NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
May 24, 2000
Summary Minutes

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The National Toxicology Program (NTP) Board of Scientific Counselors (the Board) met May 24, 2000 at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. (*Attachment 1*: *Federal Register* notice, *Attachment 2:* agenda and member roster). Members of the Board in attendance included Drs. George Bailey (chair), Clay Frederick, Lynn Goldman, Kim Hooper, Grace Lemasters, Don Mattison, and Patricia Rodier. Absent members included Drs. Norman Drinkwater, Rafael Moure-Eraso, I. Bernard Weinstein, and expert consultant, Hiroshi Yamasaki.

I. Welcome and Introduction

Dr. Kenneth Olden, Director of NIEHS and NTP, welcomed the Board. He recognized the impending retirement of Dr. George Lucier, Director of the NIEHS Environmental Toxicology Program (ETP), NIEHS, on June 30, 2000. Dr. Lucier will remain affiliated with the Institute as a consultant on special projects. Dr. Olden recognized the contributions of Dr. Lucier to the NIEHS and NTP and thanked him for his service and managerial and intellectual leadership. He recognized Dr. Lucier's role in integrating mechanism-based toxicology into NTP research, promoting the use of the best science in decision-making about public health issues, and forging partnerships between Federal agencies. Dr. Olden announced that Dr. Christopher Portier would serve as Acting ETP Director following Dr. Lucier's retirement. Dr. Olden acknowledged his confidence in the abilities of Dr. Portier and senior ETP staff and noted that the search for the ETP Director would follow replacement of the NIEHS Scientific Director. Dr. Carl Barrett left this position for the National Cancer Institute, but will remain as a permanent adjunct scientist at the NIEHS. Dr. Paul Nettesheim is the Acting Scientific Director. The search committee has identified three outstanding candidate finalists and Dr. Olden anticipates selection of a new Scientific Director by end of June 2000. Despite these changes and vacancies to fill, the NIEHS is poised with good leadership, and this is an exciting time for growth as new persons with new ideas are recruited into the NIEHS.

Dr. Bailey, on behalf of the Board, presented a certification of appreciation to Dr. Lucier in recognition of his service to the NTP. Drs. Frederick and Goldman provided remarks and tokens of appreciation on behalf of the Board and its Subcommittees.

Dr. Olden acknowledged the contributions of retiring members of the Board and presented certificates to Drs. Clay Frederick, Kim Hooper, and Patricia Rodier.

Dr. Olden reported to the Board about the process for the FY 2001 NIH budget and projected funding for the NIEHS. Increases of 14.6% and 14.8% are proposed in the House and Senate mark-ups, respectively, similar to that for the National Institutes of Health. The budget will be finalized in the latter part of 2000. The breast cancer and Parkinson's disease advocacy groups are strong advocates for environmental health research and have lobbied Congress for funds to the NIEHS. Dr. Olden believes that there is a strong support in Congress for research on

environmental health issues that is reflected in NIEHS' budgetary increases over the past few years.

II. NTP Update

Dr. George Lucier, Associate Director, NTP, expressed his appreciation to the Board for its role in providing regular and rigorous examination of the NTP, an effort that helps to strengthen the Program. He thanked Dr. Olden for providing leadership and an environment that has allowed the NTP to grow. Dr. Lucier recognized senior staff, Dr. John Bucher, ETP Deputy Director and Ms. Sandy Lange, Director for Liaison and Scientific Review for their efforts on behalf of the NTP and public health, and acknowledged the work and dedication of ETP staff. Dr. Lucier is confident about Dr. Portier's leadership for the NTP and ETP.

He identified 10 items that he believes are strengths and accomplishments of the toxicology program.

- Use of mechanism-based toxicology. This is becoming the centerpiece of the NTP and is integral for understanding the mode of action of environmental toxicants and providing regulatory agencies scientific data useful in risk assessment.
- Human studies. The NTP has expanded beyond being a rodent-testing program to include conduct of human studies; new hires have strengthened this effort.
- Alternative models for toxicological evaluations. Significant advances have been made in the development, validation, and processes by which the NTP achieves regulatory acceptance for cell systems, transgenics, and non-mammalian test systems. The success of the NTP Center for the Evaluation of Alternative Toxicological Methods is hallmark of this effort.
- Risk assessment methods. This effort led by Dr. Portier has helped the NTP to connect science to public health.
- NTP Centers. There are three new NTP Centers (Center for the Evaluation of Alternative Toxicological Methods, Center for the Evaluation of Risks to Human Reproduction and the Phototoxicology Center); each has made and is making significant contributions in connecting good science to public health. The new Phototoxicology Center is formed through collaboration with FDA.
- *Report on Carcinogens*. The NTP has continued to move forward with a commitment to bringing good and all relevant science to the evaluation of nominations.
- High priority areas. These are key areas of public health concern and are a significant commitment of NTP resources: drinking water disinfection by-products, herbal medicines, occupational mixtures, DNA-based products including gene therapies, and chemicals being studied through the NTP Phototoxicology Center.
- Excellence in pathology, chemistry, and statistics. These support activities are important to the NTP and they represent an outstanding effort by those staff.
- National Toxicology Program. The Program is a 'national' effort. Significant improvements have been made in communication with stakeholders including other agencies, academia through granting mechanisms, the public, industry, and unions.
- Sense of well being. The NTP is the essence of its staff whose dedication and talents personify the Program and its efforts.

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

A. Role of CERHR in Meeting the Goals of the NTP

Dr. Christopher Portier, Director, Office of Risk Assessment, NIEHS, provided some comments about the Center. The CERHR was established in 1998 in the Laboratory of Toxicology and is now located administratively within the Office of Risk Assessment, ETP. The Board, which oversees the Center, reviewed its activities in 1999 and prepared a report for the NTP about its strengths, weakness, and direction. Dr. Portier stated the purpose of the Center - *to provide an objective, science-based evaluation of human and experimental evidence for adverse effects on human reproduction and development caused by environmental exposures* - and noted how it falls appropriately within the mission of the NTP. The Center bases its evaluation of potential reproductive and developmental hazards on the strength of the scientific evidence. It also serves to identify major gaps for understanding the environmental causes of reproductive and development toxicity. The CERHR is the first of its kind, and will serve as a pioneer to the NTP for gaining insights about the types of studies and study designs that are most effective in evaluating reproductive and developmental toxicities and for determining how to use information about severity of effect and gradation of severity of effect when evaluating potential adversity for humans. Its target audience includes regulatory agencies, the public, and scientific and medical communities. The Center is still in its infancy and actively solicits the Board's opinion about its activities, review process, and future directions.

B. Response to the 1999 Review of the CERHR by the Board and Overview of the CERHR's Processes and Criteria

Dr. Michael Shelby, NIEHS, serves as Director for the CERHR. His presentation included a response to the Board's 1999 review of the CERHR and changes in the Center's review process and criteria. Two main components of the Center are the NIEHS/NTP staff and the contractor, Sciences International in Alexandria, Virginia. The Center's Core Committee comprised of representatives from NIEHS, EPA, NIOSH, and FDA oversees Center activities.

Dr. Shelby addressed remarks in the Board's 1999 Report about the review process for evaluation of chemicals and noted some changes. The process involves three steps: chemical nomination and selection; expert panel review (peer review and report), and NTP transmittal documents. Chemical Nomination and Selection: The nomination process is open. The Core Committee meets quarterly to review the nominations, prioritizes nominations, and makes recommendations about candidate chemicals to the NTP Associate Director. In its evaluation of nominations, the Core Committee considers production volume, human exposure information, available literature about reproductive or developmental effects, and level of public concern. The list of recommended chemicals is published in the *Federal Register* for public comment. The Core Committee then reviews public comments and recommends a selected list of chemicals for the Center's evaluation to the NTP Associate Director. Expert Panel Review: Expert panels conduct the Center's evaluations of selected chemicals. The Center maintains an expert registry database of persons nominated for service on the expert panels. The Core Committee reviews all nominations to the expert registry and evaluates them based upon their scientific qualifications. No group or affiliation is excluded and all relevant disciplines are included (*e.g.*, developmental toxicology, epidemiology, etc.). The Core Committee recommends membership of an expert panel to the NTP Associate Director for review and approval. The primary considerations for

selection of expert panel members are scientific knowledge and expertise about the chemical and literature being reviewed, experience and past performance in similar activities, and no conflict of interest relative to the chemical under review. Public comment on the expert panel and nominations of additional members are solicited. Comments are also solicited on the selected chemical(s) being evaluated. The Center is continuing to consider having an "observer" status at the expert panel meetings for members of advocacy groups that would attend and make scientific contributions relative to the chemical under review, but not be members of the panel or vote. The expert panel will review and evaluate all relevant literature and summarize its findings relative to the possible health effects for the evaluated chemical(s) in a narrative report. The expert panel report will not include quantitative risk assessment or characterization, but as available, will include a discussion about potential effects based upon comparisons of estimated human exposure with doses used in animal studies. The expert panel reports will be peer reviewed by the expert panel, NIEHS and Center scientific staff, and the Contractor's scientific staff. The expert panel report will have a standard format including information about exposure, general toxicological and biological parameters, developmental toxicity data, reproductive toxicity data, data summary and integration, and references. Public comment will be solicited on the final expert panel report. NTP Transmittal: Following completion of an expert panel's report, NIEHS/NTP staff will prepare an NTP Center Report that includes background information about the chemical's nomination and selection, a lay summary of the expert panel's findings, any new information about the chemical, and the NTP's position about the chemical. This document will be published in *Environmental Health Perspectives*, transmitted to Federal and State agencies and stakeholders (*e.g.*, public, industry, and unions), and posted on the CERHR's web site.

Dr. Shelby highlighted the various avenues for public comment to the Center relative to chemical evaluations: nomination of chemicals for evaluation, nominations for the expert panel registry and expert panel, comment on candidate chemicals, comment of selected chemicals, comments at expert panel meetings, comment on expert panel reports, and comments at the Board meeting.

Dr. Shelby responded to recommendations in the Board's 1999 report about expansion of the Center. The Center is headquartered at the NIEHS and has two part time staff. Other non-Center NIEHS staff is available to serve as resources for CERHR activities. As the Center's activities grow, a dedicated staff at the NIEHS will be needed to meet the Center's needs. This CERHR staff would direct and coordinate the Center's activities, oversee contract and budgetary issues, respond to inquiries, receive and respond to public comments, prepare *Federal Register* notices and press releases, and prepare NTP Center Reports following completion of expert panel reports.

Dr. Shelby listed the various ways for communicating with stakeholders [web site, NTP newsletter and list serves, press releases, *Federal Register* notices, scientific meeting (presentations and exhibits), direct inquiries, expert panel meetings, publication of expert panel reports, NTP Center reports transmitted and published, and a list of interested individuals/groups]. Currently, the Center's web site (http://cerhr.niehs.nih.gov) serves as its primary external communication resource and has 400-500 hits per day. The Center is working to expand its mailing list and welcomed suggestions about target groups. Consideration is also

being given to a suggestion in the Board's 1999 report for advertisements in popular magazines such as those related to parenting or housekeeping. Another idea under consideration is holding public information meetings such as town meetings. The Center is very receptive to expanding its ability to communicate information using multiple media.

