NATIONAL TOXICOLOGY PROGRAM (NTP)

# PUBLIC MEETING ON TOXICOLOGY IN THE 21ST CENTURY: THE ROLE OF THE NATIONAL TOXICOLOGY PROGRAM

January 29, 2004

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DR. CARPENTER: Good morning. I'm Hillary Carpenter with the Minnesota Department of Health. I've been asked to chair the meeting this morning, the National Toxicology Program's meeting on toxicology in the 21st century, the role of the National Toxicology Program. Welcome. We're glad to have you here. We're very interested in, in hearing what you have to say and looking forward to a lot of interaction between the public and the panel that we've assembled for today. A couple of housekeeping reminders. We do have a, a transcript, a record of attendance. If you haven't registered, please do so. Also, because of the fact that the meeting is being recorded we would like for you to use your microphones. Everybody should have a microphone right in front of you. Push the button and you get a nice little red light



that comes on and that way everybody can, everybody can hear what you're saying and the transcript can accurately reflect what you have said. At this time I'd like to introduce the panel that's been assembled for today. We have from the Board of Scientific Counselors directly on my left Dr. Sam Cohen from the University of Nebraska Medical Center where he's the Chairman of the Department of Pathology and Molecular Biology, we have Diane Birt from Iowa State University. She's the Chair of the Department of Food Science and Human Nutrition. To her left is, is Aaron Blair who's the Chief of Occupational Epidemiology with NCI. George, where's George? Oh, you moved already. We're going to be doing some shuffling here too because if you notice the arrangement of these seats it's impossible to see the slides from some of these seats so we're going to be moving back and forth. George Daston is from the Proctor & Gamble Company where he is a research fellow. Charlene is where she's supposed to be, thank you. Charlene McQueen is from the



University of Arizona where she is a Professor of Pharmacology and Toxicology and Steve Roberts, Dr. Steve Roberts of course is out of place according to my guidelines here. They put you... oh. My goodness. Steve Roberts with the University of Florida where he's a Professor in the Center for Environmental and Human Toxicology. We also have some, this is, this is the Board of Scientific Counselors portion of this group. We also have a representative from the Interagency Work Group on Vision and that's John Bucher who is sitting right there and he's not gonna acknowledge that, thank you, who is the Deputy Director of the Environmental Toxicology Program at NIEHS, and Michelle, there you are, Michelle Hooth who is a staff scientist in Environmental Toxicology at NIEHS. In addition, we have NTP Core Agency representatives, Dr. Chris Portier who is the Associate Director of NTP and the Director of the Environmental Toxicology Program at NIEHS. Mark Toraason, who's ignoring me or otherwise... there you go, thank you, who's the Science Director at



the National Institute for Occupational Safety and Health with CDC and also Dr. William Allaben from the, who's Associate Director and Science Coordinator at the National Center for Toxicological Research at the FDA. Did I miss anybody? What I would like to do now which will help everybody put names to faces and help with the transcript is to go through the, through the audience and ask you to please identify yourself and your affiliation, if you would.

DR. THAYER: Kris Thayer, NTP/NIEHS.

DR. SHANE: Barbara Shane, NTP/NIEHS.

DR. MASTEN: Scott Masten, NTP/NIEHS.

DR. TORAASON: Mark Toraason, NIOSH.

DR. ALLABEN: Bill Allaben, FDA.

DR. MENDRICK: Donna Mendrick, Gene Logic.

DR. FISHER: Joan Fisher, Proctor & Gamble.

DR. FELTER: Susan Felter, Proctor & Gamble.
DR. WOLFE: Mary Wolfe, NTP/NIEHS.
DR. SEIDLE: Troy Seidle, PETA.
DR. JAMESON: Bill Jameson, NTP/NIEHS.
DR. PHIBS: Pat Phibs, Reporter, BNA.
DR. WEDGE: Robbie Wedge, National Academy of Sciences.
DR. KI-HWA YANG: Ki-Hwa Yang, National Institute of Toxicological Research, Seoul, Korea.
DR. WRIGHT: Robert Wright, Training Lab, representing American College of Medical Toxicology.
DR. WIND: Marilyn Wind, Consumer Product Safety Commission.
DR. WILKINS: Steve Wilkins, Costella Health Sciences.
DR. SNYDER: Jack Snyder, Medical Toxicologist, Associate Director, National Library of Medicine.



DR. OKITA: Richard Okita, National Institutes of General Medical Sciences.
DR. AMUNDSON: Sara Amundson with the Doris Day Animal League.
DR. PAXTON: Mary Paxton, Institute of Medicine.
DR. JAMES: Peter James, Institute of Medicine.
DR. HOLSAPPLE: Mike Holsapple, the Executive Director of the Health and Environmental Sciences Institute.
DR. CARPENTER: Thank you all, and welcome. I would like at this time to acknowledge public comments that were submitted, written comments that were submitted. We received comments from Dr. Ki-Hwa Yang from the National Toxicology Program in Korea and Richard Becker from the American Chemistry Council. Right now I guess we go to, to Dr. Portier for a welcome from the NTP.
DR. PORTIER: Thank you, Dr. Carpenter. I want to thank you all for being here today as we launch an almost



year-long process into looking at the direction and future of the National Toxicology Program. Where is toxicology going, and how is the NTP going to contribute to that movement, potentially leading in some areas? I want to thank the members of the Board for being here. I want to thank you all for, for coming out and giving us your comment. We're a small enough group this morning. I hope that we can have a, a, an intimate discussion about the future of toxicology and its role in providing health protective public health decisions. With that I'll simply move into my presentation.

This year marks the 25th anniversary of the National Toxicology Program. In 25 years the NTP has contributed a substantial body of knowledge...well, this has got automatic changing, that's good. It will be fun. ...a substantial body of knowledge in the toxicology literature and a number of different areas in terms of evaluating public health risk for certain environmental and pharmacological and food-based exposures.



We've done a number... a lot of work in developing various assays and providing support for the development of those assays. So the Program has a long history of testing, research and evaluation of that research for guiding public health decisions. Our mission is in fact to evaluate agents of public health concern by developing and applying the tools of modern toxicology and molecular biology, and Dr. Olden when he started at NIEHS as the Director of the NTP 12 years ago, coined the, the term to sort of capture the essence of the NTP's mission and that is good science for good decisions and we still hold to that truth. NTP is a multi-agency Program. It's not just a single agency that makes up the Program. NIEHS is the home of the National Toxicology Program. There we go. Boy, we've got this worked out well. NIEHS is the home of the National Toxicology Program but two other agencies, the National Institute of Occupational Safety and Health and the National Center for Toxicological Research, one with CDC, one with FDA, both contribute

resources, time, effort and energy to the activities of the National Toxicology Program and we're very pleased to have our major partners here with us today to discuss the future directions of this Program. In addition, a number of agencies participate in the NTP activities, either on our executive committee or through some of the other activities that we have and this is a list of those agencies. Key among them are EPA, OSHA, CPSC, NCEH at CDC and NCI and ATSDR. All of those are on our executive committee and do a considerable amount of effort on behalf of the NTP.

The NTP has a number of outside guidance groups. I'm giving you a little background because it will, it'll make it clear as to how we move forward, forward with developing a road map for the vision. The NTP executive committee provides policy oversight for the Program, it's composed of the directors of ten federal agencies or their designates and it provides a forum for not only coordination of our research effort but looking at the practical appli...,



applicability of that effort and avoiding duplication of effort while also consolidating efforts to produce a bigger research portfolio from the individual parts. The NTP Board of Scientific Counselors which is amply representated here, represented here provides scientific oversight and a forum for public input for the National Toxicology Program. We have three standing subcommittee, we have two standing subcommittees for the National Toxicology Program, the Report on Carcinogens subcommittee and the Technical Reports Review subcommittee, but now we have a subcommittee on the NTP vision as well and Sam Cohen has agreed to chair that subcommittee and the people here are some of the members of that subcommittee from the NTP Board of Scientific Counselors. Let's see if I can stop it from moving forward here.

So, let's talk about creating a vision for the National Toxicology Program and where we have to go. First of all, what is a vision? So to make sure we're all talking about the same thing, a vision



is the ability to imagine how a country, society, industry, in this case, a program and a field of science could develop in the future and to plan in a suitable way. So at this point we're looking for that planning process. We're trying to lay out a road map for how we might achieve the vision we've laid out for the NTP. I'll talk about the goals strategies. Some of the questions we're asking people to consider as they think about changing, or looking for a vision for the, for toxicology for the 21st century and then some of the activities we have planned.

Why would we do this at this point? Before I, I look at the vision, why would we want to do this type of thing? I think there are two things that are over-arching and, and this is not new; these are issues that we continually work with within the National Toxicology Program. The first is to promote the scientific advances that have occurred in biomedical research in the last few years for use in the field of toxicology. Given these advances in basic



science what is the role of toxicology and what should that role look like? Are we doing the right type of science at this point or has, has science changed in such a way that we really need to look very carefully at what we're doing and consider some additional or alternative or refined methods of doing what we're doing? In addition, this type of activity after 25 years of the National Toxicology Program will help to improve our focus on the long-term needs of the public health decision-making community, the toxicological community and the scientific community, all three of which we are here to serve.

Second major issue is to improve public health decisions. We think the National Toxicology Program through its activities in the last 20 years has certainly contributed substantially to public health decisions in this country. But one can't just rest on one laurel, one's laurels forever and I think part of this is that we want to look at how we can move the field forward improving the translation of basic

research into public health decision-making arena, improve the information management tools that are necessary to capture the information that might be needed, report it and translate it in such a way that it can be understood by the people who have to make public health decisions; clinicians, heads of regulatory agencies, people in their own homes who have to decide what they are, want to or don't want to be exposed to, taking the, the real basic science and turning it into something that's usable. In doing that, in, in looking at that question, of course at the same time to look at how we can provide the data needed to guide these public health decisions, this has been a strong role for the Program and it will continue to be a strong role, what type of data do we need to provide and in what form should it be provided? And finally, overall, we would really like to see the development of a very strong scientific linkage from observations in molecular biology clean through disease onset and disease prognosis for environmental and other



di..., other disease causes that the NTP has been focused on for a number of years.

So, a vision has to be stated succinctly and so we've come up with this wording for the vision for the NTP for the 21st Century and that is to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused on a broad inclusion of target-specific, mechanism based biological observations. In 1995 the NTP held a workshop to look at mechanism-based toxicology and since that time we have contributed, many of our, our members of our Board of Scientific Counselors, many of you in the audience and many of the toxicologists that have worked around the world have contributed to the area of mechanism-based toxicology. You observe something in a disease-specific animal model and you spend time and effort trying to understand the mechanisms involved in that observation and try to take it apart as you will and really understand what is the root cause of the disease you're seeing. And



that's been done in a number of cases for a number of models. Part of this vision is to look at that process and decide whether it's time to start reversing it. To start thinking about working at the level of the mechanisms themselves and trying to predict backwards what may or may not cause disease given those types of mechanisms.

Given that that's a sort of a vision we're looking at, what type of data do we need, and where should we go to be able to create that type of vision at this point? Our strategy through looking at the road map we'd like to create for the NTP vision is achieving as much public input as we possibly can, that's part of what this meeting is. We'll have a number of other public meetings along the way. Seeking scientific input from our usual scientific partners, the NIEHS committee that Dr. Hooth is leading consists of members of the National Toxicology Program, core scientific staff, members of the Division of Intramural Research at NIEHS, our basic science staff and members of the Division of Extramural



Research and training at NIEHS, the grant-giving part of the Institute. All three of those groups are working together to look at how the NTP can function better within the, within its home agency, the National Institute of Environmental Health Sciences. We have an executive committee, subcommittee that John Bucher is chairing. This is, there are representatives from all of the major agencies that participate in the NTP. Here we're looking for synthesis across the agencies, understanding of, of what we'll have to do and how we'll have to work with the agencies to provide better scientific understanding for, for guiding public health decisions with this type of information. And finally we're looking for the, to the Board of Scientific Counselors Subcommittee chaired by Sam Cohen, and here we're looking for scientific guidance, what types of things could we do that would contribute to the overall direction of, of a more mechanism based toxicology approach that's predictive for environmental and other hazards. We're bringing in a number of outside experts in a

variety of points in the process to give us some advice. We have a, at, toward the end of this early process of, of getting as much idea into the Program as we possibly can we're gonna form an NTP work group that's going to formalize this into a road map for us and some goals and measurements along the way with that road map and we'll end with a, we'll end with a retreat where we finalize that road map and then hopefully sometime in fall we, we hope to hold a meeting here in Washington where we release that road map for public comment and have a workshop to discuss some of the implications of it. We've asked all of the groups involved and I'm giving you these questions as well, to consider certain things as you look at where toxicology might be going in the 21st Century, and these are just the broad questions, you can think of dozens of smaller questions under each of these categories, but first what information should the NTP produce, what might this information, how might this information be used in public health decisions, what would be needed to



gain acceptance of the new testing paradigm, and by testing paradigm here it doesn't have to be a single test, you can think of multiple tests as forming a, a strategy for testing. How can the NTP advance the utility of these new methods and new testing paradigms and finally, what new resources will be needed and what re..., existing resources will have to be reduced to look at these issues and looking at some of the processes we already have in place.

Just so you get some idea of the types of things that might be considered, and these are my own ideas; these are not things that have come to me yet from any of these subcommittees, but I wanted you to think about some of the things I'm looking at. Rapidly, rapid development of better models and faster screens, move from disease-specific focus to the systems mechanism-based focus, looking at issues that we historically have only looked at piecemeal like exposure timing, genetic controls on response, system-wide evaluation of the data, looking at an entire biological system as something of



interest, and development of tools for integrating the scientific data, these are bio-informatics and database management-types tools, that might help us integrate this information into a better picture of the potential for toxicity. In addition, tied with this and having to run parallel is to develop better and broader baseline information. If I'm gonna look at a variety of assays I want to be able to look at them in a large number of compounds in a fairly short period of time. So I'd like to see some high throughput methods used, some mechanistic clarity of the response so I know actually what I'm looking at. Even though it might have limited interpretation on its own, I want to make sure that interpretation is clear, clear before I start trying to interpret it in, in the light of a much broader issue like an entire animal response, and I want to look at a broad agent, array of agents and I want to use these consistently if possible.

Some other activities I think we need to consider along the line, enhanced



development of multi-disciplinary... disciplinary and multi-agency scientific teams. Toxicology is no longer one person in their lab doing one experiment with one model. Clearly the NTP has been a leader in that area and recognizes the need for multi-disciplinary teams. We've used them for a number of years very successfully and it's important to the overall success of any toxicology exercise to continue along those lines. Determine how to cross-link disease focus with mechanism focus. We've fundamentally changed that linkage to basic science enhanced both areas. And finally we clearly are going to need to develop training programs to meet the needs of both the NTP, our partners, and a broader based community that uses NTP information, so we also have to look towards that as well.

And I seem to have lost my picture. So... that's okay. This is a quote from John Sherr, "The future is not some place we are going to, but one we are creating." And at this point I think that's what we're trying to look at. How do we create a path

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such that we change both the maker and the destination and hopefully for the betterment of public health in the United States. Thanks a lot.

DR. CARPENTER: Thanks, Dr. Portier. You want to take questions? Any, anybody on the panel have any questions for Dr. Portier? Anybody in the audience? You were so clear. We'll now have brief statements or reports from the work groups for the NTP vision group and we start with the NTP Board of Scientific Counselors chair and that's Dr. Samuel Cohen.

DR. COHEN: Thanks, Hillary. On behalf of the Board of Scientific Counselors we've formed this subcommittee to assist in this process with the NTP and we're very much looking forward to working with Chris and his associates to be able to make progress in this area. Thank you.

DR. CARPENTER: And from the NIEHS group Dr. Michelle Hooth.

