

1 NATIONAL TOXICOLOGY PROGRAM (NTP)

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PUBLIC MEETING ON TOXICOLOGY

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IN THE 21ST CENTURY:

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THE ROLE OF THE NATIONAL TOXICOLOGY

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PROGRAM

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January 29, 2004

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1 NATIONAL TOXICOLOGY PROGRAM (NTP) PUBLIC
 2 MEETING ON
 3 TOXICOLOGY IN THE 21ST CENTURY: THE ROLE OF
 4 THE NATIONAL TOXICOLOGY PROGRAM
 5 January 29, 2004
 6 DR. CARPENTER: Good morning.
 7 I'm Hillary Carpenter with the Minnesota
 8 Department of Health. I've been asked to
 9 chair the meeting this morning, the National
 10 Toxicology Program's meeting on toxicology in
 11 the 21st century, the role of the National
 12 Toxicology Program. Welcome. We're glad to
 13 have you here. We're very interested in, in
 14 hearing what you have to say and looking
 15 forward to a lot of interaction between the
 16 public and the panel that we've assembled
 17 for today. A couple of housekeeping
 18 reminders. We do have a, a transcript, a
 19 record of attendance. If you haven't
 20 registered, please do so. Also, because of
 21 the fact that the meeting is being recorded
 22 we would like for you to use your
 23 microphones. Everybody should have a
 24 microphone right in front of you. Push the
 25 button and you get a nice little red light

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

1 University of Arizona where she is a
 2 Professor of Pharmacology and Toxicology and
 3 Steve Roberts, Dr. Steve Roberts of course
 4 is out of place according to my guidelines
 5 here. They put you... oh. My goodness.
 6 Steve Roberts with the University of Florida
 7 where he's a Professor in the Center for
 8 Environmental and Human Toxicology. We also
 9 have some, this is, this is the Board of
 10 Scientific Counselors portion of this group.
 11 We also have a representative from the
 12 Interagency Work Group on Vision and that's
 13 John Bucher who is sitting right there and
 14 he's not gonna acknowledge that, thank you,
 15 who is the Deputy Director of the
 16 Environmental Toxicology Program at NIEHS,
 17 and Michelle, there you are, Michelle Hooth
 18 who is a staff scientist in Environmental
 19 Toxicology at NIEHS. In addition, we have
 20 NTP Core Agency representatives, Dr. Chris
 21 Portier who is the Associate Director of NTP
 22 and the Director of the Environmental
 23 Toxicology Program at NIEHS. Mark Toraason,
 24 who's ignoring me or otherwise... there you
 25 go, thank you, who's the Science Director at

1 the National Institute for Occupational
 2 Safety and Health with CDC and also Dr.
 3 William Allaben from the, who's Associate
 4 Director and Science Coordinator at the
 5 National Center for Toxicological Research at
 6 the FDA. Did I miss anybody? What I would
 7 like to do now which will help everybody put
 8 names to faces and help with the transcript
 9 is to go through the, through the audience
 10 and ask you to please identify yourself and
 11 your affiliation, if you would.
 12 DR. THAYER: Kris Thayer,
 13 NTP/NIEHS.
 14 DR. SHANE: Barbara Shane,
 15 NTP/NIEHS.
 16 DR. MASTEN: Scott Masten,
 17 NTP/NIEHS.
 18 DR. TORAASON: Mark Toraason,
 19 NIOSH.
 20 DR. ALLABEN: Bill Allaben,
 21 FDA.
 22 DR. MENDRICK: Donna
 23 Mendrick, Gene Logic.
 24 DR. FISHER: Joan Fisher,
 25 Proctor & Gamble.

<p style="text-align: right;">Page 6</p> <p>1 DR. FELTER: Susan Felter, 2 Proctor & Gamble. 3 DR. WOLFE: Mary Wolfe, 4 NTP/NIEHS. 5 DR. SEIDLE: Troy Seidle, 6 PETA. 7 DR. JAMESON: Bill Jameson, 8 NTP/NIEHS. 9 DR. PHIBS: Pat Phibs, 10 Reporter, BNA. 11 DR. WEDGE: Robbie Wedge, 12 National Academy of Sciences. 13 DR. KI-HWA YANG: Ki-Hwa 14 Yang, National Institute of Toxicological 15 Research, Seoul, Korea. 16 DR. WRIGHT: Robert Wright, 17 Training Lab, representing American College 18 of Medical Toxicology. 19 DR. WIND: Marilyn Wind, 20 Consumer Product Safety Commission. 21 DR. WILKINS: Steve Wilkins, 22 Costella Health Sciences. 23 DR. SNYDER: Jack Snyder, 24 Medical Toxicologist, Associate Director, 25 National Library of Medicine.</p>	<p style="text-align: right;">Page 8</p> <p>1 year-long process into looking at the 2 direction and future of the National 3 Toxicology Program. Where is toxicology 4 going, and how is the NTP going to 5 contribute to that movement, potentially 6 leading in some areas? I want to thank the 7 members of the Board for being here. I want 8 to thank you all for, for coming out and 9 giving us your comment. We're a small 10 enough group this morning. I hope that we 11 can have a, a, an intimate discussion about 12 the future of toxicology and its role in 13 providing health protective public health 14 decisions. With that I'll simply move into 15 my presentation. 16 This year marks the 25th anniversary 17 of the National Toxicology Program. In 25 18 years the NTP has contributed a substantial 19 body of knowledge...well, this has got 20 automatic changing, that's good. It will be 21 fun. ...a substantial body of knowledge in 22 the toxicology literature and a number of 23 different areas in terms of evaluating public 24 health risk for certain environmental and 25 pharmacological and food-based exposures.</p>
<p style="text-align: right;">Page 7</p> <p>1 DR. OKITA: Richard Okita, 2 National Institutes of General Medical 3 Sciences. 4 DR. AMUNDSON: Sara Amundson 5 with the Doris Day Animal League. 6 DR. PAXTON: Mary Paxton, 7 Institute of Medicine. 8 DR. JAMES: Peter James, 9 Institute of Medicine. 10 DR. HOLSAPPLE: Mike 11 Holsapple, the Executive Director of the 12 Health and Environmental Sciences Institute. 13 DR. CARPENTER: Thank you 14 all, and welcome. I would like at this time 15 to acknowledge public comments that were 16 submitted, written comments that were 17 submitted. We received comments from Dr. 18 Ki-Hwa Yang from the National Toxicology 19 Program in Korea and Richard Becker from the 20 American Chemistry Council. Right now I 21 guess we go to, to Dr. Portier for a welcome 22 from the NTP. 23 DR. PORTIER: Thank you, Dr. 24 Carpenter. I want to thank you all for 25 being here today as we launch an almost</p>	<p style="text-align: right;">Page 9</p> <p>1 We've done a number... a lot of work in 2 developing various assays and providing 3 support for the development of those assays. 4 So the Program has a long history of 5 testing, research and evaluation of that 6 research for guiding public health decisions. 7 Our mission is in fact to evaluate agents of 8 public health concern by developing and 9 applying the tools of modern toxicology and 10 molecular biology, and Dr. Olden when he 11 started at NIEHS as the Director of the NTP 12 12 years ago, coined the, the term to sort 13 of capture the essence of the NTP's mission 14 and that is good science for good decisions 15 and we still hold to that truth. NTP is a 16 multi-agency Program. It's not just a 17 single agency that makes up the Program. 18 NIEHS is the home of the National Toxicology 19 Program. There we go. Boy, we've got this 20 worked out well. NIEHS is the home of the 21 National Toxicology Program but two other 22 agencies, the National Institute of 23 Occupational Safety and Health and the 24 National Center for Toxicological Research, 25 one with CDC, one with FDA, both contribute</p>

<p style="text-align: right;">Page 10</p> <p>1 resources, time, effort and energy to the 2 activities of the National Toxicology Program 3 and we're very pleased to have our major 4 partners here with us today to discuss the 5 future directions of this Program. In 6 addition, a number of agencies participate in 7 the NTP activities, either on our executive 8 committee or through some of the other 9 activities that we have and this is a list 10 of those agencies. Key among them are EPA, 11 OSHA, CPSC, NCEH at CDC and NCI and ATSDR. 12 All of those are on our executive committee 13 and do a considerable amount of effort on 14 behalf of the NTP. 15 The NTP has a number of outside 16 guidance groups. I'm giving you a little 17 background because it will, it'll make it 18 clear as to how we move forward, forward 19 with developing a road map for the vision. 20 The NTP executive committee provides policy 21 oversight for the Program, it's composed of 22 the directors of ten federal agencies or 23 their designates and it provides a forum for 24 not only coordination of our research effort 25 but looking at the practical appli...</p>	<p style="text-align: right;">Page 12</p> <p>1 is the ability to imagine how a country, 2 society, industry, in this case, a program 3 and a field of science could develop in the 4 future and to plan in a suitable way. So 5 at this point we're looking for that 6 planning process. We're trying to lay out a 7 road map for how we might achieve the vision 8 we've laid out for the NTP. I'll talk about 9 the goals strategies. Some of the questions 10 we're asking people to consider as they 11 think about changing, or looking for a 12 vision for the, for toxicology for the 21st 13 century and then some of the activities we 14 have planned. 15 Why would we do this at this point? 16 Before I, I look at the vision, why would we 17 want to do this type of thing? I think 18 there are two things that are over-arching 19 and, and this is not new; these are issues 20 that we continually work with within the 21 National Toxicology Program. The first is 22 to promote the scientific advances that have 23 occurred in biomedical research in the last 24 few years for use in the field of 25 toxicology. Given these advances in basic</p>
<p style="text-align: right;">Page 11</p> <p>1 applicability of that effort and avoiding 2 duplication of effort while also 3 consolidating efforts to produce a bigger 4 research portfolio from the individual parts. 5 The NTP Board of Scientific Counselors which 6 is amply represented here, represented here 7 provides scientific oversight and a forum for 8 public input for the National Toxicology 9 Program. We have three standing 10 subcommittee, we have two standing 11 subcommittees for the National Toxicology 12 Program, the Report on Carcinogens 13 subcommittee and the Technical Reports Review 14 subcommittee, but now we have a subcommittee 15 on the NTP vision as well and Sam Cohen has 16 agreed to chair that subcommittee and the 17 people here are some of the members of that 18 subcommittee from the NTP Board of Scientific 19 Counselors. Let's see if I can stop it from 20 moving forward here. 21 So, let's talk about creating a 22 vision for the National Toxicology Program 23 and where we have to go. First of all, 24 what is a vision? So to make sure we're 25 all talking about the same thing, a vision</p>	<p style="text-align: right;">Page 13</p> <p>1 science what is the role of toxicology and 2 what should that role look like? Are we 3 doing the right type of science at this 4 point or has, has science changed in such a 5 way that we really need to look very 6 carefully at what we're doing and consider 7 some additional or alternative or refined 8 methods of doing what we're doing? In 9 addition, this type of activity after 25 10 years of the National Toxicology Program will 11 help to improve our focus on the long-term 12 needs of the public health decision-making 13 community, the toxicological community and 14 the scientific community, all three of which 15 we are here to serve. 16 Second major issue is to improve 17 public health decisions. We think the 18 National Toxicology Program through its 19 activities in the last 20 years has 20 certainly contributed substantially to public 21 health decisions in this country. But one 22 can't just rest on one laurel, one's laurels 23 forever and I think part of this is that we 24 want to look at how we can move the field 25 forward improving the translation of basic</p>

<p style="text-align: right;">Page 14</p> <p>1 research into public health decision-making 2 arena, improve the information management 3 tools that are necessary to capture the 4 information that might be needed, report it 5 and translate it in such a way that it can 6 be understood by the people who have to make 7 public health decisions; clinicians, heads of 8 regulatory agencies, people in their own 9 homes who have to decide what they are, want 10 to or don't want to be exposed to, taking 11 the, the real basic science and turning it 12 into something that's usable. In doing 13 that, in, in looking at that question, of 14 course at the same time to look at how we 15 can provide the data needed to guide these 16 public health decisions, this has been a 17 strong role for the Program and it will 18 continue to be a strong role, what type of 19 data do we need to provide and in what form 20 should it be provided? And finally, 21 overall, we would really like to see the 22 development of a very strong scientific 23 linkage from observations in molecular 24 biology clean through disease onset and 25 disease prognosis for environmental and other</p>	<p style="text-align: right;">Page 16</p> <p>1 that's been done in a number of cases for a 2 number of models. Part of this vision is to 3 look at that process and decide whether it's 4 time to start reversing it. To start 5 thinking about working at the level of the 6 mechanisms themselves and trying to predict 7 backwards what may or may not cause disease 8 given those types of mechanisms. 9 Given that that's a sort of a vision 10 we're looking at, what type of data do we 11 need, and where should we go to be able to 12 create that type of vision at this point? 13 Our strategy through looking at the road map 14 we'd like to create for the NTP vision is 15 achieving as much public input as we 16 possibly can, that's part of what this 17 meeting is. We'll have a number of other 18 public meetings along the way. Seeking 19 scientific input from our usual scientific 20 partners, the NIEHS committee that Dr. Hooth 21 is leading consists of members of the 22 National Toxicology Program, core scientific 23 staff, members of the Division of Intramural 24 Research at NIEHS, our basic science staff 25 and members of the Division of Extramural</p>
<p style="text-align: right;">Page 15</p> <p>1 di..., other disease causes that the NTP has 2 been focused on for a number of years. 3 So, a vision has to be stated 4 succinctly and so we've come up with this 5 wording for the vision for the NTP for the 6 21st Century and that is to move toxicology 7 from a predominantly observational science at 8 the level of disease-specific models to a 9 predominantly predictive science focused on a 10 broad inclusion of target-specific, mechanism 11 based biological observations. In 1995 the 12 NTP held a workshop to look at mechanism- 13 based toxicology and since that time we have 14 contributed, many of our, our members of our 15 Board of Scientific Counselors, many of you 16 in the audience and many of the 17 toxicologists that have worked around the 18 world have contributed to the area of 19 mechanism-based toxicology. You observe 20 something in a disease-specific animal model 21 and you spend time and effort trying to 22 understand the mechanisms involved in that 23 observation and try to take it apart as you 24 will and really understand what is the root 25 cause of the disease you're seeing. And</p>	<p style="text-align: right;">Page 17</p> <p>1 Research and training at NIEHS, the grant- 2 giving part of the Institute. All three of 3 those groups are working together to look at 4 how the NTP can function better within the, 5 within its home agency, the National 6 Institute of Environmental Health Sciences. 7 We have an executive committee, subcommittee 8 that John Bucher is chairing. This is, 9 there are representatives from all of the 10 major agencies that participate in the NTP. 11 Here we're looking for synthesis across the 12 agencies, understanding of, of what we'll 13 have to do and how we'll have to work with 14 the agencies to provide better scientific 15 understanding for, for guiding public health 16 decisions with this type of information. 17 And finally we're looking for the, to the 18 Board of Scientific Counselors Subcommittee 19 chaired by Sam Cohen, and here we're looking 20 for scientific guidance, what types of things 21 could we do that would contribute to the 22 overall direction of, of a more mechanism 23 based toxicology approach that's predictive 24 for environmental and other hazards. We're 25 bringing in a number of outside experts in a</p>