Discussion: Dr. Hooper inquired whether the Center knows who is contacting it through the web site and what type of information is being solicited. Dr. Shelby responded that the system for tracking visits to the web site provides limited information about the group (*e.g.*, catalogues as EDU, ORG, or GOV) making the contact and does not capture "why". Dr. Hooper asked several questions about the breadth of nominations to the CERHR, the steps taken to solicit input, how nominated chemicals with limited/no scientific information are handled, and whether the Center would do an update if new data emerges about a previously reviewed chemical. Dr. Shelby responded that the nomination processes is geographically very wide (*i.e.* Europe, South America, United States) and highly variable relative to the level of information/knowledge for the chemical provided by the nominator. The Center will consider nominations of chemicals for which there is no scientific data; in this incidence the expert panel's evaluation might focus on research needs. Dr. Lucier noted that as an NTP Center, if toxicology information is lacking and there is a perceived need to obtain reproductive and developmental toxicity data, the NTP could move forward with a nomination for testing of the chemical. Dr. Shelby further commented that while the Center prefers published data; a special panel could be convened to peer review unpublished data on the chemical in the event it is needed by the expert panel for its evaluation. The Center would welcome the opportunity to update a report if new study information becomes available following conduct of an expert panel review. Dr. Mattison suggested that the Center consider whether a "public notification system" might be put into place that would alert the public about the inadequacies of reproductive and developmental data for particular chemicals, especially those that are produced in high volume.

Public comments: Dr. Raymond David, toxicologist, presented remarks about the CERHR process on behalf of the Chemical Manufacturer's Association (CMA) Phthalate Esters Panel. The CMA submitted written comments prior to the meeting. Dr. David thanked the NTP and Center for allowing as much open scientific dialogue as possible between CMA and the expert panel during breakout sessions at the phthalates review and encouraged continued dialogue including during the plenary sessions. He applauded the Center for the ambitious task of the phthalates review and for extending the time to complete that review. He hoped that time would be allowed for the public to review and comment on the panel's draft consensus statement and monograph and for the panel to review those comments and make changes if necessary. The CMA had four recommendations: 1) consider all expert scientists (regardless of affiliation) for membership on the panel; 2) schedule adequate time for the public to submit written comments and for the expert panel to review those comments; 3) continue to use the weight-of-the-evidence approach in the hazard characterization and place the hazard information in a context so the public can identify any uncertainties in the assumptions; and 4) identify data gaps separately from research needs.

Further Discussion: Dr. Mattison commended Dr. Shelby for his presentation and response to questions raised in the Board's 1999 Report. He suggested that the Center consider setting up an

electronic standardized format to capture data on chemicals under review for greater utility and analysis by the panel. He noted that identifying the users of the Center's information would help to guide it in developing appropriate formats. Dr. Bailey asked about the availability of resources to the CERHR as its activities grow. Dr. Lucier responded that the NIEHS would continue to provide resources in support of the Center's activities and acknowledged the CERHR's importance to the NTP's public health mission. He also noted that the Board would have ongoing opportunities to review the Center's activities and advise the NTP on its activities and priorities.

The Board noted the potentially large number of chemicals that would need evaluation by the Center and that this number would likely increase over time. There was a rather lengthy discussion about the volume of chemicals for review and whether different review processes might be followed for different chemicals. The Board offered several suggestions: 1) having different levels of review and setting up a triage system to screen the chemicals, 2) using a *Report on Carcinogens* type format for review, 3) collectively reviewing chemicals catalogued by class or mechanism and providing a summary of the information for that classification, and 4) following the current process of single chemical review (*e.g.*, phthalates). It was noted that a triage system might be especially helpful for identifying those chemicals needing testing. Dr. Bucher reminded the Board that the CERHR is a non-mandated NTP initiative and it can only address a fraction of the chemicals available for evaluation. As with other NTP activities, public health concern would help the NTP set priorities.

Dr. Shelby sought input about how the Center might use evaluations conducted by other agencies (*e.g.*, Health Canada, European Union, California EPA). Currently the CERHR web site has links to other authoritative bodies. Dr. Goldman thought that linking to other groups was good; however, she felt that the NTP or CERHR would need to make a judgement relative to the information provided in those reviews. The NTP acknowledged that it would use caution when deciding how to use reviews conducted by non-NTP panels. Dr. Portier noted that the Center's reporting process is still under development and he felt that once formats for the panel's reports and data presentations are standardized, this would enable the Center to increase its throughput. He noted that currently two reports are planned for each chemical, the expert panel report and the NTP Center report that includes the NTP's position. Dr. Frederick suggested that other panels' reports might be used as background.

Dr. Rodier asked about the testing of chemicals for which data on reproductive and developmental effects are insufficient or lacking. In response, Dr. Lucier noted that the CERHR has resources through the NIEHS and other agencies. He identified the nine agencies (EPA, ATSDR, CPSC, NIOSH, CDC, OSHA, NCI, NIEHS, and FDA) comprising the NTP Executive Committee and stated its roles in NTP policy oversight, promoting interagency interactions, and reviewing recommendations for NTP testing. Currently four of the agencies (EPA, NIEHS, NIOSH, and FDA) are members of the Center's Core Committee and as such are aware of the chemicals nominated to the CERHR for evaluation. In addition, he noted that the NIEHS conducts research in-house on reproductive and developmental toxicology. Dr. Bucher commented on current NTP initiatives. There is an NIEHS interagency agreement with NIOSH as well as an ongoing NIEHS interagency agreement with NCTR for studying endocrine

disrupting agents. Currently there are significant allocations budgeted for this research area and he felt them appropriate for covering additional new initiatives. Dr. Rodier asked how the NTP would assess a chemical with known neurological toxicity. Dr. Bucher responded that Drs. Chapin, Jahnke, and Harry have developed strategies, exposure situations, and study designs for developmental neurotoxicity studies; these are conducted through contract. The NTP is also trying to restructure its contracts to handle those needs. He noted that the NTP is expanding its concept for toxicology and carcinogenicity studies in its issuance of a task order contract that includes perinatal dosing and study designs to address developmental immunotoxicology and developmental neurotoxicology along with reproductive and developmental endpoints. Dr. Lucier further noted that for studies conducted both in-house and by contract there is a scientist who oversees and develops the protocol for the study. Another example is an interagency agreement under development between NIEHS and FDA to examine potential developmental neurotoxicity related to thimerosal exposure; this chemical is used as a preservative in vaccines. Dr. Goldman said if the substance has a commercial owner and is regulated then industry might conduct testing. She suggested that CERHR might develop industry/government partnerships for studying chemicals identified by the Center.

Several members were interested in the CERHR being better integrated with medical professionals (both obstetric/gynecologists and pediatricians) for both dissemination of information and for fielding questions and obtaining input. Dr. Shelby noted that three physicians, including a pediatrician, are on the phthalate esters expert panel and their input has been extremely valuable to the evaluation. He also commented that the Center would use Drs. Goldman (pediatrician) and Mattison (obstetrician and director, March of Dimes) as resources for identifying links to medical professionals. Dr. Nettesheim asked for suggestions about how to involve the medical community. Some of those offered included posters or presentations at national medical society meetings and a 1-800-information line. Dr. Lemasters noted that a subcommittee of the American Conference for Obstetrics and Gynecology has an environmental public health subsection. Dr. Hooper suggested that the CERHR consider having a physicians advisory committee that includes members from various societies to facilitate linkage with the medical profession. This group could be queried about the types of input its members would find useful and could serve as a liaison for these organizations with the Center.

VI. Perspectives on the Process (*e.g.* phthalate esters panel)

A. Expert Panel

Dr. Robert Kavlock, EPA and chair of the expert panel, covered three areas in his presentation: things that worked well, things that needed improvement, and things that (still) need improvement. He presented a compendium of comments, both those he received from the panel and his own. The panel complemented the NTP for establishing the CERHR and moving forward with the phthalate esters review. Dr. Kavlock noted the dedication of the expert panel members to the review. Things that worked well: 1) the interdisciplinary composition of the panel; 2) the panel getting input from industry and public interest groups; 3) the organizing and collating of material into tables; and 4) the use of e-mail for communicating among the Center, contractor, and panel. Several items that needed improvement: 1) clearly defining in the panel's charge how far it should go in assessing risk; 2) the Center taking a greater role in pre-meeting preparation of the draft documents including writing sections 1-4; 3) posting all panel report

drafts on the web so revisions could be tracked; and 4) deciding how to link information across chemicals, especially for those with common mechanisms. Dr. Kavlock also noted that some panel members were uncomfortable with all sessions being public and felt that this sometimes restricted dialogue. The final set of comments identified things that need improvement: 1) scheduling at most one day per chemical to ensure adequate discussions and panel interactions; 2) clarifying the roles and responsibilities of the Center Project Officer, expert panel chair, and panel members; 3) having the Center do more of the pre-meeting preparation including descriptive writing and collection of information; 4) having key data available to the panel for its own analysis; 5) improving the exposure information available to the panel; and 6) establishing some panel members with permanent or semi-permanent terms. One suggestion is rotating terms for reproductive and developmental experts with other expertise added ad hoc. The panel also recommended that the Center take responsibility for writing the lay summary and handling risk communication issues. Dr. Kavlock noted that Dr. Shelby said in his earlier presentation that the NTP would take responsibility for the lay summary; however, he suggested that the panel be able to review it.

B. Regulatory Agencies

Dr. Schwetz, FDA, addressed the Board via teleconference. He noted his personal support for the Center and its importance to this research field as well as to the public and Federal and State agencies. However, he noted that support within the FDA is mixed depending upon the chemical being evaluated and the FDA Product Center with responsibility for regulating the chemical. He said that the FDA is concerned that the CERHR evaluation of a chemical would be a risk assessment that might not be supportable by a specific Product Center because it might have conducted its own risk assessment that included information not available to the CERHR, such as proprietary data. This is primarily a situation with drugs because the information on a drug's label is negotiated with industry; for drugs, both benefit and risk are considered in the FDA's assessment. Any published document with a message that differs from the label would be of concern to the Product Center. In response to this concern, Dr. Schwetz recommended that FDA staff be included in the Center's chemical selection process and participate on expert panels when appropriate expertise is available. He said that the FDA is supportive of the panel's efforts to identify data gaps and research needs for chemicals and that the FDA would appreciate receiving such information. He briefly commented on the value of the Center, its reviews and products; - the independent expert panel reviews will serve as models for the scholarly interpretation of data, for integrating animal and human data, for evaluating dose-response relationships, and for defining the characteristics of available data including its limitations. Prior to the Board meeting, Dr. Schwetz spoke with Carol Kimmel, EPA, and asked for her input about the Center. Dr. Kimmel suggests that the expert panel report include dose-response characteristics, because this would provide a foundation for possible re-evaluations by the Center or regulatory agencies at a later time, as new data become available.

Discussion: Dr. Hooper inquired about the membership of agency scientists on the expert panel for the phthalates. Dr. Goldman responded that EPA is represented on the panel and Dr. Schwetz is a member of the Core Committee. Dr. Frederick inquired whether the FDA's concerns are so severe as to preclude any evaluations of drugs by the CERHR. In response, Dr. Schwetz answered no and that this issue should be dealt with on a case-by-case basis.

Dr. Teresa Schnorr, NIOSH, commended the Center's timeliness and the need for the type of uniform assessments of reproductive and development toxicants that will be conducted. NIOSH is implementing a National Occupational Research Agenda (NORA) that includes examining reproductive and developmental effects. She noted that Dr. Shelby is on the NORA team and she is on the CERHR's Core Committee. Dr. Schnorr was supportive of the multi-disciplinary approach to the expert panel's composition as she felt it enhances cross-communication between research areas. Dr. Schnorr provided several comments to the Center regarding possible future reviews of occupational chemicals. First, she recommended the inclusion of an industrial hygienist or expert familiar with occupational exposures on the panel, either ad hoc or as a member. Second, she noted that occupational exposures could occur through both manufacturing and use, and this should be taken into consideration. Third, Dr. Schnorr recommended that the expert panels examine dose-response relationships, and as appropriate, evaluate this data; this would help to focus future research efforts. She noted the important role of the Center for identifying research gaps during its reviews.

