gerberick's group. And they said some of the more like a frequency consideration they included in the use condition kind of uncertainty factor because they do have a use condition uncertainty factor and use condition because they are talking about cosmetic or some kind of a specific product. So they do have like the body of exposure or the integrity of the skin. Sometimes they have the exclusion or something. Those kind of things would be included into.

So there are more like -- these two groups they have proposed a different kind of approach. And sometimes they are overlapping in uncertainty factor. And the endpoint

selection process is also different because one is basically used strictly from the animal study and other the one is basically going to a group unless he finds a specific number for that group. So this is the difference.

So the reason that we use the matrix effect for the wood and because we -- for chromium, once it becomes a problem, then it become -- that is in the state that we consider Cr(VI) is a primary concern.

And in my presentation, I emphasized that Cr(VI) is more like water soluble. So it tends to leach out to the surface. So when you touch the surface, that includes more like a rubbing to the wood surface and those kind of things. So those kinds of things is considered more similar to the matrix effect. So we put 10 in our proposed approach. We're not saying it is exactly. This is our thinking.

DR. MCMAHON: I just would add a

little bit if we were talking about exposure. As I mentioned, the site that might be exposed on the body, I think you all know better than I about differences in skin type and susceptibility to that kind of reaction depending on where the exposure occurs. And if we're talking about chromium specifically, then we have issues with integrity of the skin as we know it's an irritant. And I think it might be able to facilitate its own penetration and subsequent reaction of that nature.

So as far as a matrix effect occurs, I think Dr. Chen is correct. It would have to be considered sometimes chemically specific. But as you've seen, there are two different approaches. One is a little more specific, and the other one is a little more general.

DR. HEERINGA: Any other questions from the Panel?

I'd like to maybe address this issue

with you a little myself because it's been one that I have struggled with over my years on the Panel, the uncertainty factors.

I think it's clear that the intent is for these factors to represent uncertainty in the extrapolation of the underlying data, not only maybe to another species or to another population, and then to somehow account for uncertainty which relates to the particular set of clinical or experimental data we have as it might extrapolate to a human population within the species.

We're not trying to build in safety margins per se. When all is said and done, we might decide on a safety margin. But we're really trying to account for quantitative uncertainty in the data that we have and are using it as a basis than for establishing the base-dose response relationship or threshold.

So in interspecies for example, we're saying that if we do a test or assay in

a rodent or a guinea pig and we now have to take that data and extrapolate it to a human population, we're going to allow an order of magnitude shift in the X-axis on the dose. And everything else remains the same because the data that's used to fit these points, that's used to fit the shape of the dose-response curve, we're just going to 10 exit essentially; on log 10, we're going to shift the axis on the dose.

In some ways that's what we're doing there. So to consider the uncertainty factors for interspecies, we're really looking at what sort of shift on that log-dose axis would we anticipate potentially just as the result of the fact that we're dealing with one species versus another.

And then intraspecies is always also a little difficult because in some ways that's a variability component and you've already made the shift for the interspecies. And so

you have a dose-response relationship which presumably should be across the population of individuals, but now we're sort of 10-Xing that at any point. Which says that over 10 trials of an individual whose dose point on this dose-response curve would be this, we're also allowing that over 10 trials to have as much as a 10-fold variability.

I've always been a little concerned over the compounding of these. It's essentially compounding these factors. If you think about, what you'd like to look at is the joint uncertainty of the extrapolation from a set of data to real population dose-response relationships. And I guess as we get these multiplicative factors, my own sense is that it is very easy to be conservative.

And in other settings, particularly carcinogenic settings as opposed to the dermal sensitization setting, I think allowing this sort of conservatism by compounding these

uncertainties and then effectively building in through that compounding of a margin of safety. I think there may be justification there.

But I think in this these types of issues, I'm concerned that we have too much compounding of uncertainty, numerical uncertainty. And, you know, very honestly, if we wanted a greater safety factor, I could see justifying that in these terms. But in looking at the actual extrapolation from a particular set of clinical or experimental data or test data into real populations, I think we have to be very careful in thinking about exactly what these factors are doing.

And I see them as essentially accounting for uncertainty, true uncertainty, in how if we could actually conduct that particular dose-response experiment with the population, in a large enough population -- if we could get the true dose-response population

that occurred in the U.S. population, set error bounds not only on the estimation of that, but the prediction of an individual outcome for an individual, I think we'd probably be satisfied with that and then set a safety margin on top.

That's just a comment. I've wandered a little bit here. I think in terms of thinking about this, the uncertainty factors themselves, am I correct in saying that we're really trying to account for essentially the statistical or measurement uncertainty in extrapolating from a set of measurements conducted in one setting to the population that we're tying to represent or to protect here?

DR. MCMAHON: I think your comment is very valuable, and I appreciate it. I think that's certainly part of the reason. I think that these factors go way back in the history of regulation. And I know that some

have, you know, questioned the basis for those at times. So I do think your comment is applicable.

And when we, for instance, looked at the human data on elicitation, we also recognized that we didn't need to always have a 10-fold. For not the same reasons, but I think what you're addressing is also relevant. But we also had issues of study population that we had to think about a little bit when you talk about trying to get a true dose response in the human population from data that we had that had obviously, you know, a limited number of volunteers.

But in recognizing that these people, with respect to at least the issue of dermal sensitizations, were already sensitized. So perhaps that in our mind took out some of that variability within humans. But then recognizing also that, you know, they didn't design the studies to try to establish

a no-effect level but could see effects doses as low as they could reasonably test to our way of thinking at the time.

But I appreciate your consideration of those other factors in the derivation and consideration of appropriate uncertainty factors in this case.

DR. HEERINGA: Dr. Jones, yes.

MR. JONES: I think you have very nicely characterized what it is that we're trying to do. Not speaking at all to your analysis of the conservatism of what we've proposed or not, but your characterization of what we're attempting to do with the uncertainty factors, I think, is right on. I think it will serve the discussion well as we go forward.

DR. HEERINGA: Right. I agree. I think the analysis, I mean, that has to be specific to the sets of data that are being incorporated into the scenario. I really

don't want to comment on this specific one. I think there will be plenty of input on that from persons who are more expert than I.

But I'm just trying to sort at as a statistician. You want to do this exactly what are we, how are we managing not just known or measurable variability in a set of experimental data but then this extrapolation, essentially the projection process.

And statistical uncertainty, I mean, it winds up being guesses, informed guesses at this point in time. But I think it still makes good sense to partition out uncertainty and sort of extrapolating a set of data to another set of conditions; and on that basis saying, yes, if we could extrapolate perfectly, this would be the dose-response curve. And having set that, then what margin of safely additional do we want to put on top of that.

I worry a little bit when we start

confounding the margin of safety issue with the uncertainty issue. I look at it as what if in a perfect world we could be given that set dose of response data that we really wanted for the U.S. population having gotten to that the point. To me, that's the point that we're trying to get to with the uncertainty factors. And then on top of that is this issue of margins of safety.

MR. JONES: If I could just add one thing.

The margin of safety discussion and analysis within the Agency will occur in the risk management of this. And that's where you get to the point that you had made, the oncogenicity and development effect may warrant a greater margin than an endpoint such as dermal irritation or dermal sensitization. That's how we attempt to manage that discussion within EPA.

DR. HEERINGA: Thank you very much,

Mr. Jones.

Any other questions or comments from the Panel?

At this point, we have an opportunity before we break for lunch but more importantly before we begin our afternoon session in which we'll begin to formally address the charge questions. And at that point in time, our focus will be fairly heavily directed to those specific questions in responding to the issues raised there and the questions posed in the charge questions.

And I'd open it up to the Panel at this point. We've had a lot of opportunity to interact and ask questions over the past day and a half. But if you have any specific questions for the EPA scientific staff or potential questions that would go back to some of the public comments, you're free at this point. Dr. Monteiro-Riviere?

DR. MONTEIRO-RIVIERE: No.

DR. HEERINGA: Dr. Siegel.

DR. SIEGEL: No.

DR. HEERINGA: Dr. Chu?

DR. CHU: I think the Panel would appreciate it -- at least I, myself, would appreciate it if either Dr. Chen or Dr. McMahon can elaborate on what are the rationales for incorporating of these uncertainty factors. I know you presented yesterday. But because this uncertainty factors have become such a important issue, if you can elaborate again, I think it would help us.

DR. HEERINGA: Dr. McMahon.

DR. MCMAHON: I hope I'm not repeating myself. Well, as I said, any time we get, for instance, experimental data in animals and as you've heard we try to look at that and how that might effect the human hazards situation. So we have to look at the kind of data that it is. And this session,

we're talking about data on dermal sensitization.

But in general, you would think that the kind of data that you have in front of you, what sort of extrapolation do I need to look at how that response might happen in humans. And, of course, as we all know, typically it's been assumed, through reasons that go way back, that we impose an 10-fold uncertainty to get from the animal to the human data.

And as we've heard also, that can vary based on the endpoint that we're concerned about. So for instance with respect to developmental toxicity or carcinogenicity, we might be a little more concerned about the uncertainty in the experimental data in animals versus what we might know about humans.

And then when we look at it in humans whether or not we have data itself in

humans on this type of response and how that response may vary within the human population, we also consider whether we need an uncertainty factor in that area which also has been traditionally set at 10 but, again, can vary. And any one of these can vary from 1 to 10 or perhaps even greater in certain circumstances.

So those are kind of two general factors. But it, again, can be based on the type of response we're interested in. And I think, as you've seen with respect to the dermal effect, it hasn't always been proposed to use the maximum factor. And in some cases, it's been proposed that one is sufficient.

I think then, again, as I mentioned, there were a couple of areas that we had wanted to get some input from the Panel on regarding what product we might be talking about. And I mean that in general. If we have a product outside of this issue with

chromium and treated wood, which is also an issue for us, obviously, but with respect to general product matrix whether or not that comes into play when we're talking about the effect that might happen with sensitization and also the effects of exposure that may occur repeatedly.

So those are sort of a little more specific to the issue before the Panel regarding uncertainties, whereas the first two can be more general. They can also apply specifically. But the other two that we've noticed or have read in the literature apply, tend to apply specifically to this type of situation.

DR. HEERINGA: Dr. Burleson?

DR. BURLESON: (Shakes head in negative.)

DR. HEERINGA: Dr. Jacobs?

DR. JACOBS: No.

DR. HEERINGA: Dr. Bailey?

DR. BAILEY: Not at this time.

DR. HEERINGA: Dr. Meade?

DR. MEADE: Possibly if you could just clarify. I think one of the questions that's come up among Panel members as we've talked about these questions is a little more clarity on the charge related to the questions.

Are you asking us to look at the first three questions in light of any pesticide application that may come in front of the EPA, and the fourth only being specific to chromium?

DR. MCMAHON: That is correct.

DR. MEADE: Okay. Thank you.

DR. HEERINGA: Dr. Pleus.

DR. PLEUS: If I can go back, Dr. Chen, to your presentation yesterday on the case study on Cr(VI), your slides. And I'm trying to get to, again, the charge questions. Because the first three, as Dr. Meade just

pointed out, that may be pertaining to pesticides in general; and, four, that also specifically goes to the Question 4. I'd be interested as it pertains just to how do you interpret the results of induction versus elicitation.

Can you just kind of comment on that from the Cr(VI) case study?

DR. CHEN: Well, I think this is a very good question. Because, in general, the Agency, we never really kind of differentiate the induction and the elicitation in our traditional approach. But at this moment, we do have a situation that what kind of population that we really need to protect from these kind of things. So we kind of focus on the elicitation phase or the induction phase.

So if we're going to differentiate these two, then we need to figure out the way to differentiate. If we based it on the induction phase, then what kind of thing that

we need to look into. If we're going to look into the elicitation phase, then what kind of thing we need to worry about. Then because there are studies that have come that out focus on the induction phase. So this one become this reason that we use the LLNA data to do the proposed risk assessment process.

And then for the three studies that we mentioned about because they all using the sensitized population. So it's more like based on the elicitation phase. And Griem, et al., he also proposed the approach that uses the LLNA data to predict the elicitation kind of threshold. And so this is the outline of my presentation. So this is the way I separate. This is the way I tried to differentiate the induction and the elicitation.

