SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

OCTOBER 23, 2001

VOLUME I

Located at: Sheraton Crystal City Hotel
1800 Jefferson Davis Highway
Arlington, VA 22202

Reported by: Frances M. Freeman

CONTENTS

DR. ROBERTS: Good morning. Welcome. I would like to open this October 23rd session of the FIFRA Scientific Advisory Panel.

Today is the first day of a three-day consultation between the agency and the panel on the OPP's preliminary evaluation of the non-dietary hazard and exposure to children from contact with chromated copper arsenate (CCA)-treated wood playground structures and CCA contaminated soil.

Before I introduce the panel, I would like to introduce our designated federal official for today's meeting, Ms. Olga Odiott, and ask if her if she has any announcements or instructions for the panel.

MS. ODIOTT: Thank you, Dr. Roberts. I would like to welcome the panel members and to thank them for agreeing to serve and for their time and for preparing for this meeting.

We also appreciate representatives from other federal agencies for their support, for their involvement and for their active role in preparing for today's SAP meeting. I also want to thank my EPA colleagues and presenters and SAP staff for their efforts in this meeting over the next several days.

We have challenging science issues being presented today and we have a full agenda. And I want to remind everybody that the

meeting times on the agenda are approximate. So it might not keep to the exact times as they are noted.

We want to ensure adequate time for everybody to do their presentations. We want to ensure adequate time also for the public comments to be presented and also for the panel deliberations.

So we ask that all the presenters and the panel members and the public commenters, that they identify themselves. Also, they speak into the microphones that are provided. This meeting is being recorded.

And of the public commenters, we ask that you limit your comments to the issues at hand and that you are as concise as possible so that as many people that want to address the panel have the opportunity to do so.

We have asked the public to provide written comments of the topics and the issues to be presented in advance of the meeting. And these comments has been provided to the panel for their review and their analysis.

All the materials that the panel has been provided are available from the EPA docket and most of them are also available from the FIFRA SAP web site. And the address for both of those places are at the top of your agenda.

As the designated federal official, I am responsible for ensuring that the provisions of the Federal Advisory Committee Act are met. And as the designated official for this meeting, I work with appropriate agency officials to ensure all appropriate ethics regulations are satisfied.

In that capacity, panel members are briefed with provisions of the federal conflict of interest laws. Each participant has filed a standard government ethics report and I, along with our deputy ethics officer for the office of prevention of pesticides and toxic substances, and in consultation with the office of the general counsel, have reviewed the report to ensure that all ethics requirements are met.

For those of you from the press that have questions about today's meeting, Mr. David Deegan (ph) from the office of media relations is available to assist you. Mr. Deegan, if you are around here, please stand.

Thank you.

At the conclusion of the meeting, the SAP will prepare a report as a response to the question posed by the agency: The background materials, the presentations and the public comments. The reports will serve as meeting minutes and we anticipate completing this report within 30 days of the meeting.

DR. ROBERTS: Thank you. We have a rather large panel with an impressive array of expertise available to us over the next three days. And I would like to introduce the panel by first starting with Dr. Freeman on my right and ask each member of the panel to indicate their name, affiliation and expertise. Dr. Freeman?

DR. FREEMAN: I'm Natalie Freeman from Robert Wood Johnson Medical School and the Environmental and Occupational Health Sciences Institute in Piscataway, New Jersey. And I study children's exposure to environmental contaminants and look at children's behavior patterns and how they contribute to exposure.

DR. MacDONALD: Peter MacDonald from the Department of Mathematics and Statistics at McMaster University in Canada. I have general expertise in applied statistics.

DR. KOSNETT: I'm Michael Kosnett. I'm a physician specializing in occupational and environmental toxicology. I'm on the clinical faculty at the University of Colorado Health Sciences Center. I have been particularly interested in the toxicology of arsenic. And I recently served on National Research Council's subcommittee on arsenic in drinking water.

DR. GINSBERG: I'm Gary Ginsberg from the Connecticut Department of Public Health. I'm also adjunct faculty at Yale and the

University of Connecticut Health Center. I have been involved in arsenic exposure issues from pressure-treated wood for a number of years since research in Connecticut showed some leaching, and also involved in some projects with EPA on children's pharmacokinetics.

DR. BRUCKNER: I'm Jim Bruckner from the University of Georgia. Areas are pharmacology, toxicology, toxicokinetics. I was a member of the original pesticides in children NRC committee and have been on several NRC committees since then, dealing with children's issues.

DR. KISSEL: I'm John Kissel from the Department of Environmental Health at the University of Washington. And my interest area is human exposure assessment.

DR. GORDON: I'm Terri Gordon from NYU School of Medicine. Inhalation toxicologist -- which looks at the effect of pressure-treated wood in the lungs.

DR. LEES: Good morning. My name is Peter Lees. I'm from the Johns Hopkins University School of Public Health. I am an industrial hygienist trained in exposure assessment issues. And I have worked actually for many years now on exposure assessment of an occupational cohort exposed to chromium.

DR. HOPENHAYN-RICH: My name is Claudia

Hopenhayn-Rich. I'm an epidemiologist at the University of Kentucky at the Department of Preventive Medicine and Environmental Health. And I have been involved for a number of years on several epidemiologic studies of arsenic exposure in drinking water.

DR. LEIDY: Good morning. I'm Ross Leidy from the Pesticide Residue Research Laboratory at North Carolina State University in Raleigh, North Carolina.

We are interested in non-food source exposures following pesticide applications in and around structures and are also interested in the movement of pesticides from urban and rural areas into public drinking water supplies.

DR. SOLO-GABRIELE: I'm Helena Solo-Gabriele. I'm an associate professor at the University of Miami. I'm a civil environmental engineer. For the past several years, I've been working on environmental issues associated with CCA-treated wood. In particular, we have been looking at issues associated with in-service and both disposal of the treated wood product.

DR. ROBERTS: Dr. Bates?

DR. BATES: I'm Michael Bates. I'm with the arsenic health effects research group at the School of Public Health, University of California at Berkeley. I'm a visiting researcher from New Zealand at

the moment. I'm involved in a number of epidemiologic studies into health effects, particularly cancer, associated with arsenic.

DR. STYBLO: Good morning. My name is Miroslav Styblo. I'm with the Department of Pediatrics and Department of Nutrition, University of North Carolina at Chapel Hill. And my expertise covers basically mechanisms responsible for biotransformation of arsenic. And I have also been involved in research of mechanisms underlying some toxic and carcinogenic effects of arsenic.

DR. STEINBERG: I'm J.J. Steinberg. I'm a professor at the Albert Einstein College of Medicine on the faculty of pathology. I work in genetic toxicology and have been involved in environmental public health.

DR. CHOU: I'm Karen Chou from Michigan State University and the Institute for Environmental Toxicology. I also assist the faculty in the Department of Animal Science, adjunct professor in the Institute for International Health, osteopathic medicine. I do research in reproductive toxicology. And I teach risk assessment and environmental toxicology, societal issues. And I also do outreach programs with the community with -- if they have contaminated problems.

DR. MUSHAK: I'm Paul Mushak. I'm a toxicologist and human

health risk assessment specialist. I direct a group in a consulting firm. I'm also visiting professor of pediatrics at the Albert Einstein College of Medicine working in John Rosen's group.

Most of my work has been involved with children over the years, working with lead, arsenic, mercury and, to some extent, the other metals.

DR. FRANCOIS: My name is Rony Francois. I'm an occupational medicine physician. I'm also an assistant professor at the University of South Florida, College of Public Health in Tampa, Florida. My areas include exposure assessment and toxicology.

DR. SMITH: My name is Andrew Smith. I'm the director of environmental toxicology program at the State of Maine Bureau of Health. We have been involved in doing some limited field work, looking at exposure to arsenic from pressure-treated wood. We're also currently involved in a joint study with CDC evaluating the significance of bathing as a route of exposure for children from arsenic in wells with elevated concentrations.

DR. SHI: I'm Xianglin Shi. I come from National Institute for Occupational Safety and Health. And also I'm a adjunct faculty at the West Virginia University.

My area of research focuses on molecular mechanisms of

chromium toxicity and carcinogenesis.

DR. MORRY: I'm David Morry. I am toxicologist and risk assessor. I work for the State of California in the Office of Environmental Health Hazard Assessment, which is part of the State of California Environmental Protection Agency.

I worked a few years ago on developing a public health goal for chromium in drinking water. And I have also worked in other hex-chrome exposure issues in the State of California.

MR. CLEWELL: I'm Harvey Clewell. I just recently became a principal with Environ. I have been doing pharmacokinetic and dose response modeling for both arsenic and chromium for a number of years, and recently have been involved in pharmacokinetic issues regarding children.

DR. HEERINGA: Good morning. I'm Steve Heeringa. I'm a biostatistician. I direct research design and operations at the Institute for Social Research at the University of Michigan. My training and specialty is in research and sampling design for population-based studies drop.

DR. MATSUMURA: I am Fumio Matsumura from the University of California at Davis. My area of expertise could be in the area such as the molecular biology, biochemistry or pesticides and

dioxins.

DR. THRALL: I'm Mary Anna Thrall. I'm a professor of veterinary pathology at Colorado State University.

DR. ROBERTS: And I'm Steve Roberts. I'm a toxicologist. I'm a professor with a joint appointment in the Colleges of Medicine and the College of Veterinary Medicine at the University of Florida. I also serve there as director for the Center for Environmental and Human Toxicology.

My research interests include mechanisms of toxicity, particularly involving the liver and immune system as well as toxicokinetics, including the measurement of bioavailability.

I'm pleased that we have with us this morning the director of the Office of Science Coordination and Policy of OPPTS, Dr. Vanessa Vu.

Good morning, Dr. Vu, and welcome.

DR. VU: Good morning. Thank you, Dr. Roberts.

Good morning, ladies and gentlemen. On behalf of the agency, I would like to welcome all of you members of the panel, distinguished panel, and the public to this important meeting in addressing very important environmental public health issues related to CCA-treated wood in playground settings, particularly children's exposure.

First, I would like to thank all the panel members for their time and effort in preparing for this meeting, and also Dr. Roberts, particularly, to chair for this meeting.

In addressing this important issue, the agency Office of Pesticide Programs has been working collaboratively with our sister agency, Consumer Product Safety Commission, as well as different parts of the agency's program within the EPA. We look forward to having our colleagues within EPA as well as CPSC and ATSDR to participate in this presentation and deliberate in discussion with the panel members the next few days.

And Mr. Jim Jones, the deputy director of the Office Pesticide Programs, would further speak on the agency's activity surrounding these issues.

As you know, this meeting is a public open meeting and the agency welcomes the public participations. And as Ms. Odiott has indicated, all the materials supporting this meeting are available on the OPP's public docket for public inspection.

With this brief introductory remark, I would like to thank Dr. Roberts for giving me this opportunity. And I am really looking forward to the agency's presentations to the panel this morning as well as tomorrow morning, and looking forward to your deliberations on

these very important issues. And all the advice and recommendations to the agency will be a very valuable asset for the agencies to deliberate further next steps in our addressing these environmental issues.

Thank you, Dr. Roberts.

DR. ROBERTS: Thank you, Dr. Vu.

As you indicated, also we have with us Mr. James Jones, who is deputy director of Office of Pesticide Programs. Good morning, Mr. Jones.

MR. JONES: Good morning. Thank you. I'm Jim Jones, deputy director of EPA's Office of Pesticide Programs. I would also like to thank members of the panel for their public service.

We are struggling with a complex set of scientific issues and we very much appreciate your willingness to provide us with your expertise and advice. I will briefly provide some of the context for this meeting and then we will get right into our presentations.

In recent months, much public attention has been focused on the potential risks to children from exposure to residues of arsenic, a known human carcinogen, from playing on play structures built with wood treated with copper chromated arsenate. Although the agency was already moving forward on a comprehensive reassessment of CCA

as part of its routine re-registration review of all pesticides, the level of public concern regarding children and playgrounds prompted a focused, expedited review of the risks associated with the use of CCA-treated wood in playground settings.

The agency has convened this SAP to obtain advice and counsel on EPA's preliminary assessment of existing data regarding the hazards of arsenic and chromium, the potential exposures of children to these chemicals as they come into contact with CCA-treated wood playground equipment and associated CCA-contaminated soil.

Given the unique exposure parameters and the resulting exposure scenarios, we are seeking expert scientific peer review to ensure the agency has taken into account all key data and methodology aspects of estimating risks to children in playground settings.

Further, OPPTS scientists believe that it would be premature to develop a risk assessment or attempt to characterize risks to children without seeking expert scientific advice from the SAP first.

Two major areas of uncertainty in the exposure assessment are existing data regarding available residues of arsenic and chromium in playground soils and untreated wood are highly variable. Secondly, there is some uncertainty as to what assumptions are best used to estimate children's behavior in playground settings.

As it relates to hazard, our assessment is unusual because laboratory animals have proven to be substantially less susceptible to arsenic than humans. Thus, the agency has developed an atypical hazard assessment for arsenic based on human epidemiology studies and case reports.

OPPTS intends to use the Office of Water's hazard endpoints for cancer effects which have undergone extensive scientific peer review, including a recent reassessment by the NRC. OPPTS has been and will continue to work closely with the Office of Water in developing the most scientifically sound approach to carcinogenic risk from exposure to inorganic arsenic.

Following this meeting and taking into consideration the comments of the panel, the agency will determine whether the existing database is sufficient to allow an accurate assessment of the risks to children from exposure to CCA from playground equipment constructed with CCA-treated wood. If so, the agency will be in a position to release a preliminary draft children's risk assessment sometime in early 2002.

Recently, EPA and the Consumer Product Safety Commission released a draft study protocol for public comment on the design and implementation of a study. The study will collect actual data

regarding available residues of arsenic and chromium in playgrounds throughout the country. The data from the playground study may be used during the risk assessment process to confirm estimated exposures calculated from the existing data that will be discussed here this week.

The EPRA/CPSC sampling efforts are expected to begin in December of this year with results available in May of 2002.