Dr. Bruce Rodan, National Center for Environmental Assessment, EPA, said his agency is supportive of the Center and the focus of efficient and targeted assessments at a single Federal agency. Dr. Rodan provided EPA's recommendations for the Center - to maintain a core staff serving on several panels to provide continuity; - to have the expert panel extend its activities; -to incorporate the best science possible, including possibly defining dose-response relationships during its chemical evaluations; - to have the panel open and responsive to public comments and to consider these in preparing the final expert panel report; - to make primary data, especially for sentinel studies, available for analysis by the panel; - and to consider having a statistician permanently staffed within the CERHR for participation on the chemical evaluations to promote consistency.

C. NTP Board of Scientific Counselors

Dr. Lynn Goldman, Johns Hopkins University and member of the NTP Board of Scientific Counselors, provided her own perspectives on the CERHR and the phthalate esters review. She has attended several of the reviews. Dr. Goldman said that the Board identified four issues during its discussion about the CERHR in 1999: science, management, public participation, and process. First in terms of the science, she believes that the CERHR has been responsive to the suggestions for adding experts (*e.g.*, in exposure, pediatrics, etc.) to the panel and that the cross-disciplinary type of evaluation being conducted by the panel is good. The reviews are covering a broad scope in terms of the types of studies, endpoints, and test systems and this will benefit the field. Second, the CERHR's roles of the contractor versus the NIEHS are now more clearly defined; however, with increased involvement by the NIEHS, Dr. Shelby needs additional staff. Dr. Goldman commented on the appropriateness of the NTP reviewing the public comments and the expert panel's report and then synthesizing its position in a separate transmittal document. This process addresses the Board's concern that the NTP take ultimate responsibility for CERHR review. Dr. Goldman believes that the expert panel is staying within its mandate for hazard identification leaving risk assessment/management issues to the regulatory agencies as discussed by the NTP Board of Scientific Counselors. Third, in terms of public participation, Dr. Goldman noted the high attendance at the expert panel meetings including the public, industry, and other

Federal agencies. She believes that the public is aware of the nomination process and noted that the Center's public outreach efforts (*e.g.*, web site, *Federal Register* notices) seem to be working. However, she is concerned about an imbalance between the number of industry versus public advocacy scientists present at the expert panel meetings. She acknowledged the greater availability of experts from industry because of their support of the science, but suggested that the NTP and the contractor would need to reach out aggressively to public groups and consider ways to involve them, especially those groups with limited financial resources. Fourth, Dr. Goldman noted that the review of phthalate esters is the first evaluation and has involved much "learning by doing." Despite difficulties with the process, the expert panel is very committed to its task, the process is transparent and open, and excellent discussions have been carried out in the public forum. One weakness has been the relative lack of availability of exposure data. Dr. Goldman is supportive of maintaining some continuity across the various expert review panels and believes that this may both decrease the "learning curve" and facilitate the panels' evaluations. She suggested considering that evaluations would be carried out by a core panel, adding chemical specific experts on an ad hoc basis for specific reviews.

Discussion: Dr. Bailey thought that the time demands being placed on the expert panel are great and commented that streamlining of the review process would likely be necessary to keep the process viable. Dr. Shelby thanked Dr. Kavlock for chairing and participating in the expert panel. Dr. Portier asked for the Board's opinion about whether expert panels should address benchmark dose and should provide information about dose-response or leave such risk issues to the regulatory agencies. Dr. Portier also noted that this would be a resource issue for the NTP. Dr. Frederick believes the panel should not do an extensive dose-response evaluation with allocation of uncertainty factors. He felt sufficient time would not be available during an expert panel meeting to cover this issue. He was agreeable that expert panels should have access to "raw data" for any needed analyses.

VII. Current Trends in Toxicological Testing

A. Overview of Topic

Dr. John Bucher, NIEHS, noted that historically the early technical reports from NTP studies focused on industrial chemicals (*e.g.*, dyes, pesticides, etc.) and drugs; beginning with reports #300/400, the studies addressed mycotoxins, physical agents like EMF, and natural products. Dr. Bucher noted that the NTP is responsive to public health concerns and as such, the nomination process for agents to study is open and public comments are routinely solicited on nominations. The NTP often holds workshops as a foundation for its initiating studies in a particular area. The subsequent presentations provide overviews about current NTP initiatives. He solicited the Board's input about the scientific merit and potential public health impact of those initiatives.

B. Safe Drinking Water

Dr. Gary Boorman, NIEHS, oversees the program and in his absence, Dr. Bucher gave the presentation. Safe drinking water represents a balance between microbial and chemical risk. The 1986 Safe Drinking Water Act (Reauthorized 1996) requires that EPA determine maximum contaminant levels or treatment techniques for substances that might have an adverse health effect and that the EPA considers effects of contaminants on sensitive subpopulations (*e.g.*,

elderly, children, sickly, etc.). There are two types of substances of concern: water disinfection by-productions (vary depending upon treatment process) and contaminant candidate list (other drinking water contaminants, *e.g.*, algae toxins, organotins). Major research issues related to possible human health effects include dose/response relationships, extrapolation of effects to humans, and many of these agents are part of a complex mixture, which complicates their study. The Safe Drinking Water Act sets regulatory deadlines for the EPA, so to obtain information for meeting those deadlines and setting drinking water standards, the EPA is coordinating a research program. The NIEHS Safe Drinking Water Initiative is a cooperative program with EPA, US Department of Defense (DoD), industry, extramural investigators, and the US Geological Survey. Dr. Bucher briefly outlined some of the areas for NTP study. The NTP has completed chronic rodent studies on a number of the major DBPs: trihalomethanes (positive studies), haloacetic acids (negative), chlorinated water (negative), and chloraminated water (negative). Chronic studies are ongoing for certain trihalomethanes, haloacetic acids, haloacetonitriles, and chlorate. The NTP is also conducting DBP studies (trihalomethanes, haloacetic acids, and bromate) in transgenic rodent models to investigate mechanism(s) of action and a broader range of doses. This initiative also includes reproductive and developmental toxicology studies, immunotoxicology studies (tier one screens), neurotoxicology studies (done at EPA), and studies in the fish model - Medaka (conducted by DoD). Besides the DBPs, the EPA and NIEHS have nominated several from the contaminant candidate list (aluminum, organotins, dichloropropanes, dichloropenes, methyl tertiary butyl ether, and microcystins) for NTP study. The studies of these contaminants will have mechanistic endpoints (dose-response and toxicokinetic evaluations) and the NTP will involve academic researchers through support of extramural RO3 grants.

Discussion: In response to a question about the types of future studies, Dr. Bucher replied that they would cover cancer, immunotoxicology, and neurotoxicology, but would depend upon the available study material and findings from earlier studies. Dr. Goldman asked that the Board be added to the mailing list for receiving the chronic toxicity reports and Dr. Wolfe replied that the Board would be added. Dr. Hooper asked about the utility of studies conducted in transgenic models and how information from those studies impacts regulatory decisions. Dr. Bucher commented that EPA is interested in knowing relative carcinogenicity of agents within a class and for which data from two-year studies exists for some member of the class. Background studies for many chemicals have been conducted in both transgenic and standard rodent models; many of the transgenic studies have shown similar responses at comparable doses to those in standard bioassays. Some current studies on TCDD using an extended dose range are looking at comparative potencies and the results of risk assessments based on cancer assays with Sprague-Dawley versus transgenic animals. Dr. Hooper also asked about studies of lifetime exposures. Dr. Bucher noted an ongoing debate about the power for detecting effects in long-term rodent studies versus the problem of rising background due to spontaneous tumors. He said survival appears to be better with the new NTP2000 diet - the NTP should consider conducting some longer (>2 years) studies. Dr. Frederick requested an update about the NTP2000 diet and its effect on background tumor rate at a future meeting. Dr. Bucher noted that the initial comparisons are now being made. Dr. Hooper asked whether transgenic mice could be used for studying early effects. Dr. Bucher remarked that mice are begun in the studies as soon as possible - five to six weeks of age; however, for example with p53 transgenics, the responses are less than were anticipated, so studies initially planned for six months are being extended to nine.

Dr. Lemasters inquired about the levels of DBPs in swimming pools and asked about the comparability between the doses being used in animal studies and exposures from swimming pools and drinking water. She noted that swimming is "whole body" immersion. Dr. Bucher replied that measurements of absorbed trihalomethane have been made and there is significant human exposure through both showering and swimming. Therefore, the NTP is conducting both skin painting and inhalation studies; toxicokinetic information will be obtained for these studies regardless of exposure route. In reference to a June article in *Environmental Health Perspectives* concerning critical windows of exposure for children's health, Dr. Lemasters asked whether it is known if toxicokinetics and pharmacokinetics differ at various developmental stages (*e.g.,* infancy vs. childhood vs. adulthood). Dr. Bucher replied that this is possible, but would differ from chemical to chemical. The NTP has conducted a sources sought solicitation to identify laboratories that could conduct perinatal dosing studies with emphasis on reproductive and developmental, neurotoxicity, and immunotoxicity endpoints. Once identified, the NTP will design studies to address these issues although he was unsure whether this would include chemicals from the Safe Drinking Water Program.

C. DNA-Based Products

Dr. Rick Irwin, NIEHS, presented the overview. He referred to an article by W. French Anderson [*Science* 288(5466): 627, 2000] that highlights the development and application of new gene therapies as well as the evaluation of potential risks with long-term exposures. The FDA nominated DNA products for NTP study for several reasons -- it has limited authority to test biologicals; -- many sponsors are small biotech companies or academic institutions without resources to support well conducted long-term studies; -- the FDA cannot disseminate proprietary information or use such knowledge to require additional testing by another company; -- and DNA based products are the fastest growing segment of the product portfolio for the FDA Center for Biologic Evaluation and Research (the FDA center responsible for evaluation and approval of these products). The nomination involves three types of DNA products: plasmid DNA vaccines (engineered to express proteins in eukaryotic cells that will elicit an immune response), synthetic oligonucleotides (antisense therapies and adjuvants), and viral based vectors (adenoviruses and retroviruses). The FDA-NIEHS initiative will address safety concerns associated with DNA products such as their long-term persistence and integration into host genome, distribution to gonadal tissues, and abnormal immune activation (*e.g.*, how this affects the host's ability to respond to subsequent antigenic challenges). There are challenges to this type of study that require non-standard protocols and evaluation of non-standard endpoints. Study design is beginning and the initial efforts will address 1) the influence of DNA products on immune homeostasis, 2) the safety and immunogenicity of DNA vaccines in pregnant females and newborns, and 3) the effect of DNA products on development of autoimmune disease.

Discussion: Dr. Bailey asked whether literature is available about integration of non-human genetic material into the human germ line. Dr. Irwin replied that one study in mice where plasmid material was injected directly into the testis reported its incorporation in sperm; there was also germ line transmission to the offspring. He also noted that some bio-distribution studies have been done, but there is limited scientific literature available. Dr. Frederick noted the potential size of this type of research program and agreed that looking at DNA vectors would be a good initial start. Dr. Irwin said DNA vaccines are a priority because of the potential impact to

third world countries of providing cheap vaccines that could be disseminated widely. Dr. Frederick asked about a timeline for conducting the initial studies. Dr. Irwin responded that some studies might start by late 2000. Dr. Bucher added that these studies would be done through a cooperative agreement with FDA and many of the analyses for tissue integration will be done at FDA; this is a cost sharing activity. Currently eleven candidate materials are identified for auto-immunity assays and tissue integration assays. The NTP is not sure exactly when this program will start, several hurdles must be overcome, such as getting representative materials for study and getting companies to agree to supply the DNA products. Dr. Mattison asked about the possibility of international harmonization for the safety evaluations. Dr. Irwin was unaware of any efforts, but suggested that such information would probably be available from FDA. Dr. Goldman noted that there is an international committee on harmonization of which FDA, Japan, and the European Union are members. She asked whether there might be other substances (*e.g.*, preservatives, additives, etc.) that might be hazardous; Dr. Irwin commented that he is only aware of these materials being administered in saline; but this may become an issue if they are formulated for widespread dissemination. Dr. Allaben noted the importance of this project to the FDA and the intellectual input that the agency needs to determine their safety. Dr. Hooper asked about the level of confidence that the studies done in animals would predict the human response for gonadal integration. He also inquired whether clinical trials would be undertaken prior to wide spread distribution of these materials. Dr. Irwin agreed that the issue of applicability of animal data to humans is always a question, and in the absence of data on integration, the study of this issue is important. He also noted that clinical trials are ongoing for some substances.