DR. HOOTH: Double click on...that's okay, thanks. Good morning. I'm Michelle Hooth, and I'm chair of the

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NIEHS work group for the NTP vision, and I'd like to tell you about our progress over the past few months. Did that. That's okay. Wait a minute. Chris, nothing's working. It's not responding.

SPEAKER: Escape that menu and go to the...

DR. HOOTH: Okay. Sorry. Yeah, oops. Okay, let's try again. So is it the up arrow? It should be just the up.

SPEAKER: Enter...no. There you go. See it?

DR. HOOTH: Okay.

SPEAKER: Down there.

DR. HOOTH: Thank you. We have 11 members of our work group. Many of us are members of the Environmental Toxicology Program and so we're directly involved in the day-to-day activities of the NTP. We also have two members from the Division of Extramural Research and Training and, as Dr. Portier mentioned, this group manages the Institute's grant program. We have several principal investigators that conduct basic research and manage

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laboratories in the Institute and this includes two members from the Environmental Diseases and Medicine Program and Dori Gramalick and Nigel Walker also have laboratories in the Institute. We have very diverse backgrounds and responsibilities in the Program and this allows us to consider the full range of the NTP activities and also to develop potential collaborations within the Institute.

The charge to the work group from Dr. Portier was to develop a road map for achieving the NTP vision and more specifically to represent the NIEHS/NTP staff, to consider all the NTP programs and activities, and to provide recommendations in a written document, and we hope to complete this document in March. We started meeting in October and we've been meeting on a regular basis and the overarching goal that we're focused on is to provide, through original research or through the assembly and analysis of research done outside the Program, the scientific underpinnings upon which decisions protective of public health

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are made about risk from exposure to environmental agents, and this is really very consistent with the NTP mission.

We started by brainstorming and then organizing our recommendations in two goals, and we realized fairly early on that our goals were falling out into three basic categories, and those are research goals or scientific goals, process goals are ways of achieving these goals and then communication and translation, and I'd like to share with you a few of our recommendations. For the past few weeks we've been split into two groups working on the research goals you see here. The first to develop a scientific rationale for the generation, analysis, and integration of data from emerging technologies into the characterization of environmental health effects, and this group has been focusing on optimizing our current efforts but also looking at ways that new methods and technology can be incorporated into the Program to look at molecular mechanisms and to screen and prioritize chemical nominations. A second group has

been looking at identifying and quantifying indicators of exposure, disease and susceptibility from animal toxicity studies that can be linked to clinical and epidemiological investigations, and in this group we've been looking at quantitative relationships between exposure, tissue dosimetry and trying to identify intermediate molecular events in environmental diseases. In the next few weeks we'll be focusing on some of our other goals and just to give you an idea of the process goals, we'll be looking at ways to evaluate mechanisms for hiring and training staff to facilitate the transfer of new technologies to the NTP; ways to increase the number and relevance of agents nominated to the Program; and, given the vast amount of data that can be generated, ways to develop improved data management methods. And then under the communication and translation goals ways to strengthen public outreach and communication programs to help regulatory agencies and the public understand the significance of the NTP findings.



The process that we've been using to flush out these goals is the SMART process; so for each of our goals we identify specific aims and then we try to define measures of accomplishments, so how will we know that we've achieved our goals. And then we've also challenged ourselves to look at the ability or the feasibility to achieve the specific aims, trying to identify what the obstacles or challenges might be and at all times we want to keep in mind the relevance to the NTP mission and the public health decisions. We're also trying to provide realistic time lines for implementations of our recommendations. We appreciate the opportunity to be able to provide recommendations and we look forward to further debate and discussion of our ideas. Thank you.

DR. CARPENTER: Does anybody on the panel have any questions for Dr. Hooth?

DR. BLAIR: Two questions actually. One, the research goals you've



laid out, I must admit I don't quite know what the research goals would be for the Program now, but these seem what I might anticipate. Are they different?

DR. HOOTH: No, I think some of them are fairly consistent with the Program, things that we're already doing. But we're trying to look at ways to optimize what we're doing. Could we be getting more information or more analysis out of the studies that we're doing? And also how can we incorporate new methodologies and, as Chris stated in his overview, ways to provide rapid and thorough analysis, ways to screen or prioritize compounds. So, yeah, I, I think it does seem like these are things that we're already doing but we're trying to really focus on more of the specifics.

DR. BLAIR: One more question.

DR. HOOTH: Sure.

DR. BLAIR: In the process goals, it, what you were talking, and I think maybe this is the, the charge of your



group to look internally but what it sort of struck me as following Dr. Portier's vision it actually means incorporating information from the extramural side that feeds into NTP and so there's sort of nothing about that in your process goals and that's because you're supposed to just look internally in the NTP?

DR. HOOTH: We're looking within NIEHS but we are also considering, as we mentioned before, DERT which is the Division of Extramural Research and Training and other groups within the Institute so that... I think when you see our written document we have also considered all of the other sources of data that we'll be inputting into the Program.

DR. CARPENTER: Dr. Birt?

DR. BIRT: Moving on to the communication and translation goal, I'm, I'm very glad to see that there, but it seems like that's going to be a major effort with NTP kind of changing its test structure. You, you lump together the regulatory agencies and public understanding. I'm just wondering are you thinking those will diverge

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at some point?
DR. HOOTH: Certainly. Yeah, and in fact in one version of these slides we had them separated. We, we are... communication is so important for having everyone understand where the Program is moving and I think this is essential. The public needs to understand that we are a resource and that they can contact members of the NTP to provide them with answers about concerns about environmental agents and the regulatory agencies. There needs to be an open dialogue at all times so that we can work together and collaborate to provide the best data and interpretation of the data.
DR. CARPENTER: I'd, I'd reinforce that, in terms of the education but I'd like to also emphasize the fact that you really are going to need to do a lot of basic education more than, more than interacting, you're gonna have to educate the public and probably a lot of the regulatory community in the important aspects of the proposals. It's, it's going to be crucial to get acceptance.

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DR. HOOTH: I agree.
DR. CARPENTER: Dr. Portier.
DR. PORTIER: Yeah, I think that's where... that's gonna be one of the strongest components that the DERT, the extramural side of the Institute, can do for us. They already have a substantial training program in a number of different areas from kindergarten clean up through post-graduate education, and I think they would be very interested in potentially forming that type of training program as part of their extramural activities. Michelle, I was wondering if you could give one or two very specific examples of things you're considering under the first two points you've already done...
DR. HOOTH: Sure.
DR. PORTIER: ...so that the audience can get a feel for what type of modifications you're thinking about or what type of research you're, you're working on.
DR. HOOTH: I can go back to that slide actually. I was involved with a smaller sub-group that worked on the second

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of these goals, and one thing that we're really looking at is, or one of the recommendations that we've made is to have ADME, Absorption, Distribution, Metabolism and Elimination for each compound under study so that we can have better information about the half-life and some of the other characteristics to help us interpretat... interpret any of the other studies that we do and focusing a lot on modeling and trying to look at our studies and see whether we can identify intermediate events, earlier morphological or molecular events in the disease process that might be predictive of the endpoint. We really want to try and be able to link chemical exposure to what's seen in the tissue and then to find molecular mechanisms that might be predictive or informative of the endpoint. I don't know if that was specific enough, but. So just to follow up a little bit more, so we've asked ourselves, you know, do we need to be collecting other samples at interim time points, would that be useful information? I want to stress that we're

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really challenging ourselves to follow our recommendations through, so will the data be useful? How, how would you interpret this result? Okay, if we make this recommendation and we say something is a priority, what is the priority? What would we list as a high priority versus a low priority? So we're, we're trying to think all the way through so that it's not just, you know, we should be doing this, this and this and we're going to have all of this data, how is that data gonna be used? What will that data tell us, how can it be interpreted?
DR. CARPENTER: Any questions from the public? Oh, Chris has got another question.
DR. PORTIER: I just want to follow up on one thing Michelle did and in terms of the ADME work that you're going to be looking towards in terms of every single chemical, are you... you're also looking at non-animal based predictions of ADME as well...
DR. HOOTH: Right, right.

DR. PORTIER: ...so that there may be some high throughput activities involved in being able to look at absorption, distribution, metabolism, elimination, right?

DR. HOOTH: Absolutely.

DR. PORTIER: And you're looking at those, great.

DR. CARPENTER: Thanks very much, Michelle.

DR. HOOTH: Thank you.

DR. CARPENTER: Now we move to the interagency work group, or sub-work group. Dr. John Bucher from NIEHS.

DR. BUCHER: Yes. Thank you. I'd like to tell you a little bit about another arm of this effort at collecting opinions and moving our vision forward through the development of a road map, and this is through the activities of the NTP executive committee work group on, on the NTP road map. We haven't made as much progress as Michelle's group, but I wanted to go over a little bit of what has happened so far with this, with this activity. In



August of 2003 Dr. Portier presented the NTP vision to the NTP executive committee, or the agencies that he mentioned on the slide that he showed that comprised the sort of oversight, government oversight, for the NTP activities. In November of 2003 Dr. Portier requested that the participating NTP agencies appoint work group participants and in December we had an orientation teleconference with those participants. Yesterday was the first time that this group met face to face, and so that gives you some idea of why I can't tell you exactly as, as much as Michelle has told you about the progress of the NIEHS group effort. We are anticipating collating all of the thoughts from the agencies and the reactions and the ideas on how we can move forward and compiling this into a completed report, hopefully in April. The work group participants, you can read through these, they are Marilyn Wind, Michael Babbage from CPSC, Bill Allaben and Paul Howard from FDA, Chris de Rosa from ATSDR, Tom Sinks, NCEH, John Howard and Mark Toraason, NIOSH; Carl Barrett, David



Longfellow and Michelle Bennett from NCI; Amanda Edans from OSHA; Jack Snyder from NLM; Bill Farland and Helen Zenick from EPA; and Scott Masten and I are the NIEH representatives to this group.

The charge to this group, as was the charge to the NIEHS group, to develop a road map for achieving the NTP vision. Specifically this group is to represent the interests of the agencies which comprise the NTP executive committee. We are also charged to consider all of the NTP programs' activities with specific reference to the interagency interactions and how our various agencies work together to promote and achieve the goals of the NTP. We are also very committed to assuring that any recommended changes that we have serve the best interests of public health and, of course, we'll be providing these recommendations in a written document. Just to give you some idea, I think the discussions that we had yesterday and on the teleconference back in December were still at the stage of, of getting ourselves oriented in to thinking



about the, the depth of impacts that changing the NTP, the way the NTP does business, the kind of data that the NTP generates, how, what kind of impacts that will have in regulatory affairs, regulatory activities. NTP has been around for 25 years and these agencies and, and, have, have had a tremendous impact in, in, in forming the programs that we, that we currently have today and we want to make sure that anything that changes within the NTP is, changes in a way that the data that are generated can be useful, remain useful to regulatory and other agencies, health research agencies and also continue to be very protective in, in the maximum of any public health decisions that could come out of the research that we do. So with that, I'm finished.

DR. CARPENTER: Thanks, John. Any questions for... George?

DR. DASTON: John, when I, when I think about this effort...let me move back a second.

DR. CARPENTER: Thank you for

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remembering to use your microphone.
DR. DASTON: John, when I, when I think about this, this effort and the way that, that Chris and Michelle and now you have described going about it, it, it complements very nicely EPA's new cancer risk assessment guideline approach to take a mode of action, to base their assessments on mode of action as much as possible and then beyond that there's also been an EPA ILSI sponsored workshop a couple of years ago on how one can also incorporate non-cancer risk assessment into the mode of action process. And I'm just wondering how much you're using the cancer risk assessment guidelines and that harmonization report that was published from that, from that workshop as guidance in moving forward in this process because, although I realize that NTP is not a regulatory agency, the data that the, that EPA and other regulatory agencies use comes to a great degree from NTP. Can you comment on, on how much you're using explicitly those documents?
DR. BUCHER: Well, I think

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those documents as we move forward will certainly enter into this, these activities. The, there is another activity that EPA has ongoing now which is the creation of an NAS committee to look at the way, and I don't want to misrepresent in any way the charge to that committee because I think it's still being formulated, but there are a lot of similarities in the goals of the EPA/NAS activity with the vision that we have put forth and I think that perhaps within the various agencies there is, we're on the same page with EPA perhaps as much or, or more so than with the other agencies that form this interagency group. So I, I think that the, there will be a tight coordination between the development of our process and, and the re-invention if, if that happens through this NAS activity.
DR. CARPENTER: Any other questions?
DR. DASTON: I have just a follow-up. Do we have any time-line for the NAS activity?
DR. BUCHER: I can't really

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answer that question.
DR. DASTON: Okay.
DR. BUCHER: I'm not sure about that.
SPEAKER: Several years.
DR. DASTON: Yeah. So, so we don't want their time-line to interfere with, with our work on the vision?
DR. BUCHER: It's not gonna interfere with it but I think that... I mean their, the initial stages certainly have benefitted from close contact between their activity and our activity. We've looked at their statement of work, they've looked at the, the guidance questions that, that we provided for, for the, you know, implementing this vision and I think that there's been a lot of benefit gained from both groups by collaborating.
DR. CARPENTER: Yes.
SPEAKER: Since I'm the Project Director for that NAS study I guess maybe I can address the time-line. It is ongoing now. We're putting the committee together and within twelve months of the

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committee approval the second report, which will be more of the road map, is due within three years.
DR. CARPENTER: Any other comments? Questions? Thank you, John. Make sure I get this. According to my agenda here... We now move into the oral comments portion which now we, now we're gonna hear from the audience. The public comments are going to present, be presented at the podium. Please, again for the benefit of the transcript that's being done, I would ask each speaker when they come up to the podium to identify themselves and their affiliation for the record. If you have written material that you'd like to see distributed that you haven't already submitted, you can do so at the registration desk and, and the NTP staff, cracker jack group that they are, will reproduce it and see that it does get distributed to the, to the entire group. The comments will be presented in the order that they, that they came in so first speaker will be Michael Holsapple from the ILSI Health and

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Environmental Sciences Institute.
DR. HOLSAPPLE: I do have my written comments. Can you all hear me? Well, good morning. My name is Dr. Mike Holsapple. I'm the Executive Director of the ILSI Health and Environmental Sciences Institute here in Washington, DC. I want to begin by thanking you for this opportunity to provide our comments on the NTP vision for the 21st century. Many of you are very familiar with HESI's work on scientific issues and its collaborative work with government, academia, and industry. However, to place our comments in the proper perspective, a few brief remarks about our organization are warranted. Given our mission and diverse scientific programs, we believe that HESI is well positioned to provide feedback and recommendation to NTP regarding its vision. I should emphasize that my use of the terms "we" and "our" is deliberate and illustrates one of HESI's op... hallmark operating principles. We rely very heavily on multi-stakeholder input. In fact, our comments today are, were developed

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by HESI staff with critical input from key industrial members and academic colleagues who are identified on the front page. I've taken the liberty of providing you with a copy of our 2003 Annual Report. The mission and strategic objectives of HESI are presented on page 4. I want to emphasize a number of key words from those objectives: partnerships, communication and transparency. These words are key because they form the cornerstones of our recommendations to the NTP as it moves forward to implement its 2004 vision. Although our objectives have not changed, HESI will engage in its own science mapping session in April of 2004 in order to identify emerging scientific issues, to maximize our efforts to contribute to the resolution of scientific issues, and to ensure that we are focused on the right scientific issues. We are committed to this effort and hope to enlist the participation of key scientists from NTP and NIEHS as valued partners in this process. Regarding our purpose today, let me emphasize at the outset that HESI strongly supports NTP's

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vision to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based biological observations. We encourage NTP to strengthen partnerships with external organizations to supplement its existing resources. These collaborations enrich the scientific knowledge base of all participants and help build consensus. In the past few years NTP and HESI have been successful partners by jointly sponsoring research, publishing scientific papers in peer-reviewed journals, and co-sponsoring technical workshops to examine and disseminate scientific data. Among the issues on which NTP and HESI have collaborated are the following: transgenic rodent models, genomics, immunotoxicology, DNA adducts, biomonitoring, biomarkers, dose-dependent transitions in mechanisms of toxicity, structure-activity relationships, and protein allergenicity. Virtually all of these areas of collaboration promote NTP's

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vision to move toward predictive science. Some of the HESI and NTP collaborations are worthy of specific mention. The HESI Alternatives to Carcinogencity Testing or ACT Technical Committee organized an international workshop in February of 2003. This workship was the culmination of an 8-year program in which 21 chemicals were tested in 3-6 model systems by 50 laboratories worldwide. The Febru... The February workshop followed a workshop in 2000 that was attended by over 350 scientists from the U.S., Europe and Japan and was co-sponsored by the NIEHS, the EPA, the Society of Toxicological Pathology and the SOT. The 2003 HESI workshop was organized in cooperation with the NTP, included a lecture by Dr. Portier, and was followed the next day by a workshop organized by NTP. Taken together, the workshops by HESI and NTP clearly advanced our understanding of how transgenic animal models can and should be applied to carcinogenistic risk assessment. The HESI Genomics Technical Committee instituted an international, multi-sector

scientific collaboration in 35 laboratories including government, industry and academia, which included Dr. Ray Tennant, the Director of the National Center for Toxicogenomics at NIEHS. This effort culminated in a workshop in June of 2003. The June workshop has resulted in twelve papers describing the HESI Committee's research. These papers will be featured in 2004 editions of the journal EHP Toxicogenomics. This research effort also resulted in the co-development and population of the first functional international toxicogenomic database - ToxArrayExpress.

