NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
May 25, 2001
Summary Minutes

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The NTP Board of Scientific Counselors met May 25, 2001 at the National Institute of Environmental Health Sciences in Research Triangle Park, NC. Dr. Donald Mattison served as Chair. He told the attendees that the meeting is being taped and also videotaped to determine feasibility for future videostreaming of Board meetings. He asked members around the table and attendees within the room to introduce themselves.

I. Recognition of Retiring Board Members

Dr. Kenneth Olden, Director of NIEHS and NTP, presented a certificate of appreciation to Dr. Clay Frederick in recognition for his service to the NTP.

II. NTP Update

Dr. Olden welcomed everyone and announced the appointment of Dr. Christopher J. Portier as director of the Environmental Toxicology Program (ETP). He acknowledged the outstanding job Dr. Portier had done in his role as acting director. Dr. Olden said that the new NIEHS scientific director had been selected and he had accepted the position. A formal announcement would be made in the near future.

Dr. Olden updated the Board about the NIH budget saying it shows overall increases through 2003 including increases for NIEHS. The Breast Cancer Coalition is lobbying for the NIEHS to receive an additional $30 M over five years. Dr. Olden recently attended a reception sponsored by the Parkinson's Network where the NIEHS' activities in this area were acknowledged. Dr. Olden believes the NIEHS is currently appropriately focused in key environmental health research areas – children's health, women's health, role of genetics and individual susceptibility, exposure, and toxicogenomics. He recently attended a reception sponsored by the Childrens' Health Environmental Coalition and the efforts of the EPA and NIEHS to co-fund eight environmental health centers for children were recognized. The NIEHS will be participating in a town meeting with Senator Clinton in New York in the future. Dr. Olden thanked the Board for its council to the NTP about current programs and future activities.

Dr. Olden recognized Sandra V. Lange who would be retiring soon. Dr. Olden thanked her for her service and contributions to the institute for 33 years. She has been a key advisor to the NIEHS and the NTP. Dr. Portier acknowledged her important role as an advisor to him about NTP issues and communication with stakeholders.

Dr. Portier provided details about areas for which he has been actively involved in his role as acting director of the ETP. Currently the NTP database is on-line for about 200 cancer studies. The NTP is expanding its efforts to place data from the remaining cancer studies and the non-cancer studies on-line. This should help to move the field of toxicogenomics forward by linking the data from toxicology studies with genomic data and help to identify patterns of gene expression that might be related to toxicity. Dr. Portier believes these databases will be useful in numerous ways for: evaluating NTP study designs, developing biomarkers, identifying commonalties in mechanism of action by chemical class and/or organ, determining their utility for predictive toxicology and mechanism-based mathematical modeling, and identifying links between different toxicology endpoints and genomic data.

Dr. Portier recognized Dr. John Pritchard as Associate Director of the ETP for Research. He will focus on strengthening the intramural ETP research program and linking it with the NTP's testing program and extramural research program. The ETP is having a retreat in August 2001 and hopes to include some of the Board as attendees. The NTP is working with the extramural division to expand the use of R03 grants – small grants program – for alternative toxicology methods, transgenics, and genomics. The NTP wants to increase the use of transgenics and toxicogenomics in its testing program and enhance its efforts for non-cancer toxicology research. In this area three new hires are proposed.

III. Chemical Disposition, Toxicokinetics, and Pharmacokinetic Modeling

A. Chemical Disposition and Toxicokinetic Studies

Dr. Tom Burka, NIEHS, covered three topics in his presentation to the Board: 1) a brief overview of how NTP studies are designed; 2) information about resources for obtaining chemical disposition, toxicokinetic, and mechanistic data; and 3) two examples of past studies.

Once a chemical is selected for study, the NTP has a formal process for study design and review. Each chemical or agent is assigned a study scientist who, with assistance of a multidisciplinary design team, designs needed studies. If the design includes toxicolinetics or chemical disposition studies, they are presented to the Toxicokinetic Faculty for its review and approval.

- Chemical disposition studies are generally done with radiolabeled compounds. These studies provide data useful in designing chronic toxicology studies – What is the appropriate dose range and route of exposure of the chemical? Is there bioaccumulation? Are there reactive metabolites? Are toxicokinetic studies practical?
- Toxicokinetic studies are generally performed with unlabeled chemicals. The goal is to perform these studies simultaneously with the 13-week studies. Additional kinetic data may also be collected during the chronic study. These studies provide data useful for the design and interpretation of chronic studies – What is the exposure versus internal dose? Are there age, sex, or species-specific effects? Does saturation of absorption or metabolism occur? Do interactions occur where the animals are dosed with multiple chemicals as with the AIDS studies?
- Special studies are designed to address specific questions that need to be answered before the toxicology studies begin or that result from findings obtained in the bioassay.