D. Medicinal Herbs (Botanicals)

Dr. Tom Burka, NIEHS provided an overview on the NTP initiative to study health effects of medicinal herbs. Much of the world relies on the use of botanicals as treatments. Many developing and developed countries (*e.g.*, Germany) have established regulatory systems covering recognized preventative and therapeutic uses of botanicals. The 1994 Dietary Supplement Health and Education Act limits the FDA's ability to regulate their use in the United States. The 1997 Presidential Commission on Dietary Supplement recommended increased research on dietary supplements including medicinal herbs. Reasons for concern about the safety and efficacy of botanicals include 1) no pre-market testing or FDA approval is required to sell botanicals, 2) substantiation of efficacy is not required, 3) no package inserts are required to inform consumers of possible adverse effects or interactions, and 4) there is minimal post-market surveillance for possible adverse or allergic reactions. The NTP studies on these botanicals take into consideration several factors about these substances: 1) many of the active ingredients are secondary metabolites influenced by climate, temperature, and stress; 2) many are mixtures; and 3) many have a short shelf life. Dr. Burka noted that even when the active ingredient is known, there are often qualitative and quantitative inconsistencies among various lots of these substances. Dr. Burka briefly summarized the botanicals currently being studied by the NTP. 1) Goldenseal is an antimicrobial agent containing the alkaloids, hydrsatine and berberine. It is recommended for NTP studies of reproductive and developmental toxicity, chronic toxicity, and carcinogenicity. 2) Comfrey is consumed in herbal tea and contains several pyrrolizidine alkaloids (*e.g.*, symphytine). A NIEHS/Duke University study is planned to measure the concentration of symphytine in plasma of comfrey tea drinkers; this information will be

compared with levels measured during the rodent bioassay. It is recommended for NTP studies of carcinogenicity and reproductive and developmental toxicity. 3) Echinacea, found in the purple coneflower, is recognized as a short-term immune system stimulant; inulin is thought to the source of its immunostimulatory properties although the active ingredient(s) are not established. It is recommended for NTP studies of immunotoxicity, subchronic and chronic toxicity, and carcinogenicity. 4) Milk thistle extract has hepatoprotective properties in animal studies and its active ingredient, silymarin, is a mixture of flavonolignans. It is recommended for NTP study of genotoxicity, metabolism, reproductive toxicity, chronic toxicity, and carcinogenicity. Dr. Burka provided a brief overview of the botanicals that are currently in the literature review and design phase for NTP study. 1) Ginko biloba extract has been used historically in Chinese medicine and is the fifth most popular botanical. The extract has been used primarily to treat headaches, depression and short-term memory loss by increasing cerebral blood flow. It is recommended for NTP study of neurotoxicity, chronic toxicity, and carcinogenicity. 2) Aloe vera gel is widely purported for its topical use in wound healing; however, more recently it is being taken internally. It is recommended for NTP study in the Tg.AC transgenic mouse model. 3) The extract from ginseng root is being marketed widely and is used for general vitality and health. It is recommended for NTP study of reproductive toxicity, neurotoxicity, chronic toxicity, and carcinogenicity. 4) Kava kava is tropical shrub native to the South Pacific and is now the most commonly used botanical in the United States. Its popularity stems from its psychoactive properties that are associated with it containing kavalactone. It is recommended for NTP study of genotoxicity, reproductive toxicity, neurotoxicity, chronic toxicity, and carcinogenicity. In addition, two chemicals, which are recognized as being toxic components of botanicals, are being studied. 1) Pulegone is the active ingredient in pennyroyal and has been most often used as a drug that causes expulsion of gas from the alimentary canal, emmenagogue (stimulant of menstrual flow), and abortifacient as well as a repellant for fleas and mosquitoes. It is recommended for NTP study of chronic toxicity and carcinogenicity. 2) The use of thujone in food in the United States is banned although the use of flavorings containing it (*e.g.*, sage) is allowed. It is found in spices, herbs, and cedarleaf oil and is mildly toxic when consumed acutely. It is recommended for NTP study of genotoxicity, reproductive toxicity, neurotoxicity, chronic toxicity, and carcinogenicity.

Discussion: Dr. Hooper asked whether there are any plans for studies that would target effects for "high risk" groups, *e.g.*, elderly, young, etc. Dr. Burka responded not specifically as the initial stages of study would be to determine whether there are toxic effects associated with exposure to these botanicals and to identify, if possible, the source of the toxicity. Dr. Frederick encouraged the use of a composite sample from major manufacturers to standardize the dose consistency throughout the studies. Dr. Bailey noted that variability is common with agricultural products, so these types of studies generally use a composite. Dr. Burka said the NTP is using wholesale suppliers as sources for the botanicals, and unless the active ingredient is known, the NTP would study the herbal as a mixture. There is concern with these studies that the herbal as a mixture may be the source of any effect and its ingredients may act differently as single components.

E. NTP Center for Phototoxicology; FDA-NIEHS Phototoxicology Research and Testing Laboratory

Dr. Paul Howard, NCTR, discussed the interagency agreement (IAG) between the NIEHS and FDA, the nomination process for study of phototoxic compounds, the facilities of the FDA-NIEHS Phototoxicology Research and Testing Laboratory, the compounds under study, and future plans. The interagency agreement is to conduct mechanistic-based toxicity and carcinogenicity studies on FDA high priority chemicals nominated to the NTP. This is to try and expedite the process of gaining scientific data for meeting the regulatory needs of the FDA. Compounds under study through this IAG: studies for chloral hydrate and fumonisin B1 are complete and technical reports have been submitted; malachite green, urethane/ethanol, and alpha- and beta-hydroxy acids were the next nominations; additional nominations are chemicals for the endocrine disruptor program and include multigenerational studies on genistein, ethinyl estradiol, nonylphenol, vinclozolin, and methoxychlor. The nomination of the alpha- and beta-hydroxy acids, which are principle components of the majority of skin care creams and lotions used in the United States, raised questions about how the study of these compounds could be modeled to mimic the human exposure paradigm. Photo-induced skin carcinogenicity and skin carcinogenicity studies were needed for study of alpha- and beta-hydroxy acids.

Briefly, the nomination process for compounds studied by the Phototoxicology Center includes review of chemicals by the FDA Phototoxicology Chemical Selection Working Group with input from NIEHS/NTP, FDA centers and several offices. The prioritized nominations go to the Interagency Committee for Chemical Evaluation and Coordination and then proceed through the NTP's nomination and selection process. Once selected, the Toxicology Study Selection and Review Committee (TSSRC: composed of NIEHS and NCTR Project Officers, NCTR Director, FDA Product Center scientists, NCTR study principle investigator, FDA scientists, and public) oversees the design and progress of studies. A NCTR staff scientist serves as the study principal investigator and works with the FDA Product Center in study design and protocol review.

The Center's mission is to meet the regulatory and testing needs of FDA and NIEHS/NTP for phototoxicity and photocarcinogenicity. The design of the facility and animal caging system was developed in collaboration with Argus Research Laboratories. The Center has two 6.5 kWatt xenon-arc lamp solar simulators, one per animal room, whose spectrum can be varied to match that of sunlight. The spectrum of the simulated solar light being used matches light in Arkansas and North Carolina in July (approximately 34-North latitude). Animals are placed two meters from the 6.5 kWatt light source resulting in a dose of light that is equivalent to approximately 15% the intensity of noon summer sunlight at 34-North latitude. The Center has had site visits by experts in photobiology and phototoxicology to evaluate the facility; the response has been favorable about the "state-of-the-art" issues of dosimetry that are being addressed. In addition, the Center can generate any combination of fluorescent radiation (*e.g.*, UVA, UVB, visible) if required for an animal study. The SKH-1 hairless mouse was selectively bred in the 1970s for the adult hairless phenotype and is the primary animal model for the photocarcinogenicity studies. Skin tumors develop primarily on the rear dorsal side of the mice. Up to 576 mice can be exposed to the simulated solar light at any given time. As a result, the facility can accommodate several studies simultaneously.

Currently the Center is studying the photocarcinogenic potential of alpha- (glycolic acid) and beta-hydroxy acids (salicylic acid) that are found in over-the-counter cosmetics as

dermatological chemoexfoliants. The impact of their continuous use for risk of solar light (*e.g.,* UV) induced skin cancer is not known. Two possible consequences of chemoexfoliation are increased proliferation of the epidermal epithelial cells and deeper penetration of electromagnetic radiation into the skin. The doses of alpha- and beta-hydroxy acids being administered topically to the mice are similar to their content in over-the-counter formulations.

The Center also has the potential as a resource for testing new animal models/transgenics and new technologies for phototoxicity and photocarcinogenicity research. The Center would like to expand its research capabilities beyond cancer and study the role of drugs in combination with solar light on ocular toxicity (*e.g.,* cataract formation), neurotoxicity, melanoma formation, and systemic toxicity. The Center can also be a research resource for other government agencies and the academic community to conduct photobiological studies that require the simulation of solar light.

Discussion: Dr. Frederick noted the limited capacity of the Laboratory and wondered whether it might be more expedient to contract out the work. In response, Dr. Howard replied that there is already interest in the use of this facility by the Office of Cosmetics for studies of other dietary supplements and herbals (St. John's wort). He noted that the laboratory is a replication of the Argus laboratories and the company is very supportive of the new Center. The Center can focus on studies that have no drug sponsor. Also, the mechanistic work will facilitate interpretation of bioassays done by Argus and support NTP activities. Dr. Allaben said a number of therapeutics administered systemically would be nominated for testing in the near future; FDA does not have leverage to get the sponsor to conduct the studies. The facility has been site-visited and the team was supportive of its design and activities. In response to a question, Dr. Howard said that pending renovation and availability of personnel, the Center could handle the start of one new compound per year; four compounds are in process at any time (six rooms) - three ongoing and a fourth finishing. The facility can be expanded and there are plans to do so. Studies are generally one year of exposure. Dr. Hooper asked if throughput might be increased by increasing the light intensity. Dr. Howard felt that this would not greatly enhance the Center's ability to test more compounds.

F. Occupational Exposures and Mixtures

Because of a declining capability, toxicological testing at NIOSH was curtailed during the 1980s and 90s. As a result, NIOSH began increasing its reliance on the NTP testing program to bolster toxicological assessment of occupational hazards. To improve NIOSH's interaction (*e.g.,* research, nominations, *Report on Carcinogens,* Technical Reports, Annual Plan, etc.), with the NTP, the agency established a steering committee. Initially, NIOSH used a systematic approach to set testing priorities for occupational chemicals. Data needs were assessed for unregulated chemicals with more than 50,000 workers potentially exposed based on NIOSH's 1981-83 National Occupational Exposure Survey (NOES). In addition, chemicals for which NIOSH was reviewing established occupational exposure guidelines were also evaluated for data needs. In all, nearly one hundred chemicals were assessed by the NIOSH/NTP steering committee. Only one nomination for chemical testing (bentonite) arose from this assessment. Though gaps in toxicological data were evident for many chemicals, they were not nominated for testing because significant occupational exposure could not be readily verified. The absence of up-to-date

exposure characterization for chemicals beyond that in the NOES spurred NIOSH to plan an on-site survey of workers and workplaces 1) to gain information on the distribution of occupational hazards and the magnitude of their exposures; 2) to track trends in exposure; and 3) to identify safety and health program components, new exposures, and new interventions. Completion of the new NIOSH occupational survey is several years away.