The importance of the HESI/NTP collaborations on transgenics and genomics is captured on page 19 of our Annual Report in the following comments by Dr. Tennant: Quote, "The organizational, coordinating, and logistical leadership provided by HESI in both the ACT and Genomics Committees has been outstanding. I believe these two projects to be prototypes of the scientific interactions needed in the development of new research and testing initiatives. The scientific community, particularly in the



broad realm of toxicology, needs the type of organizational leadership available through the aegis of HESI to deal with the increasingly complex issues related to assimul... assimilating new concepts and methodologies. I do not know of another forum in which open scientific exchange can be oriented to achieving consensus among highly disparate viewpoints and missions. It is critical that basic, translational, and regulatory scientists have a forum in which all voices and viewpoints can be raised and discussed and research formulated to resolve critical issues. I've been very pleased to participate on two such committees and view their accomplishments as highly successful."

There are other examples of previous HESI/NTP collaborations, but in the interest of time I believe I'll move on. As noted above, HESI applauds the NTP for openly communicating its new toxicology vision for the 21st century. However, HESI encourages NTP to recognize the enormous challenge that they have identified and to take concrete steps toward meeting this challenge. Without



demonstrable action, the NTP vision could be dismissed as mere rhetoric. As has been articulated in its Vision Statement for the 21st Century, NTP initiated a program in1995 to use mechanism-based toxicology to develop, evaluate and validate better toxicological test methods. The 1995 NTP program contributed to major changes in toxicology at the national and international level, and mechanism-based toxicology led to some changes in the scientific basis for public health decisions. However, the NTP accurately states that mechanism-based toxicology did not dramatically reduce the need for the classical tests developed in the 70's and 80's that were the basis for many decisions related to product safety, evaluation of environmental and occupational hazards, and prioritizations of chemicals for further testing. In another document from the NTP, their Year 2000 Current Directions and Evolving Strategies: Good Science for Good Decisions, the NTP leadership emphasized that its commitment to the concept of good science for good decisions created an



atmosphere that allows the NTP to be flexible and innovative in its approach toward addressing public health concerns related to chemical exposures at home and at work and in our environment. Their 2000 document emphasized that NTP's commitment to flexibility was manifested in its expanded scope beyond cancer to include examining the impact of chemicals on non-cancer toxicities such as those affecting reproduction and development, and the immune, respiratory and nervous systems. These efforts by NTP have had an impact, and this focus should be expanded. Nevertheless, in 2000, the NTP declared that, quote, "Nationally the NTP rodent bioassay is recognized as the standard for the identification of carcinogenic, carcinogenic agents." Perhaps this statement was valid in the year 2000. However, HESI strongly encourages the NTP to revisit this conclusion in the context of its 2004 vision statement. We urge NTP to demonstrate leadership in the area of mechanism-based toxicology by communicating an expansion of its program beyond observational testing into

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the realm of mechanism-based approaches. These approaches, some of which are used routinely by the pharmaceutical industry, are valuable predictive tools. HESI's multi-sector membership, including the pharmaceutical industry, presents a unique opportunity to sare, to share such innovative tools and approaches. One way in which NTP could move toward its vision is to explore alternative testing methods which reach beyond the current testing portfolio. For example, a big step forward would be a scientific shift in characterizing substances for potential carcinogenicity. Simply put, the NTP could move beyond the notion that the NTP rodent bioassay is recognized as the standard for the identification of carcinogenic agents. As part of HESI's 2004 strate... Emerging Issues process, we are considering a new project entitled "Strategies for Improving the Hazard Identification of Potential Carcinogens." This strategy is predicated on the following consensus statements about the current situation: Genotoxins can be detected in

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short-term assays; in bioassay protocols, compounds are tested in rodents at high doses; the background incidence of many tumor types is high in test organisms; many non-genotoxic carcinogens act by a mechanism of little or no relevance to human safety; the relevance to risk assessments of tumors produced at toxic doses of a chemical is highly questionable.

The new HESI program projects that identification of potential carcinogens can be improved by taking the following approach: Identify genotoxic carcinogens by well-characterized screens for genotoxicity potential; identify non-genotoxic carcinogens from their primary effects in sub-chronic 90-day studies; depending on the results of these preliminary tests, conduct additional mechanistic-based tests to further identify the specific mode of action; consider that a margin-of-exposure approach for all carcinogens be included to ensure that human relevance is addressed.

If the bioassay is to be replaced by a science-based assessment of potential to

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cause carcinogenicity, several requirements need to be met: the short-term tests should reliably detect genotoxic carcinogens; the critical precursor events of non-genotoxic carcinogens should be able to be detected in sub-chronic tests that may require the development of new endpoints for assessment; the nature of the dose-response curve of genotoxic carcinogens should be established at human levels of exposure.

HESI has been committed to the use of mechanistic data as the basis for risk assessments for some time. Clearly, scientific discussion and consensus would be needed if such a shift were undertaken by the NTP approach to toxicology. Consistent with our strategic objectives, HESI believes that this discussion must occur in as transparent a process as possible. HESI has learned through our Technical Committee on Agricultural Chemical Safety Assessment the important, the importance of attempting to conduct a paradigm shift in a transparent manner. The mission of the ACSA Technical Committee, which is a multi-sector,

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international group, is to provide a mechanism for reaching consensus across sectors (government, academia and industry) on the development of scientifically credible and viable methods for assessing the safety of crop protection chemicals more efficiently, with fewer animals and fewer artifacts. In 2003 the ACSA project completed a multi-year project to develop an improved testing scheme for assessing the safety of crop protection chemicals. Through the work of three active task forces, a proposal was developed with specific emphasis on integrating metabolic and kinetic data into the safety assessment process; developing a hierarchy of study types, endpoints, and triggers to cover vulnerable life stages; developing a tiered testing framework for endpoints such as neurotoxicity, immunotoxicity, carcinogenicity, and chronic toxicity; and evaluating the range of relevant human exposure situations in the context of the experimental study design. The approach approached by ACSA provides a sound

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scientific basis for determining whether a given agricultural chemical poses adverse human risk in humans, taking into account the chemical's toxicological properties and use patterns.

It has been HESI's experience that it is just about impossible to prove a negative. As such, those who espouse a commitment to mechanism-based risk assessment face a huge hurdle. It is usually very difficult to provide sufficient weight of evidence to persuade policy makers that the quantity and quality of mechanistic data are sufficient to allow the hazard data generated in traditional classical guidelines and prescribed regulatory studies to be discounted. HESI believes that if NTP proposes to be a leader in predictive science, then it will need to evaluate more challenging and perhaps more controversial alternatives. If alternatives are meant to be true refinements or replacements, they should not simply be add-ons to existing tests. To be perceived as truly committed to its new vision of toxicology for the 21st

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century, the NTP should commit to an overhaul of its carcinogenicity program in a manner consistent with the HESI ACSA program: a multi-sector partnership (government, industry, and, and academics); a commitment to communicating progress; and a commitment to transparency. HESI strongly endorses this shift in vision, but it is vital to emphasize that those who are involved in interpreting the data and making the critical judgments must be competent, evidence-driven and capable of arriving at balanced assessments of complex and sometimes contradictory data. I thank you and I'll be happy to entertain any questions.

DR. CARPENTER: Thank you, Dr. Holsapple, and, and thank you for almost making the ten minute limit that I forgot to announce before the first speaker. Speakers are asked to present their comments in a ten-minute time period and you didn't do too badly. Do we have any questions for the speaker?

DR. DASTON: Mike, I appreciate your comments and I, I think the

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spirit is very much in support of what I think we're trying to do here in terms of the vision. In terms of, of, of some of the details... You had described a potential model for assessing chemicals that comes from the pharmaceutical industry and I'm wondering whether that really fits with the larger audience that, that NTP's data goes to, given that in the, in the pharmaceutical industry there are a couple of goals to pre-clinical testing. One is to eliminate as many potential bad actors as quickly as possible, you know, with the understanding that there will be some babies thrown out with the bath water, and the second is to identify potential toxicities that could then be evaluated in the clinic and that's a different situation than many other chemicals where there is no clinic and there is no evaluation for the, the compounds get approved. Is it, is it your thinking that there would be, say a, a two-stage process depending on what the ultimate end use of the chemical is?

DR. HOLSAPPLE: I, I, I

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think you're right. I think NTP is, is facing a pretty high hurdle already with the number of chemicals that they actually have to develop a tox profile for. I think our reference to the pharmaceutical industry was more along the lines of some of their use of predictive tests, the genomics and the transgenics, and the fact that I think they've got those positioned in the right way in terms of capitalizing on that information to build the subsequent test. I think the other thing that we can derive from the pharmaceutical model is their obvious commitment to pharmacokinetics, blood levels as an estimate of dose, which is something that can be extrapolated over. I think probably a better model, if I was looking at it from an NTP perspective, would be more the ag chemical model because they're struggling with the same issues. We don't have the kind of ability to, to move into humans to derive some of the safety, just by putting the chem..., just by putting the chemical into humans, but I think what they've arrived at is trying to grab some of

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the things that can be applied from a pharmaceutical-type approach. The, the tiered system, the, the movement away from kind of a box checking sort of mentality and allow the data that you have as you develop it, kind of guide the subsequent tasks to, to maximize your efficiency, to, to minimize the number of animals that you actually have to have, and I think they've also done a good job of trying to introduce a commitment toward pharmacokinetic metabolism-type studies which right now, as we move through the safety assessment for a crop protection chemical, are way, way down the road. We've got that really out of, out of sync. We really gotta be developing some of those kinetic blood level-type dose estimates early in the assessment so that we can do a better job of at least attempting to extrapolate that back to human safety issues.

DR. CARPENTER: John?

DR. BUCHER: Mike, I think the, the, some of the heart of your comments have been consistent with some of the difficulties that we've had in establishing

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adequate negatives. I think that's what you, you were referring to in the last part of your comments, and with respect to the use of mechanistic information and, and models that give you mechanistic information, it's easier, it's always easier to generate data that you can use in a predictive sense to indicate that something is harmful or that some adverse effect is, is occurring but it's much more difficult to develop models that give you the confidence to say that a negative response in that model is a, is a true negative in all and is a, and is a health protective negative. So, are there, and, and you've obviously given this a lot of thought, are there things that you could recommend that we would try to build in from the very beginning that would give as much weight to the positive findings as validating, in essence, the negative findings?

DR. HOLSAPPLE: I think that's kind of the million-dollar question associated with any movement toward either attempting to, if it's a validation of a new

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test method or a new procedure or whatever, that's the million-dollar question as to separate the positives from the negatives. Do, do, do I, as a representative of HESI, have the answer? I don't, I don't think so. I think that what it requires though is these kinds of multi-sectored partnerships when we sit down at the table, and as much as we can, try to separate that science from, from the policy applications of it. And I think if, if we try to blend those too quickly too soon at the table, I think we're gonna lose the chance to be able to move the science forward. I think it's gonna require this kind of consensus building as to what the scientific rigor would be associated with defining positives and negative validation. Many of the things that we already have underway. But I guess I would, I would recommend that I think we try to develop it at a scientific level and then take it as a second step to try to get it into the policy level, because I think to try to do both at once is almost an impossible quest.

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DR. CARPENTER: Aaron?

DR. BLAIR: A couple of questions to get your thoughts on. One was, George raised it a bit about the pharmaceutical industry. It seems to me like there's a couple distinctions that are quite different than NTP. One is that the pharmaceutical industry is developing chemicals for direct and immediate benefit to individuals; it's personal. NTP's evaluating largely things that are out there already that benefit some people but not a lot of others, but still have exposure. That's, that's quite different, I think, in the way they have to proceed and the way society would, our citizens would want you to proceed. And the other thing is to, I think up to a large extent, that a pharmaceutical industry to, in many cases, developing something new. You know, I realize you pull things from plants and so forth, but it's not like it's already out there all over. NTP largely is looking at chemicals that are already strung around trying to decide if we need to do something about them. And so I'd

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just like to get your sense about... does that change how you need to think about the testing and so forth?

DR. HOLSAPPLE: I think that's both the legacy of NTP and perhaps the opportunity. And, again, I, I think we might be trying to make too much out of trying to pound NTP into a pharmaceutical model. It's clearly not. There are things, there are messages, there are approaches, that we can derive from a pharmaceutical-type approach and those would be to do a better job of the tier testing, to do a better emphasis on estimating what the dosimetrics are. And I guess I would contend that even with a chemical that's been out there forever, we could apply some of those principles and we've been woefully lacking in really trying to embrace that. And it is gonna require a paradigm shift if we're truly gonna move from the toxicology being just an observational science to a predictive one. It's gonna be an obser... we can, we can wave our hands and talk about how we've got, you know, such a tough mountain to

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climb, that we're never gonna get there but I guess that's the beauty of trying to formulate a vision. It really does... and a road map, it really does provide us with, with landmarks along the way that we can measure our success or begin to realize that we're, we're running astray from what we had deemed as the success. That's what I hope NTP will do with its road map. Not only set a vision out there for five, ten years or so down the road but have milestones along the way that we can judge it. And I think we can, we can learn from the pharmaceutical approach. They are developing new molecules. But I think the efficiency with which they approach developing the safety assessment is where I think we can learn some things and apply them. And they're all kind of embedded in what we've been moving toward in terms of this mechanism-based toxicology but some group is gonna have to take a major leadership role. I believe it can be NTP. I think that they can probably achieve that, especially if they're willing to engage in these kinds of

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partnerships in the commitment to communication and in the commitment to transparency. I think they're in a good position.

DR. BLAIR: One more question to get your sense, since you represent sort of a broad based group and you get information feeding in from a lot of different sectors of our society, and so the issue about the, the thing that sort of swirls in my mind is when you go to a mechanism approach and what NTP is trying to do to provide information to make societal decisions about different chemicals. Essentially, I think what you're talking about is all mechanisms for all outcomes. That actually sounds pretty daunting. It's real easy to identify a mechanism for one outcome and you don't even know whether that's all of them or not, and then sort of, so I'd like to get your sense about how your group thinks about this, and just overlaying with that is 25 years ago there was some move to this approach in carcinogenic testing and it was called "Looking at Mutagenicity,"

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and it folded in and helped but it never came close to replacing, because actually what it did was generate a phenomenal number of positives that you couldn't quite deal with and so I worry a little bit about that side also. Many mechanisms, many diseases, I, I will bet the bank that we'll generate so many more positives that we can't possibly deal with and so what do we do when we generate them?