As I mentioned earlier, the playground assessment is part of the overall reassessment of CCA that the agency is doing as part of its re-registration review process for all pesticides.

Other uses of CCA wood include decks, fences, landscaping, walkways, gazebos, boat decks, highway noise barriers, sign posts, utility posts and retaining walls.

During the overall reassessment, the aggregate risks posed to children from these various potential avenues of exposure will be considered where prudent to do so.

As you will see this week as the presentations are made by agency staff and other invited experts, tough scientific questions exist. Our goal is to ensure rigorous scientific process with ample public participation resulting in a robust regulatory decision.

With that background and context, I would like to turn it over to

Dr. Norm Cook.

DR. ROBERTS: Thank you, Mr. Jones.

Mr. Cook -- just to let the panel know, the agency has several presentations they would like to make to us regarding their preliminary evaluation. Mr. Cook will lead off, and he's with the antimicrobials division of the Office of Pesticide Programs.

Mr. Cook, judging by the materials that you have submitted to the panel in advance, I would say that you and your colleagues have been very busy over the last six months.

MR. COOK: That's correct. No vacation time.

Good morning, Mr. Chairman, members of the panel, ladies and gentlemen. My name is Norm Cook and I'm chief of the risk assessment and science support branch which is located into the antimicrobials division, Office of Pesticide Programs. This branch is responsible for the human and environmental risk assessments for chromated copper arsenate, also known as CCA.

Additionally, we are responsible for the children's risk assessment for CCA-treated playground structures.

Before I continue my remarks, I would like to introduce some key people as well as those sitting at the table with me. First, from the antimicrobials division, there are scientists and staff who are

actively involved with CCA issues present. These include Mr. Frank Sanders, director, Dr. Deborah Edwards, associate director, Ms. Connie Welsh, regulatory branch chief, and a number of scientists who are involved with me in the evaluation of children's hazards, exposures and risks. However, it is possible that the most critical person here today is Ms. Kay Montague, lead biologist for the CCA environmental issues, because she is handling our PowerPoint slides. Thank you, Kay.

Those making today's presentations include, to my far left -- and I don't believe he has arrived yet -- Dr. Charles Abernathy. He will be here a little later. He is the lead toxicologist for arsenic from the Office of Water.

To Charles' right is Dr. Bob Benson, lead toxicologist on arsenic issues from U.S. EPA region 8.

To Bob's right, we have Dr. Jonathan Chen, one of two lead toxicologists for arsenic from the antimicrobial division.

And to Jonathan's left, we have Dr. Timothy McMahon, the other lead toxicologist for arsenic from the antimicrobials division.

And last, but not least, we have Dr. Nader Elkassabany, lead biologist for overall CCA issues from this division as well.

The format for today's presentations is as follows:

First, I will start with an overview of some major points associated with the available hazards data for arsenic and chromium as well as some of our exposure assumptions.

Following my presentation, Nader Elkassabany will present an overview of CCA use patterns, followed by overview of the chemistry of arsenic and chromium.

Next, Dr. Timothy McMahon will present a description of the agency's hazard assessment and toxicology endpoints for arsenic and chromium.

Following Tim, Dr. Jonathan Chen will present an overview of existing bioavailability data for arsenic and chromium.

After these four presentations, Dr. Bob Benson and Dr. Charles Abernathy will speak. Dr. Benson will present a discussion of Superfund development and use of short-term arsenic hazard ends points.

Following Bob and closing out the presentations for today, Dr. Abernathy will present a brief overview of where the Office of Water is relative to the arsenic in drinking water rule.

In closing, to give the panel some idea of the extent of the cross-cutting aspects of the CCA review effort, I would like to point out that, in addition to those scientists working on CCA in the

antimicrobials division, we also have present scientists and staff from a variety of other programs and agencies.

Many of these scientists and staff are working with us as we develop our CCA assessments, and they have graciously agreed to participate today to provide further clarification on issues when needed.

Some of these staff are as follows: I have mentioned Dr. Bob Benson, Dr. Charles Abernathy. We also have Dr. Peter Grevatt from the Superfund program. Tomorrow, we will have staff from the Office of Solid Waste. We have also been working with the Office of Children's Health Protection, the Office of Research and Development, the immediate Office of the Director of Pesticide Programs, the Office of Science Coordination and Policy. We have been working with Dr. Vanessa Vu and Mr. Greg Shreer with the Biological and Economic Analysis Division.

Outside of the agency we have with us today Dr. Selene Chou from the Agency for Toxic Substances and Disease Registry. We also have scientists from the Consumer Product Safety Commission and scientists from Canada's Pesticide Management Regulatory Agency.

On behalf of the antimicrobials division, I want to thank all those who are participating today, with a special thanks to Dr. Benson

and Dr. Abernathy for agreeing to make presentations to the panel, as well as to Dr. Vanessa Vu and Greg Shreer for all the support and assistance they have provided us in our efforts.

Now, at this time, I will provide a brief overview of some CCA hazard and exposure points which we believe should be emphasized. Please note that these are summary points which will be discussed in more detail later today, tomorrow, and Thursday.

First slide, please.

It's probably pretty obvious why we are here for the next three days, but let me begin by emphasizing two points.

The agency always takes pesticide risk characterization or risk assessment seriously. However, for the characterization of children's risks, we become even more concerned because it is such a critical and important activity. Considering this, our goal is to develop and use the most appropriate hazard and exposure inputs in any children's risk assessment that we perform for CCA-treated wood. Of course, for this meeting, we are focused on CCA-treated playground structure and CCA-contaminated substrates such as soil.

Considering what I have just said, the agency welcomes and invites scientific as well as public and stakeholder discussion on the proposed hazard and exposure components that we plan to use in the

risk assessment for children who are exposed to CCA-treated structures and CCA-contaminated substrates. Specifically, we will be asking the panel for comments and recommendations in three major areas.

Let me provide some examples. In the area of available exposure and hazards data or ends points, we will ask, what does the panel think about the scientific soundness and uncertainties associated with these data?

In the area of using available exposure and hazards data or endpoints in a planned risk assessment, what does the panel think about appropriate ways to use these data?

Approaches to take. Should we use deterministic or probabilistic methods? Can the available data be combined or collated or is there too much variability in data sets to do so?

In the area of additional data needed to reduce the uncertainties in the planned children's risk assessment, what does the panel think about obtaining additional exposure data? Types of additional exposure data that should be obtained. And relative to this area, I will say more on a current effort underway between Consumer Product Safety Commission and U.S. EPA later in this talk.

Again, the agency believes that it is important to invite a

thorough scientific discussion prior to even attempting to characterize children's risks from exposure to CCA-treated structures and CCA-contaminated substrates. We plan to review and consider all panel as well as public and stakeholder comments as we finalize the children's risk assessment.

Now I would like to make some comments about certain exposure components of the planned children's risk assessment.

Let me talk first about routes of exposure. The agency believes there are two major routes of child exposure to CCA-treated wood or CCA-contaminated substrates such as soil: Via dermal contact and via oral contact. By oral, I mean incidental ingestion or hand-to-mouth contact where the child touches the wood or soil and then puts the hand to his or her mouth.

We don't believe that exposure via inhalation is a route of concern because it appears that neither arsenic nor chromium residues are volatile on surfaces of wood. Also, we are assuming that respirable airborne particles containing arsenic or chromium are not present in significant concentrations. Further, it appears that other risk assessors agree with this approach because today we haven't seen other assessors develop this exposure scenario for the playground setting.

Based upon our view of the major routes of exposure, we have developed four child exposure scenarios for the playground setting.

These are the two dermal and the two oral or incidental ingestion routes, each with one scenario for contact with CCA-treated wood and one for contact with a CCA-contaminated substrate such as a soil.

We recognize that attempting to assess durations of child exposure in a playground setting is difficult. To address exposures associated with non-cancer hazards, we have developed two scenarios: A short-term scenario defined as an exposure from one day to one month, and an intermediate term scenario defined as an exposure from one month to six months.

We have developed these scenarios based upon the California Department of Health Services' 1987 study which states that a child may spend up to 130 days per year in a school playground. This is based upon an exposure frequency for a child who uses a school playground five times per week and 26 weeks per year, resulting in 130 days.

We consider a child exposure of 130 days a central tendency value, recognizing that this duration likely is not representative of all playground exposure durations for a child.

To address exposures associated with cancer hazards, we have developed a child exposure duration of six years as a time a child might spend over a life time using playgrounds containing CCA-treated playground structures. We consider a child exposure duration of six years a central tendency value, which is based upon U.S. EPA's 2000 draft risk assessment guidance for Superfund.

Now I would like to make a few comments about the hazard assessment for CCA. The agency recognizes inorganic arsenic and inorganic chromium as compounds of toxicological concern.

Because copper is generally recognized as having minimal toxicity to humans, we have not considered copper in our hazard assessment for playground settings. However, copper will be considered in the agency's environmental risk assessment for CCA-treated wood structures because we recognize copper as a compound of ecotoxicological concern. Of the three, arsenic, chromium and copper, copper has been shown to be the most toxic to aquatic organisms.

For arsenic and non-cancer hazards, the agency recognizes that most laboratory animal data show that animals are less susceptible than humans to arsenic toxicity.

Considering this, OPP proposes to use the existing

epidemiological studies and case reports to develop short and immediate-term non-cancer endpoints for use in assessing the short and intermediate-term child exposure durations.

For cancer hazards, we are aware of the recent 2001 National Research Council update of the '99 arsenic in drinking water report. We believe this update is an important document that provides relevant information such as risk models used to characterize cancer risk from arsenic exposure via drinking water.

Further, OPP considers the NRC updated information as relevant to characterizing cancer risk from exposure -- arsenic exposure via CCA-treated wood. We believe that whether exposure is from drinking water or CCA-treated wood, both routes ultimately involve exposure to inorganic arsenic. Additionally, OPP intends to work closely with EPA's Office of Water to develop a scientifically sound approach to a cancer hazard assessment for inorganic arsenic.

Now I would like to present some summary points about chromium hazards.

For chromium, the available hazards data indicate that Chromium 6 exhibits more significant toxicity than Chromium 3. Of course, we recognize that there are minimal data indicating which valence state of chromium is found as dislodgeable residues or as

residues in substrates such as soil. Even so, we are considering use of the Chromium 6 toxicity database to develop short and intermediate-term non-cancer endpoints for use in assessing the short and intermediate-term child exposure durations. This approach would provide for a more conservative hazard assessment as well as a more conservative children's risk characterization than if one were to use the Chromium 3 hazards data. Our goal, obviously, is to be as protective as possible in our assessment.

For chromium cancer hazards, we note that Chromium 6 is classified as a group A or known human carcinogen via the inhalation route of exposure. Of course, we have already stated earlier that we are assuming that child exposure to chromium residues via inhalation is minimal.

For the oral route of exposure, Chromium 6 is classified as a group D, not classifiable carcinogen.

Now I would like to make some comments about a sampling efforts that the Consumer Product Safety Commission and U.S. EPA have jointly undertaken. First, let me provide some background as to how this effort evolved.

Several months ago, the two agencies began meeting to discuss the pros and cons of undertaking sampling to obtain further arsenic

and chromium and, in some cases, copper residue data that would be specific to playground settings. Both agencies recognize that a number of studies are available for dislodgeable and soil residues of arsenic and, to a lesser extent, for chromium. However, when we met, we both agreed that much of the available data had not been collected in playground settings.

The two agencies decided that residue sampling in playgrounds containing CCA-treated structures could provide data that would be useful in the development of child exposure and risk scenarios. With this in mind, the two agencies developed protocols to address dislodgeable residues of arsenic and chromium and copper on CCA-treated wood playground surfaces and residues of arsenic and chromium and copper in playground substrates such as soil, wood chips, pea gravel or shredded rubber.

The primary focus of the substrate sampling is sampling of soils, but consideration will be given to sampling of other substrates if they prove to be significant materials found in playground settings.

The two protocols were released for public comment on September 20th, 2001. At around the same time, the two agencies arranged for an external peer review of the protocols by independent peer reviewers. The public comment period ended on October 22nd

and the external peer review is now complete. Both agencies plan to incorporate all appropriate comments into the protocols and begin sampling in November 2001.

Relative to the two protocols, CPSC and U.S. EPA agreed to the following approach: CPSC is the lead for the dislodgeable residues from wood protocol. U.S. EPA is the lead for the substrate sampling protocol. CPSC will collect all dislodgeable and substrate samples, and U.S. EPA will analyze all substrate samples, whereas CPSC will analyze dislodgeable residues from wood samples.

Further, we agree that collected samples will be analyzed for total arsenic, total chromium, and copper.

Some analyses for speciated forms of arsenic, but more likely for chromium species may occur, depending on the results found in the pilot effort.

Now I would like to make a few comments about the overall design of the sampling study. First, as mentioned, sampling for dislodgeable and substrate residues of arsenic and chromium will occur at various playground sites. Before sampling begins, CPSC field staff will contact local authorities, such as school boards, county and state park departments, to obtain access to playground areas.

Once sites are located, a two-tier study is planned. For the pilot

study, the two agencies will locate three playgrounds in one geographic region and perform the planned sampling in those playgrounds. The purpose of the pilot study will be to standardize the field sampling techniques to be used in the larger field study.

Specifically, after reviewing the sampling techniques, approaches and analytical results from this pilot effort, the two agencies will address sampling procedures in the larger field study as needed.

For the larger field sampling study, the two agencies plan to locate and perform sampling in 15 playgrounds -- excuse me -- in 25 playgrounds in each of three geographic regions, such as the Northeast, the Southeast, and the Southwest of the United States.

In each of these 25 playgrounds, we are proposing to collect ten substrate residue samples from various points under CCA-treated structures and ten dislodgeable residue samples from the CCA-treated structure itself. These samples will then be analyzed by the two agencies for total arsenic, chromium and copper.

In closing, this concludes my overview of the exposure and hazards inputs the agency plans to use in the children's risk assessment for CCA-treated structures. As I indicated earlier, these points will be discussed in more detail in later presentations today and

tomorrow.