<p style="text-align: right;">Page 18</p> <p>1 variety of points in the process to give us 2 some advice. We have a, at, toward the end 3 of this early process of, of getting as much 4 idea into the Program as we possibly can 5 we're gonna form an NTP work group that's 6 going to formalize this into a road map for 7 us and some goals and measurements along the 8 way with that road map and we'll end with a, 9 we'll end with a retreat where we finalize 10 that road map and then hopefully sometime in 11 fall we, we hope to hold a meeting here in 12 Washington where we release that road map 13 for public comment and have a workshop to 14 discuss some of the implications of it. 15 We've asked all of the groups involved and 16 I'm giving you these questions as well, to 17 consider certain things as you look at where 18 toxicology might be going in the 21st 19 Century, and these are just the broad 20 questions, you can think of dozens of 21 smaller questions under each of these 22 categories, but first what information should 23 the NTP produce, what might this information, 24 how might this information be used in public 25 health decisions, what would be needed to</p>	<p style="text-align: right;">Page 20</p> <p>1 interest, and development of tools for 2 integrating the scientific data, these are 3 bio-informatics and database management-types 4 tools, that might help us integrate this 5 information into a better picture of the 6 potential for toxicity. In addition, tied 7 with this and having to run parallel is to 8 develop better and broader baseline 9 information. If I'm gonna look at a variety 10 of assays I want to be able to look at them 11 in a large number of compounds in a fairly 12 short period of time. So I'd like to see 13 some high throughput methods used, some 14 mechanistic clarity of the response so I 15 know actually what I'm looking at. Even 16 though it might have limited interpretation 17 on its own, I want to make sure that 18 interpretation is clear, clear before I start 19 trying to interpret it in, in the light of a 20 much broader issue like an entire animal 21 response, and I want to look at a broad 22 agent, array of agents and I want to use 23 these consistently if possible. 24 Some other activities I think we need 25 to consider along the line, enhanced</p>
<p style="text-align: right;">Page 19</p> <p>1 gain acceptance of the new testing paradigm, 2 and by testing paradigm here it doesn't have 3 to be a single test, you can think of 4 multiple tests as forming a, a strategy for 5 testing. How can the NTP advance the 6 utility of these new methods and new testing 7 paradigms and finally, what new resources 8 will be needed and what re..., existing 9 resources will have to be reduced to look at 10 these issues and looking at some of the 11 processes we already have in place. 12 Just so you get some idea of the 13 types of things that might be considered, 14 and these are my own ideas; these are not 15 things that have come to me yet from any of 16 these subcommittees, but I wanted you to 17 think about some of the things I'm looking 18 at. Rapidly, rapid development of better 19 models and faster screens, move from disease- 20 specific focus to the systems mechanism-based 21 focus, looking at issues that we historically 22 have only looked at piecemeal like exposure 23 timing, genetic controls on response, system- 24 wide evaluation of the data, looking at an 25 entire biological system as something of</p>	<p style="text-align: right;">Page 21</p> <p>1 development of multi-disciplinary... 2 disciplinary and multi-agency scientific 3 teams. Toxicology is no longer one person 4 in their lab doing one experiment with one 5 model. Clearly the NTP has been a leader in 6 that area and recognizes the need for multi- 7 disciplinary teams. We've used them for a 8 number of years very successfully and it's 9 important to the overall success of any 10 toxicology exercise to continue along those 11 lines. Determine how to cross-link disease 12 focus with mechanism focus. We've 13 fundamentally changed that linkage to basic 14 science enhanced both areas. And finally we 15 clearly are going to need to develop 16 training programs to meet the needs of both 17 the NTP, our partners, and a broader based 18 community that uses NTP information, so we 19 also have to look towards that as well. 20 And I seem to have lost my picture. 21 So... that's okay. This is a quote from 22 John Sherr, "The future is not some place we 23 are going to, but one we are creating." And 24 at this point I think that's what we're 25 trying to look at. How do we create a path</p>

1 such that we change both the maker and the
2 destination and hopefully for the betterment
3 of public health in the United States.

4 Thanks a lot.

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

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

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

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

1 NIEHS work group for the NTP vision, and I'd
2 like to tell you about our progress over the
3 past few months. Did that. That's okay.

4 Wait a minute. Chris, nothing's working.

5 It's not responding.

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

8 DR. HOOTH: Okay. Sorry.

9 Yeah, oops. Okay, let's try again. So is it
10 the up arrow? It should be just the up.

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

13 DR. HOOTH: Okay.

14 SPEAKER: Down there.

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

1 laboratories in the Institute and this
2 includes two members from the Environmental
3 Diseases and Medicine Program and Dori
4 Gramalick and Nigel Walker also have
5 laboratories in the Institute. We have very
6 diverse backgrounds and responsibilities in
7 the Program and this allows us to consider
8 the full range of the NTP activities and
9 also to develop potential collaborations
10 within the Institute.

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

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

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

<p style="text-align: right;">Page 26</p> <p>1 been looking at identifying and quantifying 2 indicators of exposure, disease and 3 susceptibility from animal toxicity studies 4 that can be linked to clinical and 5 epidemiological investigations, and in this 6 group we've been looking at quantitative 7 relationships between exposure, tissue 8 dosimetry and trying to identify intermediate 9 molecular events in environmental diseases. 10 In the next few weeks we'll be focusing on 11 some of our other goals and just to give you 12 an idea of the process goals, we'll be 13 looking at ways to evaluate mechanisms for 14 hiring and training staff to facilitate the 15 transfer of new technologies to the NTP; 16 ways to increase the number and relevance of 17 agents nominated to the Program; and, given 18 the vast amount of data that can be 19 generated, ways to develop improved data 20 management methods. And then under the 21 communication and translation goals ways to 22 strengthen public outreach and communication 23 programs to help regulatory agencies and the 24 public understand the significance of the NTP 25 findings.</p>	<p style="text-align: right;">Page 28</p> <p>1 laid out, I must admit I don't quite know 2 what the research goals would be for the 3 Program now, but these seem what I might 4 anticipate. Are they different? 5 DR. HOOTH: No, I think some 6 of them are fairly consistent with the 7 Program, things that we're already doing. 8 But we're trying to look at ways to optimize 9 what we're doing. Could we be getting more 10 information or more analysis out of the 11 studies that we're doing? And also how can 12 we incorporate new methodologies and, as 13 Chris stated in his overview, ways to 14 provide rapid and thorough analysis, ways to 15 screen or prioritize compounds. So, yeah, 16 I, I think it does seem like these are 17 things that we're already doing but we're 18 trying to really focus on more of the 19 specifics. 20 DR. BLAIR: One more 21 question. 22 DR. HOOTH: Sure. 23 DR. BLAIR: In the process 24 goals, it, what you were talking, and I 25 think maybe this is the, the charge of your</p>
<p style="text-align: right;">Page 27</p> <p>1 2 The process that we've been using to 3 flush out these goals is the SMART process; 4 so for each of our goals we identify 5 specific aims and then we try to define 6 measures of accomplishments, so how will we 7 know that we've achieved our goals. And 8 then we've also challenged ourselves to look 9 at the ability or the feasibility to achieve 10 the specific aims, trying to identify what 11 the obstacles or challenges might be and at 12 all times we want to keep in mind the 13 relevance to the NTP mission and the public 14 health decisions. We're also trying to 15 provide realistic time lines for 16 implementations of our recommendations. We 17 appreciate the opportunity to be able to 18 provide recommendations and we look forward 19 to further debate and discussion of our 20 ideas. Thank you. 21 DR. CARPENTER: Does anybody 22 on the panel have any questions for Dr. 23 Hooth? 24 DR. BLAIR: Two questions 25 actually. One, the research goals you've</p>	<p style="text-align: right;">Page 29</p> <p>1 group to look internally but what it sort of 2 struck me as following Dr. Portier's vision 3 it actually means incorporating information 4 from the extramural side that feeds into NTP 5 and so there's sort of nothing about that in 6 your process goals and that's because you're 7 supposed to just look internally in the NTP? 8 DR. HOOTH: We're looking 9 within NIEHS but we are also considering, as 10 we mentioned before, DERT which is the 11 Division of Extramural Research and Training 12 and other groups within the Institute so 13 that... I think when you see our written 14 document we have also considered all of the 15 other sources of data that we'll be 16 inputting into the Program. 17 DR. CARPENTER: Dr. Birt? 18 DR. BIRT: Moving on to the 19 communication and translation goal, I'm, I'm 20 very glad to see that there, but it seems 21 like that's going to be a major effort with 22 NTP kind of changing its test structure. 23 You, you lump together the regulatory 24 agencies and public understanding. I'm just 25 wondering are you thinking those will diverge</p>

<p style="text-align: right;">Page 30</p> <p>1 at some point?</p> <p>2 DR. HOOTH: Certainly. Yeah,</p> <p>3 and in fact in one version of these slides</p> <p>4 we had them separated. We, we are...</p> <p>5 communication is so important for having</p> <p>6 everyone understand where the Program is</p> <p>7 moving and I think this is essential. The</p> <p>8 public needs to understand that we are a</p> <p>9 resource and that they can contact members</p> <p>10 of the NTP to provide them with answers</p> <p>11 about concerns about environmental agents and</p> <p>12 the regulatory agencies. There needs to be</p> <p>13 an open dialogue at all times so that we can</p> <p>14 work together and collaborate to provide the</p> <p>15 best data and interpretation of the data.</p> <p>16 DR. CARPENTER: I'd, I'd</p> <p>17 reinforce that, in terms of the education</p> <p>18 but I'd like to also emphasize the fact that</p> <p>19 you really are going to need to do a lot of</p> <p>20 basic education more than, more than</p> <p>21 interacting, you're gonna have to educate the</p> <p>22 public and probably a lot of the regulatory</p> <p>23 community in the important aspects of the</p> <p>24 proposals. It's, it's going to be crucial</p> <p>25 to get acceptance.</p>	<p style="text-align: right;">Page 32</p> <p>1 of these goals, and one thing that we're</p> <p>2 really looking at is, or one of the</p> <p>3 recommendations that we've made is to have</p> <p>4 ADME, Absorption, Distribution, Metabolism</p> <p>5 and Elimination for each compound under study</p> <p>6 so that we can have better information about</p> <p>7 the half-life and some of the other</p> <p>8 characteristics to help us interpretat...</p> <p>9 interpret any of the other studies that we</p> <p>10 do and focusing a lot on modeling and trying</p> <p>11 to look at our studies and see whether we</p> <p>12 can identify intermediate events, earlier</p> <p>13 morphological or molecular events in the</p> <p>14 disease process that might be predictive of</p> <p>15 the endpoint. We really want to try and be</p> <p>16 able to link chemical exposure to what's</p> <p>17 seen in the tissue and then to find</p> <p>18 molecular mechanisms that might be predictive</p> <p>19 or informative of the endpoint. I don't</p> <p>20 know if that was specific enough, but. So</p> <p>21 just to follow up a little bit more, so</p> <p>22 we've asked ourselves, you know, do we need</p> <p>23 to be collecting other samples at interim</p> <p>24 time points, would that be useful</p> <p>25 information? I want to stress that we're</p>
<p style="text-align: right;">Page 31</p> <p>1 DR. HOOTH: I agree.</p> <p>2 DR. CARPENTER: Dr. Portier.</p> <p>3 DR. PORTIER: Yeah, I think</p> <p>4 that's where... that's gonna be one of the</p> <p>5 strongest components that the DERT, the</p> <p>6 extramural side of the Institute, can do for</p> <p>7 us. They already have a substantial</p> <p>8 training program in a number of different</p> <p>9 areas from kindergarten clean up through</p> <p>10 post-graduate education, and I think they</p> <p>11 would be very interested in potentially</p> <p>12 forming that type of training program as</p> <p>13 part of their extramural activities.</p> <p>14 Michelle, I was wondering if you could give</p> <p>15 one or two very specific examples of things</p> <p>16 you're considering under the first two points</p> <p>17 you've already done...</p> <p>18 DR. HOOTH: Sure.</p> <p>19 DR. PORTIER: ...so that the</p> <p>20 audience can get a feel for what type of</p> <p>21 modifications you're thinking about or what</p> <p>22 type of research you're, you're working on.</p> <p>23 DR. HOOTH: I can go back to</p> <p>24 that slide actually. I was involved with a</p> <p>25 smaller sub-group that worked on the second</p>	<p style="text-align: right;">Page 33</p> <p>1 really challenging ourselves to follow our</p> <p>2 recommendations through, so will the data be</p> <p>3 useful? How, how would you interpret this</p> <p>4 result? Okay, if we make this</p> <p>5 recommendation and we say something is a</p> <p>6 priority, what is the priority? What would</p> <p>7 we list as a high priority versus a low</p> <p>8 priority? So we're, we're trying to think</p> <p>9 all the way through so that it's not just,</p> <p>10 you know, we should be doing this, this and</p> <p>11 this and we're going to have all of this</p> <p>12 data, how is that data gonna be used? What</p> <p>13 will that data tell us, how can it be</p> <p>14 interpreted?</p> <p>15 DR. CARPENTER: Any questions</p> <p>16 from the public? Oh, Chris has got another</p> <p>17 question.</p> <p>18 DR. PORTIER: I just want to</p> <p>19 follow up on one thing Michelle did and in</p> <p>20 terms of the ADME work that you're going to</p> <p>21 be looking towards in terms of every single</p> <p>22 chemical, are you... you're also looking at</p> <p>23 non-animal based predictions of ADME as</p> <p>24 well...</p> <p>25 DR. HOOTH: Right, right.</p>

<p style="text-align: right;">Page 34</p> <p>1 DR. PORTIER: ...so that 2 there may be some high throughput activities 3 involved in being able to look at 4 absorption, distribution, metabolism, 5 elimination, right? 6 DR. HOOTH: Absolutely. 7 DR. PORTIER: And you're 8 looking at those, great. 9 DR. CARPENTER: Thanks very 10 much, Michelle. 11 DR. HOOTH: Thank you. 12 DR. CARPENTER: Now we move 13 to the interagency work group, or sub-work 14 group. Dr. John Bucher from NIEHS. 15 DR. BUCHER: Yes. Thank you. 16 I'd like to tell you a little bit about 17 another arm of this effort at collecting 18 opinions and moving our vision forward 19 through the development of a road map, and 20 this is through the activities of the NTP 21 executive committee work group on, on the 22 NTP road map. We haven't made as much 23 progress as Michelle's group, but I wanted 24 to go over a little bit of what has happened 25 so far with this, with this activity. In</p>	<p style="text-align: right;">Page 36</p> <p>1 Longfellow and Michelle Bennett from NCI; 2 Amanda Edans from OSHA; Jack Snyder from 3 NLM; Bill Farland and Helen Zenick from EPA; 4 and Scott Masten and I are the NIEH 5 representatives to this group. 6 The charge to this group, as was the 7 charge to the NIEHS group, to develop a road 8 map for achieving the NTP vision. 9 Specifically this group is to represent the 10 interests of the agencies which comprise the 11 NTP executive committee. We are also 12 charged to consider all of the NTP programs' 13 activities with specific reference to the 14 interagency interactions and how our various 15 agencies work together to promote and achieve 16 the goals of the NTP. We are also very 17 committed to assuring that any recommended 18 changes that we have serve the best 19 interests of public health and, of course, 20 we'll be providing these recommendations in a 21 written document. Just to give you some 22 idea, I think the discussions that we had 23 yesterday and on the teleconference back in 24 December were still at the stage of, of 25 getting ourselves oriented in to thinking</p>
<p style="text-align: right;">Page 35</p> <p>1 August of 2003 Dr. Portier presented the NTP 2 vision to the NTP executive committee, or 3 the agencies that he mentioned on the slide 4 that he showed that comprised the sort of 5 oversight, government oversight, for the NTP 6 activities. In November of 2003 Dr. Portier 7 requested that the participating NTP agencies 8 appoint work group participants and in 9 December we had an orientation teleconference 10 with those participants. Yesterday was the 11 first time that this group met face to face, 12 and so that gives you some idea of why I 13 can't tell you exactly as, as much as 14 Michelle has told you about the progress of 15 the NIEHS group effort. We are anticipating 16 collating all of the thoughts from the 17 agencies and the reactions and the ideas on 18 how we can move forward and compiling this 19 into a completed report, hopefully in April. 20 The work group participants, you can read 21 through these, they are Marilyn Wind, Michael 22 Babbage from CPSC, Bill Allaben and Paul 23 Howard from FDA, Chris de Rosa from ATSDR, 24 Tom Sinks, NCEH, John Howard and Mark 25 Toraason, NIOSH; Carl Barrett, David</p>	<p style="text-align: right;">Page 37</p> <p>1 about the, the depth of impacts that 2 changing the NTP, the way the NTP does 3 business, the kind of data that the NTP 4 generates, how, what kind of impacts that 5 will have in regulatory affairs, regulatory 6 activities. NTP has been around for 25 7 years and these agencies and, and, have, 8 have had a tremendous impact in, in, in 9 forming the programs that we, that we 10 currently have today and we want to make 11 sure that anything that changes within the 12 NTP is, changes in a way that the data that 13 are generated can be useful, remain useful 14 to regulatory and other agencies, health 15 research agencies and also continue to be 16 very protective in, in the maximum of any 17 public health decisions that could come out 18 of the research that we do. So with that, 19 I'm finished. 20 DR. CARPENTER: Thanks, John. 21 Any questions for... George? 22 DR. DASTON: John, when I, 23 when I think about this effort...let me move 24 back a second. 25 DR. CARPENTER: Thank you for</p>

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

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

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

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

<p style="text-align: right;">Page 42</p> <p>1 Environmental Sciences Institute. 2 DR. HOLSAPPLE: I do have my 3 written comments. Can you all hear me? 4 Well, good morning. My name is Dr. Mike 5 Holsapple. I'm the Executive Director of 6 the ILSI Health and Environmental Sciences 7 Institute here in Washington, DC. I want to 8 begin by thanking you for this opportunity 9 to provide our comments on the NTP vision 10 for the 21st century. Many of you are very 11 familiar with HESI's work on scientific 12 issues and its collaborative work with 13 government, academia, and industry. However, 14 to place our comments in the proper 15 perspective, a few brief remarks about our 16 organization are warranted. Given our 17 mission and diverse scientific programs, we 18 believe that HESI is well positioned to 19 provide feedback and recommendation to NTP 20 regarding its vision. I should emphasize 21 that my use of the terms "we" and "our" is 22 deliberate and illustrates one of HESI's 23 op... hallmark operating principles. We rely 24 very heavily on multi-stakeholder input. In 25 fact, our comments today are, were developed</p>	<p style="text-align: right;">Page 44</p> <p>1 vision to move toxicology from a 2 predominantly observational science at the 3 level of disease-specific models to a 4 predominantly predictive science focused upon 5 a broad inclusion of target-specific, 6 mechanism-based biological observations. We 7 encourage NTP to strengthen partnerships with 8 external organizations to supplement its 9 existing resources. These collaborations 10 enrich the scientific knowledge base of all 11 participants and help build consensus. In 12 the past few years NTP and HESI have been 13 successful partners by jointly sponsoring 14 research, publishing scientific papers in 15 peer-reviewed journals, and co-sponsoring 16 technical workshops to examine and 17 disseminate scientific data. Among the 18 issues on which NTP and HESI have 19 collaborated are the following: transgenic 20 rodent models, genomics, immunotoxicology, 21 DNA adducts, biomonitoring, biomarkers, dose- 22 dependent transitions in mechanisms of 23 toxicity, structure-activity relationships, 24 and protein allergenicity. Virtually all of 25 these areas of collaboration promote NTP's</p>
<p style="text-align: right;">Page 43</p> <p>1 by HESI staff with critical input from key 2 industrial members and academic colleagues 3 who are identified on the front page. I've 4 taken the liberty of providing you with a 5 copy of our 2003 Annual Report. The mission 6 and strategic objectives of HESI are 7 presented on page 4. I want to emphasize a 8 number of key words from those objectives: 9 partnerships, communication and transparency. 10 These words are key because they form the 11 cornerstones of our recommendations to the 12 NTP as it moves forward to implement its 13 2004 vision. Although our objectives have 14 not changed, HESI will engage in its own 15 science mapping session in April of 2004 in 16 order to identify emerging scientific issues, 17 to maximize our efforts to contribute to the 18 resolution of scientific issues, and to 19 ensure that we are focused on the right 20 scientific issues. We are committed to this 21 effort and hope to enlist the participation 22 of key scientists from NTP and NIEHS as 23 valued partners in this process. Regarding 24 our purpose today, let me emphasize at the 25 outset that HESI strongly supports NTP's</p>	<p style="text-align: right;">Page 45</p> <p>1 vision to move toward predictive science. 2 Some of the HESI and NTP collaborations are 3 worthy of specific mention. The HESI 4 Alternatives to Carcinogenicity Testing or ACT 5 Technical Committee organized an 6 international workshop in February of 2003. 7 This workshop was the culmination of an 8- 8 year program in which 21 chemicals were 9 tested in 3-6 model systems by 50 10 laboratories worldwide. The Febru... The 11 February workshop followed a workshop in 2000 12 that was attended by over 350 scientists 13 from the U.S., Europe and Japan and was co- 14 sponsored by the NIEHS, the EPA, the Society 15 of Toxicological Pathology and the SOT. The 16 2003 HESI workshop was organized in 17 cooperation with the NTP, included a lecture 18 by Dr. Portier, and was followed the next 19 day by a workshop organized by NTP. Taken 20 together, the workshops by HESI and NTP 21 clearly advanced our understanding of how 22 transgenic animal models can and should be 23 applied to carcinogenic risk assessment. 24 The HESI Genomics Technical Committee 25 instituted an international, multi-sector</p>

<p style="text-align: right;">Page 46</p> <p>1 scientific collaboration in 35 laboratories 2 including government, industry and academia, 3 which included Dr. Ray Tennant, the Director 4 of the National Center for Toxicogenomics at 5 NIEHS. This effort culminated in a workshop 6 in June of 2003. The June workshop has 7 resulted in twelve papers describing the HESI 8 Committee's research. These papers will be 9 featured in 2004 editions of the journal EHP 10 Toxicogenomics. This research effort also 11 resulted in the co-development and population 12 of the first functional international 13 toxicogenomic database - ToxArrayExpress. 14 The importance of the HESI/NTP 15 collaborations on transgenics and genomics is 16 captured on page 19 of our Annual Report in 17 the following comments by Dr. Tennant: Quote, 18 "The organizational, coordinating, and 19 logistical leadership provided by HESI in 20 both the ACT and Genomics Committees has 21 been outstanding. I believe these two 22 projects to be prototypes of the scientific 23 interactions needed in the development of new 24 research and testing initiatives. The 25 scientific community, particularly in the</p>	<p style="text-align: right;">Page 48</p> <p>1 demonstrable action, the NTP vision could be 2 dismissed as mere rhetoric. As has been 3 articulated in its Vision Statement for the 4 21st Century, NTP initiated a program in 1995 5 to use mechanism-based toxicology to develop, 6 evaluate and validate better toxicological 7 test methods. The 1995 NTP program 8 contributed to major changes in toxicology at 9 the national and international level, and 10 mechanism-based toxicology led to some 11 changes in the scientific basis for public 12 health decisions. However, the NTP 13 accurately states that mechanism-based 14 toxicology did not dramatically reduce the 15 need for the classical tests developed in 16 the 70's and 80's that were the basis for 17 many decisions related to product safety, 18 evaluation of environmental and occupational 19 hazards, and prioritizations of chemicals for 20 further testing. In another document from 21 the NTP, their Year 2000 Current Directions 22 and Evolving Strategies: Good Science for 23 Good Decisions, the NTP leadership emphasized 24 that its commitment to the concept of good 25 science for good decisions created an</p>
<p style="text-align: right;">Page 47</p> <p>1 broad realm of toxicology, needs the type of 2 organizational leadership available through 3 the aegis of HESI to deal with the 4 increasingly complex issues related to 5 assimil... assimilating new concepts and 6 methodologies. I do not know of another 7 forum in which open scientific exchange can 8 be oriented to achieving consensus among 9 highly disparate viewpoints and missions. It 10 is critical that basic, translational, and 11 regulatory scientists have a forum in which 12 all voices and viewpoints can be raised and 13 discussed and research formulated to resolve 14 critical issues. I've been very pleased to 15 participate on two such committees and view 16 their accomplishments as highly successful." 17 There are other examples of previous 18 HESI/NTP collaborations, but in the interest 19 of time I believe I'll move on. As noted 20 above, HESI applauds the NTP for openly 21 communicating its new toxicology vision for 22 the 21st century. However, HESI encourages 23 NTP to recognize the enormous challenge that 24 they have identified and to take concrete 25 steps toward meeting this challenge. Without</p>	<p style="text-align: right;">Page 49</p> <p>1 atmosphere that allows the NTP to be 2 flexible and innovative in its approach 3 toward addressing public health concerns 4 related to chemical exposures at home and at 5 work and in our environment. Their 2000 6 document emphasized that NTP's commitment to 7 flexibility was manifested in its expanded 8 scope beyond cancer to include examining the 9 impact of chemicals on non-cancer toxicities 10 such as those affecting reproduction and 11 development, and the immune, respiratory and 12 nervous systems. These efforts by NTP have 13 had an impact, and this focus should be 14 expanded. Nevertheless, in 2000, the NTP 15 declared that, quote, "Nationally the NTP 16 rodent bioassay is recognized as the standard 17 for the identification of carcinogenic, 18 carcinogenic agents." Perhaps this statement 19 was valid in the year 2000. However, HESI 20 strongly encourages the NTP to revisit this 21 conclusion in the context of its 2004 vision 22 statement. We urge NTP to demonstrate 23 leadership in the area of mechanism-based 24 toxicology by communicating an expansion of 25 its program beyond observational testing into</p>

<p style="text-align: right;">Page 50</p> <p>1 the realm of mechanism-based approaches. 2 These approaches, some of which are used 3 routinely by the pharmaceutical industry, are 4 valuable predictive tools. HESI's multi- 5 sector membership, including the 6 pharmaceutical industry, presents a unique 7 opportunity to share, to share such innovative 8 tools and approaches. One way in which NTP 9 could move toward its vision is to explore 10 alternative testing methods which reach 11 beyond the current testing portfolio. For 12 example, a big step forward would be a 13 scientific shift in characterizing substances 14 for potential carcinogenicity. Simply put, 15 the NTP could move beyond the notion that 16 the NTP rodent bioassay is recognized as the 17 standard for the identification of 18 carcinogenic agents. As part of HESI's 2004 19 strate... Emerging Issues process, we are 20 considering a new project entitled 21 "Strategies for Improving the Hazard 22 Identification of Potential Carcinogens." 23 This strategy is predicated on the following 24 consensus statements about the current 25 situation: Genotoxins can be detected in</p>	<p style="text-align: right;">Page 52</p> <p>1 cause carcinogenicity, several requirements 2 need to be met: the short-term tests should 3 reliably detect genotoxic carcinogens; the 4 critical precursor events of non-genotoxic 5 carcinogens should be able to be detected in 6 sub-chronic tests that may require the 7 development of new endpoints for assessment; 8 the nature of the dose-response curve of 9 genotoxic carcinogens should be established 10 at human levels of exposure. 11 HESI has been committed to the use 12 of mechanistic data as the basis for risk 13 assessments for some time. Clearly, 14 scientific discussion and consensus would be 15 needed if such a shift were undertaken by 16 the NTP approach to toxicology. Consistent 17 with our strategic objectives, HESI believes 18 that this discussion must occur in as 19 transparent a process as possible. HESI has 20 learned through our Technical Committee on 21 Agricultural Chemical Safety Assessment the 22 importance, the importance of attempting to 23 conduct a paradigm shift in a transparent 24 manner. The mission of the ACSA Technical 25 Committee, which is a multi-sector,</p>
<p style="text-align: right;">Page 51</p> <p>1 short-term assays; in bioassay protocols, 2 compounds are tested in rodents at high 3 doses; the background incidence of many tumor 4 types is high in test organisms; many non- 5 genotoxic carcinogens act by a mechanism of 6 little or no relevance to human safety; the 7 relevance to risk assessments of tumors 8 produced at toxic doses of a chemical is 9 highly questionable. 10 The new HESI program projects that 11 identification of potential carcinogens can 12 be improved by taking the following approach: 13 Identify genotoxic carcinogens by well- 14 characterized screens for genotoxicity 15 potential; identify non-genotoxic carcinogens 16 from their primary effects in sub-chronic 90- 17 day studies; depending on the results of 18 these preliminary tests, conduct additional 19 mechanistic-based tests to further identify 20 the specific mode of action; consider that a 21 margin-of-exposure approach for all 22 carcinogens be included to ensure that human 23 relevance is addressed. 24 If the bioassay is to be replaced by 25 a science-based assessment of potential to</p>	<p style="text-align: right;">Page 53</p> <p>1 international group, is to provide a 2 mechanism for reaching consensus across 3 sectors (government, academia and industry) 4 on the development of scientifically credible 5 and viable methods for assessing the safety 6 of crop protection chemicals more 7 efficiently, with fewer animals and fewer 8 artifacts. In 2003 the ACSA project 9 completed a multi-year project to develop an 10 improved testing scheme for assessing the 11 safety of crop protection chemicals. Through 12 the work of three active task forces, a 13 proposal was developed with specific emphasis 14 on integrating metabolic and kinetic data 15 into the safety assessment process; 16 developing a hierarchy of study types, 17 endpoints, and triggers to cover vulnerable 18 life stages; developing a tiered testing 19 framework for endpoints such as 20 neurotoxicity, immunotoxicity, 21 carcinogenicity, and chronic toxicity; and 22 evaluating the range of relevant human 23 exposure situations in the context of the 24 experimental study design. The approach 25 approached by ACSA provides a sound</p>

<p style="text-align: right;">Page 54</p> <p>1 scientific basis for determining whether a 2 given agricultural chemical poses adverse 3 human risk in humans, taking into account 4 the chemical's toxicological properties and 5 use patterns. 6 It has been HESI's experience that it 7 is just about impossible to prove a 8 negative. As such, those who espouse a 9 commitment to mechanism-based risk assessment 10 face a huge hurdle. It is usually very 11 difficult to provide sufficient weight of 12 evidence to persuade policy makers that the 13 quantity and quality of mechanistic data are 14 sufficient to allow the hazard data generated 15 in traditional classical guidelines and 16 prescribed regulatory studies to be 17 discounted. HESI believes that if NTP 18 proposes to be a leader in predictive 19 science, then it will need to evaluate more 20 challenging and perhaps more controversial 21 alternatives. If alternatives are meant to 22 be true refinements or replacements, they 23 should not simply be add-ons to existing 24 tests. To be perceived as truly committed 25 to its new vision of toxicology for the 21st</p>	<p style="text-align: right;">Page 56</p> <p>1 spirit is very much in support of what I 2 think we're trying to do here in terms of 3 the vision. In terms of, of, of some of 4 the details... You had described a 5 potential model for assessing chemicals that 6 comes from the pharmaceutical industry and 7 I'm wondering whether that really fits with 8 the larger audience that, that NTP's data 9 goes to, given that in the, in the 10 pharmaceutical industry there are a couple of 11 goals to pre-clinical testing. One is to 12 eliminate as many potential bad actors as 13 quickly as possible, you know, with the 14 understanding that there will be some babies 15 thrown out with the bath water, and the 16 second is to identify potential toxicities 17 that could then be evaluated in the clinic 18 and that's a different situation than many 19 other chemicals where there is no clinic and 20 there is no evaluation for the, the 21 compounds get approved. Is it, is it your 22 thinking that there would be, say a, a two- 23 stage process depending on what the ultimate 24 end use of the chemical is? 25 DR. HOLSAPPLE: I, I, I</p>
<p style="text-align: right;">Page 55</p> <p>1 century, the NTP should commit to an 2 overhaul of its carcinogenicity program in a 3 manner consistent with the HESI ACSA program: 4 a multi-sector partnership (government, 5 industry, and, and academics); a commitment 6 to communicating progress; and a commitment 7 to transparency. HESI strongly endorses this 8 shift in vision, but it is vital to 9 emphasize that those who are involved in 10 interpreting the data and making the critical 11 judgments must be competent, evidence-driven 12 and capable of arriving at balanced 13 assessments of complex and sometimes 14 contradictory data. I thank you and I'll be 15 happy to entertain any questions. 16 DR. CARPENTER: Thank you, 17 Dr. Holsapple, and, and thank you for almost 18 making the ten minute limit that I forgot to 19 announce before the first speaker. Speakers 20 are asked to present their comments in a 21 ten-minute time period and you didn't do too 22 badly. Do we have any questions for the 23 speaker? 24 DR. DASTON: Mike, I 25 appreciate your comments and I, I think the</p>	<p style="text-align: right;">Page 57</p> <p>1 think you're right. I think NTP is, is 2 facing a pretty high hurdle already with the 3 number of chemicals that they actually have 4 to develop a tox profile for. I think our 5 reference to the pharmaceutical industry was 6 more along the lines of some of their use of 7 predictive tests, the genomics and the 8 transgenics, and the fact that I think 9 they've got those positioned in the right 10 way in terms of capitalizing on that 11 information to build the subsequent test. I 12 think the other thing that we can derive 13 from the pharmaceutical model is their 14 obvious commitment to pharmacokinetics, blood 15 levels as an estimate of dose, which is 16 something that can be extrapolated over. I 17 think probably a better model, if I was 18 looking at it from an NTP perspective, would 19 be more the ag chemical model because 20 they're struggling with the same issues. We 21 don't have the kind of ability to, to move 22 into humans to derive some of the safety, 23 just by putting the chem...., just by putting 24 the chemical into humans, but I think what 25 they've arrived at is trying to grab some of</p>

<p style="text-align: right;">Page 58</p> <p>1 the things that can be applied from a 2 pharmaceutical-type approach. The, the 3 tiered system, the, the movement away from 4 kind of a box checking sort of mentality and 5 allow the data that you have as you develop 6 it, kind of guide the subsequent tasks to, 7 to maximize your efficiency, to, to minimize 8 the number of animals that you actually have 9 to have, and I think they've also done a 10 good job of trying to introduce a commitment 11 toward pharmacokinetic metabolism-type studies 12 which right now, as we move through the 13 safety assessment for a crop protection 14 chemical, are way, way down the road. We've 15 got that really out of, out of sync. We 16 really gotta be developing some of those 17 kinetic blood level-type dose estimates early 18 in the assessment so that we can do a better 19 job of at least attempting to extrapolate 20 that back to human safety issues. 21 DR. CARPENTER: John? 22 DR. BUCHER: Mike, I think 23 the, the, some of the heart of your comments 24 have been consistent with some of the 25 difficulties that we've had in establishing</p>	<p style="text-align: right;">Page 60</p> <p>1 test method or a new procedure or whatever, 2 that's the million-dollar question as to 3 separate the positives from the negatives. 4 Do, do, do I, as a representative of HESI, 5 have the answer? I don't, I don't think so. 6 I think that what it requires though is 7 these kinds of multi-sectored partnerships 8 when we sit down at the table, and as much 9 as we can, try to separate that science 10 from, from the policy applications of it. 11 And I think if, if we try to blend those 12 too quickly too soon at the table, I think 13 we're gonna lose the chance to be able to 14 move the science forward. I think it's 15 gonna require this kind of consensus building 16 as to what the scientific rigor would be 17 associated with defining positives and 18 negative validation. Many of the things 19 that we already have underway. But I guess 20 I would, I would recommend that I think we 21 try to develop it at a scientific level and 22 then take it as a second step to try to get 23 it into the policy level, because I think to 24 try to do both at once is almost an 25 impossible quest.</p>
<p style="text-align: right;">Page 59</p> <p>1 adequate negatives. I think that's what 2 you, you were referring to in the last part 3 of your comments, and with respect to the 4 use of mechanistic information and, and 5 models that give you mechanistic information, 6 it's easier, it's always easier to generate 7 data that you can use in a predictive sense 8 to indicate that something is harmful or 9 that some adverse effect is, is occurring 10 but it's much more difficult to develop 11 models that give you the confidence to say 12 that a negative response in that model is a, 13 is a true negative in all and is a, and is 14 a health protective negative. So, are 15 there, and, and you've obviously given this 16 a lot of thought, are there things that you 17 could recommend that we would try to build 18 in from the very beginning that would give 19 as much weight to the positive findings as 20 validating, in essence, the negative 21 findings? 22 DR. HOLSAPPLE: I think 23 that's kind of the million-dollar question 24 associated with any movement toward either 25 attempting to, if it's a validation of a new</p>	<p style="text-align: right;">Page 61</p> <p>1 DR. CARPENTER: Aaron? 2 DR. BLAIR: A couple of 3 questions to get your thoughts on. One was, 4 George raised it a bit about the 5 pharmaceutical industry. It seems to me 6 like there's a couple distinctions that are 7 quite different than NTP. One is that the 8 pharmaceutical industry is developing 9 chemicals for direct and immediate benefit to 10 individuals; it's personal. NTP's evaluating 11 largely things that are out there already 12 that benefit some people but not a lot of 13 others, but still have exposure. That's, 14 that's quite different, I think, in the way 15 they have to proceed and the way society 16 would, our citizens would want you to 17 proceed. And the other thing is to, I think 18 up to a large extent, that a pharmaceutical 19 industry to, in many cases, developing 20 something new. You know, I realize you pull 21 things from plants and so forth, but it's 22 not like it's already out there all over. 23 NTP largely is looking at chemicals that are 24 already strung around trying to decide if we 25 need to do something about them. And so I'd</p>

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

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

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

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

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

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

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

<p style="text-align: right;">Page 66</p> <p>1 portfolio or however you want to get from 2 point A to point B. If, if we're gonna 3 truly do that, then we just gotta kind of 4 bite the bullet and just start to move in 5 that direction. It's certainly not gonna be 6 simple and that's why I think I'm 7 encouraging NTP to recognize there are lots 8 of groups that are struggling with this out 9 there. Many of them we'll probably hear 10 from today, and that we should do as much as 11 we can to strengthen those kinds of 12 partnerships. We have to leverage that 13 information and that approach, that paradigm 14 shift, across not only science but a 15 societal paradigm shift, we all have to 16 contribute toward that, otherwise it's just 17 not gonna work.</p> <p>18 DR. CARPENTER: Go ahead. 19 DR. SNYDER: Jack Snyder from 20 NLM. As I work within the NIH community and 21 I attend various sessions, I hear discussions 22 throughout the institutes about attempts to 23 define a workable number of cellular targets 24 and you also hear the same kind of 25 discussions in industry. And so my, my</p>	<p style="text-align: right;">Page 68</p> <p>1 actions would lend themselves toward being 2 applied in that sort of a framework. We 3 came up with the P450 kinds of inducers, 4 both the phenol barb and the AH kind of 5 inducers. We came up with a kind of 6 receptor mediated in a hormonal-type level. 7 We came up with the metal kind of the free 8 oxygen radical generating mechanism. We came 9 up with cytotoxicity. So we had those four 10 that we felt pretty comfortable with where 11 we could draw upon existing knowledge about 12 specific chemicals that we believe would fit 13 in to that mode of action. However, we 14 still had another category that we kept 15 having to kind of dump over here on the 16 side, you know, others... And, and I think 17 the way that this is gonna have to play out 18 is we just gotta get our arms around PPA 19 alpha, P450-type, the estrogen-type of cancer 20 models, the cytotoxicity, the metal overload 21 type of models, and if we could begin to 22 build a consensus around what it would take 23 to accept that we've achieved that mode of 24 action and know what we're gonna do with 25 that, once we've interpreted that, then at</p>
<p style="text-align: right;">Page 67</p> <p>1 question to you is, with HESI and the other 2 interactions that you have, have there been 3 discussions about trying to get a handle on 4 a finite or a workable number of cellular 5 targets? And begin to define the vision to 6 some extent in that way, were it to have 7 that kind of analysis contribute to the 8 vision of where toxicology is going. Would 9 you like to comment on that?</p> <p>10 DR. HOLSAPPLE: Yeah, I'll 11 give you a real, hopefully a short example, 12 something that just recently happened within 13 the last couple of weeks. A group of us 14 got together to consider rodent liver tumors. 15 So it's strictly hepatocarcinogenicity. 16 We're not going for the adenocarcinomas or 17 anything like that, very limited kind of a 18 scope. Trying to build on that framework 19 that George made reference to where we were 20 talking about the PPAR alpha agonists as a 21 mode of action where we could develop a 22 framework to begin to know what to do with 23 the chemical once we had defined that PPAR 24 alpha mode of action. We sat down to try 25 to figure out what other kinds of mode of</p>	<p style="text-align: right;">Page 69</p> <p>1 least we've carved off a huge lay of the 2 land. Have we got everybody covered? No. 3 It just...I, I think that's getting at that 4 question that's not gonna be that simple. 5 But I think if we can begin to get our arms 6 around these modes of actions and reach a 7 consensus as to, once we have that data, 8 what are we gonna do with it in a public 9 policy kind of an application? At least 10 we've cut a lot of it away. We can 11 continue to fo..., focus our research efforts 12 on trying to develop additional modes of 13 actions. What do we do with that other bin, 14 so it's not, doesn't remain another bin?</p> <p>15 DR. SNYDER: I appreciate 16 that comment. Thanks. Because it's, it 17 jibes with what, the kinds of discussions 18 you see swirling around NIH which is silos 19 of targets and trying to define 20 intracellularly silos of targets because you 21 can't do everything with every target, but 22 it, what you just said to me, I captured 23 that as silos of targets.</p> <p>24 DR. HOLSAPPLE: I think it 25 becomes kind of how we build and define a</p>

<p style="text-align: right;">Page 70</p> <p>1 mode of action, what, what it's gonna take 2 to be actually go into one of those silos. 3 DR. SNYDER: Thank you. 4 DR. HOLSAPPLE: Knowing full 5 well that they probably, it won't be that 6 clean. As scientists, I think we get too 7 bogged down in wanting to classify everything 8 very cleanly and it rarely works that way. 9 DR. CARPENTER: Mark, go 10 ahead. 11 DR. TORAASON: You mentioned 12 consensus a couple times. Would you comment 13 on how you might include validation in your 14 process and where you see it might be an 15 impediment to moving forward or... 16 DR. HOLSAPPLE: Validation is 17 frequently kind of one of those bad words 18 that I guess as a, as event scientists we 19 want to steer away from, from test methods 20 and whatnot. I don't, I think it's to try 21 to build a definition of consensus into an 22 understanding of what validation is is almost 23 an oxymoron. I think consensus is more of a 24 reaching an understanding in, in a conceptual 25 sense and validation, I think, has got a lot</p>	<p style="text-align: right;">Page 72</p> <p>1 question. It's a comment. I want to thank 2 Mike for coming out and giving us quite a 3 substantial amount of material to look at 4 and think about and I wanted you to know 5 that we do appreciate it and I do have ideas 6 of how HESI could help. So, I'd be very 7 happy to talk with you at some point. Thank 8 you. 9 DR. HOLSAPPLE: Thank you. 10 DR. CARPENTER: Our next 11 speaker will be Dr. Ki-Hwa Yang from the 12 National Toxicology Program of Korea. 13 DR. YANG: Thank you, Dr. 14 Carpenter. Good morning, ladies and 15 gentlemen. My name is Ki-Hwa Yang from the 16 National Institute of Toxicological Research 17 in Seoul, Korea. And then I also head of 18 National Toxicological Research in Korea. 19 NTP in Korea is just three years old. We 20 started from 2002, so this year is just the 21 third year. So we have not established 22 fully, I mean, we just benchmarked the U.S. 23 NTP. However, the structure is not fully 24 developed. At the beginning of my 25 presentation, I really appreciate U.S. NTP</p>
<p style="text-align: right;">Page 71</p> <p>1 more rigor associated with it. I think that 2 what we've achieved through the ICCVAM 3 process, you know, which NIEHS and NTP have 4 been a very active participant in setting 5 that bar for what it takes to validate is, 6 is pretty much the way we ought to be 7 proceeding. I can tell you that some of the 8 feedback I get from many of my industrial 9 members is they, they want to shy away from 10 the V word, especially shy away from the 11 ICCVAM because it is such, such a rigorous 12 standard. I, I think we, we can afford to 13 have that kind of rigor to begin to accept 14 that a, that a method is validated. If we 15 can achieve that bar and then declare a 16 method is validated, I think we really have 17 done something that means it ought to be 18 integrated into, into both the science and 19 the public policy arena. I don't know if I 20 answered your question or not. That was a 21 tricky question. 22 DR. CARPENTER: Thank you, 23 Dr. Holsapple. Oh, we have one more 24 question or comment. Chris? 25 DR. PORTIER: It's not a</p>	<p style="text-align: right;">Page 73</p> <p>1 for inviting me to speak in the NTP Public 2 Meeting for its Vision. When I was 3 suggested to submit a comment, I was 4 hesitating what I would present and then I 5 decided to explain what KNTP is focusing 6 now. That is the medicinal herb problem. 7 I'm going to introduce the status regarding 8 medicinal herb in Korea. Many of you 9 figured out what I, what I'm going to talk 10 about in my written comment. In this 11 presentation I would just show you some 12 supplement. As I know, NTP also sponsored 13 the International Workshop to evaluate 14 research needs on the use and safety of 15 medicinal herbs held in 1998. After then, 16 toxicological studies for 15 items of herbs 17 and herbal, herbal complement have been 18 performing. I think this area should be 19 strengthened more by NTP because the Korea 20 import considerable amount of dietary 21 supplement from, from the U.S. Herbal 22 medicines literally growing in economic 23 importance. One market size would be about 24 43 billion dollars. The market size of 25 herbs in Korea is estimate, estimated, I, I</p>

<p style="text-align: right;">Page 74</p> <p>1 just...300 million U.S. dollars and then 2 imported sixty, 61,000 from foreign 3 countries. There are 550 items of herbs, 4 minerals and material from many more are 5 listed on the KP and then North Korea has 6 446 and in Japan and 117, China has 564 and 7 Taiwan has 364. This means so many herbs or 8 minerals are used for traditional medicine. 9 I would like to introduce the Korean 10 traditional medicine in brief. KTM was 11 ori..., originated from China but have been 12 developing independently since Dr. Jun Heo is 13 a very famous traditional, Korean traditional 14 medicinal doctor integrated it in two series 15 of books, Donguibogam, that were medical 16 encyclopedia in early 17th century. There 17 are three areas of pathology in these books: 18 internal medicine, surgery and miscellaneous. 19 The book was registered as the National 20 Treasures. He also described medicinal herb, 21 herb collection method, and examples of 22 ancient prescriptions. He also described use 23 of herb: decoction, pill, powder, extract 24 or soak. He...and also acupuncture, 25 moxibustion, exercise, et cetera. He</p>	<p style="text-align: right;">Page 76</p> <p>1 medicine. You can figure out the activity 2 in web site www.fhnm.net. The objective of 3 the forum is to promote public health by 4 recognizing and developing standards and 5 technical guidelines that aim to improve the 6 quality, safety and efficacy of herbal 7 medicine. The member countries, region of 8 FH...FFHH are China, Japan, Republic of 9 Korea, Singapore, Australia, Viet Nam and 10 Hong Kong. In this table I'm going to show 11 you what KNTP studied. KNTP performed 12 simple studies to figure out causes of toxic 13 hepatitis in Korea in 2003 from March to 14 October. During the eight month period, 55 15 patients were admitted to the hospital due 16 to toxic hepatitis. Most of them suffered 17 from using herbs, here, and then with this 18 simple study we estimated about 1,500 19 patients would be treated annually. There 20 is some difficulties handling herbal 21 poisonings such as documentation of the 22 health effect, the determination of a cause- 23 effect relationship, the identification of 24 the proprietary substances and active 25 ingredients, the characterization of the</p>
<p style="text-align: right;">Page 75</p> <p>1 organized by disease classification and each 2 illness and also described with related case 3 histories and prescriptions. In the end of 4 19th century, Dr. Je-Ma Lee, he also very 5 famous KTM doctor, established constitutional 6 medicine theories. In his theories he 7 classified human beings as four constitutions 8 and then he treated the patient differently 9 according to the type of constitution. Oh, 10 I'm sorry. Now I move...I'm moving to the 11 problem in using medicinal herbs as discussed 12 in 1994...6 International Workshop. There 13 are so many problems in using herbs such as 14 standardization, consumer education, herb/drug 15 and herb/herb interactions, potential 16 toxicity associated with high dose or 17 prolonged use and sensitive subpopulations. 18 In the case of standardization we have to 19 specify the next. First, species of plant 20 used, harvest schedule, storage methods, 21 physical characteristics of raw material, 22 methods for producing uniform extract, 23 knowing which part of plant contains the 24 desired bioactive component. Recently, WHO 25 organized a forum on harmonization of herbal</p>	<p style="text-align: right;">Page 77</p> <p>1 kinetic pattern and tox/path effect, the 2 uncertainty of the prognosis and treatment. 3 I'm going to skip this slide. There are 4 four types of risk factors of herbs. The 5 first is natural toxin. For example, 6 Chuanwu or Caowu which contains aconitine 7 could evoke neurological and cardiovascular 8 toxicity and the next is adulteration with 9 heavy metal and western medicine such as 10 steroids, NSAIDs, CNS stimulants, diuretics 11 and antibiotics. Thirdly, contamination in 12 botanical product such as pesticides, molds 13 and heavy metals. Current research areas of 14 KNTP, just like U.S. NTP because we just 15 benchmarked U.S. NTP, chemicals, 16 carcinogenesis, herbal medicines, mycotoxins 17 and toxicogenomics. We are just focusing 18 the herbal medicine part. KNTP performed 19 the five herbal tests for 90 days toxicity 20 studies in 2003, Pueriaria Root, Glycyrrhizan 21 Liquorice Root, it's very difficult to 22 pronounce, Pinellia Tuber, Safflower Seed and 23 Aristolochiae Radix. I can just, just show 24 you some, the result of the study. This is 25 the preliminary data of a toxicity testing</p>

<p style="text-align: right;">Page 78</p> <p>1 of safflower seed, seed. We did not expect 2 the result. Safflower seeds which contain 3 large amount of conjugated linoleic acid and 4 glyceride, are known to have effect on 5 osteoporosis, bone fracture and cholesterol 6 metabolism in Korea. Through the study we 7 found that there are dose dependent decrease 8 of liver weight; however, other internal 9 organs were unremarkable. I think you 10 can... here you can see that, ahhh, liver 11 weight is decreased in dose dependent. 12 Microscope, microscopically there are no 13 significant pathological changes in the liver 14 other than somewhat dilated sinusoidal space, 15 compared with the control, just seems to be 16 a little bit dilated sinusoidal space, 17 sinusoidal space and here's the just control. 18 There are no definite abnormal findings 19 including critical and anatomical pathology 20 other than dose dependent-decrease of the 21 liver weight. So we should investigate the 22 mechanism of decrease of the liver weight. 23 On second case... you may know this case. 24 Nortier reported this summary in the New 25 England Journal of Medicine in 2000.</p>	<p style="text-align: right;">Page 80</p> <p>1 occasionally in the high dose case cancerous 2 lesion in the renal pelvis on the left in 3 the high dose group. You can see the normal 4 pelvis on the left and then in this slide 5 you can see the focal hyperplasia, moderate 6 dysplasia, and even the transitional cell 7 carcinoma we observed. So with this kind of 8 experiment the KNTP plans to establish the 9 standard toxicology test for, for medicinal 10 herb to make a list of medicinal herbs for 11 toxicology, toxicology study according to 12 reviewing literatures and nationwide 13 surveillance for herb poisoning to set up 14 the standard method for preparing the medical 15 herb material, medicinal herb material, to 16 set up a special condition for investigating 17 the toxicities, and to investigate the 18 mechanism of toxicities. Thank you very 19 much for your kind attention and I really 20 appreciate the U.S. NTP for inviting me to 21 present my comment. Thank you very much. 22 DR. CARPENTER: Any questions 23 for Dr. Yang? 24 DR. BIRT: Yes, Dr. Yang. 25 What approach are you going to use to decide</p>
<p style="text-align: right;">Page 79</p> <p>1 Urothelial carcinoma associated with the use 2 of the Chinese herb Aristolochia fangchi. 3 The course of the disease or instant, the 4 company used Stephania tetrandra as the 5 source material. However, Aristolochia 6 fangchi replaced it in sometime because both 7 plants look like very similar. 18 out of 39 8 patient had urothelial carcinoma and then the 9 patient also has, had the Chinese herb 10 nephropathy, a unique type of rapidly 11 progressive renal fibrosis. It has been 12 described in 100 young Belgian women who had 13 followed a slimming regimen containing some 14 Chinese herb. Aristolochic acid became of 15 toxicological interest after the discovery of 16 its nephrotoxic, mutagenic, and antifertility 17 effect. We performed a 90-day toxicity 18 study for aristolochic contorta which 19 contained aristolochic acid. This is a 20 clinical dose, usually used for patients. 21 Here we can see the definite failure of the 22 weight gain in dose dependent. So it seems 23 to be a very effective dietary regimen. And 24 then we found, we found pre-cancerous... here 25 we can see the hyperplasia and even</p>	<p style="text-align: right;">Page 81</p> <p>1 on the doses that you're going to use of 2 your herbs, or the doses of the toxic or 3 active constituents? 4 DR. YANG: We usually used, 5 I, you mean, I mean the, use the dose at, 6 at pro..., pro..., proving that it test and 7 use the clinical dose with constant rate to 8 increase the dose and then there is, if 9 there, there, there were no toxicity just we 10 used the two gram, two gram body weight. 11 DR. BIRT: Do you begin by 12 considering human exposure? 13 DR. YANG: I'm sorry? 14 DR. BIRT: Human exposure? 15 The dose that people are taking? 16 DR. YANG: No. Actually, 17 the, the, the items we choo..., we chose was 18 the rising consumption drugs and then some, 19 some herbs was known as I mean having 20 toxicity in the literature. 21 DR. CARPENTER: Seeing no 22 other questions, thank you, Dr. Yang. I 23 think at this time I'd like to take a break 24 and have about a ten minute break, come back 25 about 10 minutes to the hour, please.</p>

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

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

1 the test methods that we utilize in the last
 2 40 or 50 years. And, and I'm, I'm trying
 3 to, to, as a toxicologist I think I ask
 4 myself why is that. And I think what, what
 5 it is is we've not engaged as effectively as
 6 we can with broader parts of our
 7 communities, including the regulatory areas,
 8 to think about understand..., how we can
 9 implement better mechanisms of, of toxicity
 10 into decision-making. And again, I, I'm
 11 pleased to see that, that NTP has planned
 12 for additional opportunities for public
 13 review, comment and, and discussions.
 14 Dialogue is always critical, and, and we've
 15 had some discussion already today about
 16 education and outreach and clearly these
 17 types of fora are, are, are critical for
 18 that. You, you can't just change, you have
 19 to plan for change. So partly what goes
 20 into this vision is the transitions that
 21 need to be made in planning for change and I
 22 think that needs to be developed with an
 23 opportunity for clear public involvement and
 24 discussions.
 25 NTP is very unique. It is an

1 interagency program and as such it has the
 2 vision that, the effort that NTP is
 3 undertaking at the present time has great
 4 promise to really promote and enhance the
 5 scientific cooperation, harmonization and
 6 efficiencies across agencies in the federal
 7 government, particularly in the development
 8 and application of new tech..., tech...,
 9 technologies, new methods in toxicology and
 10 risk assessment. We encourage and support
 11 the focus on mechanistic approaches for
 12 hazard characterization and risk assessment.
 13 And indeed, we do support and think this is
 14 another opportunity for NTP to, to
 15 demonstrate its leadership to develop
 16 standardized and validate new, revised and
 17 refined methods that can have a potential
 18 to, to reduce or replace laboratory animals.
 19 So that's at, that's kind of at the
 20 30,000 foot level. Some specific
 21 recommendations I'd like to put into focus
 22 today are, are really two here. This, as
 23 NTP looks at new technologies, new methods
 24 and, and trying to figure out how they fit
 25 into the programs, how they become utilized,

<p style="text-align: right;">Page 86</p> <p>1 how this, we've heard some discussion about 2 a paradigm shift occurs, to consider the 3 need for, for, for validation and where that 4 fits in with new test methods that they plan 5 to use. And that specifically with 6 genomics, I think genomics is a great 7 promise for all of us in this field. But 8 how could NTP, what, what additional work 9 could NTP do, plan to do today to help to 10 insure that, as it's developing, those 11 results become utilized, both within NTP 12 programs and more broadly across the other 13 agencies that are part of NTP. 14 So let me just take the first one, 15 ah, validation. Validation of new, revised 16 and refined test methods is required under 17 the ICCVAM Authorization Act of 2000. I'm 18 not a lawyer so I can't go in to all the 19 details of what that Act entails but, 20 suffice it to say that NTP through its 21 Center for Evaluation of Alternative Test 22 Methods is well situated in position to 23 conduct such high quality and scientifically 24 rigorous validation studies as they're 25 needed. As these new methods move from,</p>	<p style="text-align: right;">Page 88</p> <p>1 the, the, the test method. Strengths, 2 limitations and uncertainties in the data 3 interpretation. When you know what a 4 positive clearly is a positive, when you 5 know what a negative is and what it means, 6 and when you have some equivocal results, 7 need to be established before these test 8 methods move into routine use. And then 9 clearly here's one that, that, that is a 10 challenge to all of us in looking at moving 11 new and revised methods from the laboratory 12 bench, research bench, into a routine testing 13 program. It's providing this, this keyword 14 sufficient data to permit the appropriate 15 comparison with the proposed substitute and I 16 think Mike already mentioned this issue about 17 really looking at how you could obtain data 18 that satisfies that question so you could 19 really substitute a test method rather than 20 adding on as an additional test method. And 21 it may not be just a method, it may be a 22 battery, as we've heard earlier. 23 So that's kind of some thoughts on, 24 on... let me go back to, to validation. I 25 think one of the key take-away messages I'd</p>
<p style="text-align: right;">Page 87</p> <p>1 from the investigation bench to 2 standardization and then eventually on the, 3 on the verge of being perhaps pulled into a 4 formal testing program, there's a need to 5 make sure that the test methods are valid 6 for the purposes that they're intended. And 7 this validation, by necessity, needs to be a 8 priori not a posteriori. So it needs to be 9 conduc... completed prior to incorporating 10 these assays into the routine testing 11 programs. Why is that? Because it 12 establishes the relevance and reliability of 13 those test methods, and validation itself is 14 a process whereby the information is made 15 available that's needed to interpret and 16 understand the significance of the results. 17 Validation must address mechanistic 18 relevance of the method to the endpoint of 19 concern in humans, and here for example 20 carcinogenicity. But it could be any 21 endpoint. So you have to understand the 22 mechanistic relevance of that endpoint. I 23 spoke about reliability and reproducibility. 24 Clearly specifying the criteria for 25 appropriate use in the limits of the, of</p>	<p style="text-align: right;">Page 89</p> <p>1 like to, to leave here today, and it's in 2 the written comments but I didn't put it up 3 on the slide, is that the importance of 4 considering validation and the process of 5 validation as you're looking at development 6 of new methods. Now, now this becomes very 7 difficult in practice because you're looking 8 at something that's at the research bench 9 early and maybe later will get brought 10 forward into the routine testing program. 11 But I think NTP as they go forward with 12 thinking about the vision, needs to think 13 about some critical methods that they're, 14 they're, they're looking at. Genomics may 15 be one, there may be others as well, or high 16 throughput and think about what would be an 17 appropriate validation approach for these 18 methods and then to program in, if you 19 would, a discussion of that and 20 implementation of those validation steps 21 early in, early on in the process so that 22 when you're ready, or think you're ready to 23 implement that in a testing paradigm, that 24 information is available and there is 25 consensus that the method does what it says</p>

<p style="text-align: right;">Page 90</p> <p>1 it's supposed to do, that perhaps you can 2 indeed substitute this method for an alt..., 3 as an alternative method. But the point is 4 that this needs to be thought of early in 5 the process or, and not at the end of the 6 process, leave it at that. And I think 7 oftentimes we've, we've kind of tried to 8 tack validation on to methods development at 9 the end and then that creates problems. 10 Genomics. Genomics, as I said, has 11 great promise, but there's still a lot to 12 do. A lot is underway and I don't want to 13 give the impression that, that folks haven't, 14 these are, you know, folks haven't thought 15 about some of these ideas and that these 16 aren't already being addressed in some way, 17 shape or form by various organizations. But 18 I think that, look at these, these areas of, 19 of additional research and think about is 20 NTP as a unique entity where it's situated 21 in the federal government, how it might be 22 able to truly move the ball forward that 23 benefits not only NIEHS but also the other 24 agencies that are participants in NTP and 25 the general public and the industry as well.</p>	<p style="text-align: right;">Page 92</p> <p>1 that there are no clear guidelines for, for 2 correlating qualitative or quantitative 3 changes with potential for adverse effects. 4 So, so additional work needs to be done to 5 understand the application of these methods 6 within the toxicology and risk assessment 7 framework. But, given at the speed at which 8 the methods are evolving, it's probably not 9 appropriate to recommend standardization or 10 validation or it may be not, probably not 11 even practical at this time because of the, 12 the evolution of the technologies. But 13 what, what we do suggest is NTP or others 14 engaged in this process consider developing 15 best practice guidelines for conducting and 16 reporting these assays. And for example, on 17 noting experimental conditions in the refer, 18 research plat, platforms, robustness of the 19 information. And then guidelines for 20 communication, audience-appropriate 21 communication for the assay results. 22 So with that I'll, I'll end by just 23 saying in summary that it's appropriate for 24 EPA, or for NTP to be undertaking this, this 25 vision, discussion at the present time. We</p>
<p style="text-align: right;">Page 91</p> <p>1 So certainly looking at the framework of 2 genomics, looking at a framework for use of 3 genomics within, within the paradigm of risk 4 assessment is, is clearly needed. 5 Recognition that if you're gonna look at 6 genomics in the area of epidemiological 7 studies there needs to be an ability to 8 obtain and keep information on samples from 9 large and diverse populations. And of 10 course there are other issues related to 11 genomics that go beyond kind of the strictly 12 the science and having been made to think 13 about creating a stiu... or creating 14 appropriate fora or venues for discussion of 15 these as part of the scientific process of 16 methods development and application. So 17 focusing beyond the science is needed clearly 18 in genomics. 19 One of the areas that just... I 20 think comes down to a specific recommendation 21 where NTP I think can help in the shorter 22 term rather than a longer term, is this 23 issue of looking at platforms and, and 24 establishing best practices. We're, we're 25 faced with a situation now with genomics</p>	<p style="text-align: right;">Page 93</p> <p>1 look forward to participating in future, 2 future meetings and we think that the 3 process as, as has been described will be 4 one for which all of us within the different 5 communities that we represent will benefit 6 from, from this effort in the long term. 7 Thank you. 8 DR. CARPENTER: Thank you, 9 Dr. Becker. On his way back to his seat, 10 George is ready to ask a question. Go 11 ahead, George. 12 DR. DASTON: Rick, thank you 13 for your comments. In terms of, of the 14 genomics and standardization, you know, there 15 are the Miami standards that have been 16 developed and there is a draft of Miami 17 standards for toxicogenomics. Is there any 18 effort that you're aware of that is going to 19 move beyond those standards to provide the 20 kinds of minimum reporting requirements that, 21 that, that you'd like to see? 22 DR. BECKER: I guess, George, 23 I'm not aware of any and this is, what I'm, 24 what I'm suggesting is that there is a gap 25 there. Not only for reporting requirements</p>

<p style="text-align: right;">Page 94</p> <p>1 but think about the use of this information 2 across different agencies that comprise NTP 3 and others that might utilize the information 4 that's developed. So I think there is a 5 real opportunity here for NTP and the 6 agencies involved in NTP to take a 7 leadership role in fostering best practices 8 of use and communication of the results from 9 these new techniques and technologies. So, 10 I think it's an opportunity that, that 11 should be explored within the vision and, in 12 fact I'm sure it is, is being explored. 13 DR. CARPENTER: Bill, did you 14 have a comment? 15 DR. ALLABEN: I'd just like 16 to ask a question. Bill Allaben, FDA. You 17 focused a good deal on validation and 18 mentioned the ICCVAM process. I would like 19 to ask a question whether you believe the 20 current bioassay, as we know it, is a 21 validated process? 22 DR. BECKER: Was that a 23 loaded question or not? I think that as we 24 go forward and look at... I'll answer it 25 this way. As we go forward and look at</p>	<p style="text-align: right;">Page 96</p> <p>1 within that, that framework. So I think 2 I've answered your question along that 3 regard. I'm not sure that we're ever going 4 to say does this particular model replace 5 the rodent bioassay for all things. But 6 provided that you can get more mechanistic 7 information and use the results of that 8 model, and it is validated, use the results 9 of that model for a specific purpose that 10 it's intended, I think you can use, use that 11 information. 12 DR. ALLABEN: Could this be 13 more significant scientific agreement than a 14 validation process, then? 15 DR. BECKER: Well... 16 DR. ALLABEN: Because I see 17 if you, if you plug everything through the 18 ICCVAM mechanism you're gonna be ten years 19 or out before you really get wherever the 20 NTP wants to go. 21 DR. BECKER: Yeah, I think 22 you have to look at the ICCVAM mechanism 23 with a viewpoint of principles in mind and 24 that, yes, there is a need for scientific 25 consensus and that's essentially what ICCVAM</p>
<p style="text-align: right;">Page 95</p> <p>1 developing alternatives and substitutes, you 2 have to benchmark against something, okay. 3 And we have years and years of available 4 information on that assay. So, in 5 particular, if you're asking the question can 6 we substitute a new or alternative assay for 7 this assay, then you really have to ask the 8 question what is the information that I hope 9 to gain from this new assay that, that is 10 correlated to, or relevant to, what I 11 understand about the old assay. So clearly 12 in the case of laboratory animal models for, 13 for carcinogenicity we have established 14 relevancy to humans. You know, virtually 15 every human carcinogen does produce cancer in 16 a model or another. Now that doesn't mean 17 that every chemical that produces cancer in, 18 in, whatever dose level, by whatever 19 mechanism in an animal has a carcinogenic 20 risk, poses a carcinogenic risk to humans. 21 But there is relevancy of that model. So 22 the real question here is to tease out, as 23 is being done with transgenics and others, 24 the specific question that you're asking of 25 that model and making sure it can perform</p>	<p style="text-align: right;">Page 97</p> <p>1 provides. There also is a need, critical 2 need for quantitative data in order to judge 3 the, the reliability, the reproducibility of 4 the model. In terms of a formal ICCVAM 5 process, I think what's necessary in some, 6 what will be necessary, is to be able to 7 approach this from a, both a pragmatic and a 8 scientific mind at the same time, to 9 recognize that flexibility will be needed in 10 order to satisfy the principles of, of, as, 11 as articulated by ICCVAM method for, for 12 validation. I'm not quite sure that you 13 will ever be able to articulate, or as you 14 point out, Bill, to, to obtain the, you 15 know, an N of , of 50 or 100 for some of 16 these in vivo types of assays in a realistic 17 time-frame. So you need to be creative. 18 But I think that's where one can be flexible 19 but still be true to the principles and, and 20 that's what I would hold, hold as an 21 important goal. On the same, you know, at 22 the same time though, we don't want to end 23 up with, and this is, and others will speak 24 on it, we don't want to end up with the 25 double standard of demanding a certain level</p>

<p style="text-align: right;">Page 98</p> <p>1 of compliance for lack of a better term in a 2 validation process for a substitute, 3 particularly non-animal studies when you have 4 a different level of compliance, if you 5 would, from a scientific basis other, for 6 animal studies. So that, that's an area 7 that, that requires some balancing. But I 8 think it can be done and, and, you know, 9 obviously the, the processes that are, I 10 guess I will make it commercial, the 11 processes are in place for, for these types 12 of dialogues to occur. The, the FACA 13 committee for, for the alternative methods is 14 one place, the interagency group, ICCVAM is 15 another. Where these, these opportunity for 16 dialogue to solve some of these problems. I 17 just think that more openness and recognition 18 that some degree of flexibility is absolutely 19 necessary, is a key.</p> <p>20 DR. CARPENTER: John. 21 DR. BUCHER: Yeah, I wanted 22 to follow up a little bit on the validation 23 issue. The vision as it's stated implies a 24 movement from a disease-based model to 25 mechanisms-based models and I was wondering,</p>	<p style="text-align: right;">Page 100</p> <p>1 in, and I think what you need to do is, in 2 an evaluative framework. Not separate from 3 but within that context of the evaluative 4 framework. So this is where I was talking 5 about, it's a little hard when you're taking 6 a, a bench research methodology and trying 7 to project ahead and think about how it 8 might fit in with the framework. But if you 9 can think about the framework and then say 10 this is a type of method that we need, then 11 you can start, or we have, and then you can 12 start asking the questions about, well, what 13 does validation mean in terms of use of that 14 information within the evaluative framework 15 and I think that's probably the best way to 16 go.</p> <p>17 DR. CARPENTER: But again, I 18 would also get a plug in. I think these 19 types of discussions will be very good to 20 engage the ICCVAM FACA. I'm sorry, I don't 21 get the term right. It's a, the, the other, 22 the Alternative Methods FACA on, on, on 23 these types of discussions. Rather than 24 simply trying to say, you know, we need 25 test articles and, you know, three different</p>
<p style="text-align: right;">Page 99</p> <p>1 to me that, that provides some inherent 2 difficulties in, in validation and the way 3 that you've been talking about it. Is there 4 a, is there any thought that you've given to 5 how one would use the principles of 6 validation in developing mechanism-based 7 models that could be used for informing 8 public health on a, on a different level 9 than a disease-by-disease basis?</p> <p>10 DR. BECKER: I think there, 11 there, there are ways to go about this and 12 one, one I, I guess what I would say is 13 that I don't have specific recommendation, to 14 be honest, I don't have specific 15 recommendations to make today. But I think 16 if you look at some of the, some of the 17 work that's been done with the genetically 18 altered mice, mouse models, the transgenics, 19 and think about what, what the questions 20 that are being asked of those models in 21 terms of what they're capable of predicting 22 in, in terms of response to, to exposure, I 23 think you can begin to use that information 24 to, to ask how could we use the ICCVAM 25 principles with such, these types of models</p>	<p style="text-align: right;">Page 101</p> <p>1 laboratories, and, you know, et cetera. I 2 think that's, those types of details would 3 be, are... need to be worked out for certain 4 methods but for other approaches you need a 5 more thoughtful process.</p> <p>6 DR. SNYDER: Regarding 7 validation. How much validation should be 8 done at taxpayer expense as opposed to 9 validation that should either be done in the 10 private sector voluntarily versus be 11 required? You have any thoughts about that 12 distribution of effort?</p> <p>13 DR. BECKER: I'll reserve 14 comment on that. I haven't really thought 15 about that but I think that it's probably a 16 good question to, to, to think about as, as 17 the vision moves forward. There are 18 certainly clearly indications and 19 opportunities for partnerships and we've seen 20 this earlier, my, my memory's come back. 21 We've seen this with other alternative 22 methods that have come forward for, for 23 development, standardization and validation. 24 So I think exploring opportunities for, 25 perhaps this is a bullet under this methods</p>

1 validation effort, to explore opportunities
 2 for partnership across sectors is a very
 3 good placeholder for further discussion.
 4 DR. CARPENTER: Go ahead.
 5 DR. HOLSAPPLE: Just a
 6 comment about that. I think the, the
 7 biggest success that ICCVAM has had, this is
 8 Mike Holsapple from HESI, was the local
 9 lymph node, which was really the first time
 10 we really worked through that process, and,
 11 and a lot of that data was really developed
 12 by the private sector. A lot of the
 13 industry labs who had an interest in trying
 14 to make sure that that assay was accepted
 15 for a variety of reasons, so a lot of that
 16 work, in terms of what, what we as the
 17 public had to support, I think there were
 18 some government labs that contributed
 19 something but the yeoman's share of the data
 20 that went in to at least the local lymph
 21 node ICCVAM approval process was generated in
 22 the, in the industrial sector and the
 23 academic sector.
 24 DR. CARPENTER: Chris.
 25 DR. PORTIER: I don't

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

1 as we look at this issue and it's clear that
 2 we have to have a broad-based scientific
 3 discussion about what's gonna constitute
 4 regulatory acceptance of a testing method
 5 that may include a suite. It's a difficult
 6 issue.
 7 DR. BECKER: Let me just
 8 make, one, one last comment, if I can. I
 9 think one, one of the areas that we have to
 10 remember is, is for the purposes intended,
 11 it's kind of where you get at with this
 12 method, and, and one could well envision a
 13 particular, for example, a through... high
 14 throughput method being for priority setting
 15 or screening purposes, which, which is a
 16 different purpose, the outcome of which, you
 17 know, you, you would use that information
 18 for a different purpose than, you know,
 19 what's another example, citing a regulatory
 20 threshold. So I think that, that oftentimes
 21 because the discussion is not focused on
 22 what's the intended purpose, which gets to
 23 this issue of framework, you know, you get
 24 into a cart and horse situation of, or a
 25 chicken and egg is probably a better way of

1 saying it, which comes first. And, and so I
 2 think it's important to articulate a
 3 framework and think about the method, and
 4 that method may work in one framework or may
 5 work in different frameworks, and they may
 6 have different requirements but I, I think
 7 it's important to think about the method
 8 within the framework of use. So I, I do
 9 think that, and this is just a plug, it was
 10 very helpful when, when you presented the
 11 vision on the use of transgenics even though
 12 it's undergone some modification, I think, it
 13 was very helpful to see that because then
 14 one could then picture how that information
 15 output from the test methods would be
 16 utilized and that framework discussion has to
 17 go hand-in-hand with understanding what's
 18 necessary for validation.
 19 DR. CARPENTER: Mary.
 20 DR. WOLFE: I'd like to
 21 invite everyone to the SACATM meeting which
 22 will be the 10th and 11th of March. A
 23 Federal Register notice is in preparation and
 24 it will be held in Bethesda, at the Hyatt
 25 Hotel which is just one Metro stop down the

<p style="text-align: right;">Page 106</p> <p>1 road.</p> <p>2 DR. CARPENTER: Any other</p> <p>3 questions or comments? Aaron?</p> <p>4 DR. BLAIR: Using mechanisms</p> <p>5 and mechanistic models in a predictive sense</p> <p>6 says to me it means we don't always need a,</p> <p>7 a bioassay and so my, my question is sort of</p> <p>8 how do you think about an issue where</p> <p>9 there's quite a lot of mechanistic</p> <p>10 information and no evidence whatsoever that</p> <p>11 this substance would cause a cancer in any</p> <p>12 organism? Would that be sufficient then to</p> <p>13 conclude that it's a carcinogen?</p> <p>14 DR. BECKER: I think not. I</p> <p>15 mean I think not. And this has to do with</p> <p>16 probably the state of our understanding</p> <p>17 collectively, scientific understanding of the</p> <p>18 carcinogenic process. Remember, we're, we're</p> <p>19 moving in, we're moving our knowledge base</p> <p>20 forward in terms of what we know about the</p> <p>21 overall process at the same time we're</p> <p>22 moving forward in our knowledge about the</p> <p>23 endpoints or the, the, the effects of</p> <p>24 specific chemicals along the chain of, of</p> <p>25 causality, if you would. And so I think</p>	<p style="text-align: right;">Page 108</p> <p>1 encourage NTP to move forward, we shouldn't</p> <p>2 hold back in our research, development and</p> <p>3 application of this information, but again</p> <p>4 I'll go back to this, within the framework.</p> <p>5 So you have to use that information wisely.</p> <p>6 One of the critical areas, and this is I,</p> <p>7 you asked, so I get to get on my soapbox a</p> <p>8 little bit, one of the critical areas that's</p> <p>9 important and as we develop new information</p> <p>10 on mechanism and in bringing this forward</p> <p>11 into, into decision making is to make sure</p> <p>12 that there's scientific understanding and, I</p> <p>13 won't use the term consensus, but very</p> <p>14 strong peer review and peer comments, if you</p> <p>15 would, on the quality and the significance</p> <p>16 of that information. And that's where,</p> <p>17 where one can then start building confidence</p> <p>18 as you make decisions on the science. And I</p> <p>19 think the example of the, the ILSI/HESI</p> <p>20 example of, skipped my mind, what was the</p> <p>21 receptor mediated, RPAR, or PPAR process is</p> <p>22 a good example of that. How you can begin</p> <p>23 to, how you can build consensus on mechanism</p> <p>24 and use of that information. But, but there</p> <p>25 you're going mechanism by mechanism. I, I</p>
<p style="text-align: right;">Page 107</p> <p>1 oftentimes we've been, and this gets to I</p> <p>2 think part of the discussion that Mike</p> <p>3 talked about, this whole issue of how do we,</p> <p>4 if we don't know everything about a</p> <p>5 particular mechanism then are we in the</p> <p>6 state of knowing nothing and therefore not</p> <p>7 being able to use that information? And I</p> <p>8 think not. But I think it does create a</p> <p>9 dynamic tension because we don't always know</p> <p>10 which are the, the full steps of</p> <p>11 mechanistic, you know, mechanistic pathway or</p> <p>12 even sometimes which are the critical steps;</p> <p>13 we just know which, what a few are. But</p> <p>14 that shouldn't inhibit us from using that</p> <p>15 information but we have to use it wisely.</p> <p>16 So I'm not sure you can say if I say</p> <p>17 mechanism A then therefore, with the state</p> <p>18 of knowledge today, I can predict outcome B</p> <p>19 in even an animal model or even in a human</p> <p>20 at this, this time, whether it's</p> <p>21 carcinogenicity or reproductive toxicity or</p> <p>22 any of these other areas that we're</p> <p>23 concerned about. On the same time though,</p> <p>24 you can say that we shouldn't be held back,</p> <p>25 and this is where I wanna really, truly</p>	<p style="text-align: right;">Page 109</p> <p>1 think you're, you're stuck with that for now</p> <p>2 because that's a reflection of our current</p> <p>3 collectively understanding.</p> <p>4 DR. BLAIR: Just to sort of</p> <p>5 follow-up on that. I appreciate your</p> <p>6 comments so... In, in, I'm not, realizing</p> <p>7 having mechanistic information provides a lot</p> <p>8 of useful information in a lot of ways but</p> <p>9 then it sounds like for sort of this one</p> <p>10 narrow thing of making a, a decision about,</p> <p>11 I think about cancer but I know other</p> <p>12 outcomes would be important, on</p> <p>13 carcinogenicity, the mechanistic information</p> <p>14 is not predictive, it's explanatory. If you</p> <p>15 can't predict and say, well, yes, all right,</p> <p>16 we don't know that liver cancer develops in</p> <p>17 anything, anywhere but we think the mechanism</p> <p>18 is, you know, whatever amount of information</p> <p>19 we don't need to see it. So, sort of your</p> <p>20 thinking is that it's not likely we would</p> <p>21 have that amount of confidence just in</p> <p>22 mechanistic information so it would explain</p> <p>23 what we know occurs in the whole organism</p> <p>24 but it wouldn't predict.</p> <p>25 DR. BECKER: I think, I</p>

<p style="text-align: right;">Page 110</p> <p>1 think to a certain extent that's a good 2 statement of where we're at today. I would 3 hope that with, we'll be able to go farther 4 with, particularly with implementation I 5 think of some of the vision, of some of the 6 elements of the vision that will be 7 developed here. I, I guess I, just to make 8 one last comment in closing here. I don't 9 want to leave the impression that, with 10 respect to this point about having to be 11 predictive. It, it gets to the issue of the 12 inability to do this kind of planning or 13 vision outside of the risk assessment or the 14 toxicology framework. And one of the areas 15 that I think we've, we've, we've moved away 16 from and that we have to get back to, 17 particularly with, with the, these elements 18 of mechanistic information, is understanding 19 the relevance of, of dose response. So 20 Mike's comments about trying to build in 21 better ADME data earlier in the process and 22 using that is, is critical. But also trying 23 to think about, in the design and 24 application of these new, new technologies 25 and new test methods, where does dose</p>	<p style="text-align: right;">Page 112</p> <p>1 helpful. Thank you. Definitely. Well, I 2 too would first like to thank... 3 DR. CARPENTER: Excuse me for 4 the record. Can we get you to repeat your 5 name and your affiliation? 6 DR. AMUNDSON: Certainly. 7 DR. CARPENTER: Thank you. 8 DR. AMUNDSON: Again Sara 9 Amundson with the Doris Day Animal League 10 and I've been working on these and related 11 issues for the past 15 years, so I've seen 12 rapid progress in some areas and, much as 13 Rick articulated, very real concern over the 14 lack of new method development to in fact 15 replace those that have been utilized over 16 the past 40 to 50 years. So I do have a 17 markedly different perspective. Again, thank 18 you to the National Toxicology Program for 19 actually having the foresight to hold this 20 sort of initial public meeting. I am 21 looking forward to subsequent public meetings 22 for an opportunity for perhaps more in depth 23 comments on the basis of the reports that 24 come forward from the sub-groups that have 25 provided their initial concerns and initial</p>
<p style="text-align: right;">Page 111</p> <p>1 response fit in? Oftentimes we in the 2 current hazard characterization process of 3 carcinogen identification, we're just looking 4 at a, you know, a dichotomy or, you know, an 5 on/off kind of thing. It's either 6 carcinogenic or it's not. I mean there 7 could be equivocal evidence I guess or weak 8 or limited, but it's really a signal or not 9 a signal. But that's not how chemicals work 10 and so what we should do in the vision is 11 move away from that and look at areas of 12 understanding and better including 13 considerations of dose response. That's kind 14 of an editorial comment. Thank you. 15 DR. CARPENTER: Thank you, 16 Dr. Becker. Our next speaker is Sara 17 Amundson from the Doris Day Animal League. 18 DR. PORTIER: While Sara 19 comes up, I was asked to explain what SACATM 20 is. It's the Scientific Advisory Committee 21 for Alternative Toxicological Methods. It 22 advises NIEHS and the NTP on the ICCVAM 23 process and our research into alternative tox 24 methods. 25 DR. AMUNDSON: That was</p>	<p style="text-align: right;">Page 113</p> <p>1 testaments today as to what will be taking 2 place with this process. The proportion, 3 the largest proportion of my comments today 4 will be policy in nature, but I do have a 5 few comments to make about process and that 6 is the only reason I'm here today is I am 7 on the ICCVAM list serve. If you take a 8 look at the Federal Register notice for this 9 particular meeting, you will note that there 10 is no search term within that Federal 11 Register notice that refers specifically to 12 animal protection organizations as 13 stakeholders as part of this process, nor 14 does it specifically refer to alternative or 15 non-animal test methods. Be that the case, 16 keep in mind with the way that our federal 17 government works and the way that 18 stakeholders obtain information, we simply go 19 to the GPO site, pump in our search terms, 20 Federal Register notices that have 21 applicability to those search terms pop up 22 and we know what public meetings we need to 23 be participating in. If I'm not considered 24 a stakeholder, I'm simply not going to know 25 that this particular forum is taking place</p>

<p style="text-align: right;">Page 114</p> <p>1 today and that subsequent forums will take 2 place. Folks, that's a dramatic oversight. 3 Granted, industry, the regulatory sector, the 4 research sector of the federal and state 5 governments and the environmental protection 6 advocates and a variety of other folks are 7 specifically mentioned in any of the 8 communicating materials, but animal 9 protection organizations were left out, so I 10 hope that you will correct that in the 11 future. In addition, I greatly appreciated 12 the subcommittee reports, and the general 13 sort of discussion has been very interesting 14 from my perspective in addition to the four 15 to five, four questions that NTP put forward 16 as really provocative markers for getting us 17 started thinking about this process for 18 creating a vision for the NTP over the next 19 8 to 10 years. I'm most appreciative of 20 that, but again, what is lacking is where is 21 the three-hours component to each of these 22 subgroups as a portion of a very real vision 23 for taking toxicology forward in the 21st 24 century. Be that the case, I hope that this 25 issue will be comprehensively addressed on</p>	<p style="text-align: right;">Page 116</p> <p>1 this means is heretofore you will find that 2 any one revised or alternative method must 3 meet the same criteria and, and generate the 4 same robust data that's necessary in order 5 for it to be truly incorporated into our 6 regulatory scheme. Be that the case, as 7 evidenced by the number of test methods from 8 bench to federal regulatory recommendations 9 that NTP takes genuine responsibility for, do 10 keep in mind that there's certainly tax 11 payers dollars that are going into validation 12 efforts and those of us who closely monitor 13 what's taking place with the federal budgets 14 will certainly be supportive of those efforts 15 to insure that, whether it's a public/private 16 partnership or the federal government takes 17 responsibility for insuring that test methods 18 are assessed as valid, also have the 19 resources available to them to perform those 20 validation studies. That's truly, truly 21 important from our perspective. 22 I also greatly appreciate Chris's 23 comment with regard to high throughput 24 methods and building on that I wanna just 25 ask you folks to keep in mind with the</p>
<p style="text-align: right;">Page 115</p> <p>1 the basis of clearly NICEATM already exists 2 at NIEHS and certainly seems like it will be 3 providing great commentary on what is 4 transpiring with regard to the vision but my 5 contention is it needs to be a backbone of 6 this vision in moving forward. 7 Now at the risk of severely 8 compromising the poor man's credibility, I 9 must say that I am in large agreement with 10 the vast majority of overarching goals and 11 specific comments that Rick shared with you 12 just previously. His points with regard to 13 validation are well taken, obviously, 14 particularly in our animal protection 15 community and to that end I wanna address a 16 couple of points that were raised. Please 17 keep in mind that public law 106-545 which 18 is the ICCVAM Authorization Act has set a 19 new bar for toxicology when it comes to 20 federal regulatory agencies and that is: a 21 test method before it is recommended or 22 required must be ascertained as valid, and 23 we've got internationally agreed upon 24 criteria for what constitutes a validated 25 test method. The bar's been set and what</p>	<p style="text-align: right;">Page 117</p> <p>1 marked change in philosophy regarding 2 toxicology and the move toward mechanistic 3 approaches, do not embrace this philosophy at 4 the detriment of existing correlative methods 5 that may provide for refinements or 6 replacements or reductions of animal test 7 methods. We simply can't jump to the next 8 level without utilizing some of those 9 correlative methods that may be simply as 10 predictive of what we're currently utilizing 11 and I would hate to see, hate to see them 12 obliterated on the basis of the thrust for 13 mechanistic toxicology. I thought one of 14 the very, very important points that was 15 stated here is that the National Toxicology 16 Program truly is a regulatory and research 17 agency-wide coordinated effort. Be that the 18 case, where is that same activity being 19 built upon with NICEATM with regard to 20 development and validation of non-animal or 21 alternative test methods? We need a better 22 home for that to take place. We've got the 23 assessment validation stage covered. What we 24 don't have covered is coordinated activity 25 within the federal government for insuring</p>

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

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

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

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

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

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

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

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

18 DR. CARPENTER: Bill.

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

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

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

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

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

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

1 The American College of Medical
2 Toxicology is a professional, non-profit
3 association of physicians with recognized
4 expertise in medical toxicology. So we're a
5 different type of toxicologist than a basic
6 science toxicologist; we're all physicians.
7 Medical toxicology is a subspecialty which
8 encompasses clinical pharmacology. All of
9 our fellowships actually include pharmacology
10 training and we focus on the diagnosis,
11 management and prevention of poisoning and
12 adverse health effects due to medications,
13 occupational and environmental toxicants and
14 biological agents. This slide actually
15 doesn't include my field which is pediatrics;
16 however, there is what, what it's meant to
17 represent is there's overlap between
18 occupational medicine toxic..., in toxicology
19 in clinical effects of solvents, pesticides,
20 and heavy metals and other toxicants.

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

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

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

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

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

1 things that we need to do if we really want
 2 to understand and be able to make
 3 predictions is to look at chemical mixtures.
 4 Medical toxicologists provide
 5 professional services in a variety of
 6 settings. We actually have people both in
 7 industry and in academics. Most of us work
 8 in emergency departments, ICU's and other in-
 9 patient units. Some work in out-patient
 10 clinics like myself. Most of us are
 11 associated with the Poison Control Center and
 12 most of us also work at medical schools and
 13 universities. Some actually work for
 14 regulatory agencies and government agencies
 15 such as ATSDR, CDC, FDA and actually Dr.
 16 Snyder works for NIH at the National Library
 17 of Medicine and he's also a member. And
 18 even among physicians our group is very
 19 diverse. I put pediatricians first because
 20 that's me; however, the, the most, the most
 21 common profession is actually emergency
 22 physician probably followed by occupational
 23 medicine physician and we're probably third.
 24 Interns and pathologists are also members of
 25 ACMT and as I said, most work in academic

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

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

1 And I think getting to the issue of
 2 toxicogenomic epidemiologic studies, this,
 3 this interests me because I am an
 4 epidemiologist and I think a lot of the
 5 issues in toxicogenomics are very different
 6 than in pharmacogenomics. Obviously
 7 pharmacogenomics is going to be studied in
 8 the context of a randomized control trial
 9 where you have baseline data and you have
 10 the effect afterwards and you could look at
 11 the delta. In toxicogenomics first you have
 12 to identify someone who's been exposed.
 13 There's never gonna be a randomized control
 14 trial of a toxicant for ethical reasons, for
 15 very good ethical reasons. So they're gonna
 16 have to identify them, you're gonna have to
 17 measure the phenotype and you're gonna have
 18 to have some certainty in those measurements,
 19 as well as measuring whether or not
 20 someone's exposed. And I think it's gonna
 21 be a lot more difficult than pharmacogenomics
 22 and I think partnerships with the physicians
 23 who actually see these patients is going to
 24 at least help in some ways in both in the
 25 exposure measurements and in the phenotype

<p style="text-align: right;">Page 130</p> <p>1 measurements. 2 ACMT members have a long history of 3 serving as consultants to government 4 agencies. We actually have a contract with 5 ATSDR where we've produced some case studies 6 in environmental medicine. Other case 7 studies include immunotoxicology, especially 8 with respect to Lupus. I actually co-wrote 9 the pediatric environmental health ATSDR 10 monograph and there's also a monograph 11 pending on Iodine 131 exposure. And we've 12 also worked with the CDC. We're consultants 13 to the National Environmental Exposure Report 14 for the National Center for Environmental 15 Health and some of us have served on NIH 16 panels as well. So an example of 17 collaboration with federal agencies, ACMT has 18 had a collaborative, or cooperative, 19 agreement with ATSDR for several years now. 20 As I mentioned, this is where the teaching 21 monographs have come about. But we've also 22 worked with ATSDR and partnered with them in 23 educational symposia at national scientific 24 meetings. We've developed an Internet base 25 for a teaching resource and we've also done</p>	<p style="text-align: right;">Page 132</p> <p>1 clinical effects should be and whether or 2 not, and also in the management of patients. 3 There actually are FDA approved treatments 4 for methanol toxicity and we're very familiar 5 with the uses of those drugs and their 6 potential side effects. And we're also, 7 because this was a human reproductive 8 effects, there are pediatricians and 9 developmental toxicologists in our 10 organization, and I think we felt we could 11 have contributed quite a bit to such a 12 panel. 13 In summary, in terms of the, how the 14 ACMT and NT..., NTP could network, we are a 15 physician organization with very diverse 16 expertise in all facets of toxicology. 17 We're very dedicated to public health. We 18 already have at least the beginnings of an 19 infrastructure for collaboration in human 20 studies because we are geographically diverse 21 and we are the ones that, we are the 22 physicians that see the patients who have 23 toxic exposures. Also we can be a potential 24 source for clinical diagnosis and expertise 25 on the management of exposed populations and</p>
<p style="text-align: right;">Page 131</p> <p>1 up a national network of public health 2 consultation for incidents of mass chemical 3 exposures and chemical terrorism. Also the 4 pediatric environmental health unit that I 5 work in in Boston is partially funded by 6 ATSDR and we're to be a regional center for 7 pediatric environmental health referrals. 8 This is an example of the National 9 Consultation and Education Network. These 10 are the individual members of ACMT who are 11 responsible for different geographic regions 12 in the United States. So this is an example 13 that Michael Kosnett, who's the President of 14 ACMT, asked me to present. He had looked at 15 a recent monograph that NTP had put out on 16 methanol exposure and human reproductive 17 effects and he had some concerns that there 18 was no medical toxicologists on the panel. 19 This is not meant as a criticism but sort of 20 as to point out that ACMT expertise can 21 complement the expertise which was already on 22 the panel. ACMT members care for hundreds 23 of people annually exposed to methanol as 24 well as other toxic alcohols. So we have a 25 lot of experience in determining what the</p>	<p style="text-align: right;">Page 133</p> <p>1 a source of toxicologic, pharmacologic, and 2 epidemiologic expertise in human exposures in 3 general. This is contact information for 4 ACMT and I believe this will be in a handout 5 that will be passed out and this is contact 6 information from Michael Kosnett who is the 7 current President of ACMT. 8 DR. CARPENTER: Thank you. 9 I'm sure the NTP appreciates your offer of 10 assistance. Are there any questions for the 11 speaker? 12 DR. SNYDER: Just, just a 13 comment. First of all, nice presentation 14 letting this audience know what medical 15 toxicologists do. I serve on a couple of 16 committees of that college and I applaud 17 your presentation. It was very well done. 18 With regard to clinical toxicological data, 19 the rubber meets the road of challenge. 20 Over the last 15 years the NTP advisory 21 groups and participants ought to know about 22 is that the American Association of Poison 23 Control Centers has been sitting on a 24 mountain, a true mountain, of clinical 25 toxicological data for many years and</p>

<p style="text-align: right;">Page 134</p> <p>1 unfortunately the individuals who are in 2 charge of that database, that mountain of 3 information, have a challenge on their hands 4 because a great deal of the support for that 5 database comes from the pharmaceutical 6 industry and the pharmaceutical industry has 7 threatened, on numerous occasions, to pull 8 its, pull its support for that database 9 should too much of the data that's in that 10 database be allowed to be accessed by 11 investigators and other groups. That's the 12 challenge, the difficulty at the moment. So 13 I would alert this audience to that 14 particular challenge at the moment for, for 15 liability or for other purposes the pharma 16 has not made it easy for the, the clinical 17 toxicological data that exists in this 18 country to be mineable in the way that it 19 should be. And it is a source of great 20 concern and friction within the clinical 21 toxicology community. 22 DR. PHIBS: Actually, that's 23 interesting information for my question. I 24 was wondering if there are untapped sources 25 of the types of human data you work with</p>	<p style="text-align: right;">Page 136</p> <p>1 indicated about nine or ten sources of 2 information of clinical human data were 3 allegedly available but the problem is is 4 that virtually none of those databases are 5 searchable at the moment and again, very 6 difficult to access the, the clinical human 7 data that's out there. 8 DR. CARPENTER: Mary. 9 DR. WOLFE: Mary Wolfe. I 10 appreciate you bringing the awareness of your 11 organization to us. Is, does your website 12 have a, a registry of members with their 13 expertises and so forth identified should the 14 NTP be looking for a certain type of 15 expertise for someone to serve on some of 16 their panels? 17 DR. WRIGHT: I think probably 18 the, the best place to start if you were 19 looking for someone would be to contact Dr. 20 Kosnett and... because there is a great deal 21 of diversity in terms of our expertise and 22 we're a small enough organization with only 23 300 members that he knows just about 24 everybody. I think he picked me because I 25 have some funding through NIEHS although I</p>
<p style="text-align: right;">Page 135</p> <p>1 that could guide NTP research identifying 2 flags, chemicals of high priority. 3 DR. CARPENTER: Identify 4 yourself. 5 DR. WRIGHT: Other than... 6 DR. PHIBS: Pat Phibs, BNA. 7 DR. WRIGHT: Pardon? 8 DR. PHIBS: Pat Phibs with 9 BNA. 10 DR. WRIGHT: Other than the 11 AAPCC database, I'm not aware of a national 12 database. Certainly each individual poison 13 control center keeps its own records, but 14 they do submit them to AAPCC and they're a 15 part of the national database. 16 DR. SNYDER: I'd like to 17 respond to that to help you out here. At 18 the AAPCC clinical toxicology meetings over 19 the last two years there have been a couple 20 of abstracts where a couple of investigators 21 have gone out into cyberspace and attempted 22 to identify, internationally as well as 23 nationally, various databases of clinical 24 toxicological information including that 25 which is searchable. One of the abstracts</p>	<p style="text-align: right;">Page 137</p> <p>1 have no funding through NTP. But he knew 2 that. And, and if you had somebody with a 3 specific type of expertise in mind, if they 4 were in the American College of Medical 5 Toxicology he would likely know. Our 6 membership also has a list serve in which 7 interesting cases are presented to the 8 members in general and they get input from 9 other members. So if there is ever a 10 clinical issue that you wanted addressed, 11 even if Dr. Kosnett or others didn't know 12 directly the answer, it would be very easy 13 to disseminate that information to virtually 14 every member. 15 DR. SNYDER: Mary, that, that 16 list that he just pointed out does exist. I 17 actually helped participate in creating that 18 list a few years ago and it is updated by 19 ACMT. 20 DR. WRIGHT: It's very, it's 21 very common for a member who has a very 22 unusual case to submit that case and elicit 23 opinions from virt..., members all over the 24 world actually. 25 DR. CARPENTER: Are there</p>

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

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

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

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

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

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

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

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

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

12 DR. CARPENTER: Thank you.

13 Any questions for Dr. Seidle? George?

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

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

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

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

8 DR. CARPENTER: Go ahead.

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

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

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

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

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

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

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

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

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

1 hand if you're looking at some of the
2 animal-based tests and screens that are
3 coming on-line, we're seeing in the, the
4 OECD process, for example, for endocrine
5 disruptor tests an enormous body count coming
6 out of that. So it is a double-edged sword
7 and, you know, it's, it's always a
8 difficult balance between the science and the
9 ethics, but we've found enough cases with
10 enough animal tests where, you know, for
11 example, if you look at the Duray's
12 (phonetic) eye irritation test you might as
13 well toss a coin. The reproducibility has
14 been so bad historically that a line has to
15 be drawn and if it's a question of requiring
16 validation as the bar where you either pass
17 or you fail and if you fail you don't enter
18 the regulatory community, it's a short-term
19 cost for hopefully a long-term gain both for
20 animals and for the betterment of science.
21 DR. BLAIR: If you say that
22 the animal bioassay test, I assume you're
23 talking largely about carcinogenicity 'cause
24 that's the, what the bulk of things been
25 done all those, and other endpoints are not

1 validated then what would you, what do you
 2 suggest we use as a valid endpoint for the
 3 non-whole animal mechanisms?
 4 DR. SEIDLE: From my read of
 5 the lit...
 6 DR. BLAIR: Just let me add
 7 to it. It wouldn't seem that we would want
 8 to validate some mechanistic technique
 9 against another approach that hasn't been
 10 validated. So what would we use?
 11 DR. SEIDLE: I completely
 12 agree with you that validating one method
 13 against something which itself hasn't been
 14 validated is an enormous problem and
 15 unfortunately it's a problem that the, you
 16 know, even ICCVAM hasn't gone far to try and
 17 resolve, it simply... you know, I won't go
 18 so far as to say it's unresolvable but right
 19 now in my opinion, there isn't a valid
 20 toxicity test to evaluate carcinogenicity or
 21 virtually any other health effect to humans.
 22 You're going to get a certain false positive
 23 rate, you're going to get a certain false
 24 negative rate, and as long as you're outside
 25 the, the human animal, which of course you

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

1 So there are plans in the works but right
 2 now I don't think there is a, there is an
 3 answer to your question.
 4 DR. SASS: Jennifer Sass...
 5 DR. CARPENTER: Go ahead.
 6 DR. SASS: ...with the
 7 Natural Resources Defense Council. Troy,
 8 thank you for the talk. That was
 9 interesting. One of the speakers in the
 10 audience brought up, I, I guess to follow-up
 11 on the question that was just asked, the,
 12 the poison control center data accidental
 13 exposures, things like that... Actually, has
 14 PETA ever tried to, to release up that kind
 15 of data specifically? From the poison
 16 control centers? That's new information to
 17 me. I didn't realize that.
 18 DR. SEIDLE: It's something
 19 we haven't tried to tackle directly, just...
 20 given PETA's activist agenda, it's, it's
 21 something that we have, we're trying to
 22 pursue through international bodies such as
 23 the OECD where we can potentially get 30-
 24 member country support and if we can get
 25 that level of buy-in it would be a much more

1 effective tool than if it's being advanced
 2 by, by a single non-profit advocacy
 3 organization. So that's... we've been aware
 4 of it for some time but it's not something
 5 that we've pursued directly.
 6 DR. SASS: So you're trying
 7 to get an international push to release that
 8 accidental exposure, poison control center-
 9 type of data?
 10 DR. SEIDLE: Both...
 11 certainly having it released would be useful
 12 from some perspectives. Our focus has been
 13 squarely on its use for validation purposes.
 14 So we, we haven't looked at it from a
 15 completely holistic standpoint just because
 16 that's not our, our mandate exclusively.
 17 DR. CARPENTER: Seeing no
 18 further hands, thank you very much. Nice
 19 presentation. Our final speaker on the
 20 current list, and we've had nobody else ask
 21 to speak, so is Jennifer Sass from the
 22 Natural Resources Defense Council.
 23 DR. SASS: Are these
 24 microphones on already? Okay, I'm Jennifer
 25 Sass. I'm with the Natural Resources

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. SASS: Right.

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

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

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

16 DR. CARPENTER: Go ahead.

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

19 DR. CARPENTER: Go ahead.
20 Go ahead.

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

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

1 available to the folks that need to utilize
 2 it for validation purposes, or simply for
 3 informational purposes. What is NRDC doing
 4 to address that need?
 5 DR. SASS: I feel a
 6 collaboration coming on. Actually, in my
 7 written statement you'll notice that I
 8 actually said that, that there is limited
 9 amount of basic toxicity information publicly
 10 available and I am completely aware of this
 11 and if I had my way I would slap those
 12 people around a bit. I think it's
 13 incredibly valuable information and in fact I
 14 have a small commentary that's being
 15 published in Environmental Health
 16 Perspectives the month after next that
 17 actually compares the no-effect level that
 18 was set for a pesticide, two pesticides, I
 19 actually look at one in particular, with
 20 actual food poisoning event data where, where
 21 sensitive populations, some elderly, some
 22 not, were actually having to be treated in
 23 the hospital emergency care at levels far
 24 below what had been deemed the no-effect
 25 level from a Union Carbide animal study. So

1 I, I'm completely aware about how valuable
 2 this data is and it appalls me that it's out
 3 there and that, it's some minuscule amount
 4 that's actually being reported to collection
 5 centers and not being utilized.
 6 DR. CARPENTER: Go ahead.
 7 DR. WIND: Marilyn Wind from
 8 Consumer Product Safety Commission. I am
 9 perplexed at the constant repetition that the
 10 AAPCC data is not available. There are
 11 clearly real problems with that data because
 12 a lot of the data that's collected doesn't
 13 name products and if products are named, you
 14 may not know what the products contain, so
 15 from that point of view, that's a problem.
 16 Another problem with the data is that some
 17 industry, some industries actually use poison
 18 control centers for collecting, for
 19 responding to questions on their products and
 20 that data is not publicly available but we
 21 use the poison control center data which is
 22 not a statistical database unfortunately for
 23 looking at where poisonings are occurring so
 24 that we can decide what needs to be in
 25 poison prevention packaging, and the data

1 that is available is good from that point of
 2 view 'cause it tells us where there are
 3 exposures and stuff. But I'm a little
 4 perplexed at what it is that is not
 5 available that's needed because while they
 6 don't give away their data and you have to,
 7 you have to buy it, it has been available
 8 and we've been using it.
 9 DR. SASS: That's not a
 10 question for me, right? I don't run those
 11 things. I can't answer that question.
 12 DR. CARPENTER: It really
 13 wasn't a question. I just.
 14 DR. SASS: Okay.
 15 DR. CARPENTER: Whether you
 16 had a response or not, I was waiting... Any
 17 more questions or comments? Thank you very
 18 much, Dr. Sass. I appreciate it. Are
 19 there... Are there any more public
 20 comments? Go ahead.
 21 DR. AMUNDSON: My apologies.
 22 I just have a quick comment and that's,
 23 overall in approaching this issue I think
 24 what is missing here is strong representation
 25 from pharmaceutical companies. Oftentimes I

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

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

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

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

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

1 and participate in that public meeting by
 2 giving us some of the future directions that
 3 the Korean NTP is going. They're very
 4 interested in bringing the concept of a
 5 public meeting into toxicology in Asia and I
 6 commend him for that effort and I again
 7 thank him very much for being here today. I
 8 want to thank Dr. Carpenter and the Board
 9 for their efforts and being here today and
 10 addressing some of the issues and listening
 11 to them, the N, my NTP staff: Dr. Wolfe,
 12 who set up this meeting and made it work for
 13 all of us, and Sara, I'm sure, if I know
 14 Mary, the next time we do a public meeting
 15 announcement, it will include the animal
 16 rights community; Dr. Bucher and Dr. Hooth
 17 for chairing the two subgroups that NIEHS
 18 and NTP have; and our NTP partners for being
 19 here today as well. Again, thank you all
 20 very much. Dr. Carpenter, it's back to you.
 21 DR. CARPENTER: And because
 22 they gave this to me I have to use it.
 23 Adjourned.
 24 (WHEREUPON, the Meeting was adjourned at
 25 12:37 p.m.)

CAPTION

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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

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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.



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