DR. HOLSAPPLE: I guess I'm, I'm a little lost with the comment about one, one mechanism, one, one path forward. I, I think it's, it's more... If I've implied that I think it's gonna be a simple task, it, it certainly is not. But I, I think... I don't know how you could set a vision that says you're gonna move away from observational science and, and, and get more toward predictive without embracing a commitment toward putting an identification of the mode of action, or modes of action, for a chemical at a, at a high, at the center of what you're, what you're trying to do with your, your testing approach,

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portfolio or however you want to get from point A to point B. If, if we're gonna truly do that, then we just gotta kind of bite the bullet and just start to move in that direction. It's certainly not gonna be simple and that's why I think I'm encouraging NTP to recognize there are lots of groups that are struggling with this out there. Many of them we'll probably hear from today, and that we should do as much as we can to strengthen those kinds of partnerships. We have to leverage that information and that approach, that paradigm shift, across not only science but a societal paradigm shift, we all have to contribute toward that, otherwise it's just not gonna work.

DR. CARPENTER: Go ahead.

DR. SNYDER: Jack Snyder from NLM. As I work within the NIH community and I attend various sessions, I hear discussions throughout the institutes about attempts to define a workable number of cellular targets and you also hear the same kind of discussions in industry. And so my, my

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question to you is, with HESI and the other interactions that you have, have there been discussions about trying to get a handle on a finite or a workable number of cellular targets? And begin to define the vision to some extent in that way, were it to have that kind of analysis contribute to the vision of where toxicology is going. Would you like to comment on that?

DR. HOLSAPPLE: Yeah, I'll give you a real, hopefully a short example, something that just recently happened within the last couple of weeks. A group of us got together to consider rodent liver tumors. So it's strictly hepatocarcinogenicity. We're not going for the adenocarcinomas or anything like that, very limited kind of a scope. Trying to build on that framework that George made reference to where we were talking about the PPAR alpha agonists as a mode of action where we could develop a framework to begin to know what to do with the chemical once we had defined that PPAR alpha mode of action. We sat down to try to figure out what other kinds of mode of

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actions would lend themselves toward being applied in that sort of a framework. We came up with the P450 kinds of inducers, both the phenol barb and the AH kind of inducers. We came up with a kind of receptor mediated in a hormonal-type level. We came up with the metal kind of the free oxygen radical generating mechanism. We came up with cytotoxicity. So we had those four that we felt pretty comfortable with where we could draw upon existing knowledge about specific chemicals that we believe would fit in to that mode of action. However, we still had another category that we kept having to kind of dump over here on the side, you know, others... And, and I think the way that this is gonna have to play out is we just gotta get our arms around PPA alpha, P450-type, the estrogen-type of cancer models, the cytotoxicity, the metal overload type of models, and if we could begin to build a consensus around what it would take to accept that we've achieved that mode of action and know what we're gonna do with that, once we've interpreted that, then at

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least we've carved off a huge lay of the land. Have we got everybody covered? No. It just...I, I think that's getting at that question that's not gonna be that simple. But I think if we can begin to get our arms around these modes of actions and reach a consensus as to, once we have that data, what are we gonna do with it in a public policy kind of an application? At least we've cut a lot of it away. We can continue to fo..., focus our research efforts on trying to develop additional modes of actions. What do we do with that other bin, so it's not, doesn't remain another bin?

DR. SNYDER: I appreciate that comment. Thanks. Because it's, it jibes with what, the kinds of discussions you see swirling around NIH which is silos of targets and trying to define intracellularly silos of targets because you can't do everything with every target, but it, what you just said to me, I captured that as silos of targets.

DR. HOLSAPPLE: I think it becomes kind of how we build and define a

mode of action, what, what it's gonna take to be actually go into one of those silos.

DR. SNYDER: Thank you.

DR. HOLSAPPLE: Knowing full well that they probably, it won't be that clean. As scientists, I think we get too bogged down in wanting to classify everything very cleanly and it rarely works that way.

DR. CARPENTER: Mark, go ahead.

DR. TORAASON: You mentioned consensus a couple times. Would you comment on how you might include validation in your process and where you see it might be an impediment to moving forward or...

DR. HOLSAPPLE: Validation is frequently kind of one of those bad words that I guess as a, as event scientists we want to steer away from, from test methods and whatnot. I don't, I think it's to try to build a definition of consensus into an understanding of what validation is is almost an oxymoron. I think consensus is more of a reaching an understanding in, in a conceptual sense and validation, I think, has got a lot



more rigor associated with it. I think that what we've achieved through the ICCVAM process, you know, which NIEHS and NTP have been a very active participant in setting that bar for what it takes to validate is, is pretty much the way we ought to be proceeding. I can tell you that some of the feedback I get from many of my industrial members is they, they want to shy away from the V word, especially shy away from the ICCVAM because it is such, such a rigorous standard. I, I think we, we can afford to have that kind of rigor to begin to accept that a, that a method is validated. If we can achieve that bar and then declare a method is validated, I think we really have done something that means it ought to be integrated into, into both the science and the public policy arena. I don't know if I answered your question or not. That was a tricky question.

DR. CARPENTER: Thank you, Dr. Holsapple. Oh, we have one more question or comment. Chris?

DR. PORTIER: It's not a



question. It's a comment. I want to thank Mike for coming out and giving us quite a substantial amount of material to look at and think about and I wanted you to know that we do appreciate it and I do have ideas of how HESI could help. So, I'd be very happy to talk with you at some point. Thank you.

DR. HOLSAPPLE: Thank you.

DR. CARPENTER: Our next speaker will be Dr. Ki-Hwa Yang from the National Toxicology Program of Korea.

DR. YANG: Thank you, Dr. Carpenter. Good morning, ladies and gentlemen. My name is Ki-Hwa Yang from the National Institute of Toxicological Research in Seoul, Korea. And then I also head of National Toxicological Research in Korea. NTP in Korea is just three years old. We started from 2002, so this year is just the third year. So we have not established fully, I mean, we just benchmarked the U.S. NTP. However, the structure is not fully developed. At the beginning of my presentation, I really appreciate U.S. NTP



for inviting me to speak in the NTP Public Meeting for its Vision. When I was suggested to submit a comment, I was hesitating what I would present and then I decided to explain what KNTP is focusing now. That is the medicinal herb problem. I'm going to introduce the status regarding medicinal herb in Korea. Many of you figured out what I, what I'm going to talk about in my written comment. In this presentation I would just show you some supplement. As I know, NTP also sponsored the International Workshop to evaluate research needs on the use and safety of medicinal herbs held in 1998. After then, toxicological studies for 15 items of herbs and herbal, herbal complement have been performing. I think this area should be strengthened more by NTP because the Korea import considerable amount of dietary supplement from, from the U.S. Herbal medicines literally growing in economic importance. One market size would be about 43 billion dollars. The market size of herbs in Korea is estimate, estimated, I, I

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just...300 million U.S. dollars and then imported sixty, 61,000 from foreign countries. There are 550 items of herbs, minerals and material from many more are listed on the KP and then North Korea has 446 and in Japan and 117, China has 564 and Taiwan has 364. This means so many herbs or minerals are used for traditional medicine. I would like to introduce the Korean traditional medicine in brief. KTM was ori..., originated from China but have been developing independently since Dr. Jun Heo is a very famous traditional, Korean traditional medicinal doctor integrated it in two series of books, Donguibogam, that were medical encyclopedia in early 17th century. There are three areas of pathology in these books: internal medicine, surgery and miscellaneous. The book was registered as the National Treasures. He also described medicinal herb, herb collection method, and examples of ancient prescriptions. He also described use of herb: decoction, pill, powder, extract or soak. He...and also acupuncture, moxibustion, exercise, et cetera. He

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organized by disease classification and each illness and also described with related case histories and prescriptions. In the end of 19th century, Dr. Je-Ma Lee, he also very famous KTM doctor, established constitutional medicine theories. In his theories he classified human beings as four constitutions and then he treated the patient differently according to the type of constitution. Oh, I'm sorry. Now I move...I'm moving to the problem in using medicinal herbs as discussed in 1994...6 International Workshop. There are so many problems in using herbs such as standardization, consumer education, herb/drug and herb/herb interactions, potential toxicity associated with high dose or prolonged use and sensitive subpopulations. In the case of standardization we have to specify the next. First, species of plant used, harvest schedule, storage methods, physical characteristics of raw material, methods for producing uniform extract, knowing which part of plant contains the desired bioactive component. Recently, WHO organized a forum on harmonization of herbal

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medicine. You can figure out the activity in web site www.fhhm.net. The objective of the forum is to promote public health by recognizing and developing standards and technical guidelines that aim to improve the quality, safety and efficacy of herbal medicine. The member countries, region of FH...FFHH are China, Japan, Republic of Korea, Singapore, Australia, Viet Nam and Hong Kong. In this table I'm going to show you what KNTP studied. KNTP performed simple studies to figure out causes of toxic hepatitis in Korea in 2003 from March to October. During the eight month period, 55 patients were admitted to the hospital due to toxic hepatitis. Most of them suffered from using herbs, here, and then with this simple study we estimated about 1,500 patients would be treated annually. There is some difficulties handling herbal poisonings such as documentation of the health effect, the determination of a cause-effect relationship, the identification of the proprietary substances and active ingredients, the characterization of the

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kinetic pattern and tox/path effect, the uncertainty of the prognosis and treatment. I'm going to skip this slide. There are four types of risk factors of herbs. The first is natural toxin. For example, Chuanwu or Caowu which contains aconitine could evoke neurological and cardiovascular toxicity and the next is adulteration with heavy metal and western medicine such as steroids, NSAIDs, CNS stimulants, diuretics and antibiotics. Thirdly, contamination in botanical product such as pesticides, molds and heavy metals. Current research areas of KNTP, just like U.S. NTP because we just benchmarked U.S. NTP, chemicals, carcinogenesis, herbal medicines, mycotoxins and toxicogenomics. We are just focusing the herbal medicine part. KNTP performed the five herbal tests for 90 days toxicity studies in 2003, Pueriaria Root, Glycyrrhizan Liquorice Root, it's very difficult to pronounce, Pinellia Tuber, Safflower Seed and Aristolochiae Radix. I can just, just show you some, the result of the study. This is the preliminary data of a toxicity testing

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of safflower seed, seed. We did not expect the result. Safflower seeds which contain large amount of conjugated linoleic acid and glyceride, are known to have effect on osteoporosis, bone fracture and cholesterol metabolism in Korea. Through the study we found that there are dose dependent decrease of liver weight; however, other internal organs were unremarkable. I think you can... here you can see that, ahhh, liver weight is decreased in dose dependent. Microscope, microscopically there are no significant pathological changes in the liver other than somewhat dilated sinusoidal space, compared with the control, just seems to be a little bit dilated sinusoidal space, sinusoidal space and here's the just control. There are no definite abnormal findings including critical and anatomical pathology other than dose dependent-decrease of the liver weight. So we should investigate the mechanism of decrease of the liver weight. On second case... you may know this case. Nortier reported this summary in the New England Journal of Medicine in 2000.

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Urothelial carcinoma associated with the use of the Chinese herb Aristolochia fangchi. The course of the disease or instant, the company used Stephania tetrandra as the source material. However, Aristolochia fangchi replaced it in sometime because both plants look like very similar. 18 out of 39 patient had urotherial carcinoma and then the patient also has, had the Chinese herb nephropathy, a unique type of rapidly progressive renal fibrosis. It has been described in 100 young Belgian women who had followed a slimming regimen containing some Chinese herb. Aristolochic acid became of toxicological interest after the discovery of its nephrotoxic, mutagenic, and antifertility effect. We performed a 90-day toxicity study for aristolochic contorta which contained aristolochic acid. This is a clinical dose, usually used for patients. Here we can see the definite failure of the weight gain in dose dependent. So it seems to be a very effective dietary regimen. And then we found, we found pre-cancerous... here we can see the hyperplasia and even

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occasionally in the high dose case cancerous lesion in the renal pelvis on the left in the high dose group. You can see the normal pelvis on the left and then in this slide you can see the focal hyperplasia, moderate dysplasia, and even the transitional cell carcinoma we observed. So with this kind of experiment the KNTP plans to establish the standard toxicology test for, for medicinal herb to make a list of medicinal herbs for toxicology, toxicology study according to reviewing literatures and nationwide surveillance for herb poisoning to set up the standard method for preparing the medical herb material, medicinal herb material, to set up a special condition for investigating the toxicities, and to investigate the mechanism of toxicities. Thank you very much for your kind attention and I really appreciate the U.S. NTP for inviting me to present my comment. Thank you very much.

DR. CARPENTER: Any questions for Dr. Yang?

DR. BIRT: Yes, Dr. Yang. What approach are you going to use to decide

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on the doses that you're going to use of your herbs, or the doses of the toxic or active constituents?

DR. YANG: We usually used, I, you mean, I mean the, use the dose at, at pro..., pro..., proving that it test and use the clinical dose with constant rate to increase the dose and then there is, if there, there, there were no toxicity just we used the two gram, two gram body weight.

DR. BIRT: Do you begin by considering human exposure?

DR. YANG: I'm sorry?

DR. BIRT: Human exposure? The dose that people are taking?

DR. YANG: No. Actually, the, the, the items we choo..., we chose was the rising consumption drugs and then some, some herbs was known as I mean having toxicity in the literature.

DR. CARPENTER: Seeing no other questions, thank you, Dr. Yang. I think at this time I'd like to take a break and have about a ten minute break, come back about 10 minutes to the hour, please.

(WHEREUPON, a break was taken.)
DR. CARPENTER: Welcome back. Our next presenter is Dr. Richard Becker from the American Chemistry Council.
DR. BECKER: Thank you. Again, it's a pleasure to be here today. I want to thank NTP for their vision in organizing this meeting and other meetings along this line. I, my, my comments today... you should have received the written comments that I submitted last week or, or so ago. And those, those provide much more detail than what I'll discuss today. I'm gonna take kind of a 30,000 foot level view and then maybe a 5,000 foot level view, recognizing that there's a lot in between there. And I think that the processes that Dr. Portier talked about in terms of getting from where NTP is today to, to where he'd like them to be next fall, are well positioned to, to make the transition, to, to articulate the vision at the 30,000 foot level and to take it down to the lower level as well. So, I, the one thing I didn't, did not want to, to leave the impression



with is that the comments that I present today are, are, are simply all of the views, or the entirety of the views of, of the American Chemistry Council, or myself in particular. Obviously, as, as the, the reports are developed from the subcommittees, as new information is brought forward and others, and as, as we have an opportunity for additional stakeholder input and interactions, we and others I'm sure will engage more on, on some of the details.
But let's start with, with the... it's kind of overarching or the 30,000 foot level view. Clearly, it's both timely and important for EPA to focus, as they have indicated, on identifying new tools, techniques and capabilities utilized to bring those, those methods to bear on the important toxicological and public health issues that we're facing. I may make a little bit of an editorial comment. It is, it is amazing sometimes when we step back and look at where we're at in the field of toxicity testing and evaluation to realize how little progress we've actually made in



the test methods that we utilize in the last 40 or 50 years. And, and I'm, I'm trying to, to, as a toxicologist I think I ask myself why is that. And I think what, what it is is we've not engaged as effectively as we can with broader parts of our communities, including the regulatory areas, to think about understand..., how we can implement better mechanisms of, of toxicity into decision-making. And again, I, I'm pleased to see that, that NTP has planned for additional opportunities for public review, comment and, and discussions. Dialogue is always critical, and, and we've had some discussion already today about education and outreach and clearly these types of fora are, are, are critical for that. You, you can't just change, you have to plan for change. So partly what goes into this vision is the transitions that need to be made in planning for change and I think that needs to be developed with an opportunity for clear public involvement and discussions.
NTP is very unique. It is an



interagency program and as such it has the vision that, the effort that NTP is undertaking at the present time has great promise to really promote and enhance the scientific cooperation, harmonization and efficiencies across agencies in the federal government, particularly in the development and application of new tech..., tech..., technologies, new methods in toxicology and risk assessment. We encourage and support the focus on mechanistic approaches for hazard characterization and risk assessment. And indeed, we do support and think this is another opportunity for NTP to, to demonstrate its leadership to develop standardized and validate new, revised and refined methods that can have a potential to, to reduce or replace laboratory animals.
So that's at, that's kind of at the 30,000 foot level. Some specific recommendations I'd like to put into focus today are, are really two here. This, as NTP looks at new technologies, new methods and, and trying to figure out how they fit into the programs, how they become utilized,

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how this, we've heard some discussion about a paradigm shift occurs, to consider the need for, for, for validation and where that fits in with new test methods that they plan to use. And that specifically with genomics, I think genomics is a great promise for all of us in this field. But how could NTP, what, what additional work could NTP do, plan to do today to help to insure that, as it's developing, those results become utilized, both within NTP programs and more broadly across the other agencies that are part of NTP.