I will be happy to answer any questions at this time. However, if there are no questions, then I will turn the discussion over to Dr. Nader Elkassabany. Thank you.

DR. ROBERTS: Thank you, Mr. Cook.

Are there any questions from the panel for Mr. Cook before we proceed to the next presentation?

Dr. Mushak?

DR. MUSHAK: Just a general question about sequencing. The panel is being asked to evaluate the status of data which may change markedly when you folks do your pilot studies and full field studies.

How much of what we do carries over into what you hope to get out of these proposed future studies? It seemed like there is an element of prematurity here. I may be wrong.

MR. COOK: Well, we thought about that and I think we decided it would be better to have a panel meeting because there is such a large body of existing data.

Initially, our attempt was to use that data. And then this playground effort kind of became the priority.

So that is a good point. But I think we wanted to hear what the panel thought about the existing -- whether we could use it and how

reliable it would be For the playground setting. The other thing is we also have to do risk assessments beyond the playground setting.

DR. ROBERTS: Dr. Ginsberg?

DR. GINSBERG: To follow up on your last comment, it is a little confusing to me exactly how these risk assessments will proceed. Will there be two separate risk assessments, one focusing on all the playground data? Because, as you showed, there are some exposure assumptions that are more specific to children's use of playground; then you are going out and collecting a lot of playground data, it looks like, from these protocols. How will that all be related to maybe a different risk assessment or an add-on risk assessment that gets into a more holistic view with playgrounds added to other wood -- pressure-treated structures, and how will that change the exposure assessments and how will the data, the field data that you're generating now be applied to a more holistic risk assessment?

MR. COOK: I'm not sure how many questions were there, but I'll try.

Basically, the focus on re-registration is to do risk assessments on all pesticide uses. CCA-treated wood, obviously, is unique in that we're moving beyond actually assessing the pesticide itself, which would be the occupational. So our original plan was to assess each

use -- basically, it's almost like a modular approach or a tiering approach. You do your occupational, then you do your non-occupational, your residential.

And as a subset of the residential, we would have done the children's risk assessment for playgrounds. What happened, obviously, with the increased concern, we moved that risk assessment to the front, which we don't typically do. It kind of puts it out of sequence. We try to do it more holistically, working from the general to the specific. So we're actually trying to be flexible as we speak because, typically, we would have started with residential scenario and worked down to the children's risk assessment. But in this case, we're kind of working backwards.

Again, we were going to try to use the existing dislodgeable and substrate sampling data -- there is such a large body of data there. Unfortunately, to us, it seems to be very highly variable and lot of uncertainty to it.

So we decided sort of as -- I wouldn't say a fail-safe -- to undertake the sampling effort and, in the meantime, see what we could utilize in the existing database.

I don't know if that fully answers your question or not.

DR. GINSBERG: Well, just to help us frame our deliberations

in terms of what you need from us, are you looking for input on your exposure assumptions for both a playscape-type scenario and a residential scenario or just one or the other?

MR. COOK: Well, I think the focus is on the playground setting. Unfortunately, that's a very good point. These things have a tendency to spill over because, if you saw in our exposure docket, most of the data that we have available is on decking. There is some on playgrounds.

So you get into this -- well, you have deck data, you have soil data under decks. So it kind of spells into the residential setting, as well as you may have a playground set in someone's backyard.

So I'll admit the line is not very fine there. It may spill over into the residential setting. I guess we were asking the panel to focus more on the playground setting, realizing that we may spill over into the residential setting.

It's somewhat fuzzy to us, I can assure you.

DR. GINSBERG: And while I have the microphone in front of me, one other question. Are your risk assessments going to take into account food and water arsenic exposures, inorganic arsenic?

MR. COOK: I knew somebody was going to ask that sooner or later. The ultimate risk assessment for CCA, yes. In other words, we

are planning to do an occupational risk assessment, a residential one, or non-occupational, which will also include the playground setting risk assessment.

We have decided that we will need to do a dietary risk assessment for small home gardens. And also -- and others can probably speak to this better than I -- we will do an aggregate risk assessment where we will factor in drinking water, dietary and then the residential components.

That will be down the road somewhat, you know, next year.

MR. JONES: If I could just follow up briefly on what Norm mentioned regarding the -- the sequencing is unusual -- I think that's pretty clear. The external dynamic that we face is that a large number of our state and local partners are seeking advice about -- as are, I think, parents in general -- as to what they should be doing as it relates to playground equipment, and are very anxious to have some sense from the Environmental Protection Agency as to what we believe the risks from the playground scenario is.

And we are feeling that we need to get a little bit of peer review external advice on the current state of the exposure data and our exposure assessment plans as well as the hazard side of the equation before we go into a risk assessment.

But that initial risk assessment, if we were to proceed, would be done on the current database.

Obviously, there is some data that is being developed that could enhance that exposure assessment and thus risk assessment.

We did an unusual thing, which is change the sequence that we would normally take because of a -- we felt a very important need for us to be able to attempt to speak to the risks from the playscape scenario because of the concern that municipal and state governments have brought to our attention.

DR. ROBERTS: Thank you, Mr. Jones.

Dr. Smith, did you have a question?

DR. SMITH: Thank you. I have a question concerning the proposed studies or the studies that you are going to be doing jointly with the Consumer Product Safety Commission. We have -- some of the specific questions we were asked to respond to ask us about what additional studies we may recommend. I'm wondering, specifically in the context of the joint study you're going to do with the Consumer Product Safety Commission, are you looking for comments from us on that study design? And if not, will you welcome comments from us on that study design?

MR. COOK: We would definitely welcome comments.

This has been a dynamic, working on CCA. I think the comments raise -- the way I would put it in context, it's a continuum, in other words, if we focus today on the playground setting -- I mean, as this thing evolves, we may need other panel meetings as we get into the residential because, as you all know, this is a very complex -- there's so many variables here, it's -- but we would welcome comments, yes.

DR. ROBERTS: If there are no other questions from panel members, let's go ahead and proceed to the next presentation, which is on the use and chemistry of CCA.

DR. ELKASSABANY: Mr. Chairman, members of the panel, ladies and gentlemen, good morning.

My presentation to you this morning is on the -- it's an overview of CCA use and a brief discussion of CCA chemistry.

There are 32 registered products of CCA. CCA is used to protect wood from bacteria, fungi, molds, termites and other pests. These pests may attack the wood products. CCA pesticide are commonly applied to wood intended for use in outdoor settings such as decks, walkways, fences, gazebos, boat docks, utility posts, retaining walls and, of course, playground equipment.

The American Wood Preservers Institute's 1996 report indicated

that 144,506,900 pounds of CCA were used in 1996.

According to the latest estimate we got from the industry, 7 billion board feet of wood per year is treated with CCA. And the current demand for CCA-treated wood in playground equipment is approximately 50 million board feet per year. CCA is applied to wood used in various methods, but the most common is pressure treatment.

In the pressure treatment, the untreated wood is loaded on small rail tramway cars and the tram are pushed into a horizontal treating cylinder. The cylinder door then is sealed and a vacuum is applied to remove most of the air from the cylinder and wood cells.

CCA solution is then drawn into the cylinder and once the cylinder is filled, pressure is applied. In most cases, pressure is about 150 pounds per square inch, forcing CCA into the wood. After the treatment cycle, pressure is released and the unabsorbed solution is returned to the storage tank for reuse.

Then the cylinder door is opened and the trams are pulled out onto a drip pad and the wood is left out to dry before it is sold.

In my overview of the chemistry of CCA, I will discuss briefly the formulation, speciation, fixation, leaching and migration of CCA.

The purpose of this brief discussion will be to set the stage, if you will, for the next two days of discussion of the hazards and

children's exposures to CCA.

CCA components are chromium, copper and arsenic. The middle elements in CCA are usually present in the form of oxides. There are three CCA formulations referred to as type A, type B and type C. Type C is now the most used formulation in pressure treatment.

Chemical speciation describes the types and the concentration of chemical compounds.

Metals undergo changes in environment media, such as soil, water, plants and animals. Metals have a tendency to speciate in soil and water. Such changes, speciation of metals, depend on absorption, desorption, redox reaction in soil and water, precipitation reaction. The significance of speciation in case of CCA lies in its usefulness as a tool for interpretation of the toxicity of CCA.

Fixation is the chemical process in which the preservative metals and solution react with wood fiber molecules. It is a series of chemical binding reactions of metals with cellulosic structure of wood. Fixation results in reduction of metals leaching out of the wood.

The process is generally defined by the reduction of hexavalent chromium. And the reduction of the reactive and mobile Chromium 6

to Chromium 3 is really crucial for the formation of the insoluble complexes in CCA-treated wood.

For CCA-treated wood, once the fixation process is completed and done properly, all Chromium 6 would be reduced into Chromium 3.

There are many factors that can affect the degree of fixation. These factors include temperature, moisture content of the wood and the concentration of wood preservatives and the type of wood. Among all these parameters, temperature is considered as one of the most important factors.

CCA fixation is highly dependent -- a highly temperature-dependent event. Many investigators have demonstrated that fixation can be accelerated at higher ambient temperature. The effect of temperature as the most important factor is well-documented.

There has been a considerable amount of literature published concerning the leaching of CCA from wood. Although most of the metals bind with the internal wood structure, some remain free and have a tendency over a period of time to leach out on wood surfaces and onto environmental media like soil and water.

The rate of leaching depends on the size of wood -- the surface area, that is -- age of wood, wood type, the pH, and the fixation

process. The leaching amounts of metal follow the order, copper, then arsenic, then chromium.

Data are limited on whether metals leach out as inorganic, organic or complex species. Most analytical data estimate the total extractable metals, and individual species are not quantified.

Soil samples analyzed around the wood structures showed higher than background concentrations. Most of the work done on soil sampling is on arsenic and chromium.

As for migration, metals leached out from CCA-treated decks and playground equipment do not show a great tendency to migrate down into the soils. And metals have a tendency to remain on the surface soil and can result in high exposure.

Published literature indicated that the horizontal migration of leached metal is up to 18 inches and the vertical migration of leached metal is up to 9 inches.

And that concludes my presentation, and I will take questions at this time, if there are any.

DR. ROBERTS: Thank you. Are there any questions from the panel?

Dr. Chou?

DR. CHOU: I would like you to help me to understand that,

after the fixation in a factory, how long is the drying period if -- whether the condition of the drying period, such as temperature, moisture is controlled before the wood is sold?

DR. ELKASSABANY: You mean outside, after it's outside, how the temperature is controlled?

DR. CHOU: So it's just an outdoor condition?

DR. ELKASSABANY: Yes.

DR. CHOU: You just leave outside?

DR. ELKASSABANY: Yes.

DR. CHOU: And is there any specification on how long they should be out there before it's sold? Are we saying they can be sold right away after it's been fixed?

DR. ELKASSABANY: Actually, there is a -- AWPA has a standard for treatment and how long the treatment should be and the temperature, also. All of these are specified. And after it's outside -- now I guess we're not really -- I don't know the answer to this question. Maybe someone here from industry can answer that question.

DR. ROBERTS: Other questions?

Dr. Shi?

DR. SHI: I just want a clarification. What is the state in soil

and in wood? You said most of these are Chromium 3. But how about in soil? Is it all Chromium 6 or Chromium 3? What is the state.

DR. ELKASSABANY: I was talking about the wood after it's fixed.

DR. SHI: It all becomes Chromium 3?

DR. ELKASSABANY: Yes.

DR. SHI: How about in the soil or around the wood? Chromium 3 or Chromium 6 in the soil around the wood?

DR. ELKASSABANY: After it leaches out of the wood, we're not really sure if it's 6 or 3.

DR. SHI: So you don't know?

DR. ELKASSABANY: I personally don't know, yes.

DR. ROBERTS: Dr. MacDonald, then Dr. Morry, Dr. Styblo, then work from there.

Dr. MacDonald?

DR. MacDONALD: The diagram you showed of the pressure treatment process was showing a whole batch being put in and charged at one time. Do we have information on the variability in the amount of CCA that gets into the wood within one charging? And do we have information on the variability between different manufacturers and different products?

DR. ELKASSABANY: Once again, there is the standard for the industry to follow. And it's actually specified by the type of wood, how long each type should stay in treatment and temperature for even like different concentration, whether it's type A, B, C of CCA.

It's a very, very detailed process. And all of it is spelled out in the standard of AWPA.

DR. STEINBERG: Dr. Morry, then Dr. Styblo, Dr. Mushak.

DR. MORRY: David Morry, State of California. My understanding of the way the fixation process works is that the chromium complexes with either the lignin or the cellulose in the wood, and that the chromium helps to fix the other metals. I guess the other metals are somehow complexed with the chromium and then the chromium attaches to the substrate.

Now, in describing the process, you said that -- I guess in the fixation process, the chromium is reduced from Chrom 6 to Chrom 3.

So if the fixation process was complete, then all the chromium in the wood would be Chrome 3.

But you also said this is temperature-dependent and dependent on other conditions. So that implies that you have some data that shows how much of the chromium actually is complexed and how much is not complexed and remains as hex chrome inside the wood.

So my question is, how much do we know about the degree of completion of the process and how much do we know about how much chromium in the wood would remain as hexavalent chromium?

DR. ELKASSABANY: For the literature that I have listed here, yes, the literature indicated that if the wood is stored at the lower temperature, that you will find the Chromium 6. Now, when it is stored at a temperature according to the standard of the industry, the fixation will occur and -- but the process has to be done completely and properly according to the standard of AWPA.

Now, also Dr. Stilwell's presentation today will go in detail as far as the Chromium 6 and Chromium 3 leaching out of the wood.

DR. ROBERTS: Dr. Styblo?

DR. STYBLO: I have two questions.

First, about the technology of CCA treatment, one of the public comments we received in written form suggests that there could be an additional step involved which would remove excessive CCA solution from treated wood by vacuum pumps or a similar procedure. Is it a common step? Is it a recommended step? Would it help to prevent leaching?