In the absence of an up-to-date database on occupational exposures, an interagency agreement (IAG) between the NIEHS and NIOSH was established to characterize specific occupational exposures that would improve the design of pending laboratory toxicology and carcinogenesis studies. Under this IAG, NIOSH is presently characterizing two NTP nominations: asphalt fume and cellulose fiber exposures. NIOSH is assessing a system designed to produce asphalt fumes similar to that found in the field and is evaluating the physical and chemical characteristics of asphalt fumes generated under simulated road paving conditions. The agency will use this information to design laboratory inhalation studies of asphalt fume exposure in animals. Worker practices, exposures, and possible health effects caused by cellulose fibers have not been identified. NIOSH is characterizing workplace exposure to cellulose insulation and is evaluating health effects in cellulose insulation applicators. Results of these assessments will aid the design of laboratory studies on health effects of cellulose fibers.

A recent nomination to the NTP is 1-bromopropane, a substitute for ozone depleting chlorofluorocarbons. Currently there are not exposure limits for 1-bromopropane although the EPA has guidelines. Despite the view that 1-bromopropane use will increase dramatically in the next few years, the number of workers exposed is unknown. Under the IAG, NIOSH and NIEHS are planning an industry-wide exposure assessment. This assessment will characterize exposures to 1-bromopropane and identify exposed worker populations. If worker exposures are significant, a health assessment will be conducted. Phase I will be a clinical assessment of male and female reproductive effects and hematology. Phase II will be a population-based assessment of the associations between 1-bromopropane exposure and neurotoxicity, genotoxicity, and liver toxicity. In the future, NIOSH would like to extend occupational assessments to complex mixtures such as metal working fluids and welding fumes. While several components of metal working fluids have been tested, little is known regarding the chronic effects from formulations of metal working fluids inhaled as aerosol. Among the more than 80 different types of welding practices, those posing the greatest potential health hazard need to be identified.

Discussion: Dr. Toraason said that none of the current NTP nominations presently before the Board came from the NIOSH's efforts to do a systematic review using the NOES data. In response to a question, Dr. Toraason noted that both NIOSH and NTP are interested in studying complex mixtures. These would probably be addressed similarly to the asphalt fume studies. Dr. Bucher said this IAG allows the NTP to conduct exposure assessment through NIOSH and, as possible, can characterize an exposure in the field and then reproduce the scenario in the laboratory and determine if there are reasonable ways to study it. Dr. Goldman wondered whether workers exposed to metal working fluids and fumes have been monitored for exposure. Dr. Toraason replied that NIOSH has characterized worker exposures, but exposures vary greatly at different field sites and the chronic health effects of these exposures are unknown. In response to a question, Dr. Bucher replied that this presentation was included to inform the Board about

this initiative, to present current projects, to present some of the problems with studies of occupational exposures, and to identify areas for future studies. Dr. Frederick commented that workers are exposed to asphalt fumes, but children may also be exposed when a school's roof is re-asphalted. Dr. Lucier noted that occupational exposures and mixtures are important areas for resources and the NTP is working through strategies and experimental problems with NIOSH to address public health problems associated with them. Dr. Hooper acknowledged the current projects are worth while, but asked if consideration might be given to gasoline particulates - an inhaled complex mixture. Dr. Toraason noted that with available resources it would take considerable time to address the present list of potential exposures. He added that once the characterization and evaluation of the occupational exposures are finished, NIOSH may choose not to nominate metal working fluid or welding fume for additional studies.

VI. Concept Review

Dr. John Bucher, NIEHS, presented the concept (*Attachment 3*) and Drs. Frederick and Hooper served as principal reviewers. Dr. Bucher explained that prior to issuance of a contract, which 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 contract mechanisms as the appropriate means for carrying out much of its toxicology and carcinogenesis research and testing. This covers studies for cancer bioassays in laboratories, toxicology contracts arranged as task order contracts, and chronic and pre-chronic testing. Over the next five years, the NTP anticipates continuing its use of toxicology and carcinogenesis contracts with targeting of similar endpoints. The Program also intends to issue a Request for Contract (task order type) for carrying out routinely perinatal dosing studies; the current toxicology and carcinogenesis contracts do not allow routine perinatal dosing of animals. In addition, the NTP proposes to provide for the collection of additional tissue samples and/or chemical analyses for information that can be used in development of physiologically based toxicokinetic models. The NTP is asking for the Board's endorsement to use contract mechanisms to continue animal-based toxicology and carcinogenesis testing.

Discussion: Dr. Frederick encouraged NTP to set up satellite groups in conjunction with the 90-day studies for obtaining tissues that can be used for genomic and proteomic research projects at the NIEHS. Dr. Bucher said this task would be covered under current contract capabilities. Dr. Frederick also mentioned that special handling and tissue processing requirements should be considered and Dr. Bucher concurred. Dr. Lucier said the NTP tries to promote interactions with the extramural research community through RO3 grant mechanisms and makes available study samples. Dr. Mattison supported the NTP's study of exposure during pregnancy. He pointed out that physiologic changes vary across species in their adaptation to pregnancy and characterization of such changes should be part of the data collected in those studies. Such information would be important in development of physiologically based pharmacokinetic models. Dr. Portier said the NTP is interested in obtaining good baseline information on lifetime endpoints. He has asked the NIEHS toxicokinetic faculty headed by Dr. Ron Melnick to address this issue of obtaining such baseline data from control animals. This data will be used for evaluating development- and age-related changes. Dr. Mattison asked about the use of inhalation exposures and their general use and in pregnancy-related studies. Dr. Bucher replied

that inhalation studies are carried out in two major ways - long-term studies under contract and limited short-term vapor studies at the NIEHS facility. Because of the expense associated with inhalation studies conducted through contract, the NTP has historically selected chemicals for testing that are likely to go into two-year studies. The NIEHS has no capability to do short-term particulate studies and is interested in continuing this effort through NIOSH. Dr. Lemasters asked about the data on contract fidelity and deliverables from the previous five years. Dr. Bucher said the NTP has stringent requirements for record keeping and performance. There was general agreement that deliverables for NTP contracts is about 100%. The NTP has not had to stop a study because of inadequate performance in his memory. Dr. Hooper added that NTP has the largest body of consistent animal cancer data since 1978. Dr. Frederick moved that the concept be approved. Dr. Goldman seconded the motion that was approved unanimously by the Board (6 yes votes, 0 no votes).

IX. Testing Recommendations from the Interagency Coordinating Committee for Evaluation and Coordination (ICCEC)

Dr. Scott Masten, NIEHS, said that part of the NTP's mission is to provide toxicological testing on agents of public health concern. He briefly outlined the process for nomination and selection noting that the process is open to input from all interested parties. The ICCEC, a Federal interagency committee, meets biannually to review the nominations and makes recommendations on those nominations. Following this review, nominations are brought to the Board for review and comment. The NTP Executive Committee reviews the nominations, public comments, and votes on testing recommendations. Twelve new nominations were reviewed by the ICCEC in December 1999: six nominations are recommended for testing (*Attachment 4*), four nominations are deferred pending receipt of additional information (*Attachment 5*) and two nominations are not recommended for study (*Attachment 6*). Dr. Masten briefly went over the nominations to test; the Board and public were agreeable to no formal oral presentation about the nominations for no testing or for those deferred pending additional information. The Board supported the ICCEC recommendations for all three categories. The Board thought the highest priority for testing should go to 1-bromopropane and 2-bromopropane, DNA-based products, and radio frequency radiation emission of wireless communication devices.

Discussion: The Board had considerable discussion on several of the nominations. *1-Bromopropane and 2-bromopropane*: 2-Bromopropane is a minor contaminant in commercial formulations of 1-bromopropane and is not produced commercially. The Board believed that these chemicals should be of high priority for evaluation. Dr. Goldman noted that although industry has indicated no increase in production beyond current levels, EPA under the Toxic Substance Control Act (TSCA) could invoke a “significant no new use rule” in order to cap production at current levels. Dr. Frederick asked whether anyone had examined the EPA inventory on production of this material and said it likely is increasing due to 1-bromopropane being a substitute for other chemicals. Dr. Lucier noted that the EPA participates on the interagency committees (ICCEC and NTP Executive Committee) and reviews the nominations; the NTP would work through EPA on the "significant no new use rule" issue. Dr. Rodier inquired whether these substances are ozone depleting, and in response, Dr. Goldman thought that EPA would evaluate this prior to determining suitability as a substitute chemical. Dr.

Masten replied that 1-bromopropane is being considered as a replacement for other ozone-depleting substances. He also noted that EPA has a formal process for evaluating use of chemicals as substitutes. Dr. Toraason commented that OSHA and NIOSH nominated these substances for NTP study to fill toxicity data gaps thinking that this would be a more expedient way to obtain that information than relying on industry testing.

DNA-based products: Dr. Masten said the ICCEC endorsed this nomination recognizing that it is a non-standard nomination. The Board enthusiastically endorsed study in this area as high priority and in addition made several recommendations. Dr. Mattison noted the complexity of this issue and wondered whether it was possible to consider international standards when designing testing protocols. Dr. Rodier and others suggested that the NTP focus on DNA vaccines and vectors and not on studying bioengineered foods. The Board suggested that the NTP seek additional discussion with outside experts and possibly hold a workshop. Dr. Lucier noted that a series of meetings both in-house and interagency have been held to discuss strategies and agreed with the idea of a workshop; the NTP would report to the Board about its outcome at a future meeting. Dr. Portier concurred with Dr. Lucier and said the NTP would carefully consider the focus for future workshops and consider targeting different topics (DNA-based therapies, transgenic plants, etc.). In response to Dr. Mattison, Dr. Portier said how to study small protein products would be an appropriate topic for a workshop on transgenic plants especially how to identify those products and monitor their safety. Dr. Goldman and others recommended that the NTP broaden its expertise on the Board to include a geneticist, and suggested as a future issue that the NTP explore testing of other biotechnology products particularly the allergenicity of foods. Adding an allergist or immunologist to the Board was also suggested. Dr. Portier noted that a geneticist is currently included on the new Board slate.

Radio frequency radiation emission of wireless communication devices: From review of the public comments, the Board noted the apparently high public awareness of this issue and general support for a Federally administered testing program. The ICCEC recommendation is that the NTP establish an interagency program to study health effects that fulfills the FDA's regulatory needs if such needs are not being met currently through various international testing efforts. The Board supported the ICCEC recommendation, but provided several recommendations regarding the project. Dr. Hooper noted the difficulties with studying this area - the diversity in exposures and exposure patterns - and recommended that the NTP proceed cautiously and seek expert assistance including physicists. Dr. Portier noted to the Board the NIEHS' recent involvement with the EMF*RAPID* Program (50-60 Hz) that had included close interagency participation and identification of experts who could provide guidance to the NTP. He reported that one concern with the current international effort is the involvement of industry in co-funding this research with the European Commission and individual countries. Currently there are two large, ongoing, chronic bioassays being conducted in Europe using basically NTP protocols. The NTP must decide whether to conduct its own program or participate in the current one. The Board had considerable discussion about the public comments specifically ones from persons reporting symptoms of electrosensitivity. They noted the sincerity of these comments, but also the potential limitations of current testing and evaluation systems to assess the types of symptoms being reported. Dr. Goldman and others cautioned the NTP about carefully clarifying its program and communicating it to the public. Dr. Portier indicated that the scientific literature

about electrosensitivity was reviewed in the EMF*RAPID* Program and that there are groups within the United States who report both chemical and electrical sensitivities. The NTP acknowledged the Board's advice about taking a cautious approach with clearly defined goals and good public communication.