DR. PLEUS: Just maybe a follow-up question to me is: If your general questions on 1, 2, and 3, so to speak, are applicable

for any pesticide, it depends obviously on the data that you receive to do a quantitative risk assessment. Is that right?

DR. CHEN: Yes.

DR. PLEUS: And in the case of the Cr(VI) case study, you're just going through the exercise of doing both induction and elicitation to come up with the value.

DR. CHEN: Yes. Basically, in the first three questions, we are trying to be very general.

And there's one thing I need to make clear. Because the reason that we started to worry about this is because in some situations that the warning label and those kind of things won't be practical in some situations.

So we are not saying that we are going to, you know, apply it to everything that if we have some kind of discussion like dermal sensitization being discussed. But we do have some situation that the warning

language won't work. So we need to look into something to how to protect the general public because this kind of situation may happen.

And so the first three questions are basically more like not chromium specific. And the fourth question, if we're talking about chromium in the wood preservatives, this is more like it becomes a case study. So, basically, the discussion in the first three questions are very important to the fourth question also.

MR. JONES: If I could follow up on that as well.

For most of the products that we regulate, most of the pesticides products, we believe the existing framework as it relates to dermal sensitization, dermal irritation, is adequate. We're basically testing in a yes/no kind of way. And if there is irritation sensitization predicted, we feel that through labeling, because the user of the product, the

person who is going to be exposed can look at the label and be warned about the potential for the irritation, sensitization, potentially be advised to wear gloves or some other protective manner.

For the group of products that we regulate where there isn't any effective way of giving the consumer notice about what may happen, such as in what we refer to as a "treated article" where the pesticide is applied to wood in this example but then that wood is not regulated after that by the Agency, there's no way for the consumer to have knowledge about the potential sensitization or irritation.

So when we say that this framework would apply to all pesticides, we really mean all pesticides that have the similar kinds of potential exposures broadly to consumers as opposed to products that which would be the vast majority of products that regulate where

the existing framework which involves answering a yes/no question about this and then making some statements on the label with potentially some protective equipment to protect users.

I think actually the universe that it would potentially apply to be rather narrow. Wood preservatives would be a logical -- I think if we sat around and thought about it, we could think about some other products for which this quantitative approach may be appropriate.

DR. HEERINGA: Dr. Hayes.

DR. HAYES: Since the first three questions are general in nature, I'm going to go back to the uncertainty factors. If you go back to the original Starr and Dawson paper where the RFD was originally proposed, there were five uncertainty factors and a modification factor. You've talked about only two of those five and nothing about the

modification factor.

Is that something that this Panel should consider? Or does anybody remember that ancient paper? It was in 1986 or '87 or somewhere around there. It was an EPA publication.

MR. JONES: I know nothing about that paper. However, I would refer the Panel back to Dr. Heeringa's original framework that he spoke to about 10 minutes ago which is we follow some general practices in our extrapolation from animal and human data to determine what the population hazard may be. And I think that if you think of it in that context, that helps guide what kinds of category factors are appropriate or not. And so I wouldn't necessarily take one off the table if it helped in that extrapolation.

DR. HAYES: Much of what he said was said in that original paper. You ought to go back and find that paper and look at it.

DR. HEERINGA: Dr. Hayes, where would we locate that paper? Would that be --

DR. HAYES: Starr was the senior author on it. So I assume you could do any kind of a search and find it.

DR. HEERINGA: S-t-a-r-r.

DR. HAYES: He was in Cincinnati. And Dawson is TARE, the Toxicology Center for Excellence. I'm sure Mike could get it for us. Starr is dead, but Mike is still with us.

DR. HEERINGA: Okay. Very good. Any additional questions, Dr. Hayes? Dr. Menne?

DR. MENNE: No.

DR. HEERINGA: Dr. Foulds?

DR. FOULDS: It's probably just more sort of curiosity than anything. The thrust of this is to approve a new sort of wood preservation in the States. And yet it's not particularly new. It contains a substance which has been know about for a long period of

time, and it's known to be a sensitizer. And there's been exposure worldwide to it up to date, but maybe not in the levels that may occur in United States if it's used widely.

I suppose I'm curious from the point of view as why are you looking at it so much from the dermal sensitization point when we've heard no data showing that it causes any clinical problems in the users as such. We've obviously got concerns about people who are at the manufacturing stage. But it's in the users that we're sort of concentrating on. And why are we concentrating so much on the dermal sensitization when there is no evidence really that has been provided to show that it is a problem?

DR. MCMAHON: Maybe I can answer part of that. We don't have, to my knowledge, wide use of this particular product in that setting yet. And I think to my knowledge in an industrial setting you can certainly take

definitive measures to guard against things like dermal sensitization.

When you release a product that, as Jim Jones mentioned, you no longer regulate but which you suspect has a known sensitizer in it but for which we haven't had definitive data yet to make that decision but we are at the point of looking at science methodologies that would be appropriate to determine if that would be a problem or not once we have all the data in front of us.

So I think to my way of thinking that's where we are. We aren't making conclusions yet about that. But we are, because of the nature of the product, trying to move forward with methods that we might be able to use to make that determination for consumers.

DR. FOULDS: I suppose I'm just thinking that, you know, if we were talking about cement here, then we could have a good

reason for following this up because we know that it causes a problem. We know that if we reduce it to a certain concentration then that problem then is considerably reduced. And I suppose it's a curiosity. We don't know that there is a problem, and there are no problems reported as far as I'm aware.

DR. CHEN: I think I'm going to add something to Dr. McMahon's points. Because at this moment, we are going to introduce a product that we know before is completely fixed then Cr(VI) can kind of present on the surface of wood. And we are going to introduce a kind of more like this kind of thing into the general public.

So if we really look into all the kind of many human-related studies, most of them are basically are a sensitized population or something. So based on the group of people that they go into see dermatologists and then become a study group. And at this moment, we

are going to introduce something. So it's very possible that the general public may not have the chance to be exposed to the Cr(IV) in this kind of concentration.

What kind of concentration? We don't know yet. But in that case, would they become sensitized because of this exposure? So this is something that we need to really look into. And we are looking into kind of surface kind of data and those kind of things. And once we have those data, we'd like to have some kind of thing we can use to quantitatively assess the situation.

DR. HEERINGA: Thank you very much, Dr. Chen.

Any other questions at this point? Dr. Handwerger. We'll go down this row. I didn't mean to exclude you.

DR. HANDWERGER: My comment is a general one. It has no relation to what we've been talking about for the last two days. But

I'm really surprised about the assays that we use to assess some of the problems that we face. They are subjective. They are imprecise. They're distal to what we are really interested in in many ways. And we're not really taking advantage of genonomics and proteomics and modern molecular biology.

We know an awful lot about antigen-presenting cells at a molecular level. We know some of the genes that are clearly activated and are very specific in hypersensitization and so forth. And we could clearly develop methods, I'm sure, to look at the effects of many of these quote "antigens" and see whether they truly activate Langerhans cells in skins. We could do dose responses on those.

I mean people in cancer biology do this all the time to understand about new cancer drugs and whether they have effects on very specific genes. And I'm just surprised

that so much of the issues that we are talking about today are based on 1970 technology and not 2004 technology.

I would hope that, you know, the scientific community would really address these important health problems based on modern technology because I don't think a skin test is clearly the most sensitive way to do things and certainly is subjective and probably you could not find 100 hundred percent concordance among any three dermatologists, probably. And that's the nature of a test.

So that's the only comment that I'd like to make.

DR. HEERINGA: I also want to include my colleagues the front row here, too. Dr. Thrall, any questions?

DR. THRALL: No.

DR. HEERINGA: Dr. Isom, any questions?

DR. ISOM: No questions.

DR. HEERINGA: At this point, seeing no additional questions from the Panel. From the EPA, anything you would like to add before we break for lunch? We'll have the opportunity, obviously, during the question period to interact.

I have 11:15. And as I indicated at the start of the session this morning, the Panel had requested an early lunch, members of the Panel, to be able to digest what has been covered this morning and to consolidate comments, discuss these issues.

So we're going to take an early lunch. But I realized, too, because I don't want you to have a brunch; so we're going to plan to reconvene here at 12:45. That will give people a chance to take care of a little business possibly and come back to start again at 12:45 for the questions.

Thank you.

[Lunch recess at 11:12 a.m.

Session resumed at 12:50 p.m.]

DR. HEERINGA: Good afternoon and welcome back, everyone, to the continuation of our FIFRA Scientific Advisory Panel session on Consultation on Dermal Sensitization Issues for Exposures to Pesticides.

At this point in our agenda, we have reached the stage where the Panel will consider the specific charge questions, the four questions that have been placed before it by the Environmental Protection Agency. And I think we would like to begin.

At this point, Dr. McMahon or Dr. Chen will actually read the first question. And I believe the Panelist's have a coordinated response which will involve the use of the PowerPoint system. And we will address the first question, and then we'll ask Dr. McMahon to read the second one.

Let's begin with the first. Dr.

McMahon.

DR. MCMAHON: Thank you, Dr. Heeringa.

Our first question for the Panel is, as you know, related to proposed methods that we have presented on determination of induction thresholds to dermal sensitizing chemicals.

Specifically, the questions to the Panel are: What are the strengths and weaknesses of the proposed quantitative approaches for determination of induction thresholds to dermal sensitizing chemicals? And what other approaches does the Panel recommend the EPA consider? And which uncertainty factors does the Panel feel are the most appropriate for application to quantitative methods of induction threshold determination? What factors should be included in the determination of the magnitude of each uncertainty factor?

DR. HEERINGA: Dr. Pleus is our primary discussant on Question No. 1. And we'll let him respond at this time.

DR. PLEUS: Thank you.

Will there be someone that forwards the slides, or should I do that myself?

DR. HEERINGA: Two able AV technicians are approaching the table at this moment.

DR. PLEUS: Let me just start by saying what a pleasure it is to be a part of this Panel and working with a great group of people here all sitting up here at the front table. It's been a real pleasure to be able to work with everyone here.

I also thank the respondents for providing really good information that I found useful personally and I know that my colleagues here also found personally. So the time and energy it took to come out here is greatly appreciated.

What we have done in terms of with questions is we've divided into the charge questions that we were asked, questions that we identify as 1, 2, 3, and 4. But what we heard when the group of us were talking was some general principles and thoughts that we'd like to share with everyone here in attendance.

I think one of the questions that we had concerns on -- and these are just general questions -- is there an allergic contact dermatitis problem? On one aspect of this, Questions 1, 2, and 3 are really methodology problems or questions. So I don't think that that really answers it.

But I think an important question that was raised amongst our group is: Is Cr(VI) in treated wood a problem? And we are going to address that in Question 4.

There is a question as to allergic contact dermatitis as a disease in that should

it be assessed in a similar manner or as stringently as risk assessments for cancer, for neurodevelopmental or reproductive tox or any of the other endpoints that are typical with a risk assessment process.

In addition, allergic contact dermatitis is, I think, unique from typical endpoints in that it's reversible. And that has to be qualified. Qualified from the standpoint that signs and symptoms are reversible. In other words, you take away the exposure, signs and symptoms disappear or remove themselves. However that said, the underlying sensitization is not. It does not go away.

In terms of some underlying principles that we felt were very useful in the risk assessment process, we came up with other principles that we thought would be useful. One is it's not the content in the material, but it's the amount of the material

being released. We used as an example nickel in jewelry. The content or the concentration of nickel in a particular product is interesting information, but it's really the amount that the person will receive that's the most important metric.

The dermal dose metric ug/cm2 is the preferred dose metric. And we were very clear on that. Human studies are highly preferred over animal for the risk assessment process. I know that's consist with EPA guidelines in risk assessment. But we wanted to ensure that. In particular, the allergic contact dermatitis has a number of studies that have been done in humans, and that certainly is a useful source of information.

It was important to examine materials on a case-by-case basis. We found it somewhat difficult to start to extrapolate from using very general principles on one chemical to the next chemical to the next

chemical. And we felt that it was clear that each chemical is unique, and studies are different. They have their strengths and their weaknesses, and that should be incorporated into the process.

And then one other component to that is current animal testing methods may be overly conservative when used for the risk assessment purposes. In other words, animal testing obviously gives you good information and scientific information. But when you're extrapolating or using that for risk assessment purposes, we are of the question that it may be overly conservative.