Second question. You mentioned that most of the arsenic and chromium leaching from the wood is in organic forms. Is this based

on actual analytical data, especially in the case of arsenic? Is the involvement of microorganisms considered?

DR. ELKASSABANY: Actually, I didn't say leaching in organic form. I didn't say that. I don't think I said that. I said we don't know, you know, if it's inorganic or organic or a complex species. That's what I said.

But for the first question, did you say that this vacuuming after -- is it part of the standard treatment?

DR. STYBLO: Yes. It's a question because one of the manufacturers actually submitted a comment that suggests that they use vacuum treatment after CCA treatment. That would remove the excess of CCA solution, which sort of makes sense to me to limit leaching. Is that a common step?

DR. ELKASSABANY: Is it a common step?

DR. CHEN: I'm Jonathan Chen.

Well, for the CCA treatment plant, according to my knowledge, they do have a vacuum process and they would get most of the CCA solution out and recycle it.

And after that, the CCA-treated wood will par (ph) up more like an open area and, after a period of time, they would drill a hole and take a small piece to check the fixation step. So at that time they are

trying to make sure the fixation is completed.

But at this moment, we are not sure this process really, really 100 percent sure all the wood that come out of the plant are completely fixed because, under certain conditions, especially at a lower temperature, the fixation step may take longer. This is the reason that OPP raised this question, because most of the chromium that we have data are total chromium. We are not sure about -- it's Chrome 3 or Chrome 6. This is the reason we like to ask the panel member to help us to solve this problem. Thank you.

DR. ROBERTS: Dr. Mushak, then Dr. Solo-Gabriele, then Dr. Steinberg.

DR. MUSHAK: It seems to me, in looking at all of the literature in the aggregate, that the basic chemical mechanisms of fixation are still up in the air. A very recent paper by D.C. Bull in Wood Science and Technology establishes that, and it is supported by theoretical calculations that what you have in the matrix are chromic arsenate, chromic -- trivalent chromic hydroxide and mixed copper carboxylates.

Now, to the extent that the nature of the fixation determines the relative mobility of residues, could you comment on whether the Bull study is bull or whether it's, in fact, a challenge -- it's a challenge to

the orthodox mechanistic aspects of fixation?

DR. ELKASSABANY: I am not going to tell you that the Bull study was bull. I am not going to do that.

What I can say is that I have seen in the literature, usually when they start talking about the fixation process, they always say it's not a well-understood process and there are so many factors that affect the fixation.

But they always refer to the temperature being the most important factor. Now, the moisture of the wood does affect fixation. That we know. The type of wood does affect fixation, and how long the process is done and so forth.

So I don't know if I did answer your question, but there are so many studies out there that deal with that issue --

DR. MUSHAK: Well, the Bull study argues that, on theoretical grounds, you can't have what's claimed to be going on with the mechanism of fixation actually going on, and I think that's a serious challenge to the basic approach of orthodox fixation assumption.

DR. ROBERTS: Dr. Solo-Gabriele and then Dr. Steinberg.

DR. SOLO-GABRIELE: I had a question about the statement about limited vertical and horizontal migration because I would anticipate that horizontal migration would be dictated primarily by the

slope of the soil in the vicinity of the structure, and vertical migration would be governed by the characteristics -- the compositional characteristics of the soil, if you have a lot of organics versus non-organics.

So do these other studies look at those parameters to determine a relationship or even mention those characteristics of the surrounding area?

DR. ELKASSABANY: Is this a question or a comment about other studies?

DR. SOLO-GABRIELE: It's a question.

DR. ELKASSABANY: Okay. Well, I actually was referring to -- when I say studies, some of them are actually your studies in Florida.

And how far they migrate and -- you know, you probably know more than, you know, a lot of people here in the panel that migration, of course, is affected by all these things.

Now, whether other studies have done that or how well they discuss that, that I don't know.

DR. ROBERTS: Dr. Steinberg?

DR. STEINBERG: J.J. Steinberg. More so as a comment. A lot of very nice data, Dr. Elkassabany.

As long as we're under the area of chemistry, I assume that over the next few days we're going to have a full and robust discussion on kiln-treated wood and whether it's binding to lignins and whether the ammoniacals are involved, ammonia compounds, and looking at harder woods, and I think that will be all well and good.

Of course, on the human side, we're interested on the possibility of any biomarkers that may be helpful in risk assessment. And I'm going to ask the chemists around the table and in the room to start thinking certainly about whether these methyl and hydroxylated arsenates -- whether this arsenic that's hooked up to little carbon compounds and oxygen compounds, whether the possibility of their binding to molecules or into DNA should be considered. And I think they could be very good candidates for that.

There is a very small amount of data on that. Of course, in chromium, just the redox state makes it very interesting to see the generation of free radicals and whether that would be another potential marker. And of course, a lot of the risk assessment could be very easily understood because we have the potential of a mechanism of action, and that makes it, of course, very interesting to all of us.

DR. ROBERTS: Thank you.

Dr. Ginsberg and then Dr. Smith.

DR. GINSBERG: One of your overheads presented information that the arsenic trioxide content as a percentage of the CCA formulation changed from CCA-A to CCA-B to CCA-C. But I think I remember -- and you, I think, alluded to this -- that now CCA-C is more commonly used. But what is the history of using some of these other formulations? And I think it's relevant to the variability issue that you are going to find when you go out and sample any cohort of decks, that some are older and were treated with a different formulation.

So is it sort of like with lead, that if you look pre-1980 and you're going to have one type of exposure scenario, and then post-1980? You know, are we dealing with that kind of situation with these different formulations? Is it that clear-cut when the CCA-A and CCA-B stopped being used and CCA-C is being used?

And, also, do you know any more about which types of formulations are more leachable as the A versus B versus C? The older way they did it, those practices, were they more conducive to leaching than what's being done now?

DR. ELKASSABANY: How many questions was that?

For the history, I really don't know much of the history behind how type C became more common than A and B. But I think I have

read that type A and B are used more in other types of treatments, like remedial treatment after the wood is in service.

And if I'm incorrect or I'm wrong, please, someone from the audience or the industry can correct me.

DR. ROBERTS: Please identify yourself.

DR. AVIADO: Good morning, Mr. Chairman. I'm Doreen Aviado, and I work with my colleagues on the CCA assessment. I can help answer that issue.

The CCA-A, B and C -- the differences are not in perspective of time where one formulation may have been used over history and then changed to a different formulation. It truly has to do with the nature of the wood and the application for the treated wood.

So, therefore, in the context of CCA playground equipment, when Nader mentioned CCA type C as the predominant form, this is correct. The A and the B would be adopted for possibly commercial aquatic, highway barrier-type installation, depending on whether there is ground contact, above-ground contact. It definitely depends on nature of the wood and the application.

And these are standards set by the American Wood Preservers Association. They have a very, very full volume that depicts, for all types of applications, what wood treaters must reference and what

conditions are applicable for choosing which formulation.

So it's very well laid out. It's just in this context, CCA type C is really our focus. And that would also apply to any dimensional lumber from your Lowe's, your Home Depot -- those sorts of applications would be the CCA type C. Thank you.

DR. ELKASSABANY: What was the other question?

DR. GINSBERG: It pertained to these different treatments and how leachable they are, relative to one other.

But if you are saying that it's all CCA-C that should be within our purview, then that variability factor is really not on the table, I guess, unless you are saying that -- you know, ground contact poles in a playground might be one of these other formulations, but if it's all CCA-C, then I withdraw the other question.

DR. AVIADO: Right. And, in fact, the AWPA issues preservative standards and what they call commodity standards. There is a specific standard for playground equipment. It requires that all playground equipment, be it the vertical supports or the horizontal slats, must be treated at .40 pounds per cubic foot. It's a standardized penetration retention level.

And earlier we were mentioning about -- I believe Dr. Chou may have mentioned what was going on in the treatment plant in terms of

the treatment process related to quality control or how do they determine that fixation has occurred.

This has been the quagmire because the industry is not required to test the wood for fixation before it leaves the plant. All they are required to do is, after it comes out of that retort vessel, that round cylinder that Nader showed, when that tram comes down, they take boring samples, they take certain core samples which go into their lab. They analyze it for the chemicals. The balance of those chemicals will tell them, you know, if that fixation level -- I'm sorry -- if the penetration and retention level that they hoped to achieve has been met.

That's all it does. They then leave it on the drip pad, let it dry. And this is where the environmental conditions apply. If it is cold, if it is very moist conditions, high humidity, it may takes two or three months to fix that wood. That wood may have already left the treatment plant and gone to a warehouse for sale.

And I think the nature of the concern here may not be the commercial installations of the playground equipment so much as the potential for the residential homeowners to just buy some lumber and fabricate a play set for their child with wood that may have just recently been treated and may, in fact, not be fully fixed.

DR. ROBERTS: Thank you.

Dr. Smith has a question and I think we probably need to get on with our next presentation.

DR. SMITH: Dr. Ginsberg asked my question and I was very happy with the response.

DR. ROBERTS: All right. Thank you very much.

Let's go ahead and then move forward with the next presentation.

DR. McMAHON: Thank you. And good morning, Mr. Chairman, members of the panel, ladies and gentlemen. I'm Dr. Timothy F. McMahon, and I'm here before you this morning to present a set of issues related to hazard identification and toxicology endpoint selection for inorganic arsenic and inorganic chromium, chemical components of toxicological concern in CCA-treated lumber.

As mentioned earlier, although copper is also a component of CCA-treated lumber, it is not part of the current assessment. Copper is an essential nutrient which functions as a component of several enzymes in humans, and the toxicity of copper in humans is usually observed only through consumption of excessive doses of copper or as a result of genetic disorders.

By contrast with copper, inorganic arsenic and chromium have

been shown to demonstrate significant toxicity in mammalian organisms, including humans.

The information presented today on hazard is derived from several sources, which include the Agency for Toxic Substances and Disease Registry, toxicological profiles for arsenic and chromium, toxicological summaries from the U.S. EPA's IRIS database, the National Research Council report on arsenic in drinking water, and the published scientific literature.

I'll first present the arsenic overview and endpoint selection, followed by the chromium hazard overview and endpoint selection with the opportunity for any clarification after each presentation.

So moving into arsenic, as you can see here, arsenic is a naturally occurring element present in soil, water and food, and it exists in many forms in the organic and inorganic state.

In general, the inorganic forms are considered more toxic than the organic forms. And published case reports and epidemiology studies show humans to be more sensitive in general to the toxic effects of inorganic arsenic than experimental animal species tested for toxicity. As we all know, I'll be focusing on inorganic arsenic in today's presentation.

The acute oral toxicity of inorganic arsenic in experimental

animals shows lethal effects in the range of 15 to 175 milligrams per kilogram, while human poisoning incidence show lethality in the range of one to four milligrams per kilogram per day.

Relative to the oral route, the acute toxicity by the dermal and inhalation route for inorganic arsenic is lower. That is to say that data in animals by the dermal route show no mortality up to 1,000 milligram per kilogram. And by inhalation, there is no mortality in animals exposed to up to 20 milligrams per cubic meter and no mortality in humans exposed to up to 100 milligrams per cubic meter.

Contact dermatitis is observed in humans exposed occupationally. Animal studies are also suggestive of mild to severe dermal irritation after application of arsenic to the skin. There is no evidence of dermal sensitization for inorganic arsenic in a guinea pig animal model, and the evidence in humans is not conclusive.

Subchronic toxicity studies with arsenic in experimental animal models have produced only generalized toxicity; that is, weight loss and decreased survival, while the data from human exposures have shown more specific toxic effects, such as neurotoxicity, hyperkeratosis of the skin, of the hands and feet, and cardiovascular, hepatic and gastrointestinal toxicity.

There has also been the recent suggestion of an association

between arsenic exposure and diabetes.

The data on developmental and reproductive toxicity of inorganic arsenic in humans is not extensive. The available data in humans suggests reduced live birth weights, increased spontaneous abortion and elevation in latent fetal, neonatal, and post-natal mortality. These data are based on published scientific studies of women exposed to inorganic arsenic at a copper smelter or from exposure to arsenic in drinking water.

The animal data from laboratory exposures also show a variety of effects, including increased post-implantation loss, decreased viable fetuses and neural tube defects. However, at the doses tested in these animal studies, the significant maternal toxicity was also observed.

Overall, the analysis of the available human data on developmental and reproductive toxicity of inorganic arsenic from a variety of sources and offices, including EPA's Office of Water, ATSDR, NRC, and the published scientific literature conclude that, while evidence from human studies suggests the potential for adverse effects on several reproductive endpoints, that there are no reliable data that indicate heightened susceptibility of children to arsenic.

The neurotoxicity of inorganic arsenic is not evident in studies

with experimental animals. However, again, there is a large body of epidemiology studies and case reports describing neurotoxicity in humans which, after acute exposures, has been characterized by headache, lethargy, seizures, coma, and encephalopathy and, after repeated exposure, by peripheral neuropathy.

Four inorganic arsenic studies by the oral and inhalation route in commonly used experimental animal species have not revealed a definitive carcinogen response. However, epidemiology studies in human populations exposed to arsenic through drinking water reveal a strong association between exposure to arsenic and development of cancers of the skin, bladder, lung, liver, kidney and prostate.

The biotransformation of inorganic arsenic is sequential and involves a series of reduction and oxidative methylation reactions, which can occur enzymatically or non-enzymatically, resulting in the formation of monomethylated and dimethylated pentavalent and trivalent products. The major site of oxidative methylation appears to be the liver.

Products of inorganic arsenic biotransformation in urine have been identified as both the inorganic and mono and dimethylated forms of arsenic.

Urinary products appear similar among species studied, but the

relative proportion vary greatly, and a few animal species such as the chimpanzee, marmoset monkey and guinea pig lack the ability to methylate inorganic arsenic.

The methylation of inorganic arsenic, once thought to represent a detoxification pathway, may play a role in the carcinogenicity of inorganic arsenic.