Dr. Hooper asked the NTP what it felt might be accomplished by this program. Dr. Frederick added that while animal studies could address cancer (*e.g.,* brain) and provide information to the FDA, he concurred with earlier comments about not being able to study adequately the electrosensitivity issues. He suggested that clinical studies might be the appropriate way to investigate that topic. Dr. Lucier noted that the NTP understands the Board's concerns and indicated that the NIEHS' clinical component might facilitate conduct of human studies. Dr. Portier mentioned that Dr. Gary Boorman had oversight for the NIEHS EMF*RAPID* Program's research activities that included extramural funding of some clinical studies; he himself was responsible for the health assessment. Dr. Rodier said the initial sensory symptoms noted in the public comments could be studied in animals; however, while such studies would be of scientific value, she was unsure whether the public with clinical symptoms would feel that such research adequately addressed the issue. She reiterated the need for a carefully defined program that makes the best use of funds.
Juglone: Dr. Hooper questioned how juglone was identified as an agent for study. Dr. Masten said NCI is interested in the health effects from exposure to natural products. The NCI is also examining structures of various compounds for which chronic carcinogenicity or toxicity data might be useful. The goal would be to take the knowledge about toxicity learned from studying juglone and extrapolate it to other compounds with similar structures. The quinone structure of juglone suggests that it acts through a redox cycle and thus exposure to it has potential for toxicity and carcinogenicity effects.

The Board had no specific issues of discussion for potassium ferricyanide and chitosan.

X. Report on Carcinogens Update

Dr. C.W. (Bill) Jameson, NIEHS, first discussed the NTP's Response to Public Comments and Discussion on the Report on Carcinogens (*Attachment 7*). The NTP held a public meeting October 1999 for the public to make comments about the *Report on Carcinogens* (RoC) and its review process. Dr. Bernard Goldstein, University of Medicine and Dentistry of New Jersey, chaired the meeting and Drs. Clay Frederick, Rohm and Haas Company, and Lynn Goldman, The Johns Hopkins University, served as rapporteurs. Based upon comments from this meeting and those received over the past few years, the NTP has initiated some changes to the review process: - making background documents publicly available earlier, - setting the deadline for receipt of public comments at two weeks prior to the Subcommittee meeting so there is more time for their review by the Subcommittee and NTP staff, and - increasing time allotted for public comments from five to at least seven minutes and up to 10 minutes if time allows. Other issues under consideration are noted in the response.

The 9th RoC was released May 15, 2000 by the Department of Health and Human Services and contains 218 entries of which 47 are classified as *known* and 171 as *reasonably anticipated* to be a human carcinogen. There are 14 new entries in the 9th RoC - six are upgraded from *reasonably*

anticipated to *known* and two substances are removed (delisted) from the Report. Dr. Jameson listed the new entries to the *known* category: alcoholic beverage consumption, dyes metabolized to benzidine (benzidine dyes as a class), environmental tobacco smoke, solar radiation and exposure to sunlamps and sunbeds, smokeless tobacco, strong inorganic acid mists containing sulfuric acid, tamoxifen, and tobacco smoking. New entries to the *reasonably anticipated* category include chloroprene, diesel exhaust particulates, isoprene, phenolphthalein, tetrafluoroethylene, and trichloroethylene. Several substances were reclassified as *known*: 1,3-butadiene, cadmium and cadmium compounds, direct black 38 (this is a benzidine based dye), direct blue 6 (this is a benzidine based dyes), ethylene oxide, and silica - crystalline (respirable size). Saccharin and ethyl acrylate are delisted from the Report. Several additional nominations were reviewed for the 9th RoC, but not listed in the Report. This includes employment in the boot and shoe industry because the review groups could not resolve how to review a worker exposure circumstance. The NTP was asked to provide guidelines for review of this type of nomination, and the NTP is working on them. Employment in the boot and shoe industry remains in the Appendix as being listed by the International Agency for Research on Cancer as a *known* human carcinogen. Methyl-*t*-butyl ether was reviewed, but was not recommended for listing in the Report. The nomination of nickel and nickel compounds was deferred until the review of metallic nickel and nickel alloys is completed. 2,3,7,8-tetrachloro-*p*-dioxin was proposed for upgrading from *reasonably anticipated* to *known*; however, the proposed upgraded listing is currently in litigation and, depending upon that outcome, an addendum may be published following the Court's ruling.

Dr. Jameson noted the high public interest in the 9th RoC with 108,000 "hits" to the web site between May 15 - 23. The top listings of interest in decreasing order were alcoholic beverage consumption, environmental tobacco smoke, and solar radiation. The table listing the substances delisted from the Report received 5-6,000 "hits"; saccharin is included in that table. Dr. Lucier said he did about 62 interviews during that week with the most interest being in saccharin followed by an order similar to the web "hits".

Dr. Jameson provided an update on the actions by the NIEHS/NTP subcommittee (RG1), Interagency Working Group for the RoC (RG2) and the NTP Board of Scientific RoC Subcommittee (RoC Subcommittee) for the first group of nominations for the 10th RoC. Beryllium and beryllium compounds was recommended for listing as *known to be a human carcinogen*; 2,2-Bis-(bromomethyl)-1,3-propanediol (technical grade) was recommended for listing as *reasonably anticipated to be a human carcinogen*; 2,3,-Dibromo-1-propanol was recommended for listing as *reasonably anticipated to be a human carcinogen*; Dyes metabolized to 3,3'-Dimethylbenzidine was recommended for listing as *reasonably anticipated to be a human carcinogen*; Dyes metabolized to 3,3'-Dimethoxybenzidine was recommended for listing as *reasonably anticipated to be a human carcinogen*; IQ (2-Amino-3-methylimidazol[4,5-f]quinoline) was recommended for listing as *reasonably anticipated to be a human carcinogen*; Styrene-7,8-oxide was recommended for listing as *reasonably anticipated to be a human carcinogen*; Vinyl bromide was recommended for listing as *reasonably anticipated to be a human carcinogen* by RG1 and RG2 and as *known to be a human carcinogen* by the RoC Subcommittee; Vinyl fluoride was recommended for listing as *reasonably anticipated to be a human carcinogen* by RG1 and RG2 and as *known to be a human carcinogen* by the RoC

Subcommittee. The tentative list of remaining nominations for the 10th Report includes chloramphenicol; estrogens, steroidal; human papillomaviruses (HPVs); lead and lead compounds; methyleugenol; nickel (metallic) and nickel alloys; talc (with and without asbestiform fibers); upgrading of trichlorethylene; broad spectrum UV radiation and UVA, UVB and UVC; and wood dust. This second group will be reviewed in 2000.

Discussion: In response to a question, Dr. Jameson noted that IQ is the first of the heterocyclic amines found in grilled meats that the NTP has examined and if the data warrants, the heterocyclic amines found in grilled meats may be reviewed as a class. Dr. Bucher added that if data become available about different methods of cooking meat being carcinogenic, the NTP would explore integration of this information with available epidemiologic data about health effects associated with these processes. Dr. Frederick pointed out that the recommendations (4 yes/3 no) by the RoC Subcommittee for listing vinyl bromide and vinyl fluoride as *known* were made in the absence of any human data. He believes the rules of evidence and the listing criteria were not followed and this will warrant further discussion. Dr. Lucier commented that each review is separate and independent and the NTP would consider all review groups' actions when it formulates it recommendations for the Secretary. Dr. Frederick commented that the three persons voting against the motion supported the listings of vinyl bromide and vinyl fluoride as *reasonably anticipated to be human carcinogens*. In response to a question, Dr. Jameson stated that the public has access to the RoC background documents at the time the meeting is announced - eight weeks prior to the meeting and opportunity for submission of public comments for six weeks prior to the meeting. The background document is identified as the *document of record* at the time of its public release; it is not changed after that, but addenda can be added. Dr. Hooper asked specifically about public input to the background document prior to its release as a public document. Dr. Jameson responded that there is not public comment on the background documents prior to their release; however, prior to their preparation the NTP announces the list of nominations and its intent to review them for the RoC. The NTP then solicits public comment on the nominations and the identification of any issues that should be addressed in the background documents. In the future the NTP will also try to identify key issues about the nominations and announce these publicly. Dr. Lucier added that for each nomination, the background document is a resource and is used in preparation of the RoC. He said the RoC Subcommittee votes on the nomination and not on the background document. Dr. Hooper noted that in some ways it would be good if public input could be obtained about production of the various nominations, the quality of the background documents, and the adequacy with which each nomination's document addresses the available scientific information. It was noted that this type of information is solicited in the *Federal Register* notice.

XI. NTP Board of Scientific Counselors Technical Reports Review (TRR) Subcommittee Meeting

The TRR Subcommittee meeting was held May 18, 2000 at the NIEHS. The TRR Subcommittee reviewed two-year bioassays for six NTP Technical Reports (TR) and Dr. Rick Hailey, NIEHS, briefly summarized the levels of evidence for carcinogenicity for the Subcommittee's actions.

- Indium Phosphide (TR 499) - primarily used in semiconductor industry - exposure by inhalation - *clear evidence* in male and female rats (lung and adrenal) and male (lung and

liver) and female (lung) mice. The middle dose (0.1 mg/mm^3) is the current OSHA permissible exposure limit with occupational exposure.

- Naphthalene (TR 500) - ingredient in moth repellants and toilet bowl deodorants and intermediate in many chemical synthesis processes - exposure by inhalation - *clear evidence* in male and female rats (nose). The study was not conducted in mice because NTP had previously conducted a study in mice that was positive for carcinogenicity based on lung neoplasms. Lowest exposure concentration used is the current established threshold limit value.
- Sodium Nitrite (TR 495) - color fixative and preservative in meats and fish and used in industrial processes - exposure by drinking water - *equivocal evidence* in female mice (forestomach).
- *p-p'*-Dichlorodiphenyl Sulfone (TR 501) - component of reactive dyes and product from pesticide production and is a structural analog of DDT - *no evidence* in rats or mice.
- Chloral Hydrate (TR 502 and TR 503 feed restriction study) - sedative used in children – exposure by gavage. Two technical reports were prepared for chloral hydrate on studies conducted by NCTR/FDA through an interagency agreement with the NIEHS/NIH. First study (TR 502) examined the effect of age (included preweanling mice) and duration of dosing - *equivocal evidence* in female mice (pituitary). Since body weight affects liver tumor incidence in B6C3F1 mice, the second study (TR 503) compared *ad libitum* versus animals maintained at similar weights using an idealized body weight curve - *some evidence* in male mice (liver).

Dr. Hailey also presented a list of studies currently in various stages of pathology peer review and technical report preparation that would be reported in 2001. This includes acrylonitrile (mouse), methacrylonitrile, *o*-nitrotoluene, *p*-nitrotoluene, citral, vanadium pentoxide, riddelliine (seven doses), and urethane/ethanol

Discussion: Dr. Hooper asked whether there were positive effects at the lowest concentration of napthalene. Dr. Hailey responded affirmatively and added that since the nose neoplasms are so rare, they were considered treatment-related. In response to a question about riddelline, Dr. Bucher said it is a pyrrolizidine alkaloid. Dr. Allaben added that FDA is interested in riddelline because it appears in some herbal teas. Dr. Goldman asked about the chloral hydrate studies and the impetus for their being conducted. Dr. Allaben replied that EPA had done some studies showing no evidence of carcinogenicity in rats; therefore, NCTR focused on mice. The FDA nominated chloral hydrate for study because of an early report that it might be genotoxic and some evidence of liver carcinogenicity in male mice from an EPA study on chloral hydrate (considered as a disinfection by-product). Since it is an effective sedative used in pediatric medicine and dentistry, the FDA wanted to determine what level of risk, if any, exists.

Dr. Lucier thanked the Board for its efforts and participation at the meeting.

The meeting was adjourned at 5:15 p.m.

Prepared by
Mary S. Wolfe, Ph.D.
Executive Secretary, NTP

10/10/2000

DRAFT AGENDA
NATIONAL TOXICOLOGY PROGRAM (NTP) BOARD OF SCIENTIFIC COUNSELORS

May 24, 2000

Building 101, Rodbell Auditorium, South Campus, National Institute of Environmental Health Sciences (NIEHS)
Research Triangle Park, North Carolina

8:30 - 8:45 a.m.	Welcome	Dr. K. Olden, NIEHS Dr. G. Bailey, Oregon State Univ.
8:50 - 9:00 a.m.	NTP Update	Dr. G. Lucier, NIEHS
9:00 - 9:30 a.m.	NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)	
	· Role of CERHR in meeting the goals of the NTP	Dr. C. Portier, NIEHS
	· Response to last years Board Review of CERHR	Dr. M. Shelby, NIEHS
9:30 - 10:00 a.m.	CERHR Processes and Criteria	Dr. M. Shelby, NIEHS
	· Nomination and selection of agents for review	
	· Evaluation of selected agents	
	· Communication with public	
10:00 - 10:15 a.m.	*Break*	
10:15 - 10:30 a.m.	Public Comments	The Public
10:30 - 11:00 a.m.	Discussion	The Board
11:00 a.m. - Noon	Perspectives on the Process (*e.g.* Phthalates Review)	
	· Expert Panel (15 min)	Dr. R. Kavlock, EPA, Chair
	· Regulatory Agencies (15 min)	Dr. B.A. Schwetz, FDA Dr. T. Schnoor, NIOSH
	· NTP Board of Scientific Counselors (15 min)	Dr. L. Goldman, Johns Hopkins Univ.
	· Public Comments (15 min)	The Public
Noon - 1:00 p.m.	*Lunch*	
1:00 - 2:15 p.m.	Current Trends in NTP Toxicological Testing (15 min presentations with 10 min for discussion with the Board)	
	· Water disinfection by-products	Dr. J. Bucher, NIEHS
	· DNA-based products	Dr. R. Irwin, NIEHS
	· Herbals/dietary supplements	Dr. T. Burka, NIEHS
2:15 - 2:30 p.m.	*Break*	
2:30 - 3:20 p.m.	Current Trends in NTP Toxicological Testing (continued)	
	· Phototoxicology studies and the NTP Center	Dr. P. Howard, NCTR
	· Occupational chemicals and mixtures	Dr. M. Toraason, NIOSH
3:20 - 3:50 p.m.	Concept Review (15 min)	Dr. J. Bucher, NIEHS
	· Discussion and ACTION (15 min)	The Board
3:50 - 4:35 p.m.	Testing Recommendations from the Interagency Committee for Chemical Evaluation and Coordination (15 min)	Dr. S. Masten, NIEHS
	· Public Comments (15 min)	The Public
	· Discussion (15 min)	The Board
4:35 - 5:20 p.m.	NTP Board Subcommittee Reviews - Updates	
	· Report on Carcinogens (15 min)	Dr. C. W. Jameson, NIEHS
	· Technical Reports (15 min)	Dr. J. R. Hailey, NIEHS
	· Discussion (15 min)	The Board
5:20 p.m.	*Adjourn*	

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CONCEPT REVIEW

National Toxicology Program
Board of Scientific Counselors

May 24, 2000

Table of Contents

Background on Concept Review 1

Title: Toxicity and Carcinogenicity Studies in Animals 2
Presenter: Dr. John Bucher

BACKGROUND ON CONCEPT REVIEWS

NTP contracts, interagency agreements, and grants support a variety of activities — toxicologic characterization, testing, methods development, and program resources (i.e., chemistry, occupational health and safety, animal production, pathology, quality assurance, archives, etc.).

Prior to issuance of a Request for Proposal (RFP) or a Request for Application (RFA), a project concept review is required. These project concepts in many instances may consist of more than one contract, interagency agreement, or grant. Concept reviews are needed for new projects, recompetitions with changes in statements of work, and projects ongoing for five years or more since the last concept review.

The project concept reviews are conducted by the NTP Board of Scientific Counselors and are open to the public so long as discussions are limited to review of the general project purposes, scopes, goals, and various optional approaches to pursue the overall program objectives. The meeting will be closed to the public, however, if the concept discussions turn to the development or selection of details of the projects or RFPs/RFAs, such as specific technical approaches, protocols, statements of work, data formats, or product specifications. Closing the session is intended to protect the free exchange of the advisory group members' opinions and to avoid premature release of details of proposed contract projects or RFPs/RFAs.

The Board members are asked to review the project concepts for overall value and scientific relevance as well as for fulfilling the program goal of protecting public health. Specific areas should include:

a. scientific, technical or program significance of the proposed activity;

b. availability of the technology and other resources necessary to achieve required goals;

c. extent to which there are identified, practical scientific or clinical uses for the anticipated results; and

d. where pertinent, adequacy of the methodology to be used in performing the activity.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONCEPT TITLE: Toxicity and Carcinogenicity Studies in Animals

PRESENTER: Dr. John R. Bucher
Deputy Director, Environmental Toxicology Program, NIEHS

OBJECTIVES: To continue to employ the contract mechanism to characterize the toxicological effects of chemical, biological and physical agents through studies using animals. These studies provide a rational basis and data on which a broad array of public health decisions are based for the protection of people from exposure to hazardous substances.

BACKGROUND: The characterization of the toxicity of substances of public health concern is performed through studies using animals, typically laboratory rodents. The usual approach is the repeated administration of the substance to groups of animals for variable periods of time up to two years. The adverse health effects from short- or long-term exposures to different dose levels of the substance are evaluated clinically, by histopathology, and by a variety of toxicology endpoints through comparisons with groups of animals not administered the substance.

Because of limited laboratory space and personnel within NIEHS, the toxicology studies as well as a number of support activities are performed in non-government facilities through contracts or in other government facilities through interagency agreements. Support activities include such things as chemistry services, animal production, quality assurance, statistical services, technical report preparation, archive contracts, and others. Support contracts with a significant research and development component are reviewed individually by the Board of Scientific Counselors.

PROPOSED CHANGES TO THE CURRENT WORK STATEMENTS: The work to be performed during the next 5 years is expected to closely resemble in scope and effort the activities carried out under these contracts during the preceding period. In general, greater emphasis will be given to non-cancer toxic effects and on mechanistic investigations. One anticipated change is award of a new contract to allow specific study of the toxicity of substances given during the perinatal period with expanded assessments of developmental immunotoxicity, neurotoxicity, reproductive and developmental effects. Existing contracts have not been structured to allow comprehensive toxicological evaluations on pregnant animals and their offspring. This expanded capability is anticipated to provide information responsive to the increasing public health interest in women's and children's health issues.

Substances Nominated to the NTP for Study and Testing Recommendations Made by the ICCEC on December 13, 1999

Attachment 4 -- Substances Recommended for Testing

Substance [CAS Number]	Nominated by	ICCEC Recommendations	Study Rationale; Other information
1-Bromopropane [106-94-5] and 2-Bromopropane [75-26-3]	OSHA NIOSH	1-Bromopropane -carcinogenicity -reproductive and developmental toxicity -toxicokinetics -mechanistic studies -neurotoxicity -genotoxicity -exposure studies in workers 2-Bromopropane -subchronic toxicity	Reported increasing production and use in many industrial applications as an alternative to ozone depleting substances; available data from limited repeat dose studies indicate toxicity to multiple organ systems 2-Bromopropane is a minor contaminant in reagent grade 1-Bromopropane with known reproductive toxicity
Chitosan [9012-76-4]	NCI	-mechanistic studies to evaluate vitamin E and mineral depletion	Significant human exposure through use as a dietary supplement and other commercial applications; potential for toxicity from interference with dietary fat absorption
DNA-based products	FDA	-establish joint NIEHS/FDA program to evaluate long-term toxicity in anticipation of regulatory needs	Rapidly growing market for DNA-based therapeutic agents and a lack of adequate mechanisms and methodologies for evaluating safety
Juglone [481-39-0]	NCI	-mechanistic studies -metabolism studies -mouse lymphoma assay -mammalian mutagenicity -carcinogenicity testing pending results of preliminary studies	Potential human exposure resulting from use of walnut-based products as dietary supplements and natural dyes and stains; suspicion of carcinogenicity based on quinone structure
Potassium ferricyanide [13746-66-2]	NCI	-genotoxicity -subchronic toxicity	Potential consumer and worker exposure resulting from use in photographic processing; suspicion of toxicity based on potential for redox cycling; inadequate toxicity information available
Radio frequency radiation emissions of wireless communication devices	FDA	-establish interagency program to design studies assessing cancer and non-cancer health effects to fulfill regulatory needs	Widespread consumer and worker exposure; available data is inadequate to properly assess safety

Attachment 5 -- Substances for Which No Testing Is Recommended at this Time

Substance [CAS Number]	Nominated by	Nominated for	Rationale for not testing
Cafestol [469-83-0] and Kahweol [6894-43-5]	Private individual	-toxicity and carcinogenicity testing	Anti-carcinogenic effects demonstrated in animal studies; limited data indicate low potential for toxicity; other natural products with higher potential for toxicity and human exposure exist; ongoing research efforts as opposed to new testing may provide basis for determining relevance of metabolic modulatory effects to chronic toxicity
Plumbagin [481-42-5]	NCI	-mechanistic studies -metabolism studies -mouse lymphoma assay -mammalian mutagenicity -carcinogenicity	Structurally similar to Juglone which is selected for study; low magnitude and/or prevalence of human exposure; adequate evidence of acute and reproductive toxicity

Attachment 6 -- Substances for Which a Testing Recommendation is Deferred Pending Receipt and Consideration of Additional Information

Substance [CAS Number]	Nominated by	Nominated for	Additional information needed
Ethylenebis(tetrabromo-phthalimide) [32588-76-4]	NIEHS	-toxicity and carcinogenicity testing	Ongoing and planned industry testing efforts; better characterization of uses and potential human exposures
Terpinolene [586-62-9]	NIEHS	-toxicity and carcinogenicity testing	Ongoing and planned industry testing efforts; better characterization of uses and potential human exposures; study results for structurally related compounds
Tetrabromophthalic anhydride [632-79-1]	NIEHS	-toxicity and carcinogenicity testing	Ongoing and planned industry testing efforts; better characterization of uses and potential human exposures
Texanol benzyl phthalate [16883-83-3] or [32333-99-6]	NIEHS	-toxicity and carcinogenicity testing	Ongoing and planned industry testing efforts; better characterization of uses and potential human exposures

National Toxicology Program

NATIONAL TOXICOLOGY PROGRAM'S RESPONSE TO PUBLIC COMMENTS AND DISCUSSION ON THE PREPARATION AND REVIEW OF THE *REPORT ON CARCINOGENS*

Background

Section 301(b)(4) of the Public Health Service Act, as amended, provides that the Secretary, Department of Health and Human Services (DHHS), shall publish a report which contains a list of all substances (1) which either are *known to be human carcinogens* or may *reasonably be anticipated to be human carcinogens,* and (2) to which a significant number of persons residing in the United States (US) are exposed. Within the Department of Health and Human Services, the Secretary has delegated the responsibility for preparing these reports to the National Toxicology Program (NTP). The *Report on Carcinogens* (*RoC*) is an informational scientific and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances that may pose a carcinogenic hazard to human health. It serves as a meaningful and useful compilation of data on the (1) carcinogenicity, genotoxicity, and biologic mechanisms of the listed substances in humans and/or animals, (2) the potential for exposure to these substances, and (3) the regulations promulgated by Federal agencies to limit exposures.