And our last point here is that it should be an effort to use tests that mimic actual human exposure and conditions. And often in the studies that we have reviewed here, whether it be for chromium or other chemicals that people had studied, the exposure conditions may be overly exaggerated

or they may have special conditions may not apply to the actual human exposure. And I think that it goes without saying that getting a good sense of what human exposure is and the potential exposures would be critical.

We had some comments on the LLNA assay. And they are the following: In terms of the LLNA assay, we found it to be an objective testing method and that you can actually calculate an EC3. We also concluded that it's a good screening tool. In other words, it isn't necessarily definitive; but it helps you get experimental information that can be useful in terms of determining what other studies that could be done.

It's an alternative to the guinea pig test. It goes towards minimizing the use of the number of animals in testing.

Given equal numbers of exposures, there's an exaggeration of exposure. What I mean here, given equal numbers of exposures,

the human may be exposed more intermittently. The animal testing may be done more extensively. And so there is a mismatch between human and animal testing particularly with the LLNA assay.

It was concluded that with more research on different compounds -- and there was also a question of other laboratories -- that LLNA could you used in the future for assessing potency of different compounds. But that's with more research. This is a good tool for testing new chemicals particularly where data don't exist; if it's validated for hazards identification but not validated for testing for estimates of potency and it's not validated for metals and mixtures. And that's particularly important with Cr(VI) which is part of our Question 4.

On human data. So we're now, again, talking about general principles before we get into questions or charge questions. We

strongly agree on the preference of human data for risk assessment. Human data provides greater certainty, less uncertainty in that so fewer uncertainty factors are needed.

For the risk assessment process, we felt very strong that the vehicle needs to be consistent with exposure of the chemical in question. In other words, the careful, thoughtful approach in mimicking the materials that may be actually contaminated -- let me see if can say this. Let me switch the sentence around.

What we're trying to do here is to make sure that the vehicle is consistent with the types of exposure that a person, a human, would get. So for example, if a vehicle is something like olive oil and some other compounds or DMSO, and in the human situation the exposure is with water, to the greatest extent possible there should be a mimicking of those two conditions.

For testing, the patch test, the Panel strongly suggests using patch test through dilution of the test article to determine elicitation threshold. On the open test, there was strong consensus amongst the group that open test should be developed in the future for use in human testing. And then using different anatomical sites, different masses of materials, and using at different times, we felt that that would be a much better indicate particularly for the risk assessment process.

In terms of analysis of data, the Committee strongly suggests using the weight-of-evidence approach for analysis of materials or chemicals in determining the assessment for allergic contact dermatitis. Basically, gather all the information. And we saw some comments to this in -- I can't remember which article, but I'm sure a number of them.

And we added a few more actually in terms of getting historical data, looking at SAR, QSAR, looking at animal, clinical, toxological, and epidemiological data. That I think probably mimics what we mentioned initially in terms of looking as much as possible on a case-by-case basis to what information we have and using the best information, the best science in order to more forward on a risk assessment.

So we're now done with our kind of general comments. Again, we derived that through communication. And there was a consistency amongst all of the members in terms of describing that in describing these principles and underlying factors.

On Question 1, I'm the discussant leader on that. My colleagues are Dr. Jacobs, Dr. Burleson, Dr. Monteiro-Riviere, and Dr. Menne.

First, here is the question. It was

read. Do I need to read that again?

So, overall, if we can give you some overall conclusions; and then we'll give you just a little more specific.

Overall, we strongly agree that the scientific studies assessing for elicitation will be protective of induction. Now this question really goes towards induction. But I just wanted to add the components to it.

Do we need data on induction, then, is more of an important question from a methodological perspective. If it's for a new chemical where there are no data, then the answer is sure, absolutely. However, studies that determine induction thresholds should not be used, we felt, in the risk assessment process.

The LLNA test has shown promise as a method to assess potency of chemicals. And with further development and validation, it might be useful for risk assessment in the

future. But we don't feel from a risk assessment quantitative standpoint that it's at that point now.

We do not endorse any particular method for risk assessment. There have been a number that have been proposed. None of them we are recommending at that point.

In terms of uncertainty factors, we approached it by asking more general questions. And then we thought that adding numbers would help present our point or at least present some options. And so we've kind of presented both numbers and ideas here.

In terms of interspecies and intraspecies, at this point we felt that values between 1 and 10 really depend on experimental design. What was the experiment? What did they do? What was the matrix? You name it. Look at those studies very critically, and then make the assessment for those two uncertainty factors.

On the matrix and vehicle, we found this to be kind of an intriguing question. Because depending on the matrix, there may be an exaggeration of exposure such as in LLNA and some patch testing. Therefore, a value should range between from less than 1 to 10.

What we mean by that, and there's a couple of examples here. For example, in a study if you have a matrix or a vehicle that's being used that enhances the absorption of a chemical, then that should be taken in consideration; just as if the vehicle or the matrix is something that retards absorption, that should be taken into consideration.

For exposure in terms of needing to consider the total dose, it depends on the body site and repeated exposures. Again, from values less than 1 to 10. And again the idea really is case specific and specific related to the actual study in question.

If, for example, exposure would be

on the foot and the test article was in a particularly sensitive, thin area of the skin, we would want that to be considered in the risk assessment process. And vice versa, if the test article was on some tissue that was fairly thick which prevented absorption and exposure was on something thin, we would want that to be considered. So those are the values that we've given.

I will just open this up to my colleagues here at the front for any other questions or any other alternative views, if there are any, or any clarification.

DR. HEERINGA: If I could ask Kelly to go back to the slide that posts Question 1 as it was worded? Thank you very much.

Our first secondary discussant is Dr. Jacobs. I don't know if you have anything to add at this point.

DR. JACOBS: He said very well what we discussed and came to agreement upon.

DR. HEERINGA: Do any of the other -- I know that you worked on this. Do any of the other associate discussants on this particular question have specific comments they'd like to make following Dr. Pleus's?

Let me open it up more broadly then to any member of the Panel at this point.

MR. JONES: If I could follow up.

DR. HEERINGA: Mr. Jim Jones.

MR. JONES: Could you go back? I think it's actually go forward one slide or maybe two. That's it.

Give us a little bit of elaboration on the last point where the "Panel does not endorse any particular method for risk assessment as it relates to induction." Some further elaboration.

DR. PLEUS: Yeah, I think I can. What escapes me are the -- for example, if I can just maybe look at your document quickly. If someone else wants to start, and I'll catch

up with my --

DR. HEERINGA: Dr. Meade or Dr. Burleson.

DR. MEADE: I just wanted to add one point that I saw there that we talked about that didn't get on the slide. And I think Dr. Menne had pointed out the importance of exposure as one of the pieces of data that needs to be included in that, and it failed to make it to our slide.

Richard, are you looking for the three methods that were proposed: The 10 percent MET, the Gerberick method for using the LLNA, and then the Griem method?

DR. PLEUS: Thank you. That's my answer.

MR. JONES: If we could get a little bit of insight from the Panel's perspective is there wasn't a consensus around any one of them or all inadequate? A little bit on the failure to come to an endorsement on a

particular method.

DR. PLEUS: I think we found we would go back to the idea of weight of evidence as a way to start to look at that. I don't think there is any one particular assessment process that -- what we are saying is we aren't recommending one over one other one in particular.

If we wanted to get into some particular assessment by itself, I think in some cases we had some concern about the process assessment of uncertainty factors and things along that line.

What we, I guess, would be proposing -- and I'm looking at my colleagues here -- is I think what we have been do in our work through here is pretty much provide a pathway on the induction methodology, a roadmap, if you will.

DR. BURLESON: The discussion as I remember it was we certainly, I think, all

endorsed the local lymph node assay. It's a well-validated assay. But for example with the Gerberick method, we think it's an excellent starting point for quantitative risk assessment.

That's where we thought that more classes of compounds or classes of chemicals needed to be assessed with potency determination in mind. So rather than it being a negative, I think it's actually a positive statement in my mind.

DR. HEERINGA: Dr. Bailey.

DR. BAILEY: Gary, I didn't know if you wanted to say something about when we were also looking at the Gerberick's method, I believe that that methodology was dealing more or less with personal-care product lines

DR. BURLESON: Product specific.

DR. BAILEY: Yes, product specific. While the Griem method dealt with more of sort of a hazard identification, looking at

industrial chemicals or pollutants and so forth.

DR. BURLESON: I think the big difference, and certainly, I'm open for correction here, is the uncertainty factors.

DR. BAILEY: Right.

DR. BURLESON: So the uncertainty factors are the different. But the potency determination that Gerberick had proposed is, I think, the important starting point.

And if more classes of compounds are looked at with potency determination in mind, I think there is nothing to indicate that it wouldn't become a useful QRA.

DR. HEERINGA: Mr. Jones, does that help?

MR. JONES: Yes, thank you.

DR. HEERINGA: Please, at any point, the purpose is to try to answer these to our ability and potentially to your satisfaction.

MR. JONES: Thank you.

DR. HEERINGA: Any other comments from the Panel on response to Question No. 1? Again, this specifically deals with the induction phase and in a general sense as a method of assessing for dermal sensitivity.

DR. BURLESON: I think just to emphasize that at least I think it was a very positive feeling rather than a non-endorsement, negative feeling.

DR. HEERINGA: Let me also mention to the Panel, make sure that the report of the Panel, which will include our recommendations and response to the question, that anything we want to incorporate should be said publicly here in this meeting. I know you realize that, and it's just as a reminder. Because if there are small points or pieces of information you want to be sure to include in the final minutes of this proceeding, they should be discussed.

Dr. Meade.

DR. MEADE: I was going to bring this up in the next question but maybe since your comment, it should be brought up here as it relates to induction, too.

I think one of the major things that we came away with was not than we didn't endorse methods, again, as having good potential; but that we don't feel that sufficient data has been collected for either of them, any of the three of them, to accept them as stand-alone validated methods to move forward in risk assessment at this point.

DR. HEERINGA: Thank you, Dr. Pleus.

Any other comments or contributions on response to Question No. 1? I suspect some of this we will go through again in response to Question No. 2.

Dr. McMahon, if you would like to read Question No. 2 for us.

DR. MCMAHON: Our second question deals with the similar sort of aspect but with

respect to elicitation thresholds. And as you have seen, we had proposed a few methods for consideration. One, again, by Griem and the minimum elicitation threshold approach that used human data.

So our Question No. 2 is similar in nature to our Question No. 1. And I think you have part of it up there on the screen. I can read what you have.

That what are the strengths and weaknesses of the proposed quantitative approaches for determination of elicitation thresholds to dermal sensitizing chemicals? And, further, I think this question -- thank you.

DR. HEERINGA: Why don't you read the entire thing into the record?

DR. MCMAHON: So I've read the first part.

What other approaches does the Panel recommend that EPA consider? Which

uncertainty factors does the Panel feel are the most appropriate for application to quantitative methods of elicitation threshold determination? And what factors should be included in the determination of the magnitude of each uncertainty factor?

DR. HEERINGA: Thank you very much.

Dr. Meade is the primary discussant on this.

DR. MEADE: And the other discussants in our group were Dr. Bailey, Dr. Siegel, and Dr. Chew.

When we first looked at the first portion of the question, the strengths and the weaknesses related to the quantitative assessment, we discussed the strengths. And we felt that one of the strengths was that both the MET approach, which is based on the human data, and the local lymph node approach, which are both the Gerberick and the Griem approaches, use a mass/area as their dosing

regimen which for sensitization is appropriate. So we have that strength for both.

For the human data, a strength would be that, obviously, we don't have to have an uncertainty factor for interspecies correction. So we don't have to deal with issues of going from animals to man if, indeed, we have human data available and can utilize that data.

For the limited number of chemicals. And this was a strength both for the animal studies and for the human studies for the very limited number of chemicals where we have human and animal data available. There was a good correlation. So the animal supported the human. The human supported the animal. So those were the things that we thought were the strengths of these three approaches to risk assessment.

The weaknesses that we pointed out

were that four of the two approaches that use the local lymph node assay, especially for the elicitation response in risk assessment, we just don't have enough data at this point. The assays have not been sufficiently developed. And we feel as though that this is in the pipeline, and that very likely in the future this may be possible. But at this point, we don't think that it's ready to be used for this assay.