Data on methylation of inorganic arsenic in children are limited. One study conducted in a population of women aged 18 to 66 and children aged 3 to 15 exposed to arsenic in drinking water in Argentina showed conversion of arsenic to 47 percent dimethylated arsenic in children versus 66 percent dimethylated arsenic in women, while a second study examining the placental transfer of arsenic in pregnant women, also in Argentina, showed that essentially all arsenic in maternal and cord plasma was in the dimethylated form.

In light of the newer data on the possible role of methylation in arsenic toxicity, the toxicological implications of the findings require further examination.

The dermal absorption of inorganic arsenic is generally low and the value proposed for use by OPP is selected from the published data of Wester, et al. In this study, a dermal absorption of arsenic acid from water and soil is examined in vivo using the rhesus monkey. In

vivo, absorption of arsenic acid from water was 6.4 plus or minus 3.9 percent at the low dose and 2.0 plus or minus 1.2 percent at the high dose.

The absorption from soil in vivo was reported as 4.5 percent plus or minus 3.2 at the low dose and 3.2 plus or minus 1.9 percent at the high dose. And the value of 6.4 percent dermal absorption is proposed.

This was a well-conducted in vivo study in non-human primates. It is observed in this study that a higher dose on the skin resulted in a lower percentage of dermal absorption. But based on the variation in the dermal absorption values observed, it is felt that the use of the 6.4 percent value for dermal absorption is sufficiently, but not overly conservative.

I'll now be moving into a discussion of the dose response assessment and toxicology endpoint selection for inorganic arsenic. But first, I would like to make a few general comments.

Consistent with the practices within the Office of Pesticide Programs, the toxicity endpoint selection, to the extent possible, is matched with the temporal characteristics of the exposure scenarios selected for use in the risk assessment.

Selection of toxicity endpoints is reached by concurrence of a

committee of scientists, a hazard identification assessment review committee -- or HIARC -- within the Office of Pesticide Programs.

For both inorganic arsenic and chromium in children's playground exposures, non-cancer endpoints are proposed for short-term and intermediate-term incidental oral exposures based on contaminated soil ingestion exposure scenarios for children and oral ingestion exposure scenarios as a result of hand-to-mouth behavior in children from direct dermal contact with treated wood.

Non-cancer endpoints for short and intermediate-term dermal exposure are also proposed based on children's direct dermal contact with treated wood or dermal contact with contaminated soil.

For potential long-term non-cancer oral and dermal exposure scenarios, endpoints are available for arsenic that may be used as conservative values in the assessment of potential long term non-cancer risks.

For chromium, a chronic non-cancer endpoint is available for oral exposures. The endpoints for non-cancer dermal and inhalation exposures are a subject for discussion by the panel.

For chronic exposures used to characterize arsenic cancer risk, the U.S. EPA IRIS database has a published quantitative approach for characterization for arsenic carcinogenicity. However, as we have

heard earlier, based on newer published information, OPP considers this newer data relevant to quantifying the carcinogenic risk of inorganic arsenic and will be working with the Office of Water to develop the most scientifically sound approach.

For inorganic arsenic, the studies selected for short and immediate-term incidental oral exposure are the human case reports of Franzblau and Lilis and Mizuta, et al.

The LOAEL value of 0.05 milligrams per kilogram per day from Mizuta, et al., was selected based on observations of facial edema, gastrointestinal symptoms, peripheral neuropathy, and skin lesions observed in a poisoning incident involving the presence of arsenic contained in soy sauce. This study involved clinical symptoms reported in 220 persons out of 417 persons exposed with an age range of 15 to 69 years.

The duration of exposure was two to three weeks. The arsenic content was estimated at 0.1 milligrams per mill, and the estimated consumption was three milligrams per day. The estimated exposure was, thus, 0.05 milligrams per kilogram per day and was considered the LOAEL for this study.

In the majority of the patients, the symptoms appeared within two days of ingestion and then declined, even with continued

exposure. There was evidence of minor gastrointestinal bleeding. There was also abnormalities in the electrocardiograms. These changes were not evidence on reexamination after recovery from the clinical symptoms.

An abnormal patella reflex was evident in greater than 50 percent of the cases. This effect did not return to normal during the course of investigation.

Supporting data are from the case report of Franzblau and Lilis who reported two cases of subchronic arsenic intoxication resulting from ingestion of contaminated well water over a two-month period. Acute gastrointestinal symptoms, central and peripheral neuropathy, bone marrow suppression, hepatic toxicity and mild mucous membrane and cutaneous changes were presented. Calculated dose was from 0.03 to 0.08 milligrams per kilogram per day.

These two case reports are felt to be appropriate for both short and intermediate-term incidental oral endpoints for the following reasons:

The symptoms reported in the Mizuta study, gastrointestinal disorders, neuropathy, and liver toxicity, occurred after two to three weeks of exposure, making this endpoint appropriate for the short term, 1 to 30 days, exposure period. This study also examined

toxicity by the relevant route of exposure.

Similar symptoms were observed in the Franzblau study and are appropriate for the intermediate term endpoint as they were observed to occur after longer-term, two-month exposure within the dose range reported by Mizuta, et al.

This slide shows arsenic toxicity endpoints published by both ATSDR and U.S. EPA region 8, and are shown for comparison.

These endpoint selections are consistent with the proposed value by the Office of Pesticide Programs with respect to the dose levels at which adverse effects are observed from short and intermediate-term exposures to arsenic in humans. U.S. EPA region 8 recommended use of an NOAEL value as 0.015 milligrams per kilogram per day from a study by Mizuta, et al., for acute and subchronic referenced dose values with an uncertainty factor of 1.

Alternately, the LOAEL value of 0.05 milligrams per kilogram per day and an uncertainty factor of 3 0 for extrapolation from the LOAEL to the NOAEL could be selected.

ATSDR has published an acute provisional MRL value of 0.005 milligrams per kilogram per day based upon the data of Mizuta, et al., and an uncertainty factor of 10 for extrapolation of the LOAEL to the NOAEL.

You will see later in a presentation by Dr. Bob Benson that the arsenic database on short-term and immediate-term exposures is consistent as a whole with the choice of the proposed endpoint by the Office of Pesticide Programs.

There are differences noted in the magnitude of the uncertainty factor applied to the endpoint, and we will be asking the panel members for advice on the basis for and choice of the appropriate endpoint and uncertainty factor in this case.

With respect to the uncertainty factor, from OPP, an uncertainty factor of 100 is proposed to be used in conjunction with the selected endpoint. This value consists of a 10X factor for intra-species variation and a 10X factor for the severity of the toxic signs observed at the LOAEL.

Historically, only a factor of 3 is applied when extrapolating from the LOAEL to the NOAEL, and a 10X intra-species factor is not typically applied when adverse effects are based on human data. However, the HIARC committee recommended a 10X factor for extrapolation based not only upon the lack of NOAEL in this study, but also upon concern over the severity of the effects observed, including gastric bleeding, abnormal electrocardiograms and neurologic effects and the irreversibility of neurologic effects in some

individuals.

It was also noted from the data on toxicity of arsenic that effects seen after longer-term exposure are different from those seen after a short-term exposure, and that the uncertainty factor should take into the account the effects that are evident immediately after exposure as well as effects that appear later, such as skin lesions and neurotoxicity, but which still occur within a short-term time frame.

With regard to the 10X factor for intra-species variation, this factor was recommended based on the study of one ethnic group, composed mainly of adults, and the lack of data in this case report on potentially susceptible individuals such as persons with chronic illness.

Lacking studies by the dermal route with which to select endpoints for short-term and intermediate-term dermal exposure scenarios and consistent with OPP guidance, the endpoint and uncertainty factor selected for these scenarios was also the LOAEL value of 0.05 milligrams per kilogram per day and uncertainty factor of 100 based, again, upon the human case studies of Franzblau and Mizuta as described above for short-term and intermediate-term incidental oral exposures.

The dermal absorption factor of 6.4 percent for arsenic would

be used to correct for calculated dermal doses from the oral endpoint.

The next slide just shows you the summary of endpoint and the study selected for inorganic arsenic.

I would be happy to take questions at this time, or I can move on ahead into the chromium.

DR. ROBERTS: We have, apparently, several questions on the arsenic, SO let's go ahead with that.

Dr. Mushak, Dr. Steinberg, Dr. Styblo.

DR. MUSHAK: One quick caveat and two quick questions.

If you look at the NAS reports on arsenic, especially the prepublication copy of the 2001 update, if you read that material carefully, they are not saying that kids are not more susceptible than adults. What they are saying is kids are perhaps susceptible on the basis of dose, but since the lifetime cancer exposure endpoint is the one we're looking at, it probably doesn't make any difference.

I don't know that anywhere in those reports does the academy say -- or its committee say that kids wouldn't be more susceptible under less than chronic conditions, and Dr. Kosnett can jump in later and comment on that.

I notice that your database doesn't include the Morinaga (ph), Japan, powdered formula milk epidemic. This was a horrendous

epidemic back in the '50s. There were over 10,000 kids who were poisoned. A number of them died.

When we were putting together the 1984 EPA document on the health effects, we drew attention to the fact that kids are susceptible for CNS effects based on those studies. And if I'm not mistaken, we had those translated at the old NCIA (ph), and you may want to get those.

I don't know that that provides you a very good LOAEL because I think the studies were principally looking at hospitalizations and severe injury. But you may want to see if you get a better bite at the NOAEL that way than versus the adults.

The second quick question is, are you assuming that the intra-species of ten-fold will capture kids versus adults or kids plus adults at various -- with risk factors?

DR. McMAHON: Yes. With respect to your second question, the 10X for the intra-species is typically assumed to cover, in this situation, the variability within the human population.

DR. MUSHAK: Yeah, but you can do it two ways. You can look at a developmental difference or a risk factor presence difference -- I mean, health status, not developmental status.

DR. ROBERTS: Dr. Steinberg. Then I have Dr. Chou,

Dr. Styblo and Dr. Bates.

DR. STEINBERG: J.J. Steinberg. One quick comment about the neurotoxicology in animal studies. After having gone through the two telephone books of information that we have, I'm still unsure to be able to make the statement or reaffirm the statement that there is no neurotoxicology or neuropathology injury to the brain or nervous tissue in animals.

I think it's a very difficult and arcane specialty. There are not a lot of experts. And I think you have to really look at that data very carefully. And I suspect that, if you relooked at that data with agreed-upon parameters, you may be surprised at what you have.

I do want to underscore what Dr. Mushak said in that an uncertainty factor of children, particularly as it relates to the paradigm of nervous tissue and nervous tissue development, I think as something that, again, requires some discussion and should be entertained.

And, of course, supporting that is simply the variation and methylation amongst human populations can vary by 1,000-fold. And you can, therefore, have populations that may be more at risk. Conversely, you could also have populations that are at far lower risks. So, again, there is some various populations that one has to

consider. And, of course, we do have to take that extra moment to think about children.

DR. ROBERTS: Before we take any more questions, let me just remind the panel we'll have plenty of opportunity to provide the agency with input on this particular issue. I believe it is the first question that we are posed.

So if we could maybe mostly focus our questions on issues of clarification, at least at this point in our agenda.

Dr. Chou, I believe you were next.

DR. CHOU: I'm not sure that this is a clarification or not. I wonder if you ever considered interaction of arsenic with other trace elements such as zinc and copper?

DR. McMAHON: I'm aware of one paper that studied the interactions in vitro, but I'm not familiar with all the details right now. I looked at it a couple of times and I do understand there was some interaction of arsenic with other metals.

DR. CHOU: Like zinc would exaggerate copper's toxicity -- I'm sorry -- arsenic would exaggerate copper's toxicity. And arsenic also exaggerated zinc deficiency problems.

DR. ROBERTS: Dr. Styblo, do you have a question?

DR. STYBLO: I would definitely agree with what Dr. Chou

said about interaction of metals. There is a lot of literature on interactions of arsenic and copper which we consider for the purpose of this discussion on toxic, but it may appear -- it's not exactly non-toxic when combined with other metals.

I would like to make another point. You said -- and we heard it here before -- the focus of this session is inorganic arsenic. Don't you think we should, at least for the sake of the discussion, expand this focus on organic arsenicals that could be produced in the course of metabolism of inorganic arsenic leaching from the wood by microorganisms, fungi, bacteria, algae. Because even CCA-treated wood is colonized by these microorganisms. So is soil.

And as you mentioned, there is a legitimate concern among scientists now about what is exactly comparative toxicity of arsenic species. And there are people in this auditorium that would agree with me that the statement that inorganic arsenic is more toxic than methylated arsenicals is not true anymore.

We have data in vivo that shows that, actually, trivalent methylated arsenicals are of concern in terms of toxicity, DNA reactivity. So I would definitely suggest let's look a little bit wider and consider also presence and biologic effects of possible products of methylation of inorganic arsenic by microorganisms.

DR. McMAHON: Yes, that's a very good comment. I appreciate that.

In fact, from my point of view and our point of view of looking at risk, especially with respect to children -- I mean, the comment regarding the differences in methylation ability is certainly relevant. The exposure issue to inorganic or organic -- certainly appreciate any input on that since, generally speaking -- and I'm not familiar with all of them -- you know, the inorganic forms tended to be more toxic than organic.

But in relation to your comment regarding what happens now with respect to methylation, I think it could be an expanded picture. I just would appreciate the input of the data and the concepts behind that so that we could reliably address that question. But I agree with you.

DR. ROBERTS: Dr. Bates, did you have any clarifications you would like?

DR. BATES: Yes. I'm always slightly wary of the application of uncertainty factors on the way that toxicologists do to epidemiological data, the reason being that one of the major differences between toxicology and epidemiology studies is the uncertainty of the exposures in epidemiology.

And I was wondering whether any factor is incorporated to take that into account. Having looked at the Mizuta paper, I noticed that there's actually very little information on the exposure, how they actually arrived at their estimate. And one could argue that some factor might be incorporated in the overall uncertainly factor to take into account this exposure. The difference, of course, is that in toxicology studies, you usually know exactly what animals are being exposed to.

DR. McMAHON: That's correct. Again, that is an issue that we hope to have a discussion on with the panel members. Because, as you can see, there are various differences by -- you know, reported with uncertainty factors regarding similar data sets.