So let me just take the first one, ah, validation. Validation of new, revised and refined test methods is required under the ICCVAM Authorization Act of 2000. I'm not a lawyer so I can't go in to all the details of what that Act entails but, suffice it to say that NTP through its Center for Evaluation of Alternative Test Methods is well situated in position to conduct such high quality and scientifically rigorous validation studies as they're needed. As these new methods move from,

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from the investigation bench to standardization and then eventually on the, on the verge of being perhaps pulled into a formal testing program, there's a need to make sure that the test methods are valid for the purposes that they're intended. And this validation, by necessity, needs to be a priori not a posteri. So it needs to be conduc... completed prior to incorporating these assays into the routine testing programs. Why is that? Because it establishes the relevance and reliability of those test methods, and validation itself is a process whereby the information is made available that's needed to interpret and understand the significance of the results.

Validation must address mechanistic relevance of the method to the endpoint of concern in humans, and here for example carcinogenicity. But it could be any endpoint. So you have to understand the mechanistic relevance of that endpoint. I spoke about reliability and reproducibility. Clearly specifying the criteria for appropriate use in the limits of the, of

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the, the, the test method. Strengths, limitations and uncertainties in the data interpretation. When you know what a positive clearly is a positive, when you know what a negative is and what it means, and when you have some equivocal results, need to be established before these test methods move into routine use. And then clearly here's one that, that, that is a challenge to all of us in looking at moving new and revised methods from the laboratory bench, research bench, into a routine testing program. It's providing this, this keyword sufficient data to permit the appropriate comparison with the proposed substitute and I think Mike already mentioned this issue about really looking at how you could obtain data that satisfies that question so you could really substitute a test method rather than adding on as an additional test method. And it may not be just a method, it may be a battery, as we've heard earlier.

So that's kind of some thoughts on, on... let me go back to, to validation. I think one of the key take-away messages I'd

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like to, to leave here today, and it's in the written comments but I didn't put it up on the slide, is that the importance of considering validation and the process of validation as you're looking at development of new methods. Now, now this becomes very difficult in practice because you're looking at something that's at the research bench early and maybe later will get brought forward into the routine testing program. But I think NTP as they go forward with thinking about the vision, needs to think about some critical methods that they're, they're, they're looking at. Genomics may be one, there may be others as well, or high throughput and think about what would be an appropriate validation approach for these methods and then to program in, if you would, a discussion of that and implementation of those validation steps early in, early on in the process so that when you're ready, or think you're ready to implement that in a testing paradigm, that information is available and there is consensus that the method does what it says

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it's supposed to do, that perhaps you can indeed substitute this method for an alt..., as an alternative method. But the point is that this needs to be thought of early in the process or, and not at the end of the process, leave it at that. And I think oftentimes we've, we've kind of tried to tack validation on to methods development at the end and then that creates problems.

Genomics. Genomics, as I said, has great promise, but there's still a lot to do. A lot is underway and I don't want to give the impression that, that folks haven't, these are, you know, folks haven't thought about some of these ideas and that these aren't already being addressed in some way, shape or form by various organizations. But I think that, look at these, these areas of, of additional research and think about is NTP as a unique entity where it's situated in the federal government, how it might be able to truly move the ball forward that benefits not only NIEHS but also the other agencies that are participants in NTP and the general public and the industry as well.

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So certainly looking at the framework of genomics, looking at a framework for use of genomics within, within the paradigm of risk assessment is, is clearly needed. Recognition that if you're gonna look at genomics in the area of epidemiological studies there needs to be an ability to obtain and keep information on samples from large and diverse populations. And of course there are other issues related to genomics that go beyond kind of the strictly the science and having been made to think about creating a stiua... or creating appropriate fora or venues for discussion of these as part of the scientific process of methods development and application. So focusing beyond the science is needed clearly in genomics.

One of the areas that just... I think comes down to a specific recommendation where NTP I think can help in the shorter term rather than a longer term, is this issue of looking at platforms and, and establishing best practices. We're, we're faced with a situation now with genomics

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that there are no clear guidelines for, for correlating qualitative or quantitative changes with potential for adverse effects. So, so additional work needs to be done to understand the application of these methods within the toxicology and risk assessment framework. But, given at the speed at which the methods are evolving, it's probably not appropriate to recommend standardization or validation or it may be not, probably not even practical at this time because of the, the evolution of the technologies. But what, what we do suggest is NTP or others engaged in this process consider developing best practice guidelines for conducting and reporting these assays. And for example, on noting experimental conditions in the refer, research plat, platforms, robustness of the information. And then guidelines for communication, audience-appropriate communication for the assay results.

So with that I'll, I'll end by just saying in summary that it's appropriate for EPA, or for NTP to be undertaking this, this vision, discussion at the present time. We

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look forward to participating in future, future meetings and we think that the process as, as has been described will be one for which all of us within the different communities that we represent will benefit from, from this effort in the long term. Thank you.

DR. CARPENTER: Thank you, Dr. Becker. On his way back to his seat, George is ready to ask a question. Go ahead, George.

DR. DASTON: Rick, thank you for your comments. In terms of, of the genomics and standardization, you know, there are the Miami standards that have been developed and there is a draft of Miami standards for toxicogenomics. Is there any effort that you're aware of that is going to move beyond those standards to provide the kinds of minimum reporting requirements that, that, that you'd like to see?

DR. BECKER: I guess, George, I'm not aware of any and this is, what I'm, what I'm suggesting is that there is a gap there. Not only for reporting requirements

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but think about the use of this information across different agencies that comprise NTP and others that might utilize the information that's developed. So I think there is a real opportunity here for NTP and the agencies involved in NTP to take a leadership role in fostering best practices of use and communication of the results from these new techniques and technologies. So, I think it's an opportunity that, that should be explored within the vision and, in fact I'm sure it is, is being explored.

DR. CARPENTER: Bill, did you have a comment?

DR. ALLABEN: I'd just like to ask a question. Bill Allaben, FDA. You focused a good deal on validation and mentioned the ICCVAM process. I would like to ask a question whether you believe the current bioassay, as we know it, is a validated process?

DR. BECKER: Was that a loaded question or not? I think that as we go forward and look at... I'll answer it this way. As we go forward and look at

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developing alternatives and substitutes, you have to benchmark against something, okay. And we have years and years of available information on that assay. So, in particular, if you're asking the question can we substitute a new or alternative assay for this assay, then you really have to ask the question what is the information that I hope to gain from this new assay that, that is correlated to, or relevant to, what I understand about the old assay. So clearly in the case of laboratory animal models for, for carcinogenicity we have established relevancy to humans. You know, virtually every human carcinogen does produce cancer in a model or another. Now that doesn't mean that every chemical that produces cancer in, in, whatever dose level, by whatever mechanism in an animal has a carcinogenic risk, poses a carcinogenic risk to humans. But there is relevancy of that model. So the real question here is to tease out, as is being done with transgenics and others, the specific question that you're asking of that model and making sure it can perform

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within that, that framework. So I think I've answered your question along that regard. I'm not sure that we're ever going to say does this particular model replace the rodent bioassay for all things. But provided that you can get more mechanistic information and use the results of that model, and it is validated, use the results of that model for a specific purpose that it's intended, I think you can use, use that information.

DR. ALLABEN: Could this be more significant scientific agreement than a validation process, then?

DR. BECKER: Well...

DR. ALLABEN: Because I see if you, if you plug everything through the ICCVAM mechanism you're gonna be ten years or out before you really get wherever the NTP wants to go.

DR. BECKER: Yeah, I think you have to look at the ICCVAM mechanism with a viewpoint of principles in mind and that, yes, there is a need for scientific consensus and that's essentially what ICCVAM

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provides. There also is a need, critical need for quantitative data in order to judge the, the reliability, the reproducibility of the model. In terms of a formal ICCVAM process, I think what's necessary in some, what will be necessary, is to be able to approach this from a, both a pragmatic and a scientific mind at the same time, to recognize that flexibility will be needed in order to satisfy the principles of, of, as, as articulated by ICCVAM method for, for validation. I'm not quite sure that you will ever be able to articulate, or as you point out, Bill, to, to obtain the, you know, an N of , of 50 or 100 for some of these in vivo types of assays in a realistic time-frame. So you need to be creative. But I think that's where one can be flexible but still be true to the principles and, and that's what I would hold, hold as an important goal. On the same, you know, at the same time though, we don't want to end up with, and this is, and others will speak on it, we don't want to end up with the double standard of demanding a certain level

of compliance for lack of a better term in a validation process for a substitute, particularly non-animal studies when you have a different level of compliance, if you would, from a scientific basis other, for animal studies. So that, that's an area that, that requires some balancing. But I think it can be done and, and, you know, obviously the, the processes that are, I guess I will make it commercial, the processes are in place for, for these types of dialogues to occur. The, the FACA committee for, for the alternative methods is one place, the interagency group, ICCVAM is another. Where these, these opportunity for dialogue to solve some of these problems. I just think that more openness and recognition that some degree of flexibility is absolutely necessary, is a key.

DR. CARPENTER: John.

DR. BUCHER: Yeah, I wanted to follow up a little bit on the validation issue. The vision as it's stated implies a movement from a disease-based model to mechanisms-based models and I was wondering,



to me that, that provides some inherent difficulties in, in validation and the way that you've been talking about it. Is there a, is there any thought that you've given to how one would use the principles of validation in developing mechanism-based models that could be used for informing public health on a, on a different level than a disease-by-disease basis?

DR. BECKER: I think there, there, there are ways to go about this and one, one I, I guess what I would say is that I don't have specific recommendation, to be honest, I don't have specific recommendations to make today. But I think if you look at some of the, some of the work that's been done with the genetically altered mice, mouse models, the transgenics, and think about what, what the questions that are being asked of those models in terms of what they're capable of predicting in, in terms of response to, to exposure, I think you can begin to use that information to, to ask how could we use the ICCVAM principles with such, these types of models



in, and I think what you need to do is, in an evaluative framework. Not separate from but within that context of the evaluative framework. So this is where I was talking about, it's a little hard when you're taking a, a bench research methodology and trying to project ahead and think about how it might fit in with the framework. But if you can think about the framework and then say this is a type of method that we need, then you can start, or we have, and then you can start asking the questions about, well, what does validation mean in terms of use of that information within the evaluative framework and I think that's probably the best way to go.

DR. CARPENTER: But again, I would also get a plug in. I think these types of discussions will be very good to engage the ICCVAM FACA. I'm sorry, I don't get the term right. It's a, the, the other, the Alternative Methods FACA on, on, on these types of discussions. Rather than simply trying to say, you know, we need 20 test articles and, you know, three different



laboratories, and, you know, et cetera. I think that's, those types of details would be, are... need to be worked out for certain methods but for other approaches you need a more thoughtful process.

DR. SNYDER: Regarding validation. How much validation should be done at taxpayer expense as opposed to validation that should either be done in the private sector voluntarily versus be required? You have any thoughts about that distribution of effort?

DR. BECKER: I'll reserve comment on that. I haven't really thought about that but I think that it's probably a good question to, to, to think about as, as the vision moves forward. There are certainly clearly indications and opportunities for partnerships and we've seen this earlier, my, my memory's come back. We've seen this with other alternative methods that have come forward for, for development, standardization and validation. So I think exploring opportunities for, perhaps this is a bullet under this methods

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validation effort, to explore opportunities for partnership across sectors is a very good placeholder for further discussion.

DR. CARPENTER: Go ahead.

DR. HOLSAPPLE: Just a comment about that. I think the, the biggest success that ICCVAM has had, this is Mike Holsapple from HESI, was the local lymph node, which was really the first time we really worked through that process, and, and a lot of that data was really developed by the private sector. A lot of the industry labs who had an interest in trying to make sure that that assay was accepted for a variety of reasons, so a lot of that work, in terms of what, what we as the public had to support, I think there were some government labs that contributed something but the yeoman's share of the data that went in to at least the local lymph node ICCVAM approval process was generated in the, in the industrial sector and the academic sector.

DR. CARPENTER: Chris.

DR. PORTIER: I don't

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remember the exact date but Dr. Wolfe will I'm sure, we have a SACATM meeting sometime in March or April of which this is an agenda item on that meeting to discuss exactly those issues. I will point out a few things because validation is a very difficult concept in this regard. First, if you're thinking about high throughput versus non-high throughput, you've got a completely different concept of what might constitute a validation and I think thoughts you might have in the future on that, as you think about this, would be very useful to us. In addition, in some cases we may be specifying a target that's not necessarily linked to toxicity but linked to a particular mechanism and to what degree would you validate something like that up front versus validating its link to a particular target at a later time. Are things that would be... we will be presenting to SACATM as things that we need them to think about in terms of our overall validation process. Some of these came up when we were looking at transgenics; they again raise their head

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as we look at this issue and it's clear that we have to have a broad-based scientific discussion about what's gonna constitute regulatory acceptance of a testing method that may include a suite. It's a difficult issue.

DR. BECKER: Let me just make, one, one last comment, if I can. I think one, one of the areas that we have to remember is, is for the purposes intended, it's kind of where you get at with this method, and, and one could well envision a particular, for example, a through... high throughput method being for priority setting or screening purposes, which, which is a different purpose, the outcome of which, you know, you, you would use that information for a different purpose than, you know, what's another example, citing a regulatory threshold. So I think that, that oftentimes because the discussion is not focused on what's the intended purpose, which gets to this issue of framework, you know, you get into a cart and horse situation of, or a chicken and egg is probably a better way of

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saying it, which comes first. And, and so I think it's important to articulate a framework and think about the method, and that method may work in one framework or may work in different frameworks, and they may have different requirements but I, I think it's important to think about the method within the framework of use. So I, I do think that, and this is just a plug, it was very helpful when, when you presented the vision on the use of transgenics even though it's undergone some modification, I think, it was very helpful to see that because then one could then picture how that information output from the test methods would be utilized and that framework discussion has to go hand-in-hand with understanding what's necessary for validation.

DR. CARPENTER: Mary.

DR. WOLFE: I'd like to invite everyone to the SACATM meeting which will be the10th and 11th of March. A Federal Register notice is in preparation and it will be held in Bethesda, at the Hyatt Hotel which is just one Metro stop down the

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road.
DR. CARPENTER: Any other questions or comments? Aaron?
DR. BLAIR: Using mechanisms and mechanistic models in a predictive sense says to me it means we don't always need a, a bioassay and so my, my question is sort of how do you think about an issue where there's quite a lot of mechanistic information and no evidence whatsoever that this substance would cause a cancer in any organism? Would that be sufficient then to conclude that it's a carcinogen?
DR. BECKER: I think not. I mean I think not. And this has to do with probably the state of our understanding collectively, scientific understanding of the carcinogenic process. Remember, we're, we're moving in, we're moving our knowledge base forward in terms of what we know about the overall process at the same time we're moving forward in our knowledge about the endpoints or the, the, the effects of specific chemicals along the chain of, of causality, if you would. And so I think

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oftentimes we've been, and this gets to I think part of the discussion that Mike talked about, this whole issue of how do we, if we don't know everything about a particular mechanism then are we in the state of knowing nothing and therefore not being able to use that information? And I think not. But I think it does create a dynamic tension because we don't always know which are the, the full steps of mechanistic, you know, mechanistic pathway or even sometimes which are the critical steps; we just know which, what a few are. But that shouldn't inhibit us from using that information but we have to use it wisely. So I'm not sure you can say if I say mechanism A then therefore, with the state of knowledge today, I can predict outcome B in even an animal model or even in a human at this, this time, whether it's carcinogenicity or reproductive toxicity or any of these other areas that we're concerned about. On the same time though, you can say that we shouldn't be held back, and this is where I wanna really, truly

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encourage NTP to move forward, we shouldn't hold back in our research, development and application of this information, but again I'll go back to this, within the framework. So you have to use that information wisely. One of the critical areas, and this is I, you asked, so I get to get on my soapbox a little bit, one of the critical areas that's important and as we develop new information on mechanism and in bringing this forward into, into decision making is to make sure that there's scientific understanding and, I won't use the term consensus, but very strong peer review and peer comments, if you would, on the quality and the significance of that information. And that's where, where one can then start building confidence as you make decisions on the science. And I think the example of the, the ILSI/HESI example of, skipped my mind, what was the receptor mediated, RPAR, or PPAR process is a good example of that. How you can begin to, how you can build consensus on mechanism and use of that information. But, but there you're going mechanism by mechanism. I, I

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think you're, you're stuck with that for now because that's a reflection of our current collectively understanding.
DR. BLAIR: Just to sort of follow-up on that. I appreciate your comments so... In, in, I'm not, realizing having mechanistic information provides a lot of useful information in a lot of ways but then it sounds like for sort of this one narrow thing of making a, a decision about, I think about cancer but I know other outcomes would be important, on carcinogenicity, the mechanistic information is not predictive, it's explanatory. If you can't predict and say, well, yes, all right, we don't know that liver cancer develops in anything, anywhere but we think the mechanism is, you know, whatever amount of information we don't need to see it. So, sort of your thinking is that it's not likely we would have that amount of confidence just in mechanistic information so it would explain what we know occurs in the whole organism but it wouldn't predict.
DR. BECKER: I think, I

think to a certain extent that's a good statement of where we're at today. I would hope that with, we'll be able to go farther with, particularly with implementation I think of some of the vision, of some of the elements of the vision that will be developed here. I, I guess I, just to make one last comment in closing here. I don't want to leave the impression that, with respect to this point about having to be predictive. It, it gets to the issue of the inability to do this kind of planning or vision outside of the risk assessment or the toxicology framework. And one of the areas that I think we've, we've, we've moved away from and that we have to get back to, particularly with, with the, these elements of mechanistic information, is understanding the relevance of, of dose response. So Mike's comments about trying to build in better ADME data earlier in the process and using that is, is critical. But also trying to think about, in the design and application of these new, new technologies and new test methods, where does dose



response fit in? Oftentimes we in the current hazard characterization process of carcinogen identification, we're just looking at a, you know, a dichotomy or, you know, an on/off kind of thing. It's either carcinogenic or it's not. I mean there could be equivocal evidence I guess or weak or limited, but it's really a signal or not a signal. But that's not how chemicals work and so what we should do in the vision is move away from that and look at areas of understanding and better including considerations of dose response. That's kind of an editorial comment. Thank you.

DR. CARPENTER: Thank you, Dr. Becker. Our next speaker is Sara Amundson from the Doris Day Animal League.

DR. PORTIER: While Sara comes up, I was asked to explain what SACATM is. It's the Scientific Advisory Committee for Alternative Toxicological Methods. It advises NIEHS and the NTP on the ICCVAM process and our research into alternative tox methods.

DR. AMUNDSON: That was



helpful. Thank you. Definitely. Well, I too would first like to thank...

DR. CARPENTER: Excuse me for the record. Can we get you to repeat your name and your affiliation?

DR. AMUNDSON: Certainly.

DR. CARPENTER: Thank you.

DR. AMUNDSON: Again Sara Amundson with the Doris Day Animal League and I've been working on these and related issues for the past 15 years, so I've seen rapid progress in some areas and, much as Rick articulated, very real concern over the lack of new method development to in fact replace those that have been utilized over the past 40 to 50 years. So I do have a markedly different perspective. Again, thank you to the National Toxicology Program for actually having the foresight to hold this sort of initial public meeting. I am looking forward to subsequent public meetings for an opportunity for perhaps more in depth comments on the basis of the reports that come forward from the sub-groups that have provided their initial concerns and initial



testaments today as to what will be taking place with this process. The proportion, the largest proportion of my comments today will be policy in nature, but I do have a few comments to make about process and that is the only reason I'm here today is I am on the ICCVAM list serve. If you take a look at the Federal Register notice for this particular meeting, you will note that there is no search term within that Federal Register notice that refers specifically to animal protection organizations as stakeholders as part of this process, nor does it specifically refer to alternative or non-animal test methods. Be that the case, keep in mind with the way that our federal government works and the way that stakeholders obtain information, we simply go to the GPO site, pump in our search terms, Federal Register notices that have applicability to those search terms pop up and we know what public meetings we need to be participating in. If I'm not considered a stakeholder, I'm simply not going to know that this particular forum is taking place

today and that subsequent forums will take place. Folks, that's a dramatic oversight. Granted, industry, the regulatory sector, the research sector of the federal and state governments and the environmental protection advocates and a variety of other folks are specifically mentioned in any of the communicating materials, but animal protection organizations were left out, so I hope that you will correct that in the future. In addition, I greatly appreciated the subcommittee reports, and the general sort of discussion has been very interesting from my perspective in addition to the four to five, four questions that NTP put forward as really provocative markers for getting us started thinking about this process for creating a vision for the NTP over the next 8 to 10 years. I'm most appreciative of that, but again, what is lacking is where is the three-hours component to each of these subgroups as a portion of a very real vision for taking toxicology forward in the 21st century. Be that the case, I hope that this issue will be comprehensively addressed on



the basis of clearly NICEATM already exists at NIEHS and certainly seems like it will be providing great commentary on what is transpiring with regard to the vision but my contention is it needs to be a backbone of this vision in moving forward.

Now at the risk of severely compromising the poor man's credibility, I must say that I am in large agreement with the vast majority of overarching goals and specific comments that Rick shared with you just previously. His points with regard to validation are well taken, obviously, particularly in our animal protection community and to that end I wanna address a couple of points that were raised. Please keep in mind that public law 106-545 which is the ICCVAM Authorization Act has set a new bar for toxicology when it comes to federal regulatory agencies and that is: a test method before it is recommended or required must be ascertained as valid, and we've got internationally agreed upon criteria for what constitutes a validated test method. The bar's been set and what



this means is heretofore you will find that any one revised or alternative method must meet the same criteria and, and generate the same robust data that's necessary in order for it to be truly incorporated into our regulatory scheme. Be that the case, as evidenced by the number of test methods from bench to federal regulatory recommendations that NTP takes genuine responsibility for, do keep in mind that there's certainly tax payers dollars that are going into validation efforts and those of us who closely monitor what's taking place with the federal budgets will certainly be supportive of those efforts to insure that, whether it's a public/private partnership or the federal government takes responsibility for insuring that test methods are assessed as valid, also have the resources available to them to perform those validation studies. That's truly, truly important from our perspective.

I also greatly appreciate Chris's comment with regard to high throughput methods and building on that I wanna just ask you folks to keep in mind with the



marked change in philosophy regarding toxicology and the move toward mechanistic approaches, do not embrace this philosophy at the detriment of existing correlative methods that may provide for refinements or replacements or reductions of animal test methods. We simply can't jump to the next level without utilizing some of those correlative methods that may be simply as predictive of what we're currently utilizing and I would hate to see, hate to see them obliterated on the basis of the thrust for mechanistic toxicology. I thought one of the very, very important points that was stated here is that the National Toxicology Program truly is a regulatory and research agency-wide coordinated effort. Be that the case, where is that same activity being built upon with NICEATM with regard to development and validation of non-animal or alternative test methods? We need a better home for that to take place. We've got the assessment validation stage covered. What we don't have covered is coordinated activity within the federal government for insuring

that we have got a home for this activity around alternative test methods. Further to that point, I thought it was very interesting in Chris's opening remarks too that he mentioned the great need and the function, frankly, that NTP can perform with training programs. I would strongly, strongly advise you not only to insure that training programs on actual use of test methods and also on reading data to ensure that regulatory agencies are actually accepting them in an appropriate fashion transpire at the federal level but also at the state level. Keep in mind whether it's Cal EPA or a variety of other states that have very, very strong regulatory programs in this particular area when it comes to chemicals that those folks need some integrated training to ensure that they are with the federal government reading data correctly. So, I strongly would support that.

In addition, I have a functional question and that is who funds the NTP? If you've got buy-in from all of those



regulatory or research agencies on one level, that's fantastic and clearly you've got extremely strong buy-in from FDA and NIOSH but is it NIEHS's primary responsibility to fund the NTP? Can someone answer that question? Chris? Can you answer that question?

DR. CARPENTER: Chris, would you like to answer that question or do you want her to finish? We'll hold the question 'til you're finished.

DR. AMUNDSON: Well, I greatly appreciate it, but that feeds in to a larger discussion and that is I do want the people in this room to keep in mind the fact that over the past two administrations NIH's budget has doubled. The fact is NIEHS's portion of that budget is minuscule. So if we're gonna have this broader dialogue for a vision for the next 8 to 10 years of what transpires with the National Toxicology Program, you're absolutely right. Question 4 has got to be answered, and that is where are your resources going to come from to insure that you can adequately address the



components of the vision that you're going to put forward at the end of this year. That said, I would greatly appreciate a response to that question and then outside of that I appreciate the time for comments and I'm happy to entertain any questions too.

DR. CARPENTER: Thank you. Would you like to respond?

DR. PORTIER: I guess I'll respond. By law the, the technical support of the NTP has to come from three agencies. NI...NIH, NIEHS, CDC, AP... CDC..., NIOSH and FDA and CTR. The largest mass of that, of course, is coming from NIEHS. But whether it's our personal responsibility or not, I don't know if that's the case.

DR. CARPENTER: Bill.

DR. ALLABEN: Bill Allaben, FDA. I noted your, your concern regarding how the information is disseminated and that people who are in the loop and review the Federal Register, et cetera, are aware of these types of meetings. And you had asked for correction to increase the, the base



that this kind of information is disseminated to. How would you go about doing that? What would your recommendations be to enhance that process?

DR. AMUNDSON: Okay. I think it's very simple. I appreciate you raising the point. One of the changes that could be made is, in the existing Federal Register notice for this meeting in parens specific stakeholders are mentioned, meaning groups are mentioned. Whether it's industry, federal regulatory agencies or environmental organizations, animal protection organizations should certainly be included. Obviously on the basis of when it comes to the field of toxicology the NTP utilizes more animals probably than any other federal regulatory or research agency. We certainly have a strong interest in what transpires. In addition to that, that same Federal Register notice, I hope as the, as the issues become further addressed in this chronological series of events to get to the point in the fall where there is the vision that's released, that there will be a stronger, shall we say a

stronger editorial component with regard to the three R's and alternative or non-animal test method development as a portion of the overall vision. And that would certainly help.

DR. CARPENTER: Any other questions or comments? Thank you very much, Dr. Amundson. Our next scheduled speaker is Dr. Robert Wright from Children's Hospital in Boston.

DR. WRIGHT: Thank you. I am Dr. Robert Wright. I'm a physician, actually a pediatrician. I work at Children's Hospital, Boston. I'm also an Assistant Professor of Environmental Health at Harvard School of Public Health and I'm actually here as a member of the American College of Medical Toxicology. I was asked by the college to come here to sort of introduce the college to NTP. So most of my talk is gonna focus on what the college is, and I'm going to withhold any scientific comments that I might have because I'm not supposed to represent, I'm only supposed to represent the college.



The American College of Medical Toxicology is a professional, non-profit association of physicians with recognized expertise in medical toxicology. So we're a different type of toxicologist than a basic science toxicologist; we're all physicians. Medical toxicology is a subspecialty which encompasses clinical pharmacology. All of our fellowships actually include pharmacology training and we focus on the diagnosis, management and prevention of poisoning and adverse health effects due to medications, occupational and environmental toxicants and biological agents. This slide actually doesn't include my field which is pediatrics; however, there is what, what it's meant to represent is there's overlap between occupational medicine toxi..., in toxicology in clinical effects of solvents, pesticides, and heavy metals and other toxicants.

To give an overview of how subspecialized we are, approximately 700,000 physicians are currently practicing in the United States. Less than 400 of them have ever been board certified in medical



toxicology, so that's far less than 1 percent. There are 300 members of ACMT who are physicians. All of them are board certified in medical toxicology. And currently there's about 40 medical toxicology trainees. It's a two-year fellowship, so approximately 20 per year graduate, which makes us a pretty stable number because that's probably close to the number that retire. Our members' interests are very diverse. Some are independent-funded researchers. I'm an environmental epidemiologist as I said and I study pediatric and environmental health. What I do is actually very different than what a lot of other members do. Others are primarily clinic..., clinicians. Most care for patients actually. Probably the majority mainly care for physic..., or care for patients and are emergency physicians. We care for patients across the life-span. Some are pediatricians like myself, but I also when I take call for the poison center in Boston, I sometimes get calls about elderly individuals. So I also manage their



care. And that's true for all medical toxicologists and we deal with both acute and chronic exposures. I work in the pediatric environmental health clinic so I see a lot of children with lead poisoning. I also occasionally see some other chronic exposures. I've taken care of children with manganese poisoning and, in fact, that actually stimulated my interest in manganese and I currently have a birth cohort in Oklahoma which is meant to study manganese toxicity. And as I said, we're all clinical pharmacologists as well.

These are some examples of some of the clinical problems that ACMT members address. We take care of people with unintentional and intentional drug overdoses. We also take care of patients with hazardous exposure to chemical products, either via consults or directly in the hospital. We also take care of patients with drug abuse, also withdrawal from drug abuse. Envenomations, I have to admit since I work in Boston, I've actually never taken care of a snake bite; however, there are members who

do, particularly if say you happen to work in Arizona; ingestion of food-borne toxicants and toxins is also something we address. Botulism, marine toxins, such as paralytic shellfish poisoning and ciguatoxin. Toxic plants and mushrooms are actually a very common complaint that we address and we sometimes also do independent medical examinations. Obviously, because I'm a pediatrician that's, that's less of my particular care but those of us who are occupational physicians do do that. And one of the things I added to this list was that we do take care of people with drug/drug interactions and sort of as, as my one, my one scientific comment, one of the things that I didn't see addressed in the NTP vision was the idea that chemical exposures need to be addressed. Certainly pharmacogenomics and toxicogenomics are very important and a lot of the susceptibility to drugs is likely due to genetic susceptibility; however, other than a laboratory animal virtually no one is exposed to a single chemical and I think one of the



things that we need to do if we really want to understand and be able to make predictions is to look at chemical mixtures.

Medical toxicologists provide professional services in a variety of settings. We actually have people both in industry and in academics. Most of us work in emergency departments, ICU's and other in-patient units. Some work in out-patient clinics like myself. Most of us are associated with the Poison Control Center and most of us also work at medical schools and universities. Some actually work for regulatory agencies and government agencies such as ATSDR, CDC, FDA and actually Dr. Snyder works for NIH at the National Library of Medicine and he's also a member. And even among physicians our group is very diverse. I put pediatricians first because that's me; however, the, the most, the most common profession is actually emergency physician probably followed by occupational medicine physician and we're probably third. Interns and pathologists are also members of ACMT and as I said, most work in academic



settings, some do work for industry. And so we actually have a very broad political spectrum, I guess so to speak, in terms of what our biases may be but we all have to get together and work together and I think that makes us a little more tolerant.

So are there mutual interests between NTP and ACMT? I was sent here because we think there are. ACMT members are clinicians who care for people with toxic exposures, both acute and chronic. We believe that no other group will have such access to patients and I think the potential exists for partnerships for exposure monitoring to serve as a source of exposed patients for clinical studies. I think there are potential for collaborations to contribute to databases of clinical effects from toxic exposures. Particularly unusual toxic exposures. I can tell you that if there ever is a outbreak of an unusual toxic exposure an ACMT team member, if he is local, he or she is local, is very likely to be consulted by either the Board of Health or the hospital.



And I think getting to the issue of toxicogenomic epidemiologic studies, this, this interests me because I am an epidemiologist and I think a lot of the issues in toxicogenomics are very different than in pharmacogenomics. Obviously pharmacogenomics is going to be studied in the context of a randomized control trial where you have baseline data and you have the effect afterwards and you could look at the delta. In toxicogenomics first you have to identify someone who's been exposed. There's never gonna be a randomized control trial of a toxicant for ethical reasons, for very good ethical reasons. So they're gonna have to identify them, you're gonna have to measure the phenotype and you're gonna have to have some certainty in those measurements, as well as measuring whether or not someone's exposed. And I think it's gonna be a lot more difficult than pharmacogenomics and I think partnerships with the physicians who actually see these patients is going to at least help in some ways in both in the exposure measurements and in the phenotype

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measurements.
ACMT members have a long history of serving as consultants to government agencies. We actually have a contract with ATSDR where we've produced some case studies in environmental medicine. Other case studies include immunotoxicology, especially with respect to Lupus. I actually co-wrote the pediatric environmental health ATSDR monograph and there's also a monograph pending on Iodine 131 exposure. And we've also worked with the CDC. We're consultants to the National Environmental Exposure Report for the National Center for Environmental Health and some of us have served on NIH panels as well. So an example of collaboration with federal agencies, ACMT has had a collaborative, or cooperative, agreement with ATSDR for several years now. As I mentioned, this is where the teaching monographs have come about. But we've also worked with ATSDR and partnered with them in educational symposia at national scientific meetings. We've developed an Internet base for a teaching resource and we've also done

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up a national network of public health consultation for incidents of mass chemical exposures and chemical terrorism. Also the pediatric environmental health unit that I work in in Boston is partially funded by ATSDR and we're to be a regional center for pediatric environmental health referrals.
This is an example of the National Consultation and Education Network. These are the individual members of ACMT who are responsible for different geographic regions in the United States. So this is an example that Michael Kosnett, who's the President of ACMT, asked me to present. He had looked at a recent monograph that NTP had put out on methanol exposure and human reproductive effects and he had some concerns that there was no medical toxicologists on the panel. This is not meant as a criticism but sort of as to point out that ACMT expertise can complement the expertise which was already on the panel. ACMT members care for hundreds of people annually exposed to methanol as well as other toxic alcohols. So we have a lot of experience in determining what the

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clinical effects should be and whether or not, and also in the management of patients. There actually are FDA approved treatments for methanol toxicity and we're very familiar with the uses of those drugs and their potential side effects. And we're also, because this was a human reproductive effects, there are pediatricians and developmental toxicologists in our organization, and I think we felt we could have contributed quite a bit to such a panel.
In summary, in terms of the, how the ACMT and NT..., NTP could network, we are a physician organization with very diverse expertise in all facets of toxicology. We're very dedicated to public health. We already have at least the beginnings of an infrastructure for collaboration in human studies because we are geographically diverse and we are the ones that, we are the physicians that see the patients who have toxic exposures. Also we can be a potential source for clinical diagnosis and expertise on the management of exposed populations and

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a source of toxicologic, pharmacologic, and epidemiologic expertise in human exposures in general. This is contact information for ACMT and I believe this will be in a handout that will be passed out and this is contact information from Michael Kosnett who is the current President of ACMT.
DR. CARPENTER: Thank you. I'm sure the NTP appreciates your offer of assistance. Are there any questions for the speaker?
DR. SNYDER: Just, just a comment. First of all, nice presentation letting this audience know what medical toxicologists do. I serve on a couple of committees of that college and I applaud your presentation. It was very well done. With regard to clinical toxicological data, the rubber meets the road of challenge. Over the last 15 years the NTP advisory groups and participants ought to know about is that the American Association of Poison Control Centers has been sitting on a mountain, a true mountain, of clinical toxicological data for many years and

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unfortunately the individuals who are in charge of that database, that mountain of information, have a challenge on their hands because a great deal of the support for that database comes from the pharmaceutical industry and the pharmaceutical industry has threatened, on numerous occasions, to pull its, pull its support for that database should too much of the data that's in that database be allowed to be accessed by investigators and other groups. That's the challenge, the difficulty at the moment. So I would alert this audience to that particular challenge at the moment for, for liability or for other purposes the pharma has not made it easy for the, the clinical toxicological data that exists in this country to be mineable in the way that it should be. And it is a source of great concern and friction within the clinical toxicology community.

DR. PHIBS: Actually, that's interesting information for my question. I was wondering if there are untapped sources of the types of human data you work with

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that could guide NTP research identifying flags, chemicals of high priority.

DR. CARPENTER: Identify yourself.

DR. WRIGHT: Other than...

DR. PHIBS: Pat Phibs, BNA.

DR. WRIGHT: Pardon?

DR. PHIBS: Pat Phibs with BNA.

DR. WRIGHT: Other than the AAPCC database, I'm not aware of a national database. Certainly each individual poison control center keeps its own records, but they do submit them to AAPCC and they're a part of the national database.

DR. SNYDER: I'd like to respond to that to help you out here. At the AAPCC clinical toxicology meetings over the last two years there have been a couple of abstracts where a couple of investigators have gone out into cyberspace and attempted to identify, internationally as well as nationally, various databases of clinical toxicological information including that which is searchable. One of the abstracts

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indicated about nine or ten sources of information of clinical human data were allegedly available but the problem is is that virtually none of those databases are searchable at the moment and again, very difficult to access the, the clinical human data that's out there.

DR. CARPENTER: Mary.

DR. WOLFE: Mary Wolfe. I appreciate you bringing the awareness of your organization to us. Is, does your website have a, a registry of members with their expertises and so forth identified should the NTP be looking for a certain type of expertise for someone to serve on some of their panels?

DR. WRIGHT: I think probably the, the best place to start if you were looking for someone would be to contact Dr. Kosnett and... because there is a great deal of diversity in terms of our expertise and we're a small enough organization with only 300 members that he knows just about everybody. I think he picked me because I have some funding through NIEHS although I

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have no funding through NTP. But he knew that. And, and if you had somebody with a specific type of expertise in mind, if they were in the American College of Medical Toxicology he would likely know. Our membership also has a list serve in which interesting cases are presented to the members in general and they get input from other members. So if there is ever a clinical issue that you wanted addressed, even if Dr. Kosnett or others didn't know directly the answer, it would be very easy to disseminate that information to virtually every member.

DR. SNYDER: Mary, that, that list that he just pointed out does exist. I actually helped participate in creating that list a few years ago and it is updated by ACMT.

DR. WRIGHT: It's very, it's very common for a member who has a very unusual case to submit that case and elicit opinions from virt..., members all over the world actually.

DR. CARPENTER: Are there

anymore questions for Dr. Wright? Thank you very much. Our next scheduled speaker is Dr. Troy Seidle from the People for the Ethical Treatment of Animals.

DR. SEIDLE: All right, thank you. Again, my name is Troy Seidle. I'm science advisor with PETA and as most of you will know, PETA is opposed to all animal testing and research which has often put us at loggerheads with federal agencies in the U.S. and around the world which is why we were so delighted to see the NTP's vision document as one of the first examples of hopefully an effort in the U.S. to start moving away from traditional paradigms in toxicology and towards more humane and more scientific methods of evaluating toxicity.

As previous speakers have pointed out, the, the move towards alternatives is not always the same as moving towards non-animal test methods and clearly non-animal methods is what PETA would like to see the NTP pursue quite clearly under this vision and hopefully the, the resources that will be put forward in completing this vision



will not be insignificant in terms of the development and validation of non-animal, be they in-vitro and silico or other types of toxicity testing methods.

In particular, PETA does have concerns about the, the move towards transgenics. Although you will often see some reduction and refinement in the use of animals it is not a true placement and in terms of the prioritization of the funding and the allocation of resources we'd like to see transgenics ultimately lopped off the agenda and greater resources, certainly in the in-vitro, the computational as well as some of the omics technologies. We were very pleased to see the, the language in the vision document in terms of the development and validation of new and refined methods as being a priority for the NTP. As Sara Amundson had pointed out, this has really been a gap in the United States, whereas in Europe we have the European Center for the Validation of Alternative Methods, which serves a very valuable coordinating function among all the member countries to really



coordinate all of the research and development efforts. We really don't have that in the U.S. We have disparate federal agencies with very different priorities, very different regulatory agendas, who are all doing their own thing in the R&D side and even though we see far greater federal resources being spent on alternative method development in the U.S. than in Europe, we see much less bang for the buck because these methods are not adequately coordinated and we still have gaping gaps in the various research agendas to develop tier testing strategies that could ultimately reduce and replace the use of animals for specific endpoint studies.

So the NTP is in a unique position to help to serve this kind of coordinating function. We have seen some effort on the validation review side through NICEATM, through ICCVAM but we really don't see that on the very beginning end whether it be in the basic research side, method development, pre-validation and validation. So hopefully, as Sara had pointed out, this will become



much more prominent in future iterations of the vision document. What we would ultimately like to see with the NTP is the, far greater coordination, not only between agencies in the U.S. but also internationally. This is a global problem, animal testing, in our, in our view, and it also requires a globally coordinated solution. So, ultimately coordination through ECVAM would be extremely helpful to facilitate this process, both to identify methods and technologies that are already in use or under development in Europe as well as gaps, issues that the NTP would like to see targeted. There's a great deal of work on the in-vitro side in Europe but less so on the mechanistic. So to see how some of these gaps can be filled, how efforts can be better coordinated, we'd, we'd like to see that further developed in the future. And ultimately we'd like to see, when the final vision document is produced, some sort of, shall I say, hit list of methods, of endpoints, as targeted as possible to, to really have clear goals that can be

evaluated, the success of which down the road five or ten years from now. And, unfortunately coming at this point in the Program most of my other comments have already been relayed by Rick Becker and Sara, so I think I will stop there and again we would very much like to contribute further down the road as the vision document is further refined. But again, thank you very much. This is a good opportunity to begin a discussion.

DR. CARPENTER: Thank you. Any questions for Dr. Seidle? George?

DR. DASTON: I appreciate your comments and the support for omics technologies. I think the facts are with omics technologies that, in the immediate future, we're going to have to rely on animal studies to generate enough information and enough of a knowledge base to move to in-vitro models. Is that supportable in your philosophy?

DR. SEIDLE: It's, it's a very difficult compromise. It's something that philosophically we don't support any



animal testing. The question of whether you absolutely have, whether you need that kind of data scientifically or whether that data... Let me rephrase that. You can generate a lot of data using animal-based methods. The question always remains are these data relevant to humans, are these data relevant for, you know, extrapolation to wildlife if you're looking at an ecotox perspective. That's a question that remains to be answered. We're really not seeing that being addressed in a lot of the validation studies that have been done to date. It's simply assumed. As Rick had pointed out, and I guess a question had been raised about the, the standard rodent bioassay, is that considered valid? I think if you brought that forward to ICCVAM today and required a very... if it was held to the same rigor that non-animal methods that have gone through the ICCVAM process have been held, I think it would probably crash and burn given some of the reproducibility issues, given the questionable relevance. So whether you can generate data through an



animal-based system that you could not otherwise generate, that's probably true. Whether these data are truly relevant or whether they can potentially lead you, you know, astray is also a possibility. So I honestly don't know if that was a, a clear answer to your question.

DR. CARPENTER: Go ahead.

DR. SNYDER: Jack Snyder from NLM. One of the major questions for toxicological research today is what is the proper balance for investigation of what the toxicology community calls biological matrix, or biological matrices. That can be anything from the membrane of a cell or even a membrane inside the cell, to a single cell, to a series of cells in the Petri dish, to a tissue in a Petri dish, to a whole organ or to an intact animal and the question that I hear in a lot of forums, not only when your organization is represented but a host of different organizations in the spectrum here, the question is for, for your organization now what is the definition of animal? In other words, does it include the



biological matrix that is something less than the whole animal and indeed is there any room in your organization's approach for any type of research in a biologically-based system? I hope, I hope the question's clear.

DR. SEIDLE: I, I think I understand what you're asking. We have adopted an, an interim position that PETA, well, we're, we're less opposed shall we say, to experiments, for example, using less-developed invertebrates. I mean, typically the vertebrates is the, the very clear line. We have endorsed, for example, you know, simply as a refinement method the LLNA, simply because it is a step in the right direction. So on the one hand we do have very clear ethical standards, on the other hand we live in the real world, we're very pragmatic and if something is moving in the right direction and substantially enough, we, we certainly wouldn't take a position opposing it. So we, you know, we certainly endorse all of the, the in-vitro mutagenicity assays which are involving single-celled

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biological systems. So we wouldn't oppose that. Some of the, the work that's being done with certain aquatic invertebrates looking at some of the developmental and reproductive effects, we don't oppose that so... You know, I, I think there is a fair bit of room for compromise and as long as, you know, the intent is there to ultimately move towards replacement of vertebrates, certainly that's the path that we would like to see the toxicological community following.

DR. CARPENTER: Thank you. That's helpful to understand where you are in the spectrum. Thank you. Go ahead.

SPEAKER: I guess I'd like a little discussion of the issue of validation. I've heard quite a bit today. ILSI doesn't like the V-word. The chemical groups very much want validation. And a little bit to my surprise the animal protection advocates are also asking very strongly for validation. And then I've heard quite a bit about the ICCVAM, which I guess I need to learn more about because in nutritional toxicology it hasn't been something that has been in my

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face, so I need to learn more about that and I probably will. But my question really is, you know, and, and maybe it's different people have a little different definition here but to me validation would mean that we're going to have to develop new techniques that we compare them side-by-side with the, presumably two-year bioassay if that's been the gold standard, and that to me seems like it would use a lot more animals. So I guess that's why I'm a little surprised that the animal protection advocates are very, very strong on validation.

DR. SEIDLE: Well, I can tell you historically the reason that we are so strongly supportive of validation is because in-vitro methods with few exceptions have been met with skepticism and outright hostility in some cases. So it is important to demonstrate that the quality of the science is there. It's not merely a fly-by-night, it's not, you know, the ethics behind it are clear but the science has to be there as well to inform public health decisions.

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So that, that's not negotiable and for that reason we fully support it. We also insist, however, that the same standards be applied to animal-based methods which again you're, you're fighting 40-50 years of history where animal-based methods have never gone through a formal validation process in most cases so there's a lot of political resistance on that level. In terms of how a validation study could be conducted, there have been a number of rodent bioassays that have been, I mean, there've been hundreds, so in terms of validating a non-animal method against that or a tier testing strategy comprised of in silico, in-vitro, what have you, we would recommend simply data mining, taking existing data for chemicals, running those substances through the non-animal systems and doing comparison in that way so that if you have an already standardized set of data from an existing study, you don't need to repeat the study for the purpose of a validation effort. So in that way you ne..., you wouldn't necessarily just use any animals to validate a non-animal system. On the other

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hand if you're looking at some of the animal-based tests and screens that are coming on-line, we're seeing in the, the OECD process, for example, for endocrine disruptor tests an enormous body count coming out of that. So it is a double-edged sword and, you know, it's, it, it's always a difficult balance between the science and the ethics, but we've found enough cases with enough animal tests where, you know, for example, if you look at the Duray's (phonetic) eye irritation test you might as well toss a coin. The reproducibility has been so bad historically that a line has to be drawn and if it's a question of requiring validation as the bar where you either pass or you fail and if you fail you don't enter the regulatory community, it's a short-term cost for hopefully a long-term gain both for animals and for the betterment of science.

DR. BLAIR: If you say that the animal bioassay test, I assume you're talking largely about carcinogenicity 'cause that's the, what the bulk of things been done all those, and other endpoints are not

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validated then what would you, what do you suggest we use as a valid endpoint for the non-whole animal mechanisms?

DR. SEIDLE: From my read of the lit...

DR. BLAIR: Just let me add to it. It wouldn't seem that we would want to validate some mechanistic technique against another approach that hasn't been validated. So what would we use?

DR. SEIDLE: I completely agree with you that validating one method against something which itself hasn't been validated is an enormous problem and unfortunately it's a problem that the, you know, even ICCVAM hasn't gone far to try and resolve, it simply... you know, I won't go so far as to say it's unresolvable but right now in my opinion, there isn't a valid toxicity test to evaluate carcinogenicity or virtually any other health effect to humans. You're going to get a certain false positive rate, you're going to get a certain false negative rate, and as long as you're outside the, the human animal, which of course you

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can test chemicals for ethical reasons, as long as you, the further you move away from that, you're always going to get some margin of error so the question... and the fact that it hasn't been assessed in a formal way I, I firmly believe that there isn't a valid or you know, a scientifically validated method either for use presently or against which you can compare an alternative testing strategy. So I don't have a short and, you know, quick answer for you. I think some of the, the points that were raised regarding human toxicity data from occupational sources hold tremendous promise. There's actually an OECD workshop that's been proposed on the generation or the mining of human data for validation purposes for exactly that reason because, even though you will have some...you know, there, there will also be some scientific questions about the use of occupational data for validation purposes since dose questions will always be an issue. But can we get better, can we do better than just a traditional animal study as the, the gold standard for validation?

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So there are plans in the works but right now I don't think there is a, there is an answer to your question.

DR. SASS: Jennifer Sass...

DR. CARPENTER: Go ahead.

DR. SASS: ...with the Natural Resources Defense Council. Troy, thank you for the talk. That was interesting. One of the speakers in the audience brought up, I, I guess to follow-up on the question that was just asked, the, the poison control center data accidental exposures, things like that... Actually, has PETA ever tried to, to release up that kind of data specifically? From the poison control centers? That's new information to me. I didn't realize that.

DR. SEIDLE: It's something we haven't tried to tackle directly, just... given PETA's activist agenda, it's, it's something that we have, we're trying to pursue through international bodies such as the OECD where we can potentially get 30-member country support and if we can get that level of buy-in it would be a much more

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effective tool than if it's being advanced by, by a single non-profit advocacy organization. So that's... we've been aware of it for some time but it's not something that we've pursued directly.

DR. SASS: So you're trying to get an international push to release that accidental exposure, poison control center-type of data?

DR. SEIDLE: Both... certainly having it released would be useful from some perspectives. Our focus has been squarely on its use for validation purposes. So we, we haven't looked at it from a completely holistic standpoint just because that's not our, our mandate exclusively.

DR. CARPENTER: Seeing no further hands, thank you very much. Nice presentation. Our final speaker on the current list, and we've had nobody else ask to speak, so is Jennifer Sass from the Natural Resources Defense Council.

DR. SASS: Are these microphones on already? Okay, I'm Jennifer Sass. I'm with the Natural Resources

Defense Council. It's an environmental non-profit organization. I'm based here in Washington, D.C. I'm a scientist in the Health and Environment Program. We have comments I've handed out on paper. I assume that you have them. I think some extra copies were made for audience members; if not, I've also just last night when I completed them, sent them electronically to the NTP Program so they will be available on the website, I hope.

Three points only, so I'll be short. The first is support for a leading role for the NTP as a public health institute in the development of a strategy to integrate in-vitro toxicity data into regulatory policy. While we are well aware that policy makers will someday utilize these data for regulatory decisions, how this is to be done is still a point of discussion. Thus, we support a strong role for the NTP in the development of methodologies on the use of omics data for human risk assessment. Without this methodology, gene expression data cannot be effectively used to predict



toxicity or low-dose cancer risk. Further, we strongly support the need to include proteomics and metabonomics, in conjunction with the toxicogenomics efforts now underway in its overall strategy.

The second point. We support the validation and appropriate integration of in-vitro toxicity data. We support the NTP efforts to lead the way on the validation and appropriate integration of data from omics and in-vitro toxicity testing methods. However, we also encourage the NTP to develop clear objectives, as well as a comprehensive strategy to achieve that objective. For example, does the NTP envision the use of these data as screening strategies or as surrogates for existing in-vitro, in-vivo endpoints? If a potential goal is to develop an alternative approach to the rodent bioassay, we strongly object. We are years, if not decades, from fully understanding the cellular and subcellular mechanisms of carcinogenicity. We therefore suggest that an appropriate goal at this time be to further characterize cellular and



subcellular toxicity in order to refine our understanding of chemicals and toxic agents on health and disease. Mechanistic-based endpoints will be most useful if data can be developed in both humans, that is epidemiology and animal models, in order to make valid comparisons, obviously. We suggest that any objective include the development of biologically-based dose-response models that can be used for trans-species extrapolations of toxic or carcinogenic effects and that can address inter-individual differences in susceptibility as well as the effects of the exposure to mixtures. A good deal of these points have already been brought up today.

To achieve any of the above objectives, extensive quantitative data on time and dose dependent relationships will be needed. Studies on time dependence should cover the time interval between exposure and elimination of the agent under study, at least over a 24-hour cycle, longer for bio-accumulating agents or for agents in which continuous treatment affects their metabolic



elimination, and at multiple life stages in order to capture effects of age-related changes. Transcriptional data without information on time-dependent protein levels will be of limited value. Measurements of gene expression in conjunction with NTP sacrifice times, and that's from days extending through two years, may be useful in linking altered gene expression with clinical pathology or histopathological effects in some, in the same animals.

The strengths of the NTP studies are the consistent genetic background of animals on study and the consistency in diet. So it may be useful to apply mechanistic methods to better characterize the effects of animal variability, for example, the use of transgenics or knockout mice, and of different dietary formulations as well. Collecting and interpreting this information may not initially lead to savings in cost or time or use of animals, although I do agree with most of the speakers that have commented in the long-run, I think that it definitely will.

The validation and appropriate integration of microarray and omics technology will require a clear strategy to contribute to the design or interpretation of NTP studies and enhance the overall goals of the NTP. As the NTP develops their mechanistic endpoints they should consider incorporating these into low dose testing regimes as well and observe for appropriately sensitive endpoints.

And my third and final point. We support the NTP bioassay program as a critical and integral part of identifying and characterizing toxic agents. It is alarming to realize that with approximately 80,000 chemicals commercially available worldwide and 2,000 new ones introduced annually, less than 2 percent of these have been adequately tested for carcinogenicity. More than 2,800 chemicals are manufactured in the U.S. in quantities exceeding one million pounds annually. Of these, the EPA finds that a full set of basic toxicity information is available for only approximately 7 percent, while for approximately 43 percent no basic



toxicity information at all, neither human nor environmental is publicly available. Without the adequate laboratory testing, the default method for identifying human hazards is unfortunately epidemiology. This is neither rapid nor protective. Epidemiology studies are typically limited by insufficient follow-up time, uncertain exposure estimates, limited statistical power, confounding factors, and limited ability to do histopathology. The National Toxicology Program is widely considered to be the most trusted chemical testing program in the world, largely because of its tremendous work in establishing the bioassay as an effective method for identifying and characterizing carcinogens. The NTP bioassay is an accepted method because the vast majority of human carcinogens have also been shown to be carcinogenic to animals and many chemicals first identified as carcinogenic in animals were subsequently confirmed to be human carcinogens as well. Well-designed animal studies provide detailed dose-exposure information, repeatability, sufficient



statistical power and comprehensive behavior and histopatholo..., pathology. A baseline data set on measurements of gene expression over 24-hour intervals in different strains of rodents and at several ages from perinatal through senescence, would be valuable information to further the study designs. We encourage the NTP bioassay to more routinely capture the full age groups, including fetal stages, puberty and old age and to continue for at least two full years to allow latent tument, tumor formation to become evident. We encourage the NTP to expand this trusted methodology to handle an increased number of chemicals annually. Thank you.

DR. CARPENTER: Thank you. Any comments or questions for Dr. Sass?

DR. BLAIR: Jennifer, since the number of bioassays, no matter how much money we put in are finite in some way...

DR. SASS: Right.

DR. BLAIR: ... would you support the greater use of mechanistic data to select the chemicals that go in? I



mean, they use that now, of course, but some of it is overlain also by how many people are exposed, and you... one way to focus a little bit is not pay attention to that and focus just on the mechanistic data. What are your thoughts?

DR. SASS: I think that a tiered approach towards utilizing the bioassay is probably a way to go and so, yeah... if you can select intelligently and set up study designs that will be more focused, and, and complement them with mechanistic or other in-vitro data where available using it appropriately and from validated studies, I think that's excellent.

DR. CARPENTER: Go ahead.

DR. SASS: My motto as a scientist is never to say no to data.

DR. CARPENTER: Go ahead. Go ahead.

DR. AMUNDSON: Jennifer, Sara Amundson with the Doris Day Animal League. I really appreciate your comments, and the truth is there are a number of, I thought, invaluable points that you made that I

certainly agree with, while there are others that I do in fact disagree with. That said, your question of Troy was legitimate and I'd like to turn that on its ear a little bit. That is, first and foremost our information directly from EPA on the HPP Program as it currently exists demonstrates that there's about 6 percent of all data being generated through new testing. Gosh, folks, that means there's a tremendous amount of data that is currently out there, that's being brought forward. That said, we've had minuscule success in particular with the poison control centers in mining some of that data for some of the purposes we've had that are well outside of the tox testing realm. Just for things like how many exposures to ethylene glycol have you seen in children under six. Those simple bits of information have been available in very small increments. But this is testimony to the fact that whether it's poison control centers or it is human eye irritation data, you name it, all of this information that is out there that's been collated is certainly not



available to the folks that need to utilize it for validation purposes, or simply for informational purposes. What is NRDC doing to address that need?

DR. SASS: I feel a collaboration coming on. Actually, in my written statement you'll notice that I actually said that, that there is limited amount of basic toxicity information publicly available and I am completely aware of this and if I had my way I would slap those people around a bit. I think it's incredibly valuable information and in fact I have a small commentary that's being published in Environmental Health Perspectives the month after next that actually compares the no-effect level that was set for a pesticide, two pesticides, I actually look at one in particular, with actual food poisoning event data where, where sensitive populations, some elderly, some not, were actually having to be treated in the hospital emergency care at levels far below what had been deemed the no-effect level from a Union Carbide animal study. So



I, I'm completely aware about how valuable this data is and it appalls me that it's out there and that, it's some minuscule amount that's actually being reported to collection centers and not being utilized.

DR. CARPENTER: Go ahead.

DR. WIND: Marilyn Wind from Consumer Product Safety Commission. I am perplexed at the constant repetition that the AAPCC data is not available. There are clearly real problems with that data because a lot of the data that's collected doesn't name products and if products are named, you may not know what the products contain, so from that point of view, that's a problem. Another problem with the data is that some industry, some industries actually use poison control centers for collecting, for responding to questions on their products and that data is not publicly available but we use the poison control center data which is not a statistical database unfortunately for looking at where poisonings are occurring so that we can decide what needs to be in poison prevention packaging, and the data



that is available is good from that point of view 'cause it tells us where there are exposures and stuff. But I'm a little perplexed at what it is that is not available that's needed because while they don't give away their data and you have to, you have to buy it, it has been available and we've been using it.

DR. SASS: That's not a question for me, right? I don't run those things. I can't answer that question.

DR. CARPENTER: It really wasn't a question. I just.

DR. SASS: Okay.

DR. CARPENTER: Whether you had a response or not, I was waiting... Any more questions or comments? Thank you very much, Dr. Sass. I appreciate it. Are there... Are there any more public comments? Go ahead.

DR. AMUNDSON: My apologies. I just have a quick comment and that's, overall in approaching this issue I think what is missing here is strong representation from pharmaceutical companies. Oftentimes I

hear in these various fora when it comes to concerns about validation or mining data resources that fingers get pointed at the pharmaceutical sector and I think that ILSI, for example, could be exceedingly helpful in bringing those folks into the fold. We've got excellent representation from the industrial chemical sector but oftentimes these folks get left out and I'd prefer to have them early on in the discussion.

DR. CARPENTER: Good point. Any other comments? Well, I'd like to thank you all for coming and taking time and, and thank the speakers for putting together very nice presentations. I'd like to thank the panel for their efforts and ask Chris Portier if he'd like to make some final comments.

DR. PORTIER: Thanks, Dr. Carpenter. I really...I would like to make a couple of comments. I think it's been an interesting morning. This afternoon the subcommittee of the board will be meeting in closed session to discuss some of the things they've heard this morning and start working



out their strategy and they will also meet with some representatives from the interagency group as well to talk about linkages across their two strategies. So there will be some discussion this afternoon. We heard a lot of interesting things and I just thought I'd reiterate a few of the things I've, I've caught in terms of what we need to look at. We started off the public comments with consider partnerships which is absolutely an important part of this. Academic partners, stakeholder partners, partners in the federal community, I think all will play an important role in this and certainly we're gonna try our best to use the broadest expertise possible from all the stakeholder groups. But again, if all of our committees could think about how that would play into this, it would be very interesting. Consider validation in advance I think is a lesson we've all learned over the years and that we need to be very specific on the goals; not only the goals of this process but the goals of each and every piece of the process. I think Michelle's



point with the SMART approach at the beginning is something that helps and aids in that. And measurement for these goals: dates, targets, what are we reducing, if anything, what are we refining, are we going to replace animals, are we not going to replace animals, are we gonna replace one test, not another. A lot of issues that need to be looked at in terms of goals and how we measure these. And we even got suggestions of not only what goals we should be looking at but what goals we should not be looking at and so we'll consider all of those as well. And finally, the whole discussion about a number of different issues but it all boiled down to alternative databases and consider how we might explore these in unique ways in terms of looking at this vision is I think something we have to take very seriously and con..., consider as we move forward. I want to thank all the commenters for their insights and their discussions. I want to thank Dr. Yang for coming all the way from Korea to look at how the NTP conducts, conducts a public meeting



and participate in that public meeting by giving us some of the future directions that the Korean NTP is going. They're very interested in bringing the concept of a public meeting into toxicology in Asia and I commend him for that effort and I again thank him very much for being here today. I want to thank Dr. Carpenter and the Board for their efforts and being here today and addressing some of the issues and listening to them, the N, my NTP staff: Dr. Wolfe, who set up this meeting and made it work for all of us, and Sara, I'm sure, if I know Mary, the next time we do a public meeting announcement, it will include the animal rights community; Dr. Bucher and Dr. Hooth for chairing the two subgroups that NIEHS and NTP have; and our NTP partners for being here today as well. Again, thank you all very much. Dr. Carpenter, it's back to you.

DR. CARPENTER: And because they gave this to me I have to use it. Adjourned.

(WHEREUPON, the Meeting was adjourned at 12:37 p.m.)

CAPTION

The Meeting in the matter, on the date, and at the time and place set out on the title page hereof.

It was requested that the Meeting be taken by the reporter and that the same be reduced to typewritten form.

# CERTIFICATE OF REPORTER

STATE OF VIRGINIA AT LARGE:

I, **FRANK J. SPACEK, III,** Notary Public for the State of Virginia at Large, do hereby certify that the foregoing constitutes a true and accurate transcript to the best of my ability.

I further certify that I am not an employee of nor related to any of the parties, and I have no financial interest in the outcome of this matter.

Notary Public

My Commission Expires:

May 31, 2005