As far as the MET approach goes, the minimal elicitable threshold approach, using the human data from patch-test data, there were some questions related to the methodology in this. And that is that some of this data we're going back -- and Dr. Maibach drew attention to this yesterday in talking about old patch-test data.

When you go back into the literature, there may be questions related to subjectivity and how the scoring was done.

There may be papers where we don't have sufficient information on the method of occlusion or the actual area of dosing that was conduct. So there are somewhat nebulous data out there that we have to be cautious in terms of utilizing it.

The skin conditions of the humans, the vehicle matrix that's used for the patch testing, and then also that there needed to be adjustment for sampling variability used to estimate the MET. But that this could very likely be addressed statistically by using the standard confidence limit bounds.

So what we're talking about here is, if you have a small sample size in your patch test, how do you know if you're setting your standards based on 10 percent that your sample population is a good representation of the human population that you're trying to protect. But that if you statistically use confidence intervals, you should be able to

account for that.

And we'll talk about this, these uncertainty factors. Also, there are issues related again to selecting that population to patch test and whether uncertainty factors need to be added because of that.

And then the obvious, the MET approach, is going to be difficult to use for new chemicals because of ethical relations related to patch-testing humans. So we'll be limited somewhat in terms of what we can use there.

And there was also a question raised in some of the literature that, if you do sensitize people in using the human repeat insult patch test, whether they are really the appropriate group to then go back and test elicitation responses in because of the manner in which they were sensitized. They may not be representative of the population in general.

So for elicitation, the MET approach is most likely going to be limited to chemicals that already out there and we have a sensitized population.

The next question was: What other approaches does the Panel recommend that the EPA consider?

Well, sorry, this one is blank. We didn't come up with any novel approaches. It seems like the ones that are already in the pipeline need further work.

So our recommendation to you would be to support those efforts.

Which uncertainty factors does the Panel feel are most appropriate for application to quantitative methods for elicitation?

Intraspecies we feel is something that needs to be looked at. Repeat exposures and vehicle matrix.

And when we talk about the magnitude

of the uncertainty factors for these, well -- I hope that comes up. (Technical difficulties.)

Well, we can go on, I guess, without the slides.

For the intraspecies factor, we felt that this needed to be related to the number of people that patch-tested in relationship to the percentage of the individuals that may be sensitized and take into account the quality of the patch-test data. So were the patch tests conducted by standardized methodology? Certainly for the newer literature.

Now that we have TRUE Test, we have more specific guidelines from associations on how to score these tests. But there are different scoring systems, it's my understanding, from talking with the dermatologists. Different dermatologists may use different scoring systems, and we need somehow to harmonize the scoring system if we

want to use this in a quantitative risk assessment.

The main point that we wanted to make, that is, for all of these uncertainty factors, it's imperative that the magnitude be assessed on a case-by-case basis because they're going to vary very much dependent on the particular chemical and the use of that chemical.

So I think we've covered the intraspecies factor there. Also under the interspecies information related to when the patch testing was done, the site of exposure, and the condition of the exposes skin could cause for variability in the response.

Under exposure factors, we think that one should take into account the use of the chemical, the expected duration and repetitiveness of exposure, and the potential for occlusion.

So, you know, in the case of Cr(VI)

in treated wood, one would put a very different exposure factor to that than Cr(VI) in cement. So there's a big difference in how you're going to assess rubbing up against decking versus standing in fluid cement mixture.

And then likewise on the vehicle matrix, some of the same things that Rich introduced when he was talking about the induction of sensitization. The effects need to be considered on the nature of the matrix. Is it an irritating matrix? If so, one might need a higher uncertainty factor.

Does it contain penetration enhancers? And also the bioavailability of the chemical in the matrix. There are certainly some matrices where the recommend chemical would rather stay in the vehicle then depart and move into the body. If it's impregnated in wood, what is the chance that it's going to be bioavailable.

Okay. Those were our comments.

DR. HEERINGA: I'd like to ask if any of the associate discussants would like to add comments to Dr. Meade's summary? Dr. Siegel.

DR. SIEGEL: I'd just like to expound on some of the subjective nature for the patch testing that we have talked about.

In some of these patch tests, the TRUE Test, you have the sometimes mixtures or some of the patch tests you're tested along with other chemicals. So that can play a role into looking at some of these factors. If you titrate out where you consider where the different investigators consider the cutoffs as well as what one investigator would read as a positive versus another.

As you titrate out, you're increasing the variability in the reading in what you would call a positive test as you go down -- the one thing that really we discussed

about -- and there are no statistics on variability from reader to reader. And so this is somewhat of a subjective test.

And I just wanted to make sure that that was pointed out.

DR. HEERINGA: Do any of the other associate discussants or any of the other Panel members have anything they would like to add on this question?

Dr. McMahon, Dr. Chen, have you questions? Is this clear? Or do you need follow up?

DR. MCMAHON: Yes, we think the response has been clear.

DR. HEERINGA: At this point in time, Dr. McMahon, I think that you have the text of Question 3 in front of you. Just read that, please.

DR. MCMAHON: Yes, I do.

Question 3 relates to the potential sensitivity of children. And this question

reads: Does the Panel agree that the available scientific data suggest no significant difference in the relative sensitivity of children versus adults to the induction and/or elicitation of allergic contact dermatitis? If so, please provide scientific justification for the position.

If the Panel disagrees, please provide scientific justification including supporting data and/or uncertainties in the explanation.

DR. HEERINGA: And our primary discussant on this is Dr. Foulds.

DR. FOULDS: Thank you, Mr. Chairman.

Can I also say it's an honor for me to be here representing American dermatology. I'm not quite sure why there isn't an American dermatologist. But, hopefully, I can put a universal perspective on it.

I'm no Einstein; but, hopefully,

what will I say will have a practical purpose. I may have sort of deviated slightly from the question. Because as you saw with Howard yesterday, he was able to talk. I won't be talking for quite so long. But if I can have the next slide please.

There were a few issues that I wanted just to sort of bring to everybody's attention. And I apologize if a little bit of this is sort of anecdotal.

Looking back at my figures over the last sort of 18 months or 1,084 pack tests, we had 66 positives to potassium dichromate. That's testing at .5 percent. That's about 3 percent of all patients tested. That sort of compares not too dissimilar to the North American figure 2.4 percent that we heard about yesterday. It's not as high as the 5.9 percent that were shown in the paper -- I've forgotten the author you gave me from Kansas.

But that 5.9 percent where you were

worried about increasing levels of concentration perhaps is due to the selectivity of that population that was studied where there was a high proportion of people working in the construction industry. And, also, it's quite a small population study that was actually examined. And that may explain that slight sort of blip in the increased figures. And certainly I don't think our figures are too dissimilar from the North American figures.

Breaking that down, as roughly an equal sex incidence in the patients that I've seen, and that doesn't seem to be too dissimilar from the North American experience.

Looking at the age range, these are the age range of the patients of my dichromate-sensitive patients, age 24 to 86. No children. Does that mean that children can't be sensitized? Well, the answer to that is no.

We talked a little bit about relevance yesterday. Relevance is difficult. I always like to feel that I get closer to a hundred percent, but I'm probably sort of optimistic in my sort of relevance. We still have a lot of metal machining around in Birmingham. So there is quite a lot of high chromate exposure which is leached into metal.

We have quite a high proportion in chrome plating industry. There's also the construction industry. And there's a lot of corrosion inhibitors used to prevent rusting of metal which contain chrom as well. We do see a fair number of positives.

We also see quite a lot of coexisting reactions with nickel, cobalt, and chromate particularly in the females. And although chromate isn't in costume jewelry, this cross-reaction does seem to occur. I was interested to learn from Torkil Menne that since nickel has been banned in costume

jewelry, they've not seen this sort of triad of reactions coming up with nickel, cobalt, and chromate and that chromate has actually reduced in sensitivity along with the reduction in nickel. And Torkil may want to comment further upon that.

So we can argue about relevance. Certainly when there's a solitary dichromate reaction, I think you can usually find relevance. Now that then comes to interpretation because many people will have an erythematous reaction on their back when they're patch-tested. And perhaps 10 or 12 percent of people will have a degree of erythema underneath the chromate reaction.

I think you've picked quite a difficult substance to evaluate when you're trying to extrapolate it into some of the testing situations because it is so close to urgent levels and can give a fair number of false positive irritant reactions.

I always reckon it takes me six months to train one of my registrars to learn how to interpret patch tests. And chromate patch-test reactions are one of the more difficult ones from an interpretation point of view.

So it doesn't mean that children can't react to dichromate. My answer to that would be no. Even so, I haven't had any positive reactions in children because it really depends on the study population you're looking at and what sort of exposure that population actually has.

The threshold for patch testing amongst all dermatologists is very different. Some of us may have a much lower threshold for patch testing a child. Others of us -- and that's myself included. It takes me quite a lot to want to actually patch test a child. I will try anything possible first before patch testing.

Various reasons. Lack of space on the backs to get your hundred different allergens on it you wanted to do that. Otherwise, you're going to be very selective in what you're testing. And if you're going to be that selective, maybe you know the answer already and you don't need to patch test them in the first place.

Plus the fact that it is a little bit of discomfort. There's problems with keeping the patches in place for the duration of the readings. So from a practical point of view, that's going to act as a disincentive.

With an adult, I have a very low threshold for patch testing. Anything that's persistent and is going on, well, why not patch test and maybe we'll find an answer and then we can find a cure. So perhaps instance with increasing age of relevant positives in patch tests will diminish with increasing age. And that's why some of the studies where we've

seen higher instances in children is because we're much more selective in the children that we actually put through the patch-testing situation.

So for example, if you've got a child who's got nickel sensitivity and maybe a rash under a watch strap or under their earring, you're probably not going to patch test them because you know the answer.

If you've got a teenage who's got a rash under their belt buckle, they're not going to listen to you until you patch test them and show a positive reaction which will convenience them they're actually allergic. Telling them to take the buckle off is a waste of time. Another reason which can influence why you patch test in the first place.

So perhaps a child with a persistent hand dermatitis that's not getting better with treatment, with everything you're trying to do with avoidance methods, you're then going to

finish up patch testing them.

However, there are studies where people have deliberately gone about patch-testing children which have given more accurate figures as to instance.

So when I said we didn't get any chromate positive, that's not that I didn't patch test any children. There are children in that thousand. Not a huge number of children, but a number of people being patch-tested. Eighteen positive relevant patches. That's probably two-thirds were relevant. So that's quite a high pickup.

That's because of the selective population we were going for in the first place. And if we look at their reactions, we got nickel, thiurams, paraphenylenediamine. It's probably the commonest sensitizer that I'm seeing at the present time in children. We'll come back to that.

We have talked a lot about patch-

test reactions. Hopefully, you can see there's a filthy, great big blister on this person's back. It's not a child. But I don't think most people would have too much difficulty interpreting that as a fairly nasty reaction and probably a relevant positive patch test particularly when we know the chemical paraphenylenediamine doesn't tend to cause false positive reactions.

Now we're getting a bit more blurred. And it's probably quite useful to be blurred at this stage because then it is how do you interpret these sort of patch tests. If you look, I've graded these from A to E is supposed. They get less and less and less in the severity of reaction. I know it's sort of vague on the projection here.

On the laptop, it looks very clear that A is sort of infiltrating and there's little blisters. And that's very easy to interpret. If we're then talking about B, you

can see that there is probably a little bit a erythema there.

Now, in fact, it's a potassium dichromate reaction; is that a genuine positive? The answer to that: It probably isn't a positive unless you're doing a MET test looking for elicitation thresholds in which case then the redness that you will see could be interpreted as a positive irritation. But that doesn't necessarily equate to an allergic reaction.

The point I'm trying to make is that there is science behind patch testing. There's an awful lot involved when it comes to the interpretation. And what you interpret from one person's readings to another person's can be difficult. Even with multi-center studies, it can be difficult where there are different people interpreting reactions.

And it can also be difficult depending on the number of patch tests that

are going through a center at a particular time. The more patients going through a center, the more each individual patient acts as a control for the next patient going through. By that I mean if you're testing 20 or 30 people a year or 600, 20 or 30 people a year, allergen deteriorating -- perhaps it's got a concentrated allergen or whether or not it is a genuine positive. I'm just throwing these up here as difficults from an interpretation point of view.