DR. ROBERTS: Dr. Hopenhayn-Rich, then Dr. Ginsberg.

DR. HOPENHAYN-RICH: Expanding a little bit on what Dr. Mushak brought up, I just wondered if, in the selection of the Mizuta study, you had considered other studies that are published on acute intoxication or short-term effects and whether there was rationale for selecting this and/or if the effects were compared with other studies and the levels of exposure? That's one comment or question.

The other one is, with regards to what Dr. Styblo said on the

issue now of whether it's the inorganic or the methylated species that are more or less toxic. That would be also very relevant in terms of, if the study that you cited in Argentina of placental transfer was all methylated, whether, you know, you were implicating a level of toxicity or not, or less, or none.

DR. McMAHON: That's true. My understanding was that the more data in that area, the better with regards to the methylation differences, especially in children and even in, you know, pregnant women.

And with regard to your comment on the database, I know that when you see Dr. Benson's presentation, there is, again, a larger set of data. I can't remember exactly why we picked the Mizuta study, other than the reasons I stated in my presentation. I think a lot of the studies do show effects that fit within our short-term time frame and that consist of similar types of effects. So, indeed, the discussion of that could be expanded from what I had already written to include those other studies.

DR. ROBERTS: Dr. Ginsberg?

DR. GINSBERG: That segues into my comment perfectly. I think that there is a lot of support from the excellent review that Dr. Benson did in conjunction with what you just presented.

The one thing that I would think would be helpful for the panel would be to have some sorting of those studies based upon children's exposure and children's dose response within those.

For example, in the Chilean data by the Zaldivar (ph), et al., group, they show some lethalities in children in the .05 to .09 range which is -- you could see our LOAEL. Those are adult studies that we have got up there, you know, .05. But those weren't lethality effects; they were other effects. So that would suggest children might be more sensitive.

But then there is a NOAEL that's in Dr. Benson's paper that's also based upon children that's not that far from range.

So it would be really nice to see the variability this children's data and how much confidence we have that children are really covered by that and by that safety factor -- it might be nice to have that segregated out. Of course, you know, we're here now reviewing what we have in front of us. But that would be a good thing to sort of sort out.

DR. ROBERTS: Any other clarifications from the panel on the presentation on arsenic?

If not, I know you are ready to go into a discussion on chromium, but let me suggest that we take about a 15-minute break at

this point. And let's resume the chromium discussion in 15 minutes, at a quarter to 11:00.

(A recess was taken.)

DR. McMAHON: So now we're going to move on to chromium a bit. Chromium is also a naturally occurring element found in animals, plants, rocks and soil, and in volcanic dust and gasses. Although chromium can occur in several oxidation states, for the purposes of this presentation, we'll focus on the +3 and +6 oxidation states, as these are the most closely related to the hazards surrounding exposure to chromium in CCA-treated wood.

In humans and animals, Chromium 3 is an essential nutrient that plays a role in glucose, fat and protein metabolism. By contrast, Chromium 6 rarely occurs naturally and is associated with significant toxic effects in humans and experimental animals.

The administration of Chromium 6 is chromic acid by the oral, dermal and inhalation routes to experimental animals has resulted in significant acute toxicity is measured by lethality.

Studies reviewed by EPA show the oral LD50 in rats is 52 milligrams per kilogram. A dermal LD50 is 57 milligrams per kilogram, and inhalation LC50 is .217 milligrams per liter.

Human reports of death after ingestion of chromium show

lethality at lower dose levels.

Chromium 6 is also a significant eye and skin irritant and severe allergic reactions consisting of redness and swelling of the skin have also been noted in exposed animals and humans. Case reports of humans who have intentionally or accidentally ingested chromium have also shown severe respiratory effects.

In contrast to the acute toxicity of Chromium 6, the acute toxicity data for Chromium 3 show less severe acute toxicity with oral LD50 values in rats reported in the range of 183 to 200 milligrams per kilogram or up 2,365 milligrams per kilogram. There are no reports of lethality in experimental animals after acute inhalation or acute dermal exposure to Chromium 3. However, skin irritation and sensitization have also been observed from exposure to Chromium 3.

Subchronic toxicity studies in experimental animals have demonstrated hematologic and hepatic effects from repeated oral exposure to Chromium 6 which includes decreases in mean corpuscular volume and mean corpuscular hemoglobin, accumulation of hepatic lipids and hepatic cytoplasmic vacuolation.

Repeated inhalation exposure to chromium mists and dusts has resulted in reports of nasal tissue damage including perforated and ulcerated septum, nosebleed and inflamed mucosa. Exposure to

vapors to chromium salts has also been suspected as a cause asthma, coughing wheezing and other respiratory distress.

These signs have only been reported in occupational settings and there are no data on potential toxicity from residential inhalation exposures.

Adverse developmental effects have been observed in experimental studies with Chromium 6 in the scientific literature using rats and mice, including the absence of uterine implantation, increases in pre-implantation and post-implantation losses, dose-dependent reductions in total body weight crown-rump length, and reduced ossification of several bones. However, in a guideline rabbit development study submitted to and reviewed by OPP, no significant developmental toxicity was observed.

Reproductive toxicity studies in mice conducted by the National Toxicology Program showed slight reduction in mean body weight, slight decreases in mean corpuscular volume and mean corpuscular hemoglobin, and cytoplasmic vacuolization of the hepatocyte.

Despite the wealth of animal studies on the development and reproductive toxicity of Chromium 6, there are few human data with which to make any reliable conclusion regarding susceptibility of the developing fetus, infants or children to the toxic effects of

Chromium 6. The evidence available suggests similar toxic effects in adults and children from ingestion of Chromium 6.

Hexavalent chromium, as you have heard, is known to be carcinogenic in humans by the inhalation route of exposure, but by the oral route, there is no convincing evidence for the carcinogenicity of Chromium 6. By contrast, there is no evidence for carcinogenicity Chromium 3 by either the oral or inhalation route.

Hexavalent chromium can be reduced to the trivalent form in the epithelial lining fluid of the lungs as well as by the gastric juice of the stomach.

Once absorbed, chromium compounds are distributed to all organs of the body without any preferential distribution. However, exposure to higher levels of chromium, such as can occur in the chrome plating industry and chrome refining plants may result in accumulation of chromium in tissues.

If hexavalent chromium is absorbed, it can readily enter red blood cells through facilitated diffusion where it will be reduced to the trivalent form by glutathione. Curing reduction to the trivalent form, chromium may interact with cellular macromolecules, including DNA, or may be slowly released from the cell.

It has been hypothesized that the carcinogenesis of hexavalent

chromium may involve formation of oxidative DNA lesions during intracellular reduction.

As for inorganic arsenic, incidental oral exposure and dermal exposure of children to chromium is expected based upon the same exposures mentioned for inorganic arsenic.

The endpoint selected for short and intermediate-term incidental oral exposure is taken from the developmental toxicity study in the rabbit conducted by Tyl and submitted to and reviewed by the agency.

For both the short and intermediate-term incidental oral exposure scenarios, the NOAEL value of 0.05 milligrams per kilogram per day was selected based on increased incidence of maternal mortality and decreased body weight again at the LOAEL milligrams of 2.0 milligrams per kilogram per day.

This study and endpoint is felt to be appropriate for both short and intermediate-term incidental oral exposures in that it is a well-conducted, multi-dose study, toxic effects occur after a short-term dosing, and supporting data from the literature show similar effect levels after longer-term exposures at similar dose less.

A report by Zhang and Li in 1987 detailed the toxic effects observed in 155 human subjects exposed long-term to chromium in

drinking water at a concentration of approximately 20 milligrams per liter or 0.6 milligrams per kilogram per day. These effects included mouth sours, diarrhea, stomach ache, indigestion, vomiting and elevated white cell count.

Thus, the choice of the NOAEL value of 0.5 milligrams per kilogram per day from the developmental toxicity study is protective of the gastrointestinal effects suggested in humans at a slightly higher dose and is also protective of the non-lethal effect observed in humans based on a more severe effect observed in animals, mortality.

With respect to the dermal exposure, the 1998 EPA IRIS document on Chromium 6 states that chromium is one of the most common contact sensitizers in males in industrialized countries and is associated with occupational exposures to numerous materials and processes.

In addition, it is stated further that dermal exposure to chromium has been demonstrated to produce irritant and allergic contact dermatitis. The relative potency of this effect appears to differ between the 6 and 3 species of chromium check.

Bagden (ph) in 1991 collected skin hypersensitivity data for trivalent chromium compounds in human subjects and concluded that the threshold level for evoking hypersensitivity reactions from

trivalent chromium compounds is approximately 50-fold higher than for hexavalent chromium compounds. Nonetheless, it is apparent that both forms of chromium cause hypersensitivity reactions in humans.

Based on these data, the HIARC committee recommended that the skin irritation and skin allergenicity effects are the primary concern for Chromium 6 through the dermal exposure route, and that no endpoint would be selected for dermal risk assessment.

We will be asking the panel to comment on the issue of dermal effects as a possible basis for assessment of dermal risk from residential exposure.

And the last slide will, again, just show you the summary of the endpoints selected for the incidental, short and intermediate-term oral and the dermal exposure.

And that is the conclusion of my chromium presentation.

Again, I'll be happy to take any questions.

DR. ROBERTS: Thank you, Dr. McMahon.

The panel will get the opportunity to give the agency feedback on this aspect in questions, I believe, 4, 5 and 6 when we discuss those.

Right now, though, are there any clarifications we would like from the agency on this?

Seeing none, then we can proceed on to the next presentation, which is on bioavailability, which is going to be discussed by Dr. Chen.

DR. CHEN: Mr. Chairman, honorable panel members, ladies and gentlemen, my name is Jonathan Chen and I'm a toxicologist with the antimicrobials division.

In the following section we're going to present issues related to the relative bioavailability of the chemicals of concern in this risk assessment.

Before we discuss this topic, I would like to make sure some of the terms we are using are clearly defined. First, absolute bioavailability, ABA, is a ratio of the amount of chemical absorbed compared to the amount of chemical ingested.

For example, if 100 micrograms of chemical X dissolved in drinking water were ingested and a total of 90 micrograms enters the body, the ABA will be 90 percent.

Relative bioavailability, RBA, is the ratio of the absolute bioavailability of some test material compared to the absolute bioavailability of the reference material.

For example, if the ABA of the chemical X dissolved in drinking water is 90 percent and the ABA of X contained in the soil is

30 percent, then the RBA, the relative bioavailability of the chemical X in soil versus water would be 33 percent.

Therefore, if we are going to talk about relative bioavailability (soil versus water), it will be the percentage of the chemicals of concern, for example, inorganic arsenic absorbed into the body of a soil dosed animal compared to that of an animal receiving a single dose of arsenic in aqueous solution.

Now, why does the relative bioavailability (soil versus water) need to be discussed? The reason is that all the toxicity endpoints selected in the hazard assessment are based on the chemicals of concern in aqueous phase.

To adjust the exposure of the chemical in soil, the RBA (soil versus water) is required to define the chemical bioavailability in soil relative to water.

Therefore, four different RBA (soil versus water) need to be discussed in this SAP: The arsenic RBA (soil versus water) through oral route; arsenic RBA (soil versus water) through dermal route; chromium RBA (soil versus water) through oral route; and chromium RBA (soil versus water) through dermal route.

Now, we are going to focus on the arsenic relative bioavailability soil versus water through oral route first.

There are many published and/or unpublished studies that have been done on this issue. Based on these studies, we learn that there are many factors that may affect the arsenic RBA (soil versus water) through oral route.

For example, the animal model used in the study, the biomarker used in the study, for example, where there is arsenic in the blood as the biomarker or arsenic in the urine collected over a period of time as a biomarker, this may affect the reported results;

The soil type, whether it's a sandy type of soil or a clay type of soil;

The dosing techniques, whether animal is gavaged or fed with capsules;

The arsenic concentration in the soil;

The individual animal differences, and some other factors all may affect the RBA measure.

The animal models which have been used to study these issues include rats, rabbits, dogs, juvenile swine, and two different kinds of monkeys.

A summary of some of the literature reports of arsenic relative bioavailability (soil versus water) is presented in this table.

In this table, we can tell different types of soil have been

studied, the RBA ranging from around 8 percent to around 78 percent have been reported.

Roberts used male cebus apella monkeys to study the arsenic RBA in the soil from different waste sites in Florida, one from an electrical substation, one from a CCA treatment site, one from a pesticide application site, and one from a cattle dip vat site.

Difference in bioavailability ranging from around 11 percent to around 25 percent for these soil samples were reported.

In the in vitro study by Williams, et al., in 1998, when soil containing arsenic are incubated in simulated leaching fluid closely analogs to human stomach and a small intestine. Average stomach arsenic RBA of 11.2 percent were reported. The gross RBA increased to around 18.9 percent following translocation through a simulated small intestine regime.

In addition, there are several studies that have tried to determine the urinary and fecal recovery of arsenic.

The results indicate that arsenic excretion pattern of cebus apella monkey and that of the human are very similar.

In humans, after a single intravenous dose of arsenic, around 60.4 percent of the arsenic is excreted in the urine and around .7 percent is excreted in the feces, whereas in cebus apella monkey,

around 66.8 percent is excreted in the urine and around .6 percent excreted in the feces.

Therefore, based on the results of Roberts, et al., in 2001, an arsenic oral relative bioavailability (soil versus water) of 25 percent was recommended by OPP.

The reasons are, first, it is using appropriate animal model -- cebus apella monkeys were used in this study.

Second, appropriate soil samples.

Third, supported by other in vivo and in vitro studies.

Now, let us take a look at arsenic RBA (soil versus water) through dermal route.

As mentioned in Dr. Tim McMahon's presentation, Wester, et al., in 1993, studied the dermal absorption of arsenic from water and soil of rhesus monkey. In this study, Wester studied the dermal absorption of arsenic with water or soil as a media in two different doses. Let us compare the low dose group.

We can tell that dermal absorption of arsenic from water is not statistically different from the absorption from soil. Note: The large standard deviation in both groups.