In 1994, the NTP Director initiated a review of the *RoC* to 1) broaden the input to the preparation of the Report, 2) broaden the scope of scientific review associated with the *RoC*, and 3) provide review of the criteria used for listing substances in the *RoC*. The criteria review was open to the public and included participation of, or input from, a broad base of interested parties including academia, industry, labor, private organizations, and Federal, State, and local agencies. In 1996, revised criteria, which allow for listing decisions to be made with consideration given to all relevant information including mechanism of action, were approved by the Secretary, and the NTP Director announced revisions to the process for reviewing nominations for listing or delisting in the *RoC*. The revised process included addition of an external peer review to be conducted in public meetings with opportunity for public comment; allowed for additional public input throughout the review process; and established a formal mechanism for delisting substances from the *RoC*. The revised process and criteria were used in the preparation of the 8th *RoC* published in 1998 and in the review of nominations for the 9th Report, published in 2000.

During the preparation and review of the 8th and 9th *RoC*, the NTP received comments from interested stakeholders on proposed listings, the process and procedures used in the review, and the criteria for listing/delisting. The NTP has been deliberate in its efforts to solicit public input and to understand the concerns of stakeholders. The NTP has encouraged dialogue with stakeholders and responded, primarily in writing, to individual concerns and requests for additional information. The NTP did not hold meetings with individual stakeholders regarding their concerns because the closed nature of individual meetings is in conflict with the open review process established for the *RoC*. At the request of a private organization, the Toxicology Forum, the NTP staff attended its meeting in July 1999 and chaired a session on the *RoC*, which included an NTP panel to receive and respond to questions and comments from the attendees. The NTP also held a public meeting in October 1999 in an effort to obtain the broadest base of input and to provide all interested parties an opportunity to express their views about the review process and/or the evaluation criteria. The goal of the meeting was to create a dialogue among the stakeholders and NTP, and time was allotted for participants to present their views and to comment on the views expressed by others during the meeting. The meeting was chaired by Dr. Bernard Goldstein, Director of the Environmental and Occupational Health Sciences Institute of Rutgers and the University of Medicine and Dentistry of New Jersey. Assisting Dr. Goldstein with the identification of issues being presented were two NTP Board of Scientific Counselor members, Dr. Clayton Frederick, Rohm and Haas; and Dr. Lynn Goldman, Johns Hopkins University. Also attending were the NTP Director and his key NTP staff and other representatives from the Board of Scientific Counselors (BSC) and from each of the review groups involved in the Report's preparation. Forty-one persons registered to speak at the public meeting and they included private citizens, representatives of industry, organized labor unions, public citizen organizations, and law firms.

Public Comments and the NTP's Response

In summary, some comments received suggested that the current listing process is flawed and does not always include the best science. These comments also suggested that submission of the 9th *RoC* to the Secretary, DHHS, be delayed pending a re-review of specific substances by a revised process that contains their suggested improvements for the reviews. Other comments noted that the current process is open, scientifically sound, and fair and declared that the 9th Report should go forward as soon as possible. The NTP believes that the procedures and criteria used for review of nominations in the 9th *RoC* are basically sound and concluded that there were no issues or problems identified that should delay publication of the 9th Report.

The NTP is committed to maintaining an open and transparent process for preparation of the *RoC* that is unencumbered by special interests; includes high quality and open scientific review of substances nominated for listing/delisting; uses the best, publicly available, peer reviewed science; and allows for stakeholder input at multiple levels. However, public input did identify some areas where procedural modifications, as noted below, would strengthen the review process, enhance stakeholder involvement, and improve communication and outreach efforts. The NTP greatly appreciates the input from all parties and will move forward in implementing some changes immediately while considering other recommendations for possible implementation in the future. In making these changes to the *RoC* 's preparation and review, the NTP is committed to providing the resources needed to ensure their successful implementation.

NTP's responses to comments

1. In response to suggestions for earlier and more thorough notification of stakeholders, the NTP will identify to the extent possible, key scientific issues related to individual nominations and communicate them publicly when nominations are initially announced. This notification will occur at least six months prior to the BSC *RoC* Subcommittee's review. Stakeholders will be invited to provide written comments addressing these issues and also to identify any additional issues. This early input from stakeholders will help to ensure that all issues critical to evaluating the listing/delisting are addressed during development of the background documents and are considered throughout the review process.

2. In reply to the suggestion that the NTP respond to individual comments, the NTP will continue to revise the background documents during the deliberations by Review Groups 1 and 2 (RG1 and RG2, respectively). Following completion of RG2's review, the background documents are considered the document of record and will not be changed in response to any subsequent stakeholder input except to correct errors. The NTP will make public comments received on all nominations available on its world-wide-website. All comments received by published deadlines will continue to be made available to the BSC *RoC* Subcommittee for its use in the review of nominations. All comments received will also be provided to the NTP Executive Committee and the NTP Director. A summary of stakeholder opinion for each nomination will also continue to be provided to the Secretary.

- In response to the concerns expressed about unevenness in the quality of the background documents, the NTP will expand the use of external, compound-specific experts in their preparation. In addition, these experts will now be invited, as needed, to participate in the BSC *RoC* Subcommittee's meetings and discussions as well. Such situations would include instances where the experts contribute significantly to preparation of the background document or where the scientific issues for the nomination are unusually complex and/or controversial. The NTP believes that this addition of compound-specific expertise will strengthen the BSC *RoC* Subcommittee's review of the nominations.

- In response to concerns regarding the need to increase the time allotted for public review and comment on the background documents, the NTP will make background documents available eight weeks prior to the BSC *RoC* Subcommittee meeting. The deadline for receipt of public comments will be two weeks prior to the BSC *RoC* Subcommittee's meeting and review. Comments submitted following the deadline would be included with the materials assembled on the nominations and evaluated by the NTP, the NTP Executive Committee, and the NTP Director.

- Beginning with the 10th Report, the NTP will increase the time allotted at the BSC *RoC* Subcommittee meeting for presentation of each stakeholder's comments on a nomination from five minutes to a minimum of seven minutes, and depending upon the number of public comments and the time available, this will be increased to ten minutes when requested. Speakers will continue to be invited to submit written comments to supplement their oral presentation.

- As suggested at the October public meeting, the NTP will hold the next few BSC *RoC* Subcommittee meetings in the Washington, D.C. area to make the meetings more accessible to all stakeholders. After that time, the NTP will evaluate whether this effectively increases public participation. The January 2000 Subcommittee meeting was moved from NTP headquarters in North Carolina to the Crystal City Marriott in Arlington, VA.

- The NTP has evaluated the suggestion that the *RoC* attempt to communicate more fully the conditions under which exposure to a listed substance might be anticipated to cause cancer in humans. Currently, the doses of substances associated with cancer in experimental animal or human epidemiology studies are clearly indicated in *RoC* background documents, and dose response characteristics are an important consideration in establishing a link between exposure to a substance and cancer. The *RoC* also provides general information about human exposures, when available. The NTP believes that the Report's current level of emphasis on dose is appropriate and efforts to characterize exposures associated with cancers in greater detail would go beyond its intended focus on hazard identification and into the arena of quantitative risk assessment.

Issues under consideration

- The NTP will formally consider a recommendation that proposes creating separate groupings of substances within the *RoC* according to their intended use. Pharmaceuticals would be an example of a special grouping. Consideration would be given to other groupings based on use categories to improve the utility of the document. Formal consideration of this recommendation will include solicitation of public comments and review by the NTP's *RoC* Review Committees and the NTP Executive Committee.

- The NTP will ask the applicable regulatory agencies to consider communicating during the review process, information about the possible regulatory implications of listing or delisting a substance or exposure circumstance in the *RoC* . Currently, the *RoC* provides information about any existing Federal regulatory standards for a listing. This information is part of the profile for each listing and is updated with each edition of the Report. It is anticipated that these communications from the applicable regulatory agencies could lead to a better understanding by the public of the potential regulatory implications of a listed or delisted substance.

- The NTP will work with regulatory agencies to identify additional venues and strategies for targeting communication about the *RoC* with the broad group of stakeholders, including trade groups, and soliciting their input. Currently, information dissemination is reasonably broad-based through the NTP world-wide-website and list server, *Federal Register* notices, NTP newsletter, press advisories, and the *Environmental Health Perspectives* , a scientific environmental health research journal.

Comments or Questions should be directed to the NTP Liaison and Scientific Review Office at: Telephone: (919) 541-0530; Fax (919) 541-0295 e-mail: liaison@starbase.niehs.nih.gov

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Public Meeting Speakers
(Order of presentations)

1. David Guston
   Rutgers State University
2. Thomas Starr
   American Forest and Paper Association
3. Jim Tozzi
   Multinational Business Service
4. Stuart Cagen
   Shell Chemical Company
5. Philip Leber
   On behalf of Jim McGraw
   International Institute of Synthetic Rubber Producers
6. Emanuel Rubin
   Thomas Jefferson University
7. Peter Infante
   Occupational Safety and Health Administration
8. Adriana R. Oller
   Nickel Producers Environmental Research Association
9. Peter Lurie
   Public Citizens Health Risk Group
10. Susan Nathanson
    Y-ME National Breast Cancer Organization
11. William Kennedy
    Astra Zeneca
12. Michael Bird
    Exxon Biomedical Sciences Inc.
    Butadiene Work Group of the Olefins Panel, CMA
13. Lee Coogan
    Sorptive Minerals Institute
14. William G. Kelly, Jr.
    Federal Focus, Inc.
15. Richard Carchman
    Philip Morris USA
16. Steven Lester
    Center for Health, Environment, and Justice
17. Jackie Warren
    Private citizen
18. Carolyn Nunley
    Consumers Union, Public Service Projects
22. Sara Schotland
    Cleary, Gottlieb, Steen and Hamilton
    Ethylene Oxide Industry Council
23. Rudolph Valentine
    DuPont Dow Elastomers, LLC
24. Michael A. Gipko
    J&L Specialty Steel, Inc
    Specialty Steel Industry of North America
25. Gail Charnley
    Health Risk Strategies
    Chlorine Chemistry Council
26. Ashley B. Coffield
    Center for Children's Health and the Environment
27. Philip Leber
    The Goodyear Tire and Rubber Company
28. James Hathaway
    Rhodia Inc,
    CMA Inorganic Acid Mists Panel
29. Michael Jacobson
    Center for Science in the Public Interest
30. Donald Smith
    Private Citizen
31. Joseph Levy
    International Smart Tan Network
32. Bob Musil
    Physicians for Social Responsibility
33. Kerry Lane
    Delray Medical Center
34. Dennis A. Falgout
    The Metal Finishing Association of Southern California
35. Franklin E. Mirer
    International Union, UAW
36. Lyn O'Brien Nabors
    Calorie Control Council
37. Edward Ferguson
    Howrey & Simon
    Chroma Corp
38. Michael McCann
    The Center to Protect Workers Rights
39. William J. Waddell

19. Barry Castleman
Private citizen

20. Joseph Shapiro
Unimin Corporation
Crystalline Silica Panel

21. Ralph Gingell
Shell Chemical Company
Ethylene Oxide Industry

University of Louisville
Beverage Alcohol Industry

40. Michael Sprinker
International Chemical Workers Union

41. Al Collins
The National Association of Metal Finishers, the Metal Finishing Suppliers' Association, and the Association of Electroplating and Surface Finishing