So what really is the evidence that there is a difference in allergic contact dermatitis in children against adults? Or can children be sensitized? Well, we've answered that partially. How common is it in children? What about years of exposure? How relevant is that? And can one exposure to an allergen be sufficient to cause induction? We heard a little bit about that yesterday.

So can the children be sensitized?

And there's quite a number of published studies citing detection of allergic contact dermatitis in children. We can go back to historical studies on this.

Back in 1981 was one of the first early reviews from Niels Hjorth who, amongst others, quoted a study from Malmo where 118 children were tested and 32 percent of these children had positive reactions. So we know, therefore, that allergic contact reactions can occur even as far back as 1975.

We heard yesterday from Howard about the Epstein study with the poison ivy and the difference in age range and sensitization. So we know that children can be sensitized. Perhaps there's a suggestion from this that the younger you are, the less likely you are to become sensitized.

With this sort of universal allergen within the environment, it's always difficult to know what environmental effects this may

have on the increased rate of sensitization with increasing age. I'm not sure you can extrapolate this in the same way as you perhaps could with other allergens that you may not be exposed to in an everyday environment.

So the environmental exposure may be relevant to this, but it does raise a few questions, particularly in the very young age group under the age of one as to whether or not that can cause -- are they immunologically as competent to develop a positive reaction?

We also heard yesterday about the Wohrl study. That was a bit like me quoting figures. It was consecutive patch tests. And it was really looking at all the patients coming through. And if you looked at this, it would suggest that there was a high rate of instance in the very young and a lower instance in the very old.

But, hopefully, I've answered that

with my own evidence. It depends on what your threshold is for patch testing at different age ranges in the first place. So I don't think that can be extrapolated to mean that children get more in the way of allergic contact dermatitis than adults. It's the selectivity in the first place.

Another study, perhaps more population-based, from Klaus Anderson, looked at 1000 school children aged 10 to 14 years, patch tested them, and found that 15 percent gave positive patch test reactions. Now that's not too dissimilar from population studies in the adult population. So for this age range, there doesn't seem to be a big different in sensitivity rates.

So is there any evidence to suggest that children with atopic dermatitis, which we talked a little bit about yesterday, are more likely to suffer from allergic contact dermatitis? And the answer to that is no.

There's plenty of published evidence to support that. And there is evidence to suggest, as we heard yesterday, that those children suffering from atopic dermatitis are, in fact, less likely to develop allergic contact dermatitis in the first place. And there are many published studies which we can provide to support that.

So we conclude from the atopic dermatitis, which may be a worry for children who have active skin disease, that if they were exposed to chromate in treated woods, even if it's with exposure on damaged skin, that from all the published evidence from atopic dermatitis that there should be no increased risk for these children even with atopic skin disease.

Just going back to what is the evidence that there is a difference for allergic contact dermatitis in children as adverse to adults.

One thought that has sort of come to me is that with THIOMERSAL sensitivity, there has been a study looking at the instance of THIOMERSAL-positive reactions in Swedish recruits. I can't remember the exact numbers. But 11 percent of army recruits patch-tested showed a positive reaction to THIOMERSAL.

Now, THIOMERSAL is a preservative used in the triple vaccine. And sensitivity to THIOMERSAL is usually attributed to being immunized as a youngster usually within the first 18 months of life. Therefore, exposure at that time can induce sensitization which then remains lifelong.

What problem does that cause? It causes a bit of a swollen arm if somebody is then immunized with a vaccine containing THIOMERSAL. But the message from is that THIOMERSAL sensitivity is common in the normal adult population, thought to be attributed to immunization as a youngster. And, therefore,

when you're immunized to a potential sensitizer within the first 18 months of life, it's perfectly possible to induce sensitivity at this stage.

We talked a little bit about it yesterday. Could one single exposure induce sensitization? We heard quite a lot about the sort of safety factors with patch testing that with 60,000 patch tests performed with the TRUE Test, that there were no reports of chromate sensitivity occurring as a result of late sensitization.

And one of the problems with this type of data is that there have not been any formal studies looking at active sensitization from patch testing. Most of it is dependent on voluntary reporting and feedback when problems occur. In other words, if somebody has been patch-tested and nothing comes up and then suddenly three or four weeks later a red, itchy area appears on the back, that will

usually induce somebody to bring that to somebody's attention. But not always so.

So late reactions can occur. Induction sensitivity can occur. And does it occur in children?

Looking at reactions that I've seen coming up from people who have been patch-tested and then report back subsequently on the reactions that they've seen, paraphenylenediamine is the commonest active sensitizer with patch testing. Four out of a thousand were with some sensitization. And in practice, less than 1 percent of people patch-tested will develop active sensitization from the patch testing.

And it's always sort of said, well, should you be patch testing people in the first place if a small percentage will get active sensitization. Our answer to that is you're going to pick up more people than you're going to sensitize in the first place;

that if you don't patch test, you're not going to find the answers; and, therefore, the benefits outweigh the risks.

From a practical point of view, although I was making comments about the 60,000 people tested, I have never seen a positive chromate coming as a result of active sensitization from the patch test situation. And Torkil Menne would concur with that. And that's in all our years of experience.

So from an active sensitization point of view, chromate doesn't seem to be a problem. And I've never seen active sensitization from chromate from patch testing in a child.

Just reinforcing about can one exposure induce sensitization. Henna tattoos are become quite popular in children. Of course, it's not really a henna tatoo. It's not the henna that causes the problem. It's the black die that they put into it that

causes the problem, which is paraphenylenediamine. We patch test at 1 percent. Some of these tattoos, so-called "temporary tattoo," contain paraphenylenediamine at 20 percent. And it's quite a popular thing for children when they go off to the Mediterranean to go and see everybody lining up to have these temporary tattoos performed on them. I'm not sure whether it happens in the States or not, or it's only the Mediterranean.

And then come back from their holiday with and a sort of permanent nice mark on their arm and a sensitization from a solitary exposure. And this is a ten-year-old's arm who had the patch test.

And then on the next slide, the brother also had the same procedure performed at the same time. He developed a slightly less florid sensitization reaction which left his mark on his skin.

So from that point of view, I'd say that children can be actively sensitized. And I've certainly seen it as young as the age of four being actively sensitized from paraphenylenediamine.

With the current levels of chrome that there are in the environment, chromate sensitivity in children is rare. In fact, some people would say it's extremely rare. And in my experience, it is rare. I have seen it. But not in the last 1000 cases that we've tested.

You could say that children, however, have been for years exposed to chromate in treated woods. We can argue about whether it's CCA or ACC. These products have been used worldwide. In some countries, the ACC, I believe, in the Netherlands is in high usage. CCA is well used and still used in Scandinavia and in the UK.

And there are no reports in the

literature of either sensitization occurring in children or adults from this means of exposure, either inducing sensitization or eliciting a dermatitis in a sensitized child.

If I'm looking at my own sort of practice, that's about a thousand patients being tested every year. And that's 6,000 new patients that I'm responsible for general dermatology problems. And also that I receive referrals from about 30 other dermatologists in the West Midlands who are sort of worried. When they want people to be patch tested, they refer them to me.

I have to say, how many cases have I seen of sensitization being attributed to treated woods? And the answer to that is none, not in 25 years.

How many indications have I seen of elicitation being attributable to treated wood? The answer to that is one. And that was a patient three or four months ago that I

saw who was a man who had worked in construction all his life; had been in cement; had developed a dermatitis; gave it up; changed careers; and went into a timber-treatment yard; and within a couple of months, developed problems on his arms where he was actually lifting the bundles off the freshly wet treated wood.

Therefore, he had exposure to chromium which then resulted in a recurrence and an elicitation of his dermatitis. That did not cause a sensitization. It elicited the reaction in a previously sensitized individual.

And the reason I mention this in the child context is trying to get some sort of perspective back on what the clinical problem is at the present time and what the clinical problem might be in the future.

Now, I'm getting a little sort of -- this is not a consensus view. This is my

view. So, hopefully, we can throw this up for discussion. If I was asked this sort of question for applying the criteria of chromate reactions that we've seen in children to the same sort of question, well, would you use that as a preservative in a leave-on product for use in children, would it be banned? The answer to that probably would be no.

When I say leave, it would have been a wash-off product, by the way. Applying the same criteria to wash-off products, I would be recommending perhaps allowing it but monitoring any potential reactions that might occur. In other words, if it was shown to cause a problem then I would be recommending that we need to take some action that these reactions are reversible for the individual once we've identified the problem and the products can either been withdrawn or they can be modified.

I wouldn't say dermatologically

approved to the product. I would put a dermatologically approved on the wood product. I won't say that the wood was hypoallergenic. I wouldn't say this problem was hypoallergenic. But it wouldn't stop me from using a particular product as a preservative within perhaps a shampoo in a young child. But I would be monitoring the situation.

And that's sort of anecdotal and personal. But we can come back to it later on.

I've still got concerns as to what we're actually measuring here, and how we're going about it. We talked about mass/unit area of the available sensitizer. And I think it's important when we're looking at this whole issue is how much massive product unit/area is going to be available to either worry about sensitization in the first place in children or to cause elicitation potentially in children.

The duration of contact has to be important as well. And we can argue as to how much duration or contact is likely or how much cumulative contact is likely.

We've also mentioned about the site of contact. And palms and soles of feet for most of us are going to be, or for most children would be, the predominant source of contact, either from hanging off a bar or walking across the sort of bare timber decking. And I have less concerns about that from a clinical point of view because of the thickness of the epidermis and the relative difficulty of the allergen being able to penetrate.

You can look at the same example with nickel. We all handle nickel every day. And I suppose the Euro coin is the sort of example of a really high source of nickel. And yet most people don't become sensitized through that route. It's usually from other

sites that historically nickel has caused the problem. So the site of contact is different, as in the States that everybody likes to lie naked on their decks and particularly when it's wet and when it's been raining. Maybe that is more relevant, and there's a point that I'm missing somewhere.

DR. HEERINGA: You found us out here.

DR. FOULDS: Usually, in Scotland, we wear waterproofs and things in that situation.

And then, of course, we talked quite a bit about the modifying factors. And I think I've still got a few problems with how we extrapolate the studies with the real situation as to what the local pH is and what effect sweat may have.

And one thing we haven't mentioned is what about sun exposure reducing sensitization. Well, sun exposure does. It

reduces the ability to elicit reactions. We don't patch test people if they've exposed their back within the last fortnight because that can suppress reactions. It can reduce induction in the first place.

And I'm presuming that most people who are going out on the decks are going to pick a nice, sunny day for doing it. And from that point of view, I would say that that actually reduces the potential from sensitization in the first place. So these are issues that I'm raising, and that we might like to discuss further.

Getting back to the question that we're asked if I can have the next slide.

The consensus view was that we agree that there is no significant difference in the sensitivity of children versus adults to the induction or elicitation of allergic contact dermatitis. And, hopefully, some of the background I've put on that will give you some

of the justification for that and the fact that you do get different instances from different studies.

And there is an adequate data base on the subject, including several reviews in the last 10 years to support this evidence and that we can provide that evidence from those studies which we can provide to the Environmental Protection Agency.

So I'm sorry that I've only spent half the time that Howard spent. But actually, I think I spent longer than I was going to spend. So apologies for that, and thank you for your patience.

DR. HEERINGA: Thank you very much, Dr. Foulds. I'd like to turn to associate discussants on this particular question and see if there are any additional comments that they would like to add at this point. Dr. Menne?

DR. MENNE: I'm very happy with it.

DR. HEERINGA: Dr. Hayes.

DR. HAYES: How could we say anything?

DR. HEERINGA: Dr. Jacobs.

DR. JACOBS: It was the simplest question.

DR. HEERINGA: Very good.

May I request the scientists from the EPA if everything was clear, if there are any follow-up questions of Dr. Foulds?

DR. MCMAHON: No. We have no follow-up questions, and the answer was clear to us. Thank you.

DR. HEERINGA: Thank you. At this point in time, I think we would like to move on to Question No. 4 which is the final question in the serious of charge questions that were placed to the Panel.

DR. MENNE: I think that we need a little more time to discuss this in the group, Question 4. We need a about half an hour to

give it polish.

DR. HEERINGA: Okay. I'll take that as a recommendation of the Panel. We're at 2 o'clock, and we've made very good progress with the first three questions. I have no doubt that we will finish our deliberations and discussions on this today.

What I would like to recommend, being 2 o'clock, that we take a one-half hour break at this point in time and that we would reconvene back here again at 2:30 or slightly after and will continue with Question 4 at that point in time.

Thank you very much.

[Break taken at 2:01 p.m.

Session resumed at 2:38 p.m.]

DR. HEERINGA: And we took an extended break during which a subgroup of the Panel who is focused on Question 4 met in a working session to consolidate their response to this question. And so that consolidated

response will be presented shortly. So that was the nature of the session, a working group on Question 4.

At this point in time, I'd like to ask Dr. McMahon to read Question 4 into the record, please.

DR. MCMAHON: Thank you, Dr. Heeringa.

Question 4 for the Panel is a question specifically related to chromium. As you've seen, we've shown you data from the murine LLNA test as well as from human patch testing studies that have estimated induction as well as elicitation concentrations for hexavalent chromium.

And in our initial assessment of the level of concern, we had decided to use the Nethercott study from 1994 with the lowest dose tested in that study of .018 ug/cm2. The uncertainty factor of 10-fold for our interim purposes of calculation of a safe area dose of

.0017 ug/cm2.

So based on the data that we have and that we've presented, our question to the Panel is: To please comment on the methods used for derivation of safe area doses using the available LLNA in the human patch test, including the magnitude of the applied uncertainty factors and include a scientific rationale in support of your position. Please comment on whether it is scientifically supportable to derive separate safe area doses for protection against induction of dermal sensitization as well as elicitation in sensitized individuals by hexavalent chromium.

DR. HEERINGA: Dr. Menne will be our primary discussant for this particular response.

DR. MENNE: Thank you very much. I'd also like to express my gratitude in being here. It's been a great experience. And I really think that I have a lot of things to

take back to Europe and explain how to work in such regulatory affairs. And particularly this very open discussion is not a habit which we have on the other side of the Atlantic. So I congratulate you with this process, and I think it's extremely valuable.

And the question is: Can we use patch testing and can we use LLNA in the prevention of allergic contact dermatitis? And why not use sophisticated methods of DNA arrays and different in vitro tests, pseudotransformation tests, et cetera?

Is it because dermatologists are so stupid, or how can it be? I would say that the methods we used, actually as Howard said yesterday, invented by Jadassohn 105 years ago, and we still like to use them. And why do we still use them?

I will say for the up-coming meeting in the European Society of Contact Dermatitis, there will be two papers on the use of DNA

micro-array methods in the evaluation of allergic contact dermatitis. And one of them will be on chromate dermatitis. So we try to keep up. And all the years, there has been a lot of studies in immunology, and there's been a lot of attempts to develop in vitro methods.

And, yes, they are in the journals; they are in the textbooks. But then when we come down to earth to our daily practices, our patch testing is working wonderfully in relation to the diagnostic development in the patients.

And I think you should all realize that we have quite a fantastic tool in the patch test. Because with the patch test, we have a direct connection between exposure to a chemical and a test in the humans which is very cheap, easy to perform, that can tell us that the person has developed an allergy and is at a risk developing the disease, allergic contact dermatitis, if you continue the

exposure. And of those people testing, we can give the explanation for a disease in 50 percent of the cases. That's quite unique for a test in medical science.

This example compared with a carcinogens. Do we have any human test that can predict that the patients will have lung cancer in 10 years time? No. And I can make many other comparisons. So this is quite a unique test that the dermatologist have developed. I agree it's old, but we love it. And we will probably continue to use it in the individual patients.

Another aspect example, can it be used in preventative medicine and can it be used in predicting levels of exposure, will it be safe for the population? And as several examples, and for an example, there is in Europe a regulation of cement with hexavalent chromate. And the regulation is that hexavalent soluble chromate should be below 2

ppm. And in those countries who have introduced this legislation, we don't have chromate dermatitis in the building industry. And earlier we had a high number, up to 10 percent, of those working in this industry sensitized.

If you make a comparison between the building of the Channel Tunnel from France to Britain, they had several hundred cases of allergic contact dermatitis to chromate. In Denmark where we have similar projects between Sweden and Denmark between our islands, which have actually employed a larger number of individuals, we have used this reduced type of cement. And there has not been recorded of a single case of chromate sensitization in this very large population.

A similar example, nickel dermatitis. This is has been regulated in Europe in the same matter. It's based on human studies, human elicitation thresholds.

And based on this, there's a border on the release of nickel for being in prolonged skin contact of 0.5 ug/cm2. And this has been extremely effective. And young girls now don't have nickel dermatitis. And in Europe, this is an phenomenon of the past. And earlier it was 15 percent of the population who were sensitized to this item.

So with the patch test and what we can do with different types of modification of this, we have a powerful diagnostic tool. And we have also a tool that can be used for determination of elicitation thresholds. This has been successful in regulatory purposes.

And we had already seen the questions. And I will now try to answer it on behalf of our group. Please, next slide.

So what we can say is, that concerning the LLNA data, we have human experience. We have particularly the Nethercott study, so we don't need to consider

the LLNA study for the derivation of safe area dose. And further, as has already been discussed during this meeting, LLNA has not been validated for assessing metals. And we don't think it's needed to be applied on the actual problem. Please next slide.

So what is extremely important when we're discussing allergic contact dermatitis is the exposure scenario. And here we think we have quite a lot of data missing because there are many questions to be asked here. And, particularly, we learned yesterday that, when we are bleaching the decks with cleaners, there might be produced hexavalent chrome. And we have very, very little information concerning the leaching out of hexavalent but also trivalent chromate to the surface of the wood. And we have very little information on the exposure of the skin of chromate when you're working with this wood in an occupational setting.

And, of course, as a lot of possibilities to develop new methods when it comes to skin exposure, you can, of course, measure a release in synthetic sweat, But you can also measure, for example, nickel or chromate in nails. You can directly measure chromate in the skin by making different stripping methods. So it's possible to develop very accurate exposure measurements to validate this.

So we think that, when it comes to selection of studies, Nethercott's is absolutely outstanding, the study from '94. And first of all, we can say that allergic contact dermatitis is reversible. And allergic contact dermatitis will persist if the exposure is continued. But it will disappear if you remove the exposure, but the underlying contact allergy will persist.

We also had to realize that the Nethercott study has been done, conducted in a

sensitized population, and, thus, represents a sensitive population. It is an elicitation study in already sensitized individuals. They are using the TRUE Test which is actually more sensitive than other patch test systems when it comes to the metal. And we are thinking about chromate, nickel and cobalt.

What are the advantages of this critical study? First of all, it's a large population that is patch-tested. And then you can say, okay, 54, this is not a large population. We have to remember that this was collected among 6,000 patient's patch- tested among this group of dermatologist. They evaluated 102 individuals and called them back for retesting. So it's actually a major thing to do a study like this one.

We agreed that this was a good experimental design. It was done at several levels. And the contactality was confirmed. And it was done in a dose-response manner.

They specially developed the TRUE Test so that they were very certain on the specific dosage they used.

They were sure that all the whole population was sensitized to Cr(VI). They agreed on a conservative reading scale of the individual patch test.

There are other studies. There is the study by Hansen 2003 which also includes trivalent chromate. It's a minor study. That's only 17. It's actually very supportive, and it is coming to the same conclusion as the Nethercott study.

Further, Hansen and coworkers have made a review of the literature published in 2002. And, again, this is supportive. And if you look at the thresholds in the older literature, it's larger than the thresholds defined in the Nethercott study. So, again, by sticking to the Nethercott study, we make a conservative estimate.

Concerning the Fowler study, we discussed that yesterday. And at least some think that the conclusion of that study is not completely in agreement with the experimental data. What we could have hoped for was available was that we had a study supplementing the Nethercott study where we had an open exposure over several weeks, two to four weeks, repeated open exposure with a lower dosage to have a study more imitating the use situation.

We have not such a study available in a larger scale when it comes to chromate. That's a minor study made by my group on fingers. And that's the study by Dr. Basketter made on damaged skin. But, again, it's a relatively small population. And we have here to glean our support from other studies. For example, nickel, preservatives, and fragrances, where we have two to four weeks studies.

So in our conclusion, we considered that the threshold in the Nethercott study 0.018 ug/cm2 in one patient. And this was obviously a very sensitive patient who reacted to a lot of things. And this patient was disregarded. And, therefore, we decided to go closer to the minimal elicitation 10 percent dose which is 0.88 ug/cm2. This was 4 out of the 54 who reacted in the Nethercott study.

Then concerning the uncertainty factors in such a human chromate study, we put 0.1 on the matrix vehicle. And this is because it's an occluded exposure. It is so that it is generally an increase of activity at least to the effect of 10. But then we have to realize that in real life we will have a repeated open exposure which cannot really overcome this factor.

The inter- and intraspecies is at 1. And concerning the exposure factor, that's significant uncertainty. And we have placed

this from 3 up to 10.

So our estimated range would be a figure between 0.03 to 0.09 ug/cm2. And this is also pretty close to the data which was coming up also using the local lymph node assay. And it's quite also interesting to see that it is not so far from the regulation which we have on nickel, for example, which is 0.5 ug/cm2.

And here we have to remember that nickel is estimated to be a moderately potent sensitizer while chromate is a potent sensitizer. So we feel quite confident that this might be a reasonable level to suggest.

Thank you very much.

DR. HEERINGA: Thank you Dr. Menne.

At this point, I'd like to ask the associate discussants if they have any points to add to the presentation and comments that Dr. Menne has just offered on Question 4. Dr. Pleus.

DR. PLEUS: Yes, just a minor comment. In that the one thing that I felt -- and I'll speak personally on this one -- was that the 0.088 was a conservative number. And I think that that was explained in the slide, but I just wanted to make sure it was stated.

In addition, the uncertainty factors, obviously, the exposure was one that had a range of values. And I think given maybe more time and maybe a closer look at some of the studies, we might have been able to refine that. I'm not sure. But that's my only comment.

DR. HEERINGA: With regard to the conservatism of the.088 value in your thinking, what were the elements that you think?

DR. PLEUS: Well, I think they've all been said before. You're looking at a sensitive population to begin with, them being sensitized. And I think that presents a new

arena at least in one aspect of the risk assessment approach.

We're always looking as risk assessors as what is the sensitive population. And in this one, that was directly measured.

I'm trying to still understand what does this represent to the total population. And that I still am not clear about. So like I said, maybe with more studies, I'd be clearer about that.

DR. HEERINGA: Thank you.

DR. PLEUS: May I ask one other question?

DR. HEERINGA: Absolutely.

DR. PLEUS: I would look to ask the EPA just for clarification if I could.

DR. HEERINGA: Certainly.

DR. PLEUS: There's a reference dose, the so-called SRFD. And the definition of that RFD, do you have a definition for that? Or is the same as a reference dose?

DR. MCMAHON: It's similar. But I think it was defined in the publications as related to a dose on the skin that would not cause this kind of specific adverse effect. So it was termed in the scientific literature. We don't have an Agency definition for that kind of specific yet. But it was a proposal.

DR. PLEUS: What I'm referring to, I think, and I don't have the definition of an RFD. But there's some degree of, I don't know, uncertainty between the value that is chosen, and it can be a magnitude higher or lower and something along that line. I'm only paraphrasing from the words of a reference dose. Does that make sense?

DR. MCMAHON: Yeah. I think, generally, it would refer to a dose below which we would not expect to see adverse effects over a lifetime is usually how they're set. They're set for different durations, of course, since we have acute and chronic.

But, yeah, I understand your point about the nature of the uncertainty. And I don't know if I remember it exactly myself. But it relates to how much uncertainty we apply to the level of concern that we derive. And then, you know, that's put into words. And, generally, the definition considers what you just got at in general versus specific RFDs, that we have various uncertainty applied to where we discuss specifically what we mean in that analysis.

You are correct. That is part of the definition.

DR. PLEUS: Thank you.

DR. HEERINGA: Any other comments from the associate discussants or any other members of the Panel? Dr. Foulds.

DR. FOULDS: Dr. Menne mentioned the reversibility of the contact dermatitis which I would agree with if there was a clearly defined cause for the chromate exposure, for

example, shoe dermatitis which can be easily avoided.

I'd just like to mention the occupationally induced chromate dermatitis which where apparent, withdrawal from the chromate exposure , i.e., cement or plaster, there can be a significant problem for a proportion of people exposed which, in some studies, has been reported up to 10 percent of individuals that may develop a persistent occupational dermatitis.

But that's in the occupational context. There's no evidence to suggest that, as far as I'm aware, in the nonoccupational exposure that there may be such a persistent problem from withdrawal from the allergen.

DR. HEERINGA: Dr. Meade.

DR. MEADE: I just wanted to make one comment about one of the bullets on the slide related to the local lymph node assay. And the point was made again that the local

lymph node assay has not been validated for metals.

I'd like to draw the Panel's attention and the group's attention to the fact that, at the time of the ICVAAM peer review was done, there was not sufficient data to include metals in this evaluation. And since that time, studies have been added. And we have shown that we can, indeed, induce sensitization to metals.

It has not gone back through rigorous validation or a validation exercise at all. But I'd also like to call the attention that using the human patch test for elicitation of responses has never been validated nor has the guinea pig maximization test or many of the other tests that we use.

So I think that always putting in front of us the lack of validation for some portion for use of local lymph node assay is holding it to a standard that no other tests

are. And again I'd point out that we do not feel that this assay is ready to be used in quantitative risk assessment but that the data is in pretty close agreement with the human data. And we do feel that there is promise for this assay down the road.

DR. HEERINGA: I'd like to go back to the last slide. I want to make sure that our calculations as presented are correct. Can you bring that back up?

I may be off base here, but I want to make sure that what was put up there is a range, that there was a consideration of a 10-fold factor for exposure and then a potential lower 3-fold factor. And I think those should be divisors instead of multipliers.

Let me just think out loud here. With a 10-fold uncertainty for exposure, the denominator here is 1 with a 3-fold factor on exposure is the denominator .3. So we should

be at .088 divided by .3 which is closer to 2.44 or 2.5.

I just -- does everybody follow me on this?

DR. HAYES: You did the math in the room.

DR. HEERINGA: Yeah, I helped. Dr. Hayes pointed out that, when I was walking through the room, somebody asked me to do the math; and I did the multiplication instead of the division. So I'm being sent back to school. I did recover I think here, unfortunately.

It's .088 divided by .3. I just want to be clear that, since there was a range put up here, we were absolutely correct on this range. And my understanding of the use of these uncertainty factors is exactly that, that they are divisors on this to essentially lower the exposure thresholds.

DR. JACOBS: You divide by 1 or you

divide by 3? No. Divide by .3.

(General discussion among Panel members.)

DR. HEERINGA: I don't have my calculator on me.

DR. JACOBSON: But it needs to get smaller.

DR. HEERINGA: I've since lost the ability to --

(General discussion among Panel members.)

DR. HEERINGA: It's .3 though. So the product of the uncertainty factors is either .3 or .1. Excuse me.

DR. PLEUS: Is this correct?

DR. HEERINGA: Does everyone agree that that is correct as you apply the uncertainty factors? Sorry for the confusion.

Dr. Hayes is right. That as I was walking by the screen, I was asked to do the multiplication in my head. And I did the

multiplication. Any other comments? Dr. Siegel.

DR. SIEGEL: I have one comment. On the .1, I agree with that as far as for wood. But would you agree that that's probably not generalizable to other materials such as leather gloves or shoes where that would come closer to being occluded and that you would wear for longer times for repeated exposure? Is there any discussion on that?

DR. HAYES: I think that we specifically did this for wood chromate. That was the question that was asked.

DR. HEERINGA: Dr. Meade.

DR. MEADE: Just one other point that we discussed, and I don't think that it has come out in this. And correct me if I'm wrong. The remainder of the Panel, we said that we were entering this into the weight-of-evidence; that we weren't suggesting that the Nethercott study by itself be taken

as the sole analysis. But this is one part of the weight-of-evidence.

DR. HEERINGA: That's a good point. Thank you. Dr. McMahon.

DR. MCMAHON: Yes, I just have a clarifying question. I just wanted to make sure I understood the selection of 1 as the intraspecies variation factor. And my understanding of that would be that it was based on the use of a sensitized population and what you consider a fairly large study size for this type of study.

I just wanted to make sure I understood. And the selection of the 10 percent response level, am I correct in my reasoning as to what led you to that factor?

DR. HEERINGA: Dr. Menne, would you like to address that?

DR. MENNE: I think you're right. That's in accordance with our discussions.

DR. HEERINGA: Are there any other

comments with regard to Question No. 4. Mr. Jones.

MR. JONES: Just a little bit more. Maybe it could be just repeating what you said. It takes a while for me to absorb it all.

That the science behind the rationale of the matrix factor of, is it, .1 would be interesting to hear what the Panel was thinking. What size sort of supports that value versus .2 or .3 or any other number? I understand the why less than 1 part.

DR. HEERINGA: Dr. Menne, do you want to start with this?

DR. MENNE: You know, if you're asking whether it should be 0.1 or 0.3, I have no science to support that. But it's a general thing, that when we are making the patch testing and compare it, for example, with a repeated doses, then we need approximately 10 times higher concentration

for the occluded -- 10 times lower concentration for the occluded patch test. But, of course, this depends very much on the hapten. So it might differ from one hapten to the other.

And if you ask me how many studies have been done in this area, I would say it's few. So this statement is not very well supported.

MR. JONES: Okay. And then similarly in the factor for exposure, you suggested 3 or 10. In advice to us, how would you suggest we sort of weigh the one versus the other in the exposure factor that you recommended?

DR. HEERINGA: Dr. Pleus, would you like to address that?

DR. PLEUS: Well, I think with much of this in terms of uncertainty factors it's using best professional judgment. And the range is there because of -- the range is

there, I think, effectively because we judged that when you're considering -- let me kind of rephrase it.

In the best of all worlds, the type of study that we would prefer in this kind of an evaluation is an open test with repeated exposures. And the suggestion would have been four weeks, for example. So what the attempt in this uncertainty factor is to adjust for that to get a better understanding of what that might mean and then base that on best professional judgment with what was done in the Nethercott, et al., study. And so with some flexibility, we have 3 or 10.

MR. JONES: That's helpful.

The last question I had, just to make sure I'm understanding the totality, really, of what you talked all afternoon -- and correct me if I've not understood it well -- is that the data that exists doesn't really support this kind of quantitative analysis for

induction, but that it does for elicitation; and elicitation to -- it will be protective of induction. I think I got that part right.

And then sort of going back to a comment you made a few minutes ago, Dr. Pleus. You also had some questions about what the elicitation quantitative analysis says to induction. And I just wanted to get the sense of a broader group as to any thoughts that you may have about this risk analysis around elicitation, what it does tell us about the general population or not.

It sounded like there isn't much you're able to say other than it's protective of the general population for induction.

DR. HEERINGA: Dr. Menne.

DR. MENNE: I can try to answer it.

You can say that here you're taking the most sensitive population probably you have out of the total population. Because these individuals, they have been sensitized.

And there can be two reasons for it. Either they are particularly sensitive because of genetics, enzymatic, polymorphism or whatever it can be; or they have had a specific high exposure. So they have been sensitized as far as the individual level and the exposure level. And that's the reason why they have ended up at the dermatologist, been patch tested, and ended up in this trial here.

So we can say that it's probably the best possible population we can have because they have been sensitized, not but one reason but by several reasons, by the sum of chromate exposure in the society. And probably they represent a special sensitive group because they have shown they are able to be sensitized.

We could speculate that we could have another group. We could, for example, take a group of 200 individuals, and then we could experimentally sensitize them and make

the same study. But we cannot be sure that this will be as good a marker as this one. Because those experimentally sensitized, they are probably exposed to a much higher dosage and this might come out with another result.

So I think that by doing it this way, you have a kind of natural selection of the population. You have the people who are sensitive, and you have the diversity of different exposures in the population. And in that way, you have the kind of worse-case scenario.

And if during this exercise, you can protect this group of individuals, you should have a very fair chance to protect the rest.

So that's the thinking behind it. It's maybe not big science. But it's because we really don't know what is making an individual sensitive to sensitization. We haven't figured out the genes yet. We will do it. I'm sure that we will come up with these

genes that make -- so that we can define the group of individuals who are particularly sensitive to chromate sensitization.

And I think when we have done that, you will see that some will have a propensity for chromate sensitization; others, probably to other allergens; and a subgroup of the population will have a propensity to multiple sensitizations.

MR. JONES: Thanks.

DR. HEERINGA: Dr. Meade and then Dr. Hayes.

DR. MEADE: Actually, if Wally's addressing this, he can go ahead.

DR. HEERINGA: Dr. Hayes first, please.

DR. HAYES: We have said all along that the human data should take precedence. If I remember correctly, if you look at the LLNA data, the local lymph node assay, it gives the same answer from the induction side

of the equation. So when we put the weight of the evidence together, you have increased the support for all of this.

DR. HEERINGA: Thank you. Dr. Meade.

DR. MEADE: Jim, I just wanted to add something to the question that you had asked about why we gave range for the uncertainty factor related to exposure. And I think you'll be able to narrow that down more when you get your exposure data. Part of that is because we don't have any information on what the exposure is going to be at this point.

Once you get the wipe data, you may find that people won't be repeatedly exposed to a given deck once it's built after two weeks or whatever. But we don't know that. So you'll have a very a different, I would think, uncertainty factor related to exposure if you find you can no longer recover chromium

from wood once it is been cured for two months versus if you find it's going to leach out every time you clean it or every time it rains.

So I think that's part of the reason for the breadth of the uncertainty. We don't know what exposures are at this point.

DR. HEERINGA: Dr. Hayes.

DR. HAYES: I hate to disagree with my good friend, but that's not the exposure part of the equation. This is a different exposure if I understood correctly. This is the size area, the place that it's located, and not the actual exposure coming off of the product.

DR. MEADE: I thought it related to repeat exposure. And that's where I was coming from. You eliminate the possibility for repeat exposure if, indeed, it's not coming out of the wood.

DR. HAYES: That's part of it. But

it's not the actual exposure from the product itself.

DR. MEADE: No. It's not the exposure numbers.

DR. HAYES: I just want to be sure that's --

DR. MEADE: It's just whether you have the potential for repeat exposure or you have not is what I was referring to.

MR. JONES: I'm sorry. Let me make sure I get this. That if the wipe data shows that the Cr(VI) you can be exposed to six or eight weeks later, then, obviously, a repeat exposure is possible if not likely. If it only is going to occur for six hours or six days, then you may not -- the likelihood of a repeat exposure is less.

DR. HAYES: And you go with the smaller number.

MR. JONES: You go with the smaller number. I see.

DR. HEERINGA: Additional comments? Dr. Pleus.

DR. PLEUS: Again, as we sit and deliberate and produce our report, we may have an opportunity to pull some more studies that might be useful in helping delineate that or support that.

DR. HEERINGA: Just a comment on that, too. Of course, we'll only cover things that have been presented here. But if we have references in direct support of that, they may be cited in the literature. But we won't be introducing any new data beyond what's been covered here.

DR. MEADE: And I guess with that in mind, I will just -- I had asked about this earlier. We spoke in generalities, I guess, Jim, when you had asked earlier about why we didn't support any of the three methodologies.

And just so we can get the literature in the report, I would like to make

reference to the Gerberick papers, the Basketter papers, and others that have looked at potency comparison data for the local lymph node EC3 value in setting group's potency groups for local lymph node data in comparison to the human data because those will be cited in the report.

DR. HEERINGA: Dr. Pleus.

DR. PLEUS: And in lieu of your comment, although I don't have any studies in my mind in particular, I guess there is probably a literature out there that talks about behavior of people and their use of outdoor equipment and things of that.

DR. HEERINGA: Actually, there is a good source for that literature. It's been fairly extensively addressed in this series of SAP meetings on CCA-treated wood. And, in fact, those exposures, including children's exposure, I think the minutes of those previous meetings of the SAP on CCA, while

they are not necessarily relevant to chromium exposures from ACC in terms of activity patterns, I think those issues have been very heavily addressed. And so it would be a very good source of references on those activities.

Any other comments from the Panel on Question No. 4? From the EPA scientists? Yes, Mr. Merenda.

DR. MERENDA: This is just checking back on something that I may have misunderstood that was mentioned earlier in the discussion. But there seemed to be some conversation about cross-sensitization between chromium and nickel and should the Agency be in any way be considering that in this process. I presume that the study that we're using here was limited to people who were identified as chromium sensitive. Would it make any difference for someone who is nickel sensitive?

DR. HEERINGA: Dr. Menne.

DR. MENNE: No. There's no cross-sensitivity between chromate and nickel.

DR. MERRILL: Good. Thank you.

DR. HEERINGA: Any additional questions or comments on Question No. 4?

Okay. At this point in time, I'd like to move on to just a wrap-up. And we've had a lot of material presented. We've discussed a lot of issues. And I would like to give the members of the Panel and then researches and administrators from the EPA a chance to make some additional comments.

There will be, in addition to the response to the four directed questions to the Panel, a general set of recommendations, an overview, that is, and part of the minutes in the report. If there are other things that you would like to see included in the minutes of these proceedings or as part of that report, I would be happy to have you give those at this point. Maybe I can start with

Dr. Foulds.

DR. FOULDS: I don't think I've got anything additional to add on. I think I've brought everything out in my presentation. Thank you.

DR. HEERINGA: Dr. Menne, the same?

DR. MENNE: Thank you.

DR. HEERINGA: The same. Dr. Hayes?

DR. HAYES: (Shakes head in negative.)

DR. HEERINGA: Dr. Pleus?

DR. PLEUS: Nope. The same.

DR. HEERINGA: Dr. Isom? Okay. Dr. Thrall? Dr. Meade? Dr. Bailey? We've been successful here. Dr. Burleson? Dr. Chu? Dr. Siegel?

DR. SIEGEL: Did you want us to address Dr. Burgess's questions?

DR. HEERINGA: There are -- we'll pick that up in a moment. There were some questions that were presented, the OSWER

questions. Is that what you're referring to?

DR. SIEGEL: Yes.

DR. HEERINGA: Yeah, If I could get back to those in just a moment. Let's maybe just focus on the EPA.

DR. SIEGEL: Nothing.

DR. MONTEIRO-RIVIERE: Nothing.

DR. HEERINGA: We were in a position which is little unusual for the SAP, but I think is beneficial, potentially, to the Agency. And that is in the presentation yesterday by Dr. Michele Burgess, she had posed two questions at the end of her talk. And if I could read the first. And if there are any contributions from the Panel.

Mr. Jones, you don't mind if we do this at this point.

MR. JONES: Please, please.

DR. HEERINGA: Let me just read them. And if there are any contributions from the Panel, I think the first one might be

answered with a very simple answer. But I'll let somebody more knowledgeable that I do that.

And that is: Does the SAP agree that environmental matrix variables will influence the acceptable area dermal dose to induce, elicit contact dermal sensitization in an individual when exposed to a chemical incorporated in an environmental media?

Dr. Burgess is joining us here, too.

DR. BURGESS: Thank you.

DR. HEERINGA: Does anybody want to give an answer to that? Yes, Dr. Monteiro-Riviere.

DR. MONTEIRO-RIVIERE: I guess, based on everything that was presented here today, you can see that we probably do agree that matrix variables can influence the amount of a compound that could be available to penetrate through the stratum conium. It's been redundant all day long here. So I think

it's sufficient.

DR. HEERINGA: The first one is easy. I think the answer is yes. Dr. Siegel.

DR. SIEGEL: I would also like to mention that it could go either way. It can bind so it can't absorb or facilitate absorption.

DR. HEERINGA: And the second part the Dr. Burgess's question to the Panel in her presentation was: Please describe how media-specific characteristics have or do not have a substantial impact on determining an environmentally acceptable dose for a chemical incorporated in an environmental media?

Now there's a complex kind of chemistry question. I think that's a little tougher to answer.

DR. PLEUS: I'm not going to answer it. But could I just ask Dr. Burgess to explain it, please?

DR. BURGESS: Yes. That's not as

simple a question, is it.

I guess it kind of goes back to what Dr. Siegel was saying. And that is, if the Panel had decided that, no, these were not important environmental -- and when I'm talking about vehicle, I'm only speaking of the media, so soil, wood, and water. Those matrix variables that would, as you were saying, either facilitate or abate the absorption. And, therefore, I guess I was just wanting to see that if, no, then why; and if yes, then why.

And I know that's kind of complicated. And I guess I'm just wondering. In the deliberations that I'm hearing today, it seems that there are certain factors that may link to sensitivity analysis. In other words, the pH may be incredibly important factor. I think you were bringing up, Dr. Pleus, that the sweat, the chemistry of the sweat, may be an important factor for that

being taken up by the skin.

And I guess I was just wondering if anyone had recommendations in their vast experience here at the table as to which factors they think may really be important factors to look at.

DR. HEERINGA: Dr. Burgess, you mentioned as media, soil, water, and wood, wood particles, and probably any derivative thereof. Dr. Monteiro-Riviere.

DR. MONTEIRO-RIVIERE: Yeah, I'll give it a try.

For example, if you're talking soil, dry soil may be different than wet soil. Wet soil providing a hydration effect on the skin that would then make a compound more assessable. Ph definitely would make it a factor. Metal speciation of the compound itself, the Cr(VI) versus the Cr(III), that would all have an affect.

Perspiration, I guess you talked

about sweat, Wally. That definitely could have an effect. Whether the compound is lipophilic or not would also have an effect. A lot of compounds have different configurations. So the molecular weight of a compound would also have an effect. Fixation.

DR. BURGESS: Right. In the wood.

DR. MONTEIRO-RIVIERE: Moisture content. All of that would have an effect. And also exposure site. Where it is applied to could have an effect. Like where hand exposed versus your abdomen being exposed based on the blood flow under the skin that would then have uptake of the substance. And also the thickness which varies over the body regions.

DR. BURGESS: Okay. Thank you.

DR. MONTEIRO-RIVIERE: Or even specific body sites such as axillary region versus other regions that may have more sweat glands, that would have more production of

sweat, that would increase the rate of absorption which would be an extremely moist area.

I think all that would happen.

DR. HEERINGA: Dr. Burgess, I think you've probably seen them. But I would also refer you to the same reports of the SAP proceedings that were published on the CCA reviews. I think there's a fair amount of discussion in those reports on the effect of speciation of particular compounds. It may be arsenic. But it may also touch on chromium. And I would refer you to those, too, for literature and discussion by the Panel experts that were present there.

DR. BURGESS: Thank you. Great.

DR. HEERINGA: Any other comments in response to these two items? Thank you very much, Dr. Burgess. I hope we -- oh, yes, please.

DR. BURGESS: Thank you. Again, I

wanted to ask a question again about the uncertainty factor that you all have been talking about with regards to matrix and vehicle effects. Is that directly related to environmental exposures or just simply to the test method?

GROUP: Test method.

DR. BURGESS: Test method only.

DR. MONTEIRO-RIVIERE: From the DMSO.

DR. BURGESS: From the DMSO.

DR. MONTEIRO-RIVIERE: I think that's what we concluded, that that would be a great penetration enhancer for a compound.

DR. HEERINGA: Let's make sure. I think the answer is that it was related to the test method. And Dr. Meade.

DR. MEADE: Maybe I misunderstand, then, because I thought, as we used the wood-impregnated chromium as an example, it really looked at both. We were testing in

DMSO, but it was going to be in impregnated wood. And we said if, indeed, it was going to be in wet cement, then maybe we wouldn't have used that same factor. So it seems to me that both play a role.

DR. HEERINGA: Dr. Pleus.

DR. PLEUS: In one way, I think if you -- I think it depends on how you're looking at this. And I think on one level when we were looking at the studies that we have all reviewed here and trying to derive, let's say, a critical study and the critical value and things along that line, it was important to take a look at the vehicle for the administration of the chemical in question, Cr(VI). And so in that way, I think an uncertainty factor, that's where we applied that.

At the same time, I think Dr. Meade, what you're saying here is, if you were doing a risk assessment now that that part is over

and I think that's what you're speaking towards more of that. Right?

DR. BURGESS: Right. Sort of. What I had heard. And it was exactly what Dr. Meade had said with regards to you kind of need to be sure that the matrix that you're doing the test method will match the scenario that you are expecting. Like she was saying, wet cement. And I also heard you say a very similar thing. But yet when you put your numbers up, that was where I was hearing that that attributed to the test method. Is that correct?

DR. PLEUS: That is where we have, I think, focused our effort on is on the uncertainty for the test method. But I understood from where you were coming from you were looking at it as a risk assessment standpoint.

DR. BURGESS: Yes, yes. Ultimately, yes, that's where I'm coming from. But I just

wanted to be sure I understood what you all had to say.

DR. HEERINGA: Dr. Chu.

DR. BURGESS: Thank you.

DR. CHU: Much of this answer has been said by Nancy.

Yes, the nature of environmental media does have impact on the dermal dose. For instance, in the case of chromium embedded in ACC-treated wood, it is considered less bioavailable. However, if a chemical such as a pH is mixed with soil, then it would depend on the nature of the soil; and the bioavailability would probably be less available to penetrate. In fact, there was one, maybe more papers, published in Dr. Howard's laboratory by Ron Wester which has proven to this effect. Thank you.

DR. HEERINGA: Any additional questions?

DR. BURGESS: No more questions,

thank you. I appreciate it.

DR. HEERINGA: Thank you very much, Dr. Burgess. And thank you, Panel members, for that.

At this point, I'd like to turn to the scientific and administrative staff of the EPA to see if they have any additional questions that they'd like to ask for clarification on with the Panel or comments. Dr. McMahon or Dr. Chen?

DR. MCMAHON: No. We appreciate the answers of the Panel. And we feel that they've addressed the questions appropriately and have given us the scientific input based on what we've been able to present.

We don't have anymore clarifying questions for the Panel.

DR. HEERINGA: Dr. Handwerger? Mr. Jones?

MR. JONES: If I could just for a moment. On behalf of the Office of Pesticides

Programs, I'd just like to thank you, this Panel, for the help that you have provided to us in sorting out one of the several very difficult issues we face as it relates to our regulatory decision-making around chromium.

I have not certainly been to nearly as many of these meeting as my colleague Joe Merenda or Paul Lewis. But I think it is -- after just talking with Joe briefly, I think it's been somewhat unique the degree to which we have gotten so much direct response in the meeting. And that's greatly appreciated.

And I think we've got a general sense as to -- not a general sense. I think we have a pretty clear sense as to the Panel's recommendations here, although we do look forward to the final report.

So thank you very much for your help in this efforts.

DR. HEERINGA: Thank you. On behalf on the Panel, too, I would like to thank your

staff for its presentations and the organization and for your involvement as well in the past two days. And I want to thank all the public commenters for their contributions to this session.

And on behalf of myself and the permanent members of the SAP, I would like to thank all of the SAP members who joined us for this session and provided their expertise. I think it was exceptionally well handled.

And at this point in time before we conclude, I'd like to turn it over Paul Lewis, the Designated Federal Official, to see if he has additional comments.

MR. LEWIS: Well, thank you, Dr. Heeringa. And, again, I appreciate your guidance over these past few days in terms of preparing the Panel for the discussions we had. And for the Panel to be actively engaged in terms of preparing the slides that we saw to summarize the Panel's thoughts and

recommendations, I think that was a very useful exercise for all of us to really capture the essence of their thoughts.

Half of our work is down now. The other half is for us to prepare a report. And the Panel will be preparing that report and will make it available in approximately 60 days. Again, this serves as meeting minutes which summarizes the Panel's recommendations that occurred on this afternoon, the four charge questions, and other comments they had.

I want to thank members of the Panel here for working with me in terms of getting prepared for this meeting and for your excellent deliberation and for members of the public who participated in this meeting over the past two days and being actively engaged in the deliberations we heard here.

But also I want to thank members, colleagues, and the SAP, sitting over here to my left, who really helped make the operations

of this meeting be successful and with our meeting contractors who, again, help arrange administrative support and other arrangements.

Thank you, Dr. Heeringa.

DR. HEERINGA: Just one final note. We've made a number of references to papers and materials. Any available copies of those materials and those papers will be available in the docket for these meetings and can be accessed there if not directly from the original source.

At this point in time, if there's no remaining questions, I'd like to draw this meeting to a close and thank everybody for their attendance and participation over the last two days.

Thank you very much.

[The meeting was adjourned at 3:40 p.m.]

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I, Jane F. Hoffman Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

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