Therefore, an arsenic dermal RBA (soil versus water) of 100 percent was proposed by OPP.

In other words, via dermal exposure, the magnitude of absorption of arsenic is equal whether the arsenic is in water or in soil.

Next slide.

We are going to talk about relative bioavailability (soil versus water) for chromium -- we're talking about both Chromium 3 and Chromium 6 -- through either oral or dermal route because there is no study regarding the relative bioavailability of chromium in soil when compared with in water through either oral or dermal exposure route and it is known that either dermal or oral absolute bioavailability of chromium is very low.

Therefore, OPP is proposing a RBA value for both soil versus water of 100 percent for both oral and dermal exposure routes for both Chromium 3 and Chromium 6.

In other words, via either oral or dermal exposure routes, the magnitude of absorption of chromium is equal whether the chromium is in water or in soil.

In summary, all the OPP recommended RBA (soil versus water) are summarized in this slide. Thank you.

I'll be happy to address any question.

DR. ROBERTS: Dr. Mushak, would you like to begin?

DR. MUSHAK: Just a quick clarification on criteria for animal models and comparability across models for uptake of arsenic.

Is it the case that you are assuming that there is no developmental difference in arsenic uptake, kids versus adults, therefore, don't worry about developmental differences in stages or ages or stages for the appropriate animal model?

The reason the young pig is popular with region 8 and region 10 and other regions is that, in the case of lead at least, it seems to do a pretty good job of predicting what the case is with humans. And it also compares pretty well with the in vitro studies of Drexler, Ruby, et cetera.

So could you commend on whether development comes in the picture or not.

DR. CHEN: Well, actually, at this moment, if you notice, the reported RBA value for arsenic through oral exposure route -- and you will notice that the reported data varies a lot.

And the juvenile swine is a very good model for lead and, besides that, juvenile swine, we think about it because dietary pattern is similar to humans.

Well, at this moment, we are not excluding the other animal model being used. The reason that we present it here is that the cebus

apella monkey, based on the result we have, shows it's a good model, but we are not saying other models are bad.

At this moment, we didn't really think about whether people with different ages need to be thought about. I think this would be a very good question for the panel to discuss about.

DR. ROBERTS: Dr. Hopenhayn-Rich, then Dr. Gordon, then Dr. Kosnett.

DR. HOPENHAYN-RICH: I'm not a toxicologist, so some of these questions might have an easy answer or maybe not.

I had two questions. One is with respect to the urinary recovery of arsenic after the intravenous dose, comparing humans and the different kinds of monkeys. Was there a similar comparison done or could a similar comparison be done for ingested rather than intravenous dose and whether -- my question is whether that would be more relevant? I know that Buchet and his group did several studies related to single dose and doses over a few days of arsenic. I don't know if a similar study has been done with the cebus apella monkey or not. That's one question.

And the other one is the conclusion that the water and soil dermal -- the RBA for arsenic dermal (soil and water) is pretty much the same based on this Wester study that we just got a copy of, so

we'll have a chance to review it, hopefully, today in more depth.

The fact -- I think you mentioned that there was no significant difference between the groups. At the same time, you said the confidence intervals were large, and I would add the numbers of animals in each group were very small, so the fact that they were not statistically significant is clearly a function of that, and whether there is really no difference would depend how large your sample size is.

DR. ROBERTS: Would you like me to answer one of those questions?

DR. CHEN: I think you would be the better person.

DR. ROBERTS: To answer your question about a comparison with ingestion in humans, data are available for that comparison. They weren't presented by the agency, but we have those data.

And I have had some requests for information from this study because, as the agency pointed out -- this study at this point has been written up. It's been submitted for peer-reviewed publication, but that process isn't completed yet. It was presented at the annual meeting of the Society of Toxicology, and the agency is relying on the presentation of data there. I have the panels from that presentation, the slides from that presentation, and I can distribute those to the panel and put that on the public docket if that will help the panel take

a look at this study. And also I can answer any methodological questions regarding that study which I think might be helpful.

Then also as an aside, the other study that was mentioned by the agency for the dermal absorption was the Wester paper, and I happen to have -- happened to bring a copy of that with me, so I have made a copy of that and that is being distributed if you would like to take a look at that one as well.

I had Dr. Gordon, Dr. Kosnett and then Dr. Ginsberg.

DR. GORDON: Given the uncertainty and maybe controversy in understanding the chemistry of the CCA in the wood and what might be there in the dislodgeable or worn wood particles, have any of the absorption studies, dermal or oral, used soil from contaminated sites at a playground, not a CCA-treated plant soil, but the actual stuff that we're concerned with?

DR. CHEN: You mean use soil in the CCA-treated site?

DR. GORDON: Soil from a playground structure, which might be very different than the soil contaminated with arsenic and chromium at a CCA treatment plant site, given the uncertainties and the chemistry of it all. Have any studies used that kind of soil?

DR. CHEN: Well, at this moment we are focused on the soil, and from my understanding, there is no real -- current use of CCA

directly. No study.

DR. ROBERTS: Dr. Kosnett?

DR. KOSNETT: Dr. Chen, I just had a couple of questions. Besides the study of Dr. Roberts, which we're looking forward to finding out more about, does the agency have any other studies or data on the cebus apella monkey with respect to the pharmacokinetics and the metabolism of inorganic arsenic in that species?

DR. CHEN: No. The information I have, it's just an abstract from the Society of Toxicology. So maybe Dr. Roberts may be able to answer the question better than I do.

DR. ROBERTS: I'm not aware of any other studies other than ours that have used this money for studying arsenic.

DR. KOSNETT: Okay. And on your slide, in addition to indicating that that -- you listed three criteria for selecting the relative bioavailability findings based on that abstract. One was the appropriate animal model. The second was appropriate soil samples. And that study mentions, on a previous slide, that there were four different waste sites in Florida.

Did the agency exercise some criteria in saying that these particular soil types were more appropriate than perhaps the other studies which they also listed with --

DR. CHEN: Well, the reason that I state this is because of the opinion (ph) of this task because there are so many studies and there are so many different kind of soils involved. So basically we classified the different types of soil into three different kinds.

And one is soil from the mining area. So the background soil is already going to have high arsenic content.

The second one is soil that the arsenic is from the contamination part, like the soil used in this study.

And the third type is house dust.

And if we go through these, then we notice that other soil types used in this study, it goes to the soil type that is more equivalent to how we are going to talk about the CCA contamination of this site soil.

This is the reason that we say it's appropriate soil type.

DR. KOSNETT: Is that based on the fact that, of the four types that were studied in Dr. Roberts' study, one of them particularly was from a CCA treatment site?

DR. CHEN: Yes.

DR. KOSNETT: And that none of the other -- that was the only animal model that you had available in the entire data set that referred to CCA?

DR. CHEN: If you really think back, all those other type of soil, they are soil, but is from the arsenic contamination from different sources, like pesticide application.

So I include all those soil types in the consideration. These soil are not the soil from the mining area soil. So, to me, these soil samples are more appropriate.

DR. KOSNETT: Maybe I don't want to belabor the point, but you did study soils from other sites that were not mining but are available on the data set?

DR. CHEN: Yes.

DR. KOSNETT: I was just -- I guess what I'm getting at is I just wanted to get more information on why you selected this one particular study for your relative bioavailability when, in fact, there is a very rich data set on other bioavailability as well? And as was mentioned, region 8, for instance, has done studies, as has region 10, on the swine model.

DR. CHEN: Well, to me, I think this is very good question. Actually, we go through all those studies. And when we compare these studies, it becomes very difficult to really kind of say which is the most appropriate one.

And the region 10 study has used juvenile swine, but the

biomarker check that region 10 use is arsenic in the blood as a biomarker.

And from the information we have from other biomarkers, like arsenic in the blood, it's not so sensitive as the arsenic in the urine collected over a period of time. It varies a lot.

This is the reason that we -- besides that, region 10 study is using a mining area. And for that reason, we kind of mentioned that, but we didn't use that.

The second thing is that in the in vitro study, if you notice that, the highest number that is reported in the region 10 is about 78 percent, and in the in vitro study, it's around 20 percent in the small intestine area. So this is the reason we think the cebus apella monkey model, the result is more appropriate.

And we are not excluding other studies. To me, I think this is -- we open this because this is something that we really need the panel members to give us advice.

DR. ROBERTS: Dr. Ginsberg?

DR. GINSBERG: Something I've always been curious about in these studies. Children are ingesting small quantities of soil, 100 milligrams a day. In these studies, are they trying to simulate that type of soil amount going down or are we talking about higher

amounts so you can get sensitive amounts in urine, et cetera? Maybe -- I invite Steve Roberts and Dr. Chen to comment on the methodology. How much soil is involved in these in putting into these animals?

DR. ROBERTS: No, we can't measure bioavailability on the kinds of soils that we typically talk about when we are talking about, you know, 100 milligrams, 200 milligrams per day in a child. The problem just has to do with analytical sensitivity.

Because the problem is you have to -- we have to work with arsenic soil samples that are in a reasonable concentration range, and we have to provide them with a arsenic dose that's high enough that we can measure with some reliability. Frankly, what we wind up is giving doses that are probably much larger than an individual would get on a --

DR. GINSBERG: So are we on a gram level?

DR. ROBERTS: Yes, gram-level doses, right, to get an arsenic dose that you can reliably measure the bioavailability. Gram doses of soil, not gram doses of arsenic.

Dr. Mushak?

DR. MUSHAK: Two quick follow-ups from comments by Drs. Kosnett and Ginsberg.

One is that as soils age with the contaminants, then the principal determinant of what the arsenic is going to behave like is going to be the nature of the soil, not the incoming medium. So I think over time -- if we're looking at the behavior of these residues over time, I think we need to be looking what types of soils are involved.

And If you look at the mining data, you know, a lot of those soils are not materially different than others. So I think to say that CCA went into one soil, makes that a better soil -- you know, I don't buy that.

The second thing is that kids, in fact, do -- if you look at hand transfer studies, et cetera, kids ingest small quantities over the course of the day. Studies that use a bolus basically that swamp out the mobilizing apparatus of a child's stomach, I think are largely irrelevant to uptake rates. I mean, it's just an artifactual situation.

So I think your comment about, you know, you have to simulate how kids ingest stuff is critical.

DR. ROBERTS: Dr. Bates. And, again, we'll have plenty of opportunity to discuss this provide our input if there is a question specifically addressing this.

Dr. Bates, did you have a clarification for Dr. Chen?

DR. BATES: This is slightly different to what was just being discussed. Just going back to the relative biological availability, dermally, for soil, arsenic in soil, the figure of 100 percent is being used based on this study using rhesus monkeys, a fairly small number.

In fact, if you look at the data, it seems to ne that the data is actually compatible to a very wide range of estimates. And 100 percent has been selected.

So I was wondering if -- has any sort of sensitivity analysis been done to look to see what are the implications if you varied this -- say, took 50 percent or 25 percent?

And looking broader than that, I was wondering, based on a sensitivity analysis, what are the most important of these parameters that we should be looking at? We could spend a lot of time looking at some of these things and trying to refine the levels, the estimates, to get them more precise, maybe calling for more data. But which are the most important of these absorption factors and so forth?

Has that sort of exercise been done?

DR. CHEN: Well, if you go to other results from all these studies, you will notice that all these studies, the standard deviation is kind of big. So -- there are so many factors that can affect it.

This is the reason that OPP is proposing 25 percent, but we do

know that it varies a lot. I don't know whether we can -- any sensitivity of the research techniques are really being studied, but many researchers report in their documents that many factors can affect the results.

But in the risk assessment, we do need something to make the comparison. This is the reason this question becomes so important to the panels. And I don't know.

DR. ROBERTS: I had a question, Dr. Chen.

I understand the concept of using relative bioavailability when you are measuring absorption and risk from oral exposures. But typically when you are measuring risk from dermal exposure, often what is used is the absolute bioavailability to calculate an internal dose, which is then compared with an internal version or form of a toxicity value, which may be derived, for example, from oral exposure and gastrointestinal absorption, or something like that.

Can you explain for me or help me understand a little better the concept of the use of relative bioavailability for dermal absorption.

DR. CHEN: Well, at this moment, because in the risk assessment we do have two different concentrations. One is that we don't have the dermal toxicity studies or something.

So we basically we kind of go through from the oral --

extrapolate from the oral exposure toxicity endpoint to the dermal toxicity endpoint. At that time, the toxicity we are comparing compares the toxicity through the oral route versus toxicity through the dermal route.

So the relative bioavailability issue, that is compared the oral route to the dermal route.

But if we are using the dermal toxicity studies, the toxicity endpoint is directly from the dermal study, but the study is using the chemical in the aqueous phase. Then, if we are going to compare that to the dermal as a media, then we do need dermal the relative bioavailability to make the conversion.

This is the point that we are going to use.

DR. ROBERTS: Thank you.

Any other follow-up questions on bioavailability?

If not, thank you very much, Dr. Chen.

Let's move on to our next presentation. I believe Dr. Benson is going to tell us about the Superfund short-term approach in assessing risks.

Welcome, Dr. Benson.

DR. BENSON: Good morning, Mr. Chairman and members of the panel.

I obviously didn't get the memo about standard background in my slides, so it's different from the rest.

I am Bob Benson. I'm a toxicologist in the drinking water program in EPA region 8.

I'm here today to discuss some work I did for the Superfund program concerning the acute and subchronic reference values for arsenic.

You might wonder why a regional toxicologist who works in the drinking program got involved in this in the first place.

Well, as it turns out, many of you probably realize, arsenic has quite a great deal of interest in region 8. It frequently occurs at mining sites, and we have some very large Superfund mining sites in region 8, some of them larger than some of the -- in area, some of them larger than a few of the eastern states, actually.

So I'm going to talk about how we evaluated the acute and subchronic data available on arsenic and derived reference values.

In mid 1999, because of some issues that were raised at a Superfund site in metropolitan Denver, I volunteered to help the Superfund program try to resolve some issues between EPA and ATSDR concerning the possible health effects from exposure to arsenic from residential soils at this site in Denver.