There are two major sources of support for conducting these types of studies – chemistry support contracts and chemical disposition contracts/in-house laboratories. Chemistry support contracts do bioanalytical work and provide toxicokinetic data. The chemical disposition contracts do absorption, disposition, metabolism and elimination (ADME) studies and comparative metabolism studies. Mechanistic studies, evaluations of new methods, and special studies are generally done in-house.

Dr. Burka presented brief synopses of the chemical disposition and toxicokinetic studies that were conducted for anthraquinone (a dosed feed study) and methyleugenol (gavage study). The

toxicokinetic data for anthraquinone showed a difference in response for rats versus mice. The mice data suggested saturation of absorption at the higher dose and provided guidance to the NTP about dose setting. The chemical disposition data for methyleugenol given IV versus orally showed almost complete absorption and rapid excretion. Additional mechanistic studies were conducted for methyleugenol to determine whether nongenotoxic mechanisms might be responsible for the forestomach neoplasms observed in the bioassay. Human exposure to methyleugenol was also investigated by measuring its content in plasma samples from the NHANES and a wide range was found. In collaboration with Duke University, the NTP conducted a feeding study in humans; rapid absorption and elimination were found similar to that observed in the toxicokinetic studies in rodents.

Discussion: Dr. Frederick noted the importance of the contract laboratories being timely in providing information to the NTP so it can be most useful in the design of the toxicology bioassay. Dr. Allaben, NCTR, told the Board that the FDA supports this effort as it provides the agency information needed for assessing potential risks for public health from exposures. Dr. Daston agreed that these data are important for interpreting how hazard data from cancer studies translate for human risk assessment. Dr. Frederick identified three areas for which he believes these data are useful – 1) designing studies; 2) providing mechanistic information used for interpreting the hazard data; and 3) integrating this information with human exposure data. In response to a question, Dr. Portier said the Centers for Disease Control and Prevention (CDC) developed the methods used for measuring methyleugenol concentrations in the human samples. He noted the NTP makes recommendations to CDC about agents that it would like evaluated and hopes to expand these efforts.

Dr. Drinkwater asked how the data are used in dose setting for the chronic bioassay. Dr. Burka responded that they are generally used to confirm the chosen doses. Both pathology and chemical disposition information are used for dose setting.

B. Pharmacokinetic Modeling of Disposition of Lipophilic Chemicals

Dr. Portier presented information about role of pharmacokinetic (PBPK) modeling in the analysis of toxicokinetic (TK) data from NTP studies. Dr. Portier presented this talk for Dr. Michael Kohn who was unable to attend the meeting.

Most analyses done, to date, of TK data and ADME data are either simple one or two compartment pharmacokinetic models or PBPK models done in-house. The NTP is moving toward having the statistical contractor conduct these analyses. The goal is to develop a consist method of analysis for TK and ADME data. Currently modeling is done as a research activity and NTP wants to move toward modeling as a testing activity. As possible, the NTP would like to have the results in advance of starting chronic studies so information from the modeling can be used in design considerations, such as dose setting.

He enumerated advantages of PBPK models as compared to simple pharmacokinetic modeling – more physiologically realistic and incorporates mechanisms of action into the model. He also

identified some disadvantages - requires greater computing power and more extensive data including more anatomical detail about the animals (e.g., body weight, respiratory rates), time course data of uptake and clearance, and biochemical measurements (e.g., enzymatic activities).

Dr. Portier presented PBPK modeling for the same examples as Dr. Burka, methyleugenol and anthraquinone. He showed a basic diagram of a PBPK model and discussed how it was simplified relative to data available for methyleugenol. Modeling confirmed that methyleugenol is rapidly cleared from the body and also provided other information about its metabolism: 1) absorption of oral doses in mice and rats is rapid and complete and the same across species and genders; 2) distribution of methyleugenol to tissues is not hampered by tissue permeability and occurs by simple diffusion; and 3) metabolism is saturable and includes an extrahepatic component for the mouse.

The second example was anthraquinone. Although both compounds are lipophilic, the methyleugenol model did not fit the data for anthraquinone. More detailed information about biliary secretion and urinary and fecal elimination were available for anthraquinone than for methyleugenol. Modeling provided specific information about anthraquinone's metabolism: 1) it has a long residence time in blood, 2) it is slowly extracted from blood into tissues, and 3) both absorption and metabolism are saturable. Dr. Portier identified differences in the anthraquinone model versus the methyleugenol model. Such differences highlight the importance of having information from modeling available when designing the bioassay.

Discussion: Dr. Moure-Eraso asked about the relevance of models to long-term carcinogenicity outcomes. Dr. Portier said these models help predict what might occur with chronic exposure. He added that for some chemicals, TK studies are being conducted during chronic exposure. This information, in addition to the single-dose, pre-chronic studies will be used for design of future chronic bioassays. Dr. Moure-Eraso asked if modeling is repeated over an animal's lifetime during chronic exposure. In response, Dr. Portier said tissue concentrations of a chemical are measured during the bioassay and those data are used to determine how well the model predicts the outcome.

Dr. Carpenter asked whether there are plans to expand efforts in modeling by looking at *in utero* exposures or exposures in young animals. Dr. Portier said non-cancer toxicology is a priority for the program and currently there is an opening for a modeler who would focus on reproductive and/or developmental toxicology. Dr. Carpenter felt this is an important area relative to children's health and asked if such modeling might become a routine NTP effort. Dr. Portier agreed about its importance, but added that currently this type of data analysis for reproductive toxicology is limited and is primarily a research activity and not routine like the PBPK modeling done in adult animals. It will take time before is becomes a routine NTP analysis.

Dr. Mattison asked about the strategy for developing PBPK models for non-static organ systems such as would be found in a developing animal. Dr. Portier said the models for both anthraquinone and methyleugenol had growth components. He would like to initiate an effort that would develop the baseline data needed to address questions about genetic, enzymatic, and metabolic changes occurring during development. Dr. Frederick suggested that the NTP think about developing four basic models: young animal, preadolescent/adolescent, adult, and

geriatric. Dr. Goldman thought this might be a useful approach, but cautioned about the variability in developmental rates among species and noted the importance of considering this when making cross-species extrapolations.

Dr. Bonney asked if the NTP had considered computer simulation of physiological processes for obtaining information beyond that available through mathematical modeling. Dr. Portier said the PBPK models are used in a simulation mode and are challenged with questions about dose, applicability to humans, etc. Dr. Daston commented that models are insightful for identifying data gaps for future biological research. He commended the program for its work in toxicokinetics and for using this information in bioassay design. In response to a question, Dr. Portier hopes that modeling, in addition to pathology, will provide scientific input that is useful to a study design team when designing a bioassay. Dr. Drinkwater questioned whether PBPK modeling could to be done on a routine basis successfully by a contractor citing creativity as a limiting factor. Dr. Portier responded that there would be some limitations to PBPK modeling being done through a contractor, but he is confident that with appropriate guidance it can be successful. Dr. Toraason asked if the NTP has considered how it might approach modeling of complex mixtures. Dr. Portier said the NTP is exploring how to approach modeling of mixtures through its ongoing studies of dioxins and PCBs.

Dr. Frederick encouraged the NTP to examine the ADME information obtained historically and to focus resources on collecting those data of greatest utility for hazard identification. Dr. Bucher said that the NTP has done this. As an example, the NTP found that TK data collected at 15 months of age did not provide additional information that warranted it being collected, so the measurement was dropped. Dr. Mattison told the Board that Dr. Frederick and Carpenter would prepare a write-up for the NTP on this session and invited members to send them any additional comments.

IV. Concept Review: Studies of Chemical Disposition in Mammals

Dr. Tom Burka, NIEHS, presented the concept and Drs. Frederick and Carpenter served as principal reviewers. Dr. Don Gulla, Contracts Officer, NIEHS, provided the Board guidance about the scope of the discussion. Prior to issuance of a contract that contains a significant research and development component, the NTP is required by law to take the concept before its advisory committee and gain concept approval for use of the contract mechanism. Also every five years, the NTP must get re-endorsement of the concept for using the contract mechanisms as the appropriate means for carrying out chemical disposition studies. Dr. Burka explained that this concept is for continuation of the current activity of conducting chemical disposition studies and additional special studies, as needed, and expands the task of providing biochemical parameters from *in vitro* studies. Dr. Bucher outlined how chemical disposition contracts fit within the study design scheme and added that they generate the data about ADME and other basic information about biochemical parameters, solubility characteristics, etc. used in development of models such as those described earlier. The modeling would be done by other means.

Discussion: Dr. Frederick said he believes the NTP should evaluate the utility of the chemistry support contract and he questioned whether the NTP in the future might consider combining the chemical disposition and chemistry support contracts. This might facilitate contract management and integration and use of the data and be cost saving. Dr. Frederick said he was very supportive of the chemical disposition studies and special mechanistic studies especially the special toxicity work because it extends collection of information beyond the bioassay and helps identify areas for additional research within the intramural program. He believes the contract mechanism is the appropriate mechanism to carry out that work. Dr. Burka replied he was not sure whether that might not restrict competition because of the level of expertise that would be required to fulfill the contract's requirements and it might result in greater expense. Dr. Goldman thought Dr. Frederick's question about whether it would be beneficial and more efficient for the work to be done under one contract was reasonable and the Board might ask the NTP to evaluate this issue.

Dr. Mattison asked if the Board had any issues related to data integration. Dr. Frederick thought timeliness of pharmacokinetic data availability would be very important if the information is being used for dose setting. He also commented that doing toxicokinetic studies should go beyond only addressing metabolism of the parent compound and also include a study of the kinetics of metabolites of the parent. Dr. Burka agreed that including an evaluation of metabolites is generally more informative; however, this is not always possible because of limitations of time and cost. He added that once the kinetic studies begin, there is currently no lag in getting the data; lab reports are submitted to him quarterly and he forwards the results to the study scientist. Dr. Portier asked Dr. Frederick his opinion about priorities for the program with respect to determining chemical disposition over time and metabolites prior to the bioassay for use in its design as opposed to conducting these analyses as follow-up to the bioassay. Dr. Frederick feels that studies for setting doses should be conducted first so the bioassay's start is not delayed. He added that determining the toxicokinetics of metabolites might not be necessary for dose setting and could occur later or in parallel with the bioassay.

Dr. Carpenter said the Board seemed in favor of continued contract support for chemical disposition and special mechanistic studies. However, he would like the program to consider how they might be used for other areas such as including in non-cancer studies, addressing low-dose issues, and not limiting special studies to just ADME. Dr. Allaben noted the importance of the data from these studies to the FDA.

Dr. Portier commented that the use and development of methods to track nonlabeled compounds in rodents would be useful for human monitoring. Dr. Frederick agreed, but thought this effort could be done as adjunct to the chemical disposition contract.

Dr. Frederick moved that the concept for continuing support of the chemical disposition work be approved. Dr. Carpenter seconded the motion and it was approved unanimously by the Board (6 yes votes, 0 no votes).

V. NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)

A. Guidelines for Expert Panel Reviews

Dr. Michael Shelby, Director of CERHR presented the draft guidelines to the Board. In addition to the Board there were three ad hoc reviewers, Dr. George Daston, Dr. Kim Boekelheide, and Dr. Germaine Buck; however, at the last minute Dr. Buck was unable to attend. Dr. Shelby said the CERHR strives to be a center of excellence for the evaluation of hazards and risks to reproduction and children's health. To facilitate its expert panel reviews, the CERHR developed guidelines. These were distributed to the Board prior to the meeting and public comments on them were solicited through a Federal Register notice.

As background, Dr. Shelby told the Board about the phthalates review that consisted of three expert panel meetings followed by release of the expert panel reports for public comment. The reports have been well received. As the first evaluation conducted by the CERHR, lessons were learned during the phthalates review that resulted in the development of guidelines - their goal being to standardize the format of the reports and to provide guidance about the wording of the conclusions. Dr. Shelby explained that prior to this meeting, the guidelines had undergone several levels of review, both internal and external to the NTP, and were presented to the NTP Executive Committee at its meeting in March 2001. Comments from those reviews were incorporated into the current draft that went out for 60-day public comment beginning April 25.

The guidelines are intended to 1) provide guidance on the processes involved in preparation of the expert panel reports, 2) increase efficiency and promote understanding about the process among expert panel members, and 3) provide consistency among reports. They have three basic parts: 1) information about process for preparation and review of expert panel reports; 2) an outline and guidance about content of individual sections, conclusions, and data needs; and 3) guidance about the evaluation of individual studies. Dr. Shelby briefly discussed the template for the hazard statement found at the end of the reproductive and developmental toxicity sections. It was taken from the NRC report on evaluating reproductive and developmental toxicity and is intended as guidance on the information that should be included. Dr. Shelby also discussed the risk statement that would be included in section 5 (summary and conclusions). He noted that predetermined categories are not given for the panels to use in qualifying their conclusions. The panels will be asked to integrate the toxicity and exposure information and reach a conclusion regarding whether or not the agent is a human health hazard under current or established exposure levels. Dr. Shelby noted that two questions were sent to the Board prior to the meeting asking for the members' opinion about the clarity and utility of the guidelines and about using a narrative format for giving conclusions about the likelihood of hazard as opposed to having classification categories.

Dr. Shelby updated the Board about the status of CERHR evaluations - the NTP center report on phthalates is in process, an evaluation of methanol is underway, and the evaluations of 1- and 2-bromopranes and ethylene glycol are being scheduled. The methanol meeting is October 15-17, 2001 at the Radisson Hotel Old Town, Alexandria, Virginia.

The CERHR has been working to update the Internet links between its site and others. Currently CERHR's web site has links to 45 sites and eight sites provide links to CERHR.

Discussion: Drs. Drinkwater asked about the system proposed for classifying hazard by the expert panels and if the CERHR had considered using the NTP's level of evidence categories for carcinogenicity of "clear, some, equivocal, or no" instead of "sufficient" or "insufficient". Dr. Frederick agreed that the CERHR should consider using the categories established for the NTP technical reports' reviews. Dr. Shelby replied that the panel is not restricted to choosing "sufficient" or "insufficient" and those descriptors could be used. Dr. Goldman said the NAS report on reproductive toxicology was used as background for these guidelines because it reflects the current thinking of experts in the field about how to evaluate this information. The NTP wants to ensure that the process is credible, consistent, and informative.

Dr. Daston pointed out the important role of CERHR in providing information on reproductive health risks and noted it fills a critical need for stakeholders and the public. He acknowledged Dr. Shelby's role in setting up CERHR and in carrying out the phthalates review. He believed the guidelines address many issues identified by Dr. Robert Kavlock at the May 24, 2000 Board meeting. Dr. Daston noted a few areas for further clarification: 1) identify in the pre-meeting preparation section how many experts will review each study; 2) include a description of the nature of the effect(s) observed in the templates for the developmental and reproductive hazard statements; and 3) when possible, address in the overall conclusions the likelihood of risk in typical exposure scenarios; and provide a quantitative comparison of hazard and exposure data (e.g., margin of exposure). Dr. Daston considered the narrative conclusion an ideal form to communicate hazard and risk information about reproductive toxicants and believes this format would be useful to the end users, e.g., clinicians, risk managers, parents.

Dr. Torasson asked how the panel would handle the statement of risk if there were a disparity between occupational and residential. Dr. Shelby said there can be multiple statements of risk and this was done in the phthalates expert panel reports. Dr. Toraason asked if any consideration had been given to expediting or shortening the review process to increase output. Dr. Shelby said the Core Committee had discussed it. He acknowledged that in some incidences, it might be expeditious to review a class of chemicals instead of individuals; however, the CERHR is moving cautiously because it wants to ensure that the process for all reviews remains scientifically credible.

Dr. Boekelheide acknowledged the uniqueness of the CERHR and its important role in efforts to provide authoritative assessments of human risks associated with exposure to reproductive/ developmental toxicants. He thought the guidelines balance the need for a consistent approach to the evaluation of reproductive/developmental toxicants with flexibility for dealing with different compounds and effects. Dr. Boekelheide said using a narrative format for the conclusions is the best approach because it would allow the expert panels to present the hazard evaluation in the context of the best available science. He commented that although the guidelines separate reproductive and developmental toxicities although for some chemicals, e.g., phthalates, they have common origins and overlapping effects. He encouraged the CERHR to periodically review and, if necessary, revise the guidelines to reflect the merging of these two fields. Dr. Shelby agreed. In response to a question about the composition of the expert panels,

Dr. Shelby said the CERHR has addressed trying to maintain continuity across panels and is considering having a core that would be participate in multiple reviews. Dr. Boekelheide felt that the success of the phthalates review would facilitate persons agreeing to serve on several panels. Dr. Torasson noted that one recommendation from NIOSH at the May 24, 2000 meeting is to include an industrial hygienist on the expert panels.

Dr. Moure-Eraso felt the guidelines are comprehensive, but suggested that the sections 1.2 (use and human exposure), 3.1 (human data for developmental toxicity) and 4.1 (human data for reproductive toxicity) specify residential and occupational (production and manufacturing) separately in order to broaden the databases examined. Dr. Goldman concurred saying the phthalates review included exposure information primarily for production and to consumers, but had little information about occupational exposures for persons involved in the manufacture of products containing phthalates. Dr. Daston said he believes that the HPV testing program will be a source for exposure data and that industry will make this information publicly available. He asked Dr. Toraason about a new NIOSH occupational survey getting underway. Dr. Toraason said it now in the planning stages.

Dr. Goldman provided the Board with a brief summary of the Board's report on CERHR from the May 24th meeting. She noted that the Board felt much progress had been made achieved since its review in 1999 and its concerns had been addressed by CERHR. The guidelines address many of the issues that deal with the report preparation process, consistency of reports, and putting the hazard assessment into context with exposure. The Board recommended that the CERHR establish a core of expert panel members with rotational terms and consider inclusion of an industrial hygienist on the panels. The Board supported CERHR exploring ways to increase the number of chemical evaluations. Dr. Goldman felt it was important to establish good guidelines and get broad participation outside NTP before increasing the number of reviews. Dr. Goodman said the Board felt continued improvements are needed in outreach - both with involving NTP agencies in CERHR activities and in publicizing CERHR. She believes the guidelines provide a good foundation for CERHR reviews, but feels the Board would want to revisit the guidelines in the future to find out if they are useful and if process issues have improved.

Dr. Frederick asked if the review of 1- and 2-bromopropane would occur prior to the NTP completing its toxicology testing. Dr. Shelby believes there is a sufficient reproductive and developmental database for review of these chemicals.

VI. NTP Testing Activities

A. ICCEC Recommendations for Future NTP Studies

Dr. Scott Masten, NIEHS, presented the nominations proposed for study by the NTP. He prefaced his presentation with a brief overview of the process for nomination and selection. The process includes comment by the NTP Board and several opportunities for public comment. He asked for the Board's input about the nominations, the specific types of testing recommended by the Interagency Committee for Chemical Evaluation and Coordination (ICCEC), and any issues the NTP should consider when making selections and designing studies. The ICCEC reviewed

and made testing recommendations for 18 nominations including 28 total substances at its October 2000 meeting: 22 were recommended for testing (Att. 5-Tbl. 1) and six were deferred pending receipt and consideration of additional information (Att. 5-Tbl. 2). The nominations fit into five general categories: drinking water contaminants, therapeutic agents, phototoxicity nominations, dietary supplements, and industrial chemicals. Dr. Masten briefly reviewed the nominations and testing recommendations. He noted the NTP received a large volume of information on S-adenosylmethionine from manufacturers during the public comment period. The NTP will review this information and determine if any of the testing recommendations have been met.

Discussion: Dr. Daston asked how the NTP plans to characterize the dietary supplements and get representative materials for study. Dr. Masten said Dr. Burka oversees the dietary supplement testing and he has been working with manufacturers to get representative material. The NTP is also trying to determine if there is an active ingredient or marker constituent that would allow a substance to be characterized chemically and standardized for study. Dr. Frederick supported the NTP using a composite sample. Dr. Bucher commented that the NTP contacted the trade associations and organizations and invited them to provide the materials (particular product, unnamed product or composite) to be used for testing and so far there has been little interest. Dr. Drinkwater asked if the NTP had considered testing the active ingredients instead of or in addition to the dietary supplements. Dr. Masten said this is being done in one situation; however, the NTP is somewhat concerned with this approach because it might not be the "right" active ingredient or the ingredient's biological activity might differ in the mixture versus when pure.

Dr. Frederick encouraged the NTP to talk with industry about ways to characterize the methyl organotin test materials. He noted for the record that his company bought another that makes organotin stabilizers.

Public Comments: Dr. Esther Patrick presented comments on behalf of L'Oreal USA and L'Oreal SA. She asked the Board to consider three questions in its deliberations about whether the photo(co)carcinogenicity studies on all-trans-retinyl palmitate should be supported. 1) Does the proposed photo(co)carcinogenicity study of all-trans-retinyl palmitate provide additional information or address the conflicting results of existing studies? 2) Does the proposed study meet the nomination principles for NTP studies? 3) Is the conduct of the photo(co)carcinogenicity study of all-trans-retinyl palmitate a prudent use of the NTP and NCTR resources available to investigate photo(co)carcinogenicity?

Discussion: Dr. Frederick asked Dr. Patrick to clarify the downside of doing the proposed study. She replied that the downside is not specific to this study, but to continuing to conduct photo(co)carcinogenicity studies without addressing the basic criticisms of the method. Dr. Patrick added that at the time the facility was built, there was a commitment to study mechanisms and to conduct basic research on photo(co)carcinogenicity. Dr. Allaben said that the FDA's Center for Food Safety and Applied Nutrition had done a thorough review about the research needs prior to submitting this nomination to the ICCEC.

Dr. Carpenter referred to comments from ATOFINA Chemicals, Inc. about the testing program sponsored by the Organotin Environmental Programme Association and the availability of data from existing or planned studies for testing materials included in the list nominated to the NTP. He asked about how this might affect NTP testing plans and if the NTP would use the information if it were proprietary. Dr. Masten replied there is a current dialogue with the organotin industry, and the NTP will work with this industry group to fill the data gaps. Dr. Portier added that the NTP would look at proprietary data differently than publicly available information regarding whether additional testing is needed. The NTP assesses the public health and scientific needs for a proposed study and always tries to take advantage of any opportunities to examine existing data that might advise the program regarding its testing decisions. This helps the NTP maximizes the use of its resources. Dr. Frederick acknowledged his understanding that the industry is committed to making data available and cooperating in trying to fill data gaps.

Dr. Moure-Eraso asked about the rationale for studying dietary supplements. Dr. Mattison said dietary supplements are uniquely regulated within the United States and are generally considered safe until proven otherwise. They are broadly available and used without studies that demonstrate safety or efficacy. Dr. Allaben added that under the 1994 DSHEA [Dietary Supplement Health and Education Act of 1994], the FDA has only limited regulatory authority for dietary supplements although the agency is required to respond to any identified public health harm. The NTP serves as a resource for the FDA to get information about potential health risks associated with normal use patterns for dietary supplements. Dr. Portier said the NTP is also using resources to characterize the dietary supplements and their variation because they are not uniformly produced.

Dr. Carpenter asked a general question about selection of chemicals for testing. He said an area of concern by state agencies is evaluation of pesticide breakdown products. He asked if this might be an area for NTP nomination. Dr. Portier said the NTP would welcome such a nomination, but added that in this instance, the NTP would consult with the EPA about the types of any mandated testing before the NTP moved forward. Dr. Goldman said pesticide breakdown products are routinely tested as part of pesticide registration although the information might not be readily available to state agencies. If it is an obsolete pesticide and does not have a current owner (registrant), then there is no regulator and NTP testing would be appropriate. Specifically for atrazine, the pesticide of concern, Dr. Goldman said the EPA has information on atrazine breakdown products that is publicly available.

Dr. Moure-Eraso asked about nominations that are not acted upon. Dr. Portier said the NTP keeps an active list of all nominations and proposed testing strategies andhe program routinely reviews this list. In response to a question, Dr. Masten said the NTP is working to make this list publicly available on the web.

Dr. Goldman asked what the NTP might know about fluorosilicates and fluorosilic acids. Dr. Portier said the NTP met with two concerned individuals to get clarification about why they believe exposure to these compounds is different than to the various fluorides used in water. [They propose to the agency initiated the NTP's discussion with this group-syntax unclear]. Dr. Daston noted for the record that his company uses fluoride compounds. He said it seems

appropriate to do toxicokinetic studies on the various fluoride compounds to see if their metabolism is similar or different from that observed in NTP studies of sodium fluoride. This might advise the NTP on how the body handles different forms of fluoride and whether 2-year bioassays are needed. Dr. Portier said he believes that toxicokinetic studies will be very important in evaluating these compounds.

B. Hexavalent Chromium

Dr. John Bucher, NIEHS, provided information to the Board about the nomination of hexavalent chromium (Cr VI) and the proposed study plans. The NTP received a nomination for study of Cr VI from State Senator Adam Schiff and Dr. Joseph Landolph. This was followed by support from the California EPA, the Department of Health Services, and 11 members of the California Congressional delegation. The rationale for its nomination is 1) Cr VI might be a carcinogen in drinking water, 2) recent findings show measurable levels of Cr VI in source water for several California cities, 3) there is an inadequacy of data from long-term animal studies of Cr VI administered orally, and 4) these is a need for data on Cr VI's gastrointestinal absorption during a chronic exposure. Cr VI is a known human carcinogen by inhalation exposure and more toxic than Cr III. Cr VI is reduced to Cr III in the gastrointestinal tract. Controversy exists about whether this reduction is protective or complete and whether the intermediates Cr V and Cr IV might be carcinogenic for site of contact effects. Given these uncertainties, the NTP will perform traditional oral rodent cancer studies using Cr VI administered in drinking water and incorporate measures of systemic Cr to evaluate absorption and reduction. A future public meeting in California is planned for review and discussion of more detailed study designs.

Discussion: In response to a question about the extent of this issue, Dr. Bucher noted that the Cr VI issue is probably national. However, it is acute for California because Cal EPA is recommending decreasing the permissible drinking water limit from 50 ppb for total Cr to 2.5 ppb, which is lower than the current handling capacity of local water treatment systems. Dr. Portier added that the meeting is being held in California because there is scientific expertise for Cr VI and one of the NIEHS' extramural research centers having a focus on exposure assessment is there.

Public comments: Mr. Russ Morgan, Occidental Chemical, provided comments on behalf of the Chrome Coalition. His group is concerned that the NTP proposes to use an animal model with a forestomach for these studies although humans do not have a forestomach. He also commented that a number of agencies have reviewed the data and said there is insufficient evidence for oral carcinogenicity of Cr VI.

Discussion: Dr. Frederick commented that the Coalition's suggestion that the NTP use guinea pigs is problematic because these animals do not make Vitamin C and supplementation would complicate the study. He noted the importance of the ADME contract discussed earlier to this study. He proposed the NTP consider including metabolic studies in dogs or nonhuman primates at the same exposure conditions as the bioassay and compare Cr VI's steady state conversion and bioavailability with rodents. In response to a question, Dr. Bucher said the formal study proposal, once completed, would be submitted for public comment.

Board Endorsement: The Board supported the testing recommendations for the substances nominated to the NTP.

VII. NTP Board of Scientific Counselors' Subcommittees

A. Report on Carcinogens

Dr. C. W. Jameson, NIEHS, presented an update on the Report on Carcinogens (RoC). He noted that the 9th Edition of the RoC was published in May 2000. The recommended upgrading of the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) listing to a *known to be human carcinogen* in the 9th RoC was deferred pending litigation. Following dismissal of the injunction to prevent the listing of TCDD as "known" by the U.S. Court of Appeals, an addendum to the 9th RoC was published by the NTP on January 19, 2001, that changed the listing of TCDD from *reasonably anticipated to be a human carcinogen* to a *known to be human carcinogen* .

Dr. Jameson reported that the second set of nominations for the 10th RoC had completed its three scientific reviews and gone out for final public comment. Upon receipt of final public comments the NTP Executive Committee will review the nominations and recommendations of the three scientific review committees along with all public comments. Dr. Jameson briefly summarized the recommendations of the Board's RoC Subcommittee that met December 13-15, 2001 in Washington, DC. The nominations and subcommittee recommendations are as follows:

(1) Broad Spectrum UV Radiation was recommended for listing as *known to be a human carcinogen* and UVA, and UVB, and UVC were each recommended for listing as *reasonably anticipated to be a human carcinogen*;
(2) Chloramphenicol was recommended for listing as *reasonably anticipated to be a human carcinogen*;
(3) Estrogens, Steroidal were recommended for listing as *known human carcinogens*;
(4) Methyleugenol was recommended for listing as *reasonably anticipated to be a human carcinogen*;
(5) Metallic Nickel was recommended for listing as *reasonably anticipated to be a human carcinogen* and Certain Nickel Alloys was recommended to not be listed in the RoC;
(6) the motion to recommend that Talc containing Asbestiform Fibers be listed as *reasonably anticipated to be a human carcinogen* resulted in a tie vote and Talc not containing Asbestiform Fibers was recommended to not be listed in the RoC;
(7) Trichloroethylene was recommended to remain listed as *reasonably anticipated to be a human carcinogen*; and
(8) Wood Dust was recommended for listing as *known to be a human carcinogen*.

The initial list of nominations for the 11th Edition of the RoC includes the following: 1-Amino-2,4-dibromoanthraquinone, 2-Amino-3,4-dimethylimidazo[4,5-f]quinoline (MeIQ), Caffeic Acid, Cobalt Sulfate, Diazoaminobenzene, Diethanolamine, Hepatitis B Virus, Hepatitis C Virus, High Risk Human Papillomaviruses, X-Radiation and GAMMA-Radiation, Neutrons, Occupational Exposure to Lead or Lead Compounds, Naphthalene, Nitrobenzene, Nitromethane, Phenylimidazopyridine (PhIP), and 4,4'-Thiodianiline. Dr. Jameson said the NTP would solicit public comments through the Federal Register and based upon the comments received, the list

might be modified. Review of these nominations will begin in 2001. Additional information about these nominations is provided on the NTP web site (http://ntp-server.niehs.nih.gov/, see Report on Carcinogens).

Discussion: Dr. Goldman commended the NIEHS on how it handled the TCDD litigation and communications around this issue. She thought it encouraging that the RoC review process having been tested by the court was victorious and it points to the overall integrity of the program. Dr. Portier mentioned that the NTP would continue to work on improving the quality of the background documents and some changes would be made in how those documents are produced. In response to a question about the nominations for the 11th RoC, Dr. Jameson said that at the time Dr. Olden initiated review of the RoC criteria, the NTP sought legal advice about the intent of Congress concerning what should be included in the RoC. It was determined that Congress intended that everything known or reasonably anticipated to cause cancer in humans should be included in the RoC and therefore it is appropriate to review viruses and exposure circumstances for possible listing in the Report. Dr. Frederick asked the NTP to be sensitive to the special needs of individuals who use some of the agents listed in the RoC for therapeutic reasons (e.g., tamoxifen) and to acknowledge the merits of those applications when identifying the cancer hazard associated with an exposure.

B. Technical Reports Review (TRR) Subcommittee

Dr. Rick Hailey, NIEHS, provided information about the meeting held May 3, 2001 at the NIEHS. The TRR Subcommittee reviewed two-year bioassays for five NTP Technical Reports (TR) and Dr. Hailey summarized the levels of evidence for carcinogenicity for the Subcommittee's actions.

- Acrylonitrile (TR-506) - primarily used in the production of acrylic fibers, elastomers, and resins - exposure by gavage - *clear evidence* in male and female mice (forestomach and harderian gland).
- Methacrylonitrile (TR-497) - used as an alternative or replacement for acrylonitrile in some of the same applications - exposure by gavage - *no evidence* in male and female rats or mice.
- Citral (TR-505) - lemon flavoring and fragrance used widely in foods, cosmetics, and other consumer products - exposure by microcapsules mixed in animals' feed - *equivocal evidence* in female mice (lymphomas) and *no evidence* in male mice and male and female rats.
- *o*-Nitrotoluene (TR-504) - widely used in the synthesis of dyes, rubber, and agricultural chemicals - exposure in animals' feed - *clear evidence* in male (mesothelioma; skin, liver, and mammary gland neoplasms) and female rats (skin and mammary gland) and in male (hemangiosarcomas and large intestine neoplasms) and female (hemangiosarcomas, liver and large intestine neoplasms) mice.
- *p*-Nitrotoluene (TR-498) - widely used in the synthesis of dyes, rubber, and agricultural chemicals - exposure in animals' feed -*some evidence* in female rats (clitoral gland), *equivocal evidence* in male (skin) rats and male (lung) mice, and *no evidence* in female mice.

The next subcommittee meeting is October 18, 2001.

VIII. Other Business

The NTP asked the Board for feedback about the agenda for future meetings. The two subcommittees are very focused and handle specific elements of the program - the review of draft NTP Technical Reports and the review of nominations to the Report on Carcinogens. The Board would like to use these meetings for substantive discussions about program issues. Suggestions included NTP research directions and testing activities e.g., links with toxicogenomics or extramural research, emerging issues for which the NTP is considering action, and addressing susceptible subpopulations in testing activities. The Board was agreeable to more frequent meetings.

In response to a question, Dr. Portier briefly updated the Board about the low-dose peer review on endocrine disruptors. The report is complete and is in a public comment period before it is transmitted to the US EPA. He acknowledged the tremendous effort by one subpanel headed by Dr. Joe Haseman, NIEHS, to reanalyze data from primary studies evaluated at the peer review. Dr. Portier said the findings from the meeting would provide guidance to the NTP about future studies.