During this same time, the ATSDR was in the process of updating its toxicological profile on arsenic.

So to try to resolve some of these issues between the two agencies, EPA and ATSDR formed an interagency work group, and the members of the work group are shown on the slide.

Because the two agencies have some overlapping responsibilities at Superfund sites, the original plan was to try to publish a joint document that both agencies could support. This ultimately didn't happen, for reasons which I'll mention later.

Peter Grevatt chaired the work group. I was the primary author of the final document.

Most of the staff work was done by myself and Selene Chou and David Mellard from ATSDR. Dr. Chou is in the audience, so if you have questions about the ATSDR involvement, we can defer those to her.

The other scientists from both of the agencies participated in various discussions and review of the documents as it was finally being developed.

The next slide shows the external peer reviewers that were used to review the document. We actually did two rounds of peer review, one an earlier draft, and then, after we had made substantial changes

to the document and incorporated comments, both from the first round of peer reviewers and agency comments, we sent the document back to the peer reviewers for another round of review.

The criteria that we used for including studies are listed on this slide. The first criterion was that the study concerned non-cancer health effects in humans rather than in laboratory animals and that the publication concerned relatively low doses. In other words, we excluded studies that only reported death or other very serious toxicity as the only endpoints in the study.

The second criterion was that the study provide specific information on the duration of exposure, as we were trying to sort out effects from acute exposure and subchronic exposure or exposure lasting in the order of several months to several years.

The third criterion was that the study provide a sufficient amount of information that we could estimate the daily exposure with some reasonable degree of confidence. And in the document that I prepared, we list all of the assumptions that we needed to make in order to get to an exposure in milligrams per kilogram body weight per day. Some of the studies had more information than others on that.

This slide lists the areas of agreement and disagreement that we

had between the members of the work group and the differences between EPA scientists and the ATSDR scientists.

The areas of agreement included what data we should use to derive reference values. This turned out to be fairly easy for us to do. We also agreed on the effect levels that were observed in the studies.

The two primary areas of disagreement included what the NOAELs were in some of the studies. ATSDR essentially didn't agree with a couple of NOAELs that I assigned to the studies.

Also, there was a difference of opinion about what uncertainty factor to apply to the endpoints in the Mizuta study. The ATSDR wanted to use a factor of ten -- an uncertainty factor of ten on the Mizuta study, and EPA wanted to use only a factor of three on the NOAEL in that same study.

And as you heard earlier, OPP has proposed a different uncertainty factor on the same study, and it's one of the principal areas that I think the agency -- OPP is asking for your advice on.

There was also a difference in the definition of exposure durations between EPA Superfund and ATSDR.

The Superfund exposure durations that we used are listed on this slide. An acute exposure is from 1 to 14 days, subchronic exposure from 15 days to about 7 years, and chronic exposure, an

exposure greater than about 7 years. And this applies to human exposures, at least in the durations definitions.

The next slide shows the exposure duration that the ATSDR uses in their toxicological profiles, where an acute exposure is from 1 to 14 days, an intermediate exposure is from 15 days to 365 days, and chronic exposure, something greater than 365 days. The way the ATSDR uses these definitions is that the exposure duration applies to both laboratory animals and to humans.

The next slide shows the definitions that OPP is using where their short-term exposure is an exposure from 1 to 30 days, their intermediate-term exposure is from 1 to 6 months.

The next slide shows the list of adverse health effects, non-cancer health effects that have been attributed to inorganic arsenic. And as you can see, there is a large variety of effects that have been reported in the literature in human studies, or studies in humans anyway.

The most characteristic lesion from across the entire database are the skin lesions, usually characterized as hyperpigmentation and hyperkeratosis. But the exposure or the effects that are observed depend on the magnitude of the exposure and its duration, to some extent.

What I'm going to do now is kind of walk through the exposure response assessment that is summarized in the paper I wrote. And I understand that the panel has been given a copy of this paper in the background document, background material, so I'm going to go through this relatively quickly.

The next series of slides are a series of tables organized by exposure duration. The first two acute exposure studies are shown here.

Dr. McMahon discussed earlier in detail the results from the -- that were presented from the Mizuta study, the soy sauce incident, so I'm not going to go through that in detail. But in general, we agree completely with the endpoints that he reported and the LOAEL in the study, which is 0.05 milligrams per kilogram body weight per day.

One thing I should point out is that in all of these studies, we're talking about exposure from relatively bioavailable sources of arsenic, soy sauce, drinking water and fowler solution. There are no studies in the database where adverse health effects have been observed from an exposure to soil, at least as far as I'm aware.

One of the things I should mention is that in the Mizuta study, the author estimated the exposure, and I actually have some question as to how accurate that estimate is. The exposure was estimated as 3

milligrams per day based on the daily consumption of 30 milliliters of soy sauce containing 0.1 milligrams per milliliter of arsenic. A small error in the estimate of either one of those two input points could cause a fairly significant change in the estimated exposure, particularly since we're operating in what appears to be a very narrow range for adverse health effects, particularly the neurological symptoms that are reported in some of the studies.

The same thing could be said of the Franzblau and Lilis dose reconstruction or exposure reconstruction. It's not entirely clear from the publication when, in the course of the exposure, the neurological symptoms developed. But it was clear that, at the early exposures, there were fairly substantial gastrointestinal effects.

The next slide has results from the use of inorganic arsenic as intravenous treatment for leukemia. I put this discussion in the paper I wrote to indicate that, in this particular study, even though the exposures were in the same range as the earlier soy sauce and drinking water study, there is no clear evidence of neurological effects in this study. However, it is a fairly small study and there were some neurological effects preexisting in some of these patients that complicates the issue. And I have not seen more recent follow-up of any other case reports from these workers. There may be some, but I

have not seen them.

Next slide has a series on subchronic exposure from arsenic. Some of these are case reports, single case reports from the use of fowler solution, which is arsenic trioxide in potassium bicarbonate solutions. It was used historically for the treatment of asthma, I understand.

The results of these various studies are at least, I think, fairly consistent, all showing low effect levels in the range of an exposure of 0.05 to 0.06 milligrams per kilogram body weight per day.

The effects that you most commonly see across this entire series of results is the skin lesions, sometimes with neurological effects also reported, and also gastrointestinal effects. But the most characteristic are the skin lesions that were reported.

The next couple of slides have some reports of exposure in children, which is one of the areas of interest here. We specifically tried to pull out, when we were doing this work, studies that had exposure to children that we could clearly determine what the exposure was and the duration of exposure, and tried to compare those results with what had been observed in some of the other studies where only adult populations were seen.

The second entry here is study in South America that involved a

study of children, school-aged children that had been exposed for about ten years. A fairly large study, there were 27,000 children involved in this particular study.

Again, the low effect level for the lowest observed adverse effect level reported occurred in an exposure of about 0.06 milligrams per kilogram body weight per day.

The next slide has two more studies where our emphasis here was on exposure to children. The first one is, again, from the South American workers -- actually, it was the same population group, essentially, as the Borgano study on the previous slide. This one is somewhat smaller. 37 out of 300 children examined who were ten years of age or less showed the characteristic arsenical skin lesions. And, again, the exposure was about 0.05 milligrams per kilogram body weight per day.

The next study is from Mazumder, et al., that was published in 1998. This was a study that was conducted in either India or Bangladesh -- I can't remember which right now -- where, again, the target population that we pulled out from this larger study was the age group zero to 9 years old. These children had been exposed to arsenic since birth.

There was a clear indication of skin lesions in the -- what the

workers had from the exposure groups that they had pulled out from the measurements that they had made. The low effect level, lowest observed adverse effect level occurred in the range of 0.0149 up to 0.0739 milligrams per kilogram body weight per day.

The way I looked at this study, the lower exposure, less than 0.0159, there was a very low incidence of skin lesions, depending on how you look at studies in another parts of the world, whether 1 out of 66 was a background incidence of skin lesions or whether it's related to arsenic. I don't think you can really say. I chose to call it a no-effect level in this particular study, and it was one of the areas where ATSDR and EPA Superfund did not agree.

The next slide pulls out some exposure information, again, from children in two larger studies where the exposure was lifetime exposure.

What I did for this particular paper was to focus on the reports in these two publications, exposure to children, again, zero to 9 years old because that's the only -- that's the way it was reported in the study.

In the Cebrian study, at least the way I interpreted the data, there was no evidence of significant skin effects, and the exposure I pulled out was at 0.04 milligrams per kilogram body weight per day.

Similarly, the Tseng study in Taiwan, the zero to 9 year old group, no significant effects in approximately 14,000 children that were examined. Again, in both of these studies, the children had been exposed from birth up to 9 years of age.

The NOAEL effect level that I pulled out from this study was 0.03 milligrams per kilogram body weight per day.

The way that I determined the exposure levels was to take into account the difference in drinking water consumption between children and adults, and I relied on the EPA exposure factors handbook showing that, in that population group, the consumption of water was about 1.9 times higher than an adult based on their body weight. This is explained in the document that I wrote.

So, essentially, I multiplied the exposure that was reported for adults in this study by 1.9 to get the estimated exposure based on body weight to children. Not everybody would agree with what I did here, I will admit, but I'm trying to present the way I did it, anyway.

The next slide shows two studies that were used by EPA to derive our chronic reference dose. Again, the lifetime exposure of skin effects were observed. In the Cebrian study, the lowest observed adverse effect level -- this is averaged across the entire exposed group -- was 0.022 milligrams per kilogram body weight per day.

In the Tseng study, again, lifetime exposure, where the -- at least EPA tried to take into account exposure from both drinking water and food. There was a clear lowest observed adverse effect level for skin lesions in the approximately 40,000 people that were involved in this study at an average exposure of 0.014 milligrams per kilogram body weight per day. And EPA assigned no observed adverse effect level at 0.0008 milligrams per kilogram body weight per day.

And there were some 7,000 people that were examined in a different population that had been exposed to lower amounts of arsenic from the -- where the lowest observed adverse effect level was assigned.

There has been controversy over the exposure reconstruction, particularly for the no-effect level, since long before I became involved in arsenic, a considerable amount of debate about whether the concentration of the arsenic in the drinking water wells, particularly at the lower exposures, was reconstructed accurately. And there are also some significant questions about the amount of arsenic that was in the diet of these individuals.

The next slides shows the conclusions on exposure response across this entire data set that we looked at.

The first one is that the exposure at 0.05 to 0.06 milligrams per kilogram body weight per day will cause adverse effects from either acute or subchronic exposure.

The skin lesions are the most consistently found effect, with some suggestion of gastrointestinal and neurological effects in some of these studies.

An exposure at 0.014 milligrams per kilogram body weight per day will cause adverse effects, again, skin lesions, from chronic exposure.

The next slide shows a couple of points. There is -- at least the way we looked at the data, there is no evidence that young children or malnourished individuals are a sensitive subpopulation for non-cancer health effects.

As far as I could tell from looking at the data sets, you see the same effects in children and adults, and they occur at approximately the same exposure levels in both children and in adults.

And whether you are looking at acute one or two times exposure or subchronic exposure up to seven to ten years, the effect levels seem to be in the same range.

A no-observed adverse effect level from subchronic exposure is approximately 0.0149 milligrams per kilogram body weight per day.

The next slide shows that there is other evidence from other studies that a no-observed adverse effect level might be as high as 0.03 to 0.04 milligrams per kilogram body weight per day in children when the exposure is ten years or less.

A fairly significant uncertainty across this entire data set, I think, is whether these skin lesions are latent effects that could appear after ten years of exposure without additional exposure to arsenic.

There is some anecdotal reports that the skin lesions tend to disappear or lessen with continued exposure. And there's other reports indicating that some of the effects might appear later.

There has never been a study done where we know for sure that children are exposed for ten years and then you stop the exposure and then follow them for a significant period of time after that to see whether there is adverse effects that might occur latently. There is just nothing in the literature on that as far as I can tell.

The next slide shows how we derived our reference values based on a no-effect level of 0.0149 and an uncertainty factor of 1, the acute and subchronic reference values that we have in the paper is 0.015 milligrams per kilogram body weight per day, and I rounded that value up to make it a little bit easier to work with for the regional risk assessors.

An uncertainty factor for intra-species variability is not used in the derivation of these reference values because we have a very large population of people examined in -- across the database in these various studies, probably one of the largest data sets available for human exposure to a chemical that EPA deals with.

The next slide shows a different -- an alternative way of deriving acute and subchronic exposure reference values using the lowest observed adverse effect level in the range of 0.05 to 0.06 and an uncertainty factor of 3. After rounding, the acute and subchronic reference value turns up at 0.02 milligrams per kilogram body weight per day.

The uncertainty factor here of 3 is used for the LOAEL to NOAEL extrapolation. And, again, an uncertainty factor for intra-species variability is not used, again, because of the large population examined in these various studies across the range of human exposures.

That concludes my formal presentation. I'll try to answer any questions that the panel might have at this time.

DR. ROBERTS: Thank you, Dr. Benson.

Before we get to questions, let me ask the panel to please hold any comments, suggestions, opinions or remarks regarding this

analysis until our discussion of question 1 tomorrow.

Are there any questions of clarification only for Dr. Benson?

Dr. Steinberg, Dr. Chou, Dr. Mushak, and then Dr. Ginsberg.

(Volume I of II concluded.)

CERTIFICATE OF STENOTYPE REPORTER

I, Frances M. Freeman, 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.

_____

FRANCES M. FREEMAN

I-N-V-O-I-C-E**** ****I-N-V-O-I-C-E****

FRANCES M. FREEMAN
21168 Wildflower Square
Ashburn, VA 20147
703/723-3550

TODAY'S DATE: 11/19/01

DATE TAKEN: 10/23/01

CASE NAME: Fifra SAP conference

DEPONENTS:

TOTAL: -- PAGES: 172

ATTORNEY TAKING DEPO:

COPY SALES To:

DELIVERY:

COMPRESSED:

DISK:

E-MAIL:

EXHIBITS:

TRIAL DATE:

**SIGNATURE: