NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
Committee Meeting
September 10-11, 2003
Summary Minutes

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Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors ("the Board") met on September 10 and 11, 2003, in the Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. (*Attachment 1*: *Federal Register* meeting announcement; *Attachments 2* and *3*: Agenda and Roster of Members). Members of the Board who attended the meeting were Drs. Donald Mattison (Chairperson), Diane Birt, Aaron Blair, Kim Boekelheide, Hillary Carpenter, Harvey Checkoway, Samuel Cohen, Barbara Pence George Daston, Thomas Gasiewicz, Shuk-Mei Ho, Maria Morandi, Charlene McQueen, Stephen Roberts, Richard Storer, Cheryl Walker and Bruce Weir. The following Board members Drs. George Bonney, Gail Charnley, John Froines, Howard Frumkin, John Giesy, Irva Hertz-Picciotto, Margaret Karagas, Jim Klaunig, James Popp, Alan Smith, Mary Anna Thrall and Mary Vore were absent.

I. Welcome

Dr Mattison welcomed everyone to the meeting and asked the Board members and attendees within the room to introduce themselves.

Dr. Christopher Portier, Director, Environmental Toxicology Program (ETP), and Associate Director, NTP, NIEHS, welcomed and thanked the Board members for their efforts and advice as this input helps the NTP set priorities and directions for research that potentially impacts public health. He expressed Dr. Olden's regrets for being unable to attend the meeting due to a conflicting commitment. He mentioned that three members of the Board were retiring this year and seven new members had been appointed. He welcomed the new members of the Board who were attending their first meeting. Dr. Portier presented a certificate and acknowledged the contribution of Dr. Mattison, who was retiring from the Board.

II. NTP Update

A. Changes in Personnel

Dr. Portier reported that Dr. Olden was stepping down as the Director of NIEHS and the NTP after 12 years of service as he felt that new leadership was important. He acknowledged Dr. Olden's numerous contributions to NIEHS and his support of the NTP that has helped to maintain the program as a leader in toxicology. Dr. Portier then briefly mentioned changes in personnel within the NTP. He was pleased to announce that Dr. William Stokes had been appointed as the Chief Veterinary Officer of the Public Health Service. He thanked Dr. Mary Wolfe for her service over the past three years in the Liaison Office and Scientific Review and welcomed Dr. Barbara Shane to the office as executive secretary. He said a second executive

secretary has been selected and the hiring was progressing. He said that the executive secretary is a scientific position in accord with other federal agencies.

B. Transgenics

Dr. Portier reported on a workshop held in February 2002 that focused on the use of genetically modified mouse (GMM) models in the NTP testing program. Representatives from federal agencies, members of NTP advisory committees including the NTP Board and the Scientific Advisory Committee on Alternative Toxicological Methods, and scientists from academia and industry attended. The focus of the meeting was to discuss the proper interpretation and reporting of studies conducted in GMM models. At the meeting, the attendees addressed hypothetical cases with examples from studies conducted in $p53^{+/-}$, Tg.AC and Hras2 mice. These case studies were designed to stimulate discussion that might reveal the current level of acceptance of these models for cancer hazard identification. The attendees did not willingly accept that results from these studies are equivalent to traditional 2-year rodent studies. The majority of attendees accepted the terminology used in 2-year studies for describing the strength of response in $p53^{+/-}$ and Hras2 models where the altered gene is in a pathway leading to a carcinogenic outcome. The attendees struggled with appropriate language for describing findings in the Tg.AC mouse model. Based on advice from the NTP Board and participants at the workshop, the NTP decided to initiate a separate technical report series named the GMM series, for reporting studies using GMM models. The NTP now has 3 report series – NTP Technical Reports, NTP Toxicity Reports and NTP GMM Reports. To date, draft reports for two chemicals, aspartame and acesulfame potassium, have been reviewed by the Technical Reports Review Subcommittee of the NTP Board. He said presently 20-25 substances are undergoing testing in transgenic animals. The NTP also organized a session at the Toxicology Forum meeting in Aspen CO in July 2003 to discuss the future of transgenic animals in testing.

C. Report on Carcinogens (RoC)

Dr. Portier mentioned that the next NTP Board of Scientific Counselors RoC Subcommittee meeting to discuss the second group of nominations for the 11th RoC would be held on October 14-15, 2003, in Bethesda, MD.

D. NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

Dr. Portier commented on the NICEATM and for edification of the new Board members, he briefly described the role of NICEATM. The NICEATM was established to provide scientific and operational support for the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the federal government's focal point for the development, validation, acceptance and harmonization of new, revised, and alternative toxicological methods that reduce, replace or refine the use of animals in testing. The first meeting of the Scientific Advisory Committee for Alternative Toxicological Methods (SACATM) was held in Washington, DC in December 2002 and the second SACATM meeting was held in August 2003,

in Research Triangle Park, NC where information on research activities using alternative tests was presented by different federal agencies. At this meeting, Dr. Thomas Hartung, head of the European Center for the Validation of Alternative Methods (ECVAM) provided an update on ECVAM activities. He reported that in the next 5-7 years, testing for cosmetic preparations would require the use of *in vitro* methods only; no animal testing would be permitted. Dr. Portier noted the NTP's concern about this directive and the importance of the NTP continuing to communicate and collaborate with the ECVAM and staying abreast of their future directions.

Dr. Portier highlighted some NICEATM/ICCVAM activities. ICCVAM has published guidelines for acute oral toxicity testing, which although not performed by the NTP, are required by some federal agencies. The NICEATM has compiled background review documents on estrogen and androgen binding and transcriptional activation assays and held a peer review in May 2002 to evaluate the status of these types of assays. The ICCVAM and NICEATM have published minimal procedural standards for three types of methods to assess dermal corrosivity. These methods differ from those proposed by the ECVAM and the Organization for Economic Co-operation and Development (OECD). Presently the NICEATM is directing a study evaluating methods for acute oral toxicity testing as a means of estimating LD_{50} values of substances. A joint validation study on the measurement of *in vitro* oral toxicity is underway with laboratories in the United States and Europe. Recently revised guidelines for submission of test methods have been published. Dr. Portier noted that NIEHS/NTP has appropriated additional funds to NICEATM to support the preparation of background documents for nominated methods. These funds might be used for developing additional background information on submissions that contain limited scientific information.

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

Dr Portier reported on an expert panel meeting convened by the CERHR on February 11-13, 2003, to review the reproductive and developmental effects of ethylene and propylene glycols. He mentioned a workshop held in August 2003 to discuss compounds that might affect the thyroid gland, and have a potential impact on reproduction. He noted that the meeting report would be published in *Environmental Health Perspectives*. Six of the seven NTP-CERHR monographs on phthalates have been published and the last monograph, diethylhexyl phthalate (DEHP), is expected in October 2003. Two expert panel meetings are planned for 2004 - one to discuss Fluoxetine (Prozac®) and the other to review acrylamide. There is concern about the potential reproductive and/or developmental hazard of Prozac, because the FDA has approved its use for children 7 to 17 years of age.

F. NTP Testing Program

Dr. Portier provided information about the estimated new starts for studies through the end of August 2003:

10 cancer studies, 3 reproductive toxicity studies, 3 neurotoxicity studies, 4 immunotoxicity studies, 21 sub-chronic toxicity studies, 4 transgenic studies and a number of genetic toxicology studies.

As of April 2003, the number of ongoing studies is:
50 cancer studies, 30 reproductive toxicity studies, 7 neurotoxicity studies, 20 immunotoxicity studies, 10-12 subchronic toxicity studies, 4 transgenic studies and a number of genetic toxicology studies.

G. Other Activities

Dr. Portier mentioned the digitized atlas of rat kidney lesions prepared by Dr. Robert Maronpot and the satellite symposium he organized at the Toxicologic Pathology meeting. Dr. Portier noted that Dr. William Eastin would report on the new databases that NTP is compiling and would welcome feedback on them.

He briefly reported on the formal agreement between the NIEHS/NTP and the Korean National Toxicology Program that will enable Korean scientists to visit the NIEHS and learn about the NTP. This interaction should avoid duplication in testing efforts by the Koreans and the NTP.

Dr. Portier attended a meeting with scientists from the European community to discuss linkages with the NTP. The European community is concentrating on testing substances produced in large volumes using alternate *in vitro* assays. He will attend the EUROTOX meetings at the end of September and meet with ECVAM.

Dr. Portier identified NTP-sponsored meetings: the Society of Toxicology, Toxicologic Pathology, EUROTOX, and a World Health Organization's meeting on cellular telephones. The NTP also had booths at annual meetings of the Society of Toxicology, American Public Health Association, and Pathologic Toxicology.

The NTP has implemented an initiative using *Caenorhabditis elegans* where high throughput robotics is being used to screen 100-200 substances for their neurotoxic effects in adult worms and in the developing embryo. Dr. Portier hopes to report on data on 10-12 compounds at the next Board meeting.

Dr. Portier mentioned that the Office of Management and Budget has promulgated new guidelines for advisory committees relating to conflict of interest and balance issues.

The NTP is working closely with the National Center for Toxicogenomics (NCT) to develop draft guidelines for toxicogenomic studies. The NCT will be hiring, under contract, new staff trained in bioinformatics to work with scientists in the NCT to develop a database of toxicogenomic data that will be publicly available through the Internet. *Environmental Health Perspectives* has published a new edition, entitled Toxicogenomics. An announcement on the availability of data on studies performed by the NCT will appear periodically in the journal.

Dr. Portier mentioned a study on Agent Orange in Vietnam that the NTP is sponsoring with EPA. The NTP will be co-sponsoring with other government agencies a meeting on the medical uses of mercury and is presently working with the National Institute for Dental and Craniofacial Research of the NIH to investigate the health effects associated with the leaching of mercury from dental amalgam fillings and resin ingredients of composites.

Dr. Portier said Dr. Olden has a number of advisory groups, including a public interest group consisting of representatives of environmental and advocacy groups. Dr. Portier made a presentation about the NTP to this group in September 2002 in New York. Senator Hillary Clinton and Representatives from more than 50 environmental advocacy groups attended and expressed enthusiasm about the NTP's activities.

Dr. Portier attended the Division of Intramural Research (DIR), NIEHS, retreat where an effort is underway to improve coordination between the NTP and the basic scientists at the Institute. The NTP is planning a retreat in July 2004 as part of the activities for development of the roadmap for the Vision for the 21st Century; the Board will have a role at this retreat.

The NTP in collaboration with the Division of Extramural Research and Training (DERT) is supporting the further development of a database that the International Agency on Research on Cancer began compiling on mutations in the p53 gene. The NTP will also support the development of new databases on mutations in similar genes.

Board Discussion

Dr. Blair asked about the structure of the Board and other federal committees that interact with the NTP. Dr Portier responded that the Board is comprised of up to 35 members who give general guidance on the scientific activities being undertaken by the NTP. The Board has two standing subcommittees, the Report on Carcinogens (RoC) Subcommittee and the Technical Reports Review (TRR) Subcommittee. The RoC Subcommittee makes recommendations to the NTP regarding which substances should or should not be listed in the RoC, and the TRR Subcommittee advises the NTP on the final conclusions regarding the carcinogenicity of chemical and physical agents tested by the NTP. The SACATM composed of 15 members is Congressionally mandated, and consists of representatives of animal welfare, and scientists from industry academia, and state government; the 15 members of ICCVAM are *ad hoc* members. The NTP Executive Committee consists of the heads (or their designees) of nine federal agencies, including the Agency for Toxic Substances and Disease Registry, the National Cancer Institute, the Environmental Protection Agency, the NIEHS, the Food and Drug Administration, the National Institute for Occupational Safety and Health, the Consumer Product Safety Commission, the National Center for Environmental Health, the Center for Disease Control, and the Occupational Safety and Health Association. This committee provides input to the NTP on policy issues.

Dr. Daston was pleased that NTP is forging a relationship with the ECVAM, because the European Union has promulgated laws that will prevent the marketing of products tested in

animals after 2009 and 2013. He is concerned as to how the European Union will handle the use of a chemical tested in animals by the NTP after these deadlines. He went on to say that validation is a lengthy process, because the review and regulatory and legal acceptance of new methods can take up to four years. He proposed that the ICCVAM develop a method to streamline test method validation.

Dr. Mattison was impressed with the breadth and diversity of the activities in which the NTP has been involved. He asked Dr. Portier to convey to program scientists the Board's appreciation and acknowledgement of their accomplishments.

III. A Vision for the NTP

Dr. Portier introduced the NTP Vision for the 21st Century ("the vision") and gave a perspective on past activities that have helped the program evolve and remain a leader in toxicology testing. In 1995, the NTP began efforts toward a more mechanistically based toxicological approach.

Dr. Portier described the vision. Its major goal is to improve the way in which public health decisions are made and to improve the scientific information used in making those decisions. He said the NTP must work to define and improve the role of toxicology for translating basic research into public health decisions. Internationally, toxicology testing is changing and the NTP must be involved in guiding scientific perspective and development of new policies. The NTP needs to improve the tools for toxicology testing, provide guidance on the use of scientific information obtained from these new tools, and educate regulatory agencies regarding the use of this information in developing public health policies.

Dr. Portier raised questions regarding a few areas that the NTP might pursue and asked for guidance on them from the Board. Specifically, are there models using human cell lines or other animal species that the NTP might use that are more predictive of human risk than currently used models? Should the NTP analyze human blood as a means of determining biomarkers of exposure or effect alongside epidemiological evaluations? Would data from such studies strengthen/complement data that NTP is presently generating? Should the NTP continue its interaction with other federal agencies and its ongoing studies? Should the NTP focus more on epidemiological studies?

With the changing face of toxicology, Dr. Portier noted the importance of the NTP developing a strong framework for achieving the vision. He noted a number of elements that are needed to keep the program moving forward: additional databases, new models for toxicology testing including more rapid screens, non-cancer endpoints, and incorporation of molecular biology techniques. The NTP program has been oriented towards testing for specific disease outcomes and it is now time to move toward a more systems/mechanism-based approach. Many diseases are caused by environmental exposures that have similar mechanisms, and the NTP should concentrate on finding a linkage between these mechanisms and disease outcome. The NTP approach must be multidisciplinary and strive to bridge basic intramural research with the testing program. Dr. Portier also noted that training staff in these new techniques is integral to

implementing the vision as is educating the NTP's federal partners on the appropriate use of the data obtained from studies using these new methods.

Dr. Portier said the NTP plans to provide several opportunities for public input to the vision and roadmap. He asked the Board for guidance regarding goals for the vision and their priority as well as elements for the roadmap. The NTP will keep the Board informed about the vision/roadmap activities.

Board Discussion

The Board applauded Dr. Portier for developing a vision to guide the NTP's future. Prior to the meeting, four members of the Board, namely Drs. Gasiewicz, Mattison, Cohen and Roberts were asked to serve as lead discussants for this topic and to prepare a short commentary on the vision for presentation to the Board.

Dr. Gasiewicz complimented Dr. Portier on the vision and said the NTP cannot develop the vision alone, but provides an ideal focal point for coordinating efforts across agencies. He did not think it possible for NTP to develop all the needed assays and should involve other agencies. He agreed that mechanism-based assays could replace the empirical assays presently being used, but the chosen mechanism-based assays must be validated for their sensitivity and specificity. He asked which mechanism-based assay(s) would be adopted and what methods would be used for their validation. He suggested that perhaps several assays might be used in combination, for example QSARS, transgenic animals, metabolism studies. He asked how these mechanism-based assays would be integrated into decision-making. He felt that before results from mechanism-based assays can be integrated into public health decision-making, their predictability must be compared to currently used assays and a cost analysis must be done. He thought it important to obtain buy-in from industry and the public on these assays, and to show their comparability and/or improvement over conventional assays. He cited the possible use of *in vitro* estrogen receptor binding assays as a replacement for *in vivo* reproductive assays.

Dr. Cohen applauded Dr. Portier's efforts on the vision and enumerated the changes in toxicology that he envisions for the future. He cautioned that the NTP not lose sight of its legal requirements. He said that there must be a greater focus on science rather than on technology in the future training of toxicologists. However, training in bioinformatics and its interpretation is most important. The NTP must maintain its advantage as the coordinator of programs across federal agencies and must educate the agencies on the new scientific approaches and their applicability to hazard assessment. He stated that the NTP must emphasize human relevance and use more models to predict outcomes. He encouraged the development of computer-based databases. He said the NTP must educate the public in toxicology. He said that the NTP must remain focused on what it does well and prioritize its efforts in any new endeavors. One of the challenges will be the development of a plan to achieve these objectives. Such a plan will require coordination, collaboration and inclusion of all agencies. Since it will be impossible to implement all of the potential areas, the Board must help the NTP set priorities on the most appropriate areas into which it should expand.

Dr. Roberts said that the development of a vision statement is needed periodically. If the NTP wants to maintain a leadership role in toxicological sciences, it must develop tests that have more predictive value. The NTP must be in the forefront of molecular biology and information sciences. The Program must not loose sight of the fact that regulatory agencies are relying on the data it generates and reassure the agencies that their needs will be met. In future studies, the NTP must integrate dose and exposure times, besides mechanistic approaches, into their experimental designs. Because dose and time affect the carcinogenicity of substances, stop studies should also be incorporated into the testing protocols. He suggested that a working group be constituted to develop a strategy for the design of assays in which dose and time intervals and mechanisms are considered.

Dr. Mattison said that the vision document had adequately described a focus for the future. The challenge lay in the path that needs to be traversed to achieve the goals of improving public health decisions and guiding regulatory policy. It will be important for the NTP to concentrate on the coordination, collaboration and inclusion of other federal agencies and other stakeholders in implementing its goals. He suggested that more emphasis be the placed on understanding how metabolic pathways change during the life cycle as a result of changes in the expression of receptors or signaling pathways. He expressed frustration because so little is known about juvenile humans and rodents, and the transitions from infancy to childhood and childhood to adulthood. The NTP should consider the incorporation of studies on young rodents.

After these presentations, other members of the Board commented on the vision. Dr. Daston said he is pleased with the outline of the vision. He said there is a need to better define the studies that can and should be undertaken to address public health issues. He said Dr. Portier addressed this in the vision and stated that there is a vexing gap between the number of chemicals that have been tested and those in commerce. Dr. Daston stressed coordination between the different groups. He said this is the right time to make a change in the scientific approach to toxicology and that the NTP is uniquely placed to implement the vision. He added that it is important to put down in "black and white" what NTP can do to revolutionize science.

Dr. Birt was pleased to read that the NTP plans to place more emphasis on mechanism-based rather than disease-based approaches. She suggested that the term "bioinformatics" be included in the vision as well as a statement about the global reach of the NTP.

Dr. Ho suggested that the NTP develop a standardized process for collecting microarray data and assume a leadership role in developing a genomic database repository for access by the scientific community. However, Dr. Pence cautioned the NTP of the difficulty in the interpretation and relevance of microarray data, and in relating this information to an outcome.

Dr. Bucher said the NTP has an opportunity to influence regulatory processes through the RoC and the CERHR and to offer an opinion on the relevance of particular chemicals to human risk. In the future, mechanistic-based findings may play a larger role in the evaluation of individual chemicals.

Drs. Walker and Carpenter suggested that the NTP be proactive to bring other stakeholders into the development of the vision, including scientists, public health agencies, schools of public health and the public. Dr. Mattison concurred.

Dr. Blair said the NTP must maintain the right balance between a disease-focus and mechanism-based focus. He said it is the NTP's responsibility to study chemicals that may pose a public health risk and that the NTP must continue with the present carcinogenicity assays. Dr. Daston responded to Dr. Blair and said there cannot be an end to the two-year bioassays but more information must be collected during these two-year studies beyond the identification of hazard.

Dr. Ho was pleased that the NTP is taking a global approach and interacting with developing countries such as Korea. She emphasized the importance of building alliances with China, Singapore and Japan. She said IBM is entering the bioinformatics arena and the NTP might want to be linked into their database. She said the translation of effects to humans "is easier said than done" and one approach to this challenge would be the identification and collection of human samples from populations exposed to chemicals.

Dr. Boekelheide said Dr. Bucher raised the issue of an advisory role for the RoC Subcommittee. He went on to say that CERHR has filled the gap somewhat by providing needed information about adverse effects of chemicals on reproduction and development.

Dr. Portier summed up the deliberations and said the NTP would consider the incorporation of dose and time as well as the investigation of mechanisms into future studies. He said the exposure of juveniles would be considered. He asked whether any quick screening tests exist that might provide insight about potential targets for toxicity that the program could perform on a chemical before designing the chronic studies.

Dr. Toraasen stated that Dr. Portier had asked the NTP Executive Committee for their input on the vision. He noted that NIOSH would provide input on the vision and roadmap. Dr. Allaben said he was pleased with the interaction between the FDA and the NTP in designing studies on agents of interest to the FDA. He said FDA regulators that would eventually make regulatory decisions about a chemical are included in the design phase of a study and provide input to NTP scientists.

Dr. Mattison asked the Board for input on strategies to implement the vision. Dr. Roberts thought an easy approach would be to add mechanistic and gene array studies to the 2-year bioassay protocol. Because of potential increases in cost and time, the NTP would need to be selective as to when these additional studies would be added. Dr. Gasiewicz added that the NTP should only include those endpoints for which the mechanism is known. Dr. Ho said there must be follow-up on the studies so that a connection is made between disease and mechanisms and suggested that intramural NIEHS scientists might undertake the mechanism-based studies.

Dr. Portier answered the questions regarding the types of activities he envisaged to develop the vision further. He said that there would be meetings of small focused groups, interagency discussions, and workshops to develop a list of priorities. The NTP will consider all comments and incorporate as many as possible. He thought that adding mechanistic experiments to existing studies would be a good approach and that these studies could then be followed by retrospective analyses. He asked whether new studies needed to be implemented and if so, which ones. He was supportive of involving DIR scientists in mechanistic studies and asked for creative suggestions as to how this might be accomplished.

Dr. Portier said the goal is to obtain input to the vision through July 2004 and then to hold an NTP retreat to discuss the roadmap. He asked the Board what role they would want to play in formulating the vision's roadmap; whether they would want to discuss it at a future meeting or establish a working group to address the issue. Dr. Daston responded that the Board should be apprised of the progress of the document midway in the process. He suggested establishment of a working group of the Board to compile a document for review by the entire Board. After the Board's approval, the document could be sent to Dr. Portier. Dr. Cohen thought the formation of a working group worthwhile. Dr. Portier agreed to the formation of a working group and he would update the group at the Society of Toxicology Annual Meeting in Baltimore in March 2004.

Dr. Mattison asked Dr. Cohen to chair the working group and he agreed. Drs. Birt, Carpenter, Cohen, Roberts, McQueen, and Daston volunteered to serve on the working group. Dr. Cohen was concerned about the chasm between toxicology and epidemiology and how the NTP should bride that gap. Dr. Blair, an epidemiologist, agreed to serve on the working group.

IV. NTP databases

Dr. William Eastin, NIEHS, presented information on the development of new, publicly accessible, electronic databases for NTP studies. The goal of the project is to expand the availability of data in the NTP databases for the public. This is achieved by migrating study data from its original source to an on-site searchable database, the development of web-based access to the database and a mechanism to download the data. Two databases are being developed: one containing data on the 2-year bioassay, and second containing information from special studies including immunotoxicology, genetic toxicology, teratology and reproductive toxicology. Information on clinical chemistry and pathology will also be accessible. The database on the 2-year bioassays contains incidence rates and pathology data for completed pre-chronic and chronic studies. Currently the NTP is developing programming tools for accessing the data, and has requested feedback from the public on the use of the new search engines. The data on a study can be accessed by CAS number or by chemical name. Once a specific chemical has been selected the user can access information on a specific study, or specific information on the study such as the end point evaluated, the species and sex of the animals used, body weight changes etc. The user can also request information about a specific study, e.g., a 13-week study on a specific substance and obtain an abstract, if there is one. The information can be downloaded to a desktop computer in Excel although other formats for the data are being developed.

Information on genetic toxicology data will also be available. Future efforts are directed at the loading of study data from studies prior to 1993 when information was collected in a different format from that used presently.

The project was started 18 months ago and data from 300 bioassays have been entered over the last 6 months. The NTP is hopeful that it will be able to obtain carcinogenicity information on the 200 chemicals that have been tested at the Rammazini Institute in Italy for incorporation into the NTP database. Plans to include a link to the genomic database of the NCT website are being developed.

Board Discussion

Dr. McQueen congratulated the NTP on the progress that has been made on developing the databases on NTP studies. She asked how Dr. Eastin is defining the public, whether the databases are geared to the scientific community or whether the information is in a format that the public at large can access and understand. She said in general, the public does not understand how scientists test a compound. She added that the NIH is addressing this issue, but wanted to know what NTP is doing to make the database more understandable to the lay public. She suggested that it might be useful to link the NTP database with the NCI webpage, which has two tracts, one for the research community and one for the non-scientific public. Dr. Eastin responded that the NTP is in the process of awarding a new contract and that this would be an ideal opportunity to make changes to the contract to incorporate this suggestion. Dr. Bucher added that the NTP is in the process of adding a lay description of the general purpose of each study to make the information more understandable to the public.

Dr. Carpenter mentioned that he had difficulty navigating through the site and obtaining the information he was seeking. He said that it is important that the NTP pay attention to the user. He suggested that the addition of glossaries and acronyms would be useful particularly for the general public. Dr. Eastin said these suggestions would be adopted and added that he and his staff have spent time ensuring that the site is 508 compliant for use by people with disabilities.

Dr. Storer asked whether a query tool would be included to permit a search for all the compounds tested in one species that elicited a tumor in a specific tissue. The ability to aggregate data in such a manner would be most useful to scientists. For the lay public, the source of the exposure and the incorporation of the current regulatory status of chemicals in commerce would be useful. Dr. Eastin responded that a new tool to access data across studies is being developed. Dr. Portier added that under the new contract access to the database would be made more "user friendly" and it could be linked, for example, to the ATSDR toxicity profile database. The NTP will also explore the possibility of linking its databases to toxicity databases at other federal agency sites to avoid duplication.

Dr. Daston said he frequently used the information on the NTP website and allowing access across studies would be a very powerful tool. He had a concern that harmonized terminology has not been used in all the studies and suggested that a thesaurus be added. Although searching

for information on a chemical usually begins with the chemical name or CAS number, a search term by chemical structure would be extremely useful, because of the use of different names for the same or similar chemicals. Dr. Eastin responded that the NTP is cognizant of the problem of terminology and has had some difficulty in matching units in the expression of the data across studies.

Dr. Carpenter asked whether the conclusions of a study and an explanation of the statistics used in the analysis were on the web site. Dr. Eastin responded that if there is a published abstract it is on the first page before linking to the data and there is an explanation of the statistics used in the 2-year bioassays, but not for other assays, e.g., immunotoxicology.

Dr. Ho suggested that a tutorial be offered to explain access to the databases and that the statistical data be available in another format besides Excel, because it is difficult to import data from Excel into many statistical programs. She asked whether there is a user lock so that the investigator could continue with a search at a later date without loosing all the information that had been collected. She was concerned about security of the database and whether it could be corrupted. Dr. Eastin responded that a single person handles the database; most of the information in the databases is a copy and "aid screens" are being developed. The NTP has relied on statisticians for guidance on the format of the data, but the raw data will be available in the future in comma-delimited-format that could be imported into any statistical program. The NTP is looking into the possibility of the user being able to save a search and return to it at a later date.

Dr. Storer stated that a reference list to published data on a particular chemical or a hyperlink to PubMed and other literature databases would be useful. Dr. Portier responded that the NTP is planning on linking the technical reports to the PubMed database, so that relevant publications on a chemical from a study, not published by NIEHS scientists, will be accessible.

Dr. Mattison asked the Board members if the databases are being used for teaching. Dr. McQueen responded that the information on the technical reports is useful for teaching purposes.

Dr. Portier asked Dr. Daston for his input on whether the background documents for the RoC, technical reports, and the hundreds of chemicals nominated over the years should be on the web site. For him, NTP data on immunotoxicology and reproductive toxicology studies are of high priority, but reviews become out dated so access to them is not as important. In contrast, Dr. Carpenter said having information on all nominated substances and the reviews would be a useful reference for state agencies and the public.
Dr. Mattison concluded this discussion by stating that the Board had given Dr. Portier competing types of advice regarding the inclusion of reviews and information on all the substances nominated over the years. He appreciated both perspectives because different users have different needs. Dr. Portier responded that in future all the study data would be on the web. An object-oriented design, which automatically dumps the data into the databases and create links, will be used. It will be important to have the background review documents on the web for public access of nominations proposed in the past.

V. 2-D Imaging Technology for Pathological Evaluations

Dr. Robert Maronpot presented information on scanning histology slides, managing images, and developing access capabilities for the public to view the slides over the Internet. He demonstrated the interactive, web-based, 2-D imaging system using the rodent cerebellum as an example. He said one can obtain an image of the whole cerebellum using a web-based interface and then zoom into a specific area to obtain more detailed information. The tool functions as a virtual microscope and is accessible over the Internet with free downloadable software, which is both PC and Mac compatible. At present 92 slides have been scanned, hyperlinked, and being examined by 10-15 pathologists in preparation for a pathology working group meeting. The pathologists have the advantage of viewing the slides before they arrive for a meeting or having a discussion simultaneously on a specific slide before or during a meeting. Thus, pathologists off-site can address a question relating to individual structures on a specific slide. The software program allows a pathologist to annotate the slide, add notes to which the other pathologists can respond, add labels to specific areas and identify "hotspots". The difficulty is how to mange such a large amount of data and how to make the database searchable by others. Not only will this technological approach be useful for pathologists, but also it will be important for evaluating microarray data and other imaging outputs such as cell sorting. The NTP pathologists are in the beginning stages of integrating these pathology images seamlessly into the NTP toxicology databases.

There is still a certain amount of manual scanning of a slide to obtain an image for its subsequent posting on a server for Internet access. Presently, the pathology group is using a Scanscope® production model that scans faster than an older manual method, but it too is manual. The development and use of the annotation has just begun. It is envisioned that implementation of this system will enhance the interaction of pathologists worldwide. Dr. Maronpot hopes that the scanning technique will improve so that the images can be integrated rapidly into the Oracle toxicity databases. Dr. Maronpot suggested that he could give an update at the next Board meeting.

Board Discussion

The Board was impressed with the presentation by Dr. Maronpot and endorsed the continuance of the program. They asked about a time line for linking the images with the other NTP databases and Dr. Maronpot responded that this would be accomplished in a few months. Dr. Ho wanted to know whether one could superimpose images from immunostaining for a specific protein such as p53, with a pathology slide. Dr. Maronpot stated that one could do that with serial sections because superimposed serial sections would look alike. Dr. Walker asked about sending the images through the Internet and Dr. Maronpot responded that the Scanscope® images are stored on a local server that can be accessed through the web. Dr. Portier responded that the objective of this endeavor will be to read a large number of slides automatically, since a single bioassay generates about 25,0000 slides. This technique will revolutionize pathology.

Dr. Walker asked about focusing a slide and Dr. Maronpot responded that this is a technical issue that is performed automatically by placing focal points on a slide, breaking up the image into small squares known as tiles, scanning each tile and digitizing and storing each image.

VI. Research Highlights of the NTP

A. Carbonyl Sulfide

Dr. Robert Sills presented the latest information on the neurotoxicity of carbonyl sulfide in Fisher 344 rats. EPA nominated carbon disulfide for testing because it is a high volume chemical used in the manufacture of dicarbamate pesticides for which minimal toxicology data are available. It is not regulated by OSHA and has a half-life of 2 years. In two preliminary studies, Monsanto and ITRI found that carbonyl sulfide when administered at 600 ppm caused neurotoxicity, manifest as ataxia with brain lesions in the cerebellum.

The NTP decided to repeat the studies, but also included magnetic resonance microscopy (MRM), electrophysiology, and cellular and molecular studies. MRM would aid in understanding the relationship between exposure and micro-anatomical changes. This technique acquires information on 200 or more brain slices in three dimensions, compared to the 3 to 5 sections that are usually examined, and offers a greater opportunity than any other technique of linking changes in anatomical sites to clinical and functional disturbances. Rats were exposed for 12 weeks to 200-600 ppm for 6 hours/day for 5 days a week. Groups were sacrificed at 4, 8, 12 weeks and the brain examined for neuropathological changes. Clinically, animals exposed to 400 ppm showed no motor abnormalities and easily righted themselves. Using MRM, areas of microgliosis were observed in the posterior colliculus and macrophages accumulated in the anterior auditory nucleus. Loss of neurons was observed in the frontal parietal cortex and other areas of the brain associated with hearing. Since it appeared that carbonyl sulfide is affecting the auditory pathway, an electrophysiology evaluation was needed. Carbonyl sulfide appears to alter the brainstem auditory response. Because the posterior colliculus has one of the highest metabolic rates, it was hypothesized that perhaps carbonyl sulfide is interfering with oxidation or oxidative phosphorylation. *In vitro* studies showed that carbonyl sulfide inhibits cytochrome C oxidase, particularly in cells of the posterior colliculus. Pathologically, the investigators observed degeneration of neurons in the posterior colliculus manifest as disintegrating dendrites and axons. These pathological changes correlated with a decrease in cytochrome oxidase levels in this area of the brain. Based on these observations, Dr. Sills and his group concluded that their preliminary data suggest that carbonyl sulfide affects the auditory system of the brain, possibly through its effects on cytochrome oxidase, resulting in ATP depletion and neuronal injury.

Board Discussion

Dr. Mattison thanked Dr. Sills for an exciting presentation. Dr Cohen asked about the limits of sensitivity and the size of the lesions. Dr Sills responded that MGM allows the researcher to identify neuroanatomical areas of the brain that might be damaged. He said they were able to see lesions that were 100 microns in thickness and that the MRM easily identified the lesions in

specific areas. Dr. Daston asked how widely this technology could be applied since a huge magnet is required, how many animals are needed to detect lesions, and why this area of the brain is targeted by carbonyl sulfide? Dr Sills replied that they had used 6 animals /group and were able to consistently pick up the lesions in the animals. As far as he knew, there are three laboratories in the country that have MRM capability - Duke, UCLA and Sloan Kettering. Researchers can arrange to have a limited number of animals sent to these centers for evaluation. He stated that from a strategic point of view, chemicals should be studied using these techniques only if the target tissue is known. In the case of the brain, it might be difficult to identify the area of the brain that is affected unless there is prior information on the target area. Dr. Sills thought that the posterior colliculus is targeted by carbon disulfide because this area of the brain has one of highest metabolic rates in the body.

Dr. Morandi stated that there is a strong suspicion that exposure to solvent and noise can affect hearing and this technique might be useful tool for evaluating hearing loss. Dr. Sills replied that the next phase of the study will be the development of biomarkers to monitor early events that occur in the interaction between solvents and the brain.

Dr. Roberts asked if this technology could be applied to live animals. Dr. Bucher responded that the difficulty of using live animals is movement, even during breathing, which interferes with the scanning. Efforts are underway to develop computer programs that can compensate for this movement.

B. Endocrine Disrupting Agents

Retha Newbold presented information on the NTP interagency efforts on endocrine disrupting agents. The goal of the interagency study is to evaluate a number of endpoints over a wide range of doses of a series of compounds with a range of potencies. The working hypothesis is that exposure to relatively low doses of endocrine disrupting agents may have long lasting consequences including altered reproductive function and an increased incidence of neoplasia. The interagency study involves the performance of studies to determine whether life-long exposure of animals starting in gestation has subtle effects that can be passed on to subsequent generations. Range finding studies were undertaken with five compounds: genistein, ethinyl estradiol, nonylphenol, methoxychlor and vinclozolin. Multigenerational studies followed only with genistein, ethinyl estradiol and nonylphenol. Only genistein and ethinyl estradiol were studied in a chronic study.

Ms. Newbold described the results of the multigenerational and chronic study with Sprague Dawley rats that were fed 5, 100, 500 mg/kg/day of genistein. These concentrations span the range of the daily intake of this isoflavone by people consuming an Asian diet, a Western diet and soy-based infant formula. Estrogenic effects were noted in this multigenerational study with a reduction in litter size, acceleration in vaginal opening, induction of abnormal estrus cycles in young animals, early onset of abnormal cycling in older animals, and altered immune responses in young animals manifested as an enhanced T-cell response. No increase in neoplastic lesions of the reproductive tract was observed possibly due to the low concentration of genistein found

in the pups; however, an increased incidence of malignant mammary tumors was seen. Minimal behavioral effects were noted, and there were indications of sexual dimorphism.

In a study with CD-1 mice, abnormalities were observed in mice treated with genistein at doses comparable to human exposure levels. The mice were exposed as neonates from days 1 through 5 after birth to 5 or 50 mg/kg/day of genistein and alterations in reproductive tract and ovarian development were monitored. Multi-oocyte follicles in the ovary were observed in genistein treated mice at puberty apparently as the result of abnormal differentiation of the ovary. Since genistein has a high affinity for estrogen receptor (ER) and ER is strongly expressed in ovarian granulosa cells, one potential hypothesis for the abnormal follicles could be that genistein interferes with the normal function of ER. None of the mice on the high dose of genistein was fertile and all the mice on the lower dose became sub-fertile by 4 months of age probably as the result of early senescence of the ovary. By 19 months of age, 35% of the mice on the high dose of genistein developed uterine adenocarcinoma, the same tumor type and incidence found in animals treated with an equal estrogenic dose of diethylstilbestrol.

Ms. Newbold concluded her talk by stating that exposure during critical stages of development to substances with estrogenic activity can cause permanent long-lasting effects in mice. She expressed concern that similar adverse effects might occur in humans exposed at a young age to high doses of soy protein.

Board Discussion

Dr. Birt recalled an epidemiological study performed about ten years ago where children fed soy-based formulae showed no adverse reproductive effects. Ms. Newbold responded that a similar study performed more recently suggested similar findings, but on further analysis, it was apparent that some girls experienced menstrual irregularities, autoimmune diseases as indicated by allergies, and gave birth to an abnormally high percentage of twins.

Dr. Ho questioned whether exposure of neonates at days 1 to 5 days is meaningful since the level of ER is very low at this age. Ms. Newbold responded that their data confirmed the presence of ER in the ovary of neonates and intratubular testicular cells of males and sperm counts were presently ongoing in males.

Dr. Storer questioned the differential bioavailability of genistein when administered in the diet compared to the subcutaneous route used in the mouse study. Ms. Newbold replied that serum levels of genistein were similar following both routes of exposure. Dr. Carpenter asked whether the affinity of genistein for the ER and ER receptors was similar in mice and humans. Ms. Newbold stated that genistein preferentially binds to ER in both species. Dr. Blair asked whether adverse effects were noted in adult rats fed genistein and Ms. Newbold responded that uterine hyperplasia was observed, but not neoplasia. She hypothesized that there is a developmental window when exposure to genistein will result in uterine cancer and that the rats received very little genistein as neonates from lactational exposure. She also pointed out that even with these very low levels of genistein, an increased incidence in malignant mammary

tumors was observed. Dr. Mattison asked how the results with one isoflavone, genistein, could be predictive of the response of a complex mixture of isoflavones found in soy. Ms. Newbold said one goal of her studies is to investigate the interaction between two or more isoflavones such as daidzein and genistein. Dr. Mattison said an epidemiological study in children that consumed soy suggested that the incidence of lymphoma might be increased. Ms. Newbold replied that the Pathology Working Group would be evaluating whether the rats fed genistein developed lymphoma.

Dr. Mattison commented on prevention studies at NIH where a single component from a complex foodstuff has been found to elicit a response that is "upside down" when compared to the mixture. Since the studies reported by Newbold suggested a mechanism for the effect of genistein on reproduction, this model would be ideal to study the interaction of individual isoflavones in soy. He continued by stating that it is unfortunate that not many studies have investigated the effects of mixtures and perhaps scientists are "missing the boat" because humans are exposed to a number of substances simultaneously. Ms. Newbold added that a study with genistein and diadzein is underway in her lab.

Dr. Bucher pointed out that the interagency studies involve the evaluation of five generations of animals, which is a huge undertaking. Two of the studies (genistein and ethinyl estradiol) include subsets of animals evaluated for carcinogenicity. Dr. Bucher stated that when the results of the studies are reported to the Board, the members will appreciate the complexity of the interagency initiative.

Dr Storer commented on a study with the p53 transgenic mouse model that developed pituitary and testicular tumors following exposure to diethylstilbestrol. Since these tumors developed in the mice in six months, Dr. Storer asked whether this model would be appropriate for the study of soy and soy components. Ms. Newbold responded that such studies are being performed at NCTR with genistein.

Dr. Ho suggested that the effects of equol should be investigated because it was a common isoflavone metabolite and has one of the longest half lives of this class of substances. Ms. Newbold said studies with equol are being planned at NIEHS.

Dr Mattison asked whether exposure to these soy components altered hypothalamic programming or patterning in mice. Ms. Newbold said there are indications in mice that high doses of isoflavones certainly alter hypothalamic programming, but that with low doses, the ovary is a primary target.

C. Future Research Highlights

Dr, Portier stated that the last three presentations were made to the Board to acquaint them with the bridging research that the NTP is performing with DIR. Dr. Maronpot's work is directly linked to the NTP because pathology assessment is major NTP activity. It is hoped that the development of these imaging capabilities will facilitate the pathology working groups enabling them to discuss slides and diagnoses remotely. Dr. Sills' work is a follow-up to a finding of

brain lesions in animals exposed to carbonyl sulfide. The third presentation by Ms. Newbold is hypothesis-driven research that is part of the large multigenerational studies. He asked the Board for their opinion on these types of research and whether the Board would want similar presentations on other projects at future meetings.

Board Discussion

Dr Walker asked whether another group evaluates the research efforts of these scientists at another level. Dr. Portier responded that it depends on the proportion of the research undertaken for the NTP. Dr. Maronpot's efforts will not reviewed by another group. The DIR Scientific Advisory Board that reviews DIR research scientists recently reviewed Ms. Newbold's program. He added that the NTP is trying to forge closer ties with DIR scientists, some of whom are part of the Environmental Toxicology Program. Some scientists in DIR are fairly closely aligned with the NTP, but there is no formal linkage. Ms. Newbold and other staff scientists have a dual responsibility; they coordinate research for NTP by being project officers for contracts and they manage a small research laboratory. Dr. Roberts requested that those scientists in DIR that interact closely with the NTP have the opportunity to present their work at future Board meetings.

Drs. Daston and Boekelheide thought strategically it would be advantageous for the NTP to develop a more formal relationship with DIR. Dr. Portier said he is not sure how to accomplish that goal and whether a subgroup of this Board should meet with the DIR Scientific Advisory Board. Drs. Walker and Storer stated that they enjoyed the presentations and would like to hear presentations by other scientists interacting with the NTP to get a broader perspective of the program. Dr. Portier said the NTP would like to forge closer ties and collaborate with the DIR possibly by offering resources to encourage DIR scientists to undertake studies important to the NTP.

Dr. Walker said an interaction with the NTP should be extended to the extramural community through the Division of Extramural Research and Training (DERT). Dr. Portier responded that the NTP has a good relationship with DERT evident by the number of SBIR grants that NTP funds. The NTP is also involved with the mouse consortium, participates on the NCT meetings, and is strengthening its connection to the toxicokinetics faculty. He stated that it is a requirement of all DIR scientists to participate on the NIEHS RoC Review Committee, if asked to do so.

VII. NTP Study Updates

A. Cellular Telephone Emissions

Dr. Ronald Melnick presented an experimental design for studies to determine whether exposure to cell phone radiofrequency radiation (RFR) produces any adverse health effects and to characterize dose-response relationships. FDA's Center for Devices and Radiological Health had nominated RFR emissions from cellular devices for study because of the increasing number of Americans using wireless communication devices. There are no regulatory standards *per se* for

RFR although the FCC has developed exposure guidelines for protection from acute injury from thermal effects. Little is known about any long-term effects and the follow-up time in epidemiological studies is too short to make conclusive determinations of cancer risks.

Before initiating experimental studies, the NTP established an interagency agreement with the National Institute of Standards and Technology (NIST) to determine the feasibility of performing RFR exposures in reverberation chambers. A reverberation chamber is a large shielded room with excitation antennae and a paddle to create a homogeneous electromagnetic environment. An advantage of this approach compared to previous studies is that animals can be individually caged and free roaming during the exposure periods. The studies at NIST demonstrated that uniform electric fields are produced in empty chambers; field uniformity is only slightly diminished when water bottles containing a biological simulation fluid are added to the chamber, and the RFR dose in these fluid-filled bottles (expressed as the specific absorption rate, SAR) is consistent at multiple locations in the chamber.

As an extension of the NIST IAG, simulation models were developed at IT'IS in Zurich to estimate organ specific dosimetry in rats and mice exposed to RFR at 900 MHz and 1.9 GHz. The models indicated that in mice exposed to 900 MHz RFR and rats to 1.9 GHz, the predominant site of RFR absorption is the tail. To obtain a more even distribution of dose to internal organs, it was recommended that mice be exposed to 900 MHz RFR and rats to 1.9 GHz.

Sprague-Dawley rats will be used rather than Fisher rats, because there will be less background interference from leukemia in Sprague Dawley rats. The conventional B6C3F1 mouse strain will be used although a brain cancer transgenic mouse model is sought. A pilot study will be performed to determine the SAR at which animals lose their ability to thermoregulate. The prechronic studies will use four dose levels at which animals maintain their ability to thermoregulate plus a sham control group. Exposures will begin on gestation day 6 and continue until animals are 7 weeks of age. The chronic studies (3 dose levels plus a sham control) will also begin on gestation day 6, but continue until animals are 110 weeks of age. Exposures (5 days/week) are planned for 20 hours/day with intermittent cycling of 10 minutes on and 10 minutes off throughout the daily exposure period. Parameters that will be measured include body weight, clinical signs, core body temperature, and organ weights at the end of the perinatal study and at a 19-week interim sacrifice. Complete necropsy and histopathology will be performed. Additional evaluations will include blood brain barrier permeability, lens optical quality, micronuclei frequency, DNA strand breaks in brain cells, urinary metabonomic profiles, and excretion of melatonin metabolites.

Board Discussion

Dr. Storer asked whether the NTP will evaluate any potential behavioral changes in the animals. Dr. Melnick responded that the NTP has considered this issue but decided that it would not be wise to remove animals from the chambers during exposure. Rather they might design a parallel experiment to investigate behavioral changes and possible effects on cognitive function.

Dr. Walker asked why the NTP decided that electromagnetic radiation from cellular phones should be studied. Dr. Melnick responded that the FDA asked for the study to be undertaken and the ICCEC supported these studies. In addition, the GAO is interested in this nomination. Dr. Portier elaborated on this response stating that the NTP considers three basic reasons for studying a nomination and that studies might be halted any time if the question being posed is answered. First, if there is a gap in the scientific knowledge, second, if there is some unique finding that will aid in the understanding of the mechanism of action of a broader class of substances and third, if the exposure is widespread. The last reason applies in this case. There is the potential for hazard and no independent group has studied RFR.

Dr. Walker asked why the NTP is planning such an extensive group of studies on RFR as the scope of the studies seems much broader than those usually conducted on a chemical. Dr. Melnick responded that there has been so much controversy and concern about RFR. By conducting the proposed studies, he anticipates that the NTP can come to a definitive conclusion as to whether or not RFR causes an adverse effect. Dr. Portier stated that the NTP wants to be sure that if RFR causes an adverse effect, the NTP is able to identify it.

Dr. Daston was intrigued with the differences in the absorption of RFR by rats and mice, which seems related to size. He said it appears that the choice of animal models is focused on biology rather than on dosimetry. He asked whether there is a relationship between SAR in organs and health effects that can be translated to human SAR dosimetry and whether any modeling could be done to determine which of the models would be the best to assess dosimetry for humans. Dr. Melnick responded that the NTP studies would provide dose-response information regarding relationships between organ SAR levels and health effects.

Dr. Daston asked about the expectations of the studies and whether there is a hypothesis as to how RFR might cause damage beyond a thermal effect. He asked why NTP would study the effect of absorbed energy and not some other electromagnetic radiation like a magnetic field. Dr. Melnick responded that the energy absorbed is a combination of both electrical and magnetic fields and they cannot be distinguished.

Dr. Daston asked whether there is a postulated mechanism for an adverse health effect. Dr. Melnick responded that there is no postulated mechanism, but published studies have shown induction of heat shock proteins and changes in protein conformation at non-thermal exposures. NTP plans on keeping exposure levels below those that might cause significant thermal effects. Dr Portier stated that the NTP could not rule out an effect from small temperature changes.

A question was posed regarding whether noise will be heard in the chambers. Dr. Melnick responded that there will be noise from the RFR generator, but no significant noise penetrates the chambers from the outside. Control animals will be sham-exposed in a similar chamber with an antenna and a paddle rotating at the same rate as in the RFR exposure chambers. To avoid a position effect, cages will be rotated in the chambers.

The Board did not raise any objections to moving forward with this project.

B. NTP-NIOSH Collaborations

Dr. Toraason presented an overview of the projects NIOSH is conducting under the interagency agreement with the NTP. He also discussed atypical testing nominations to the NTP that involve toxicological assessment of complex mixtures to which workers are exposed.

Under the NTP interagency agreement, NIOSH characterized worker exposure to cellulose insulation and identified work practices posing the highest risks for exposure. NIOSH found that the cellulose insulation contains mostly particles and the few fibers in air-blown insulation are too large to be inhaled into the lung. In the absence of significant exposure to respirable cellulose fibers among insulation workers, it was recommended that chronic bioassays on cellulose fibers not be conducted.

In the early 1980s, NIOSH conducted chronic bioassays on fractions of roofing asphalt fumes. NIOSH received criticism because the materials used in the bioassays were considered not to be representative of what roofers are exposed to at the worksite. In 1998, NIOSH nominated paving asphalt fumes for testing by the NTP. This nomination included a proposal to generate fumes in a laboratory setting comparable to those produced at road paving operations. Under an interagency agreement with NTP, NIOSH developed a paving apparatus to generate and characterize the materials that volatilized from asphalt during paving. Acute toxicity studies were performed with rodents exposed in real time to the fumes generated by the laboratory paving apparatus. Based on the outcome from these studies, NIOSH recommended that NTP not proceed with a chronic study because of the expense and because the Fraunhofer Institute in Germany is presently performing a chronic bioassay with fumes similar to those produced by NIOSH's paving apparatus.

Dr. Toraason discussed the testing of 1-bromopropane (1-BP), a substitute for ozone depleting agents. EPA has accepted the use of 1-BP to replace methylene chloride and set the occupational exposure levels at 25 ppm. NIOSH found in some occupational settings that exposures can be as high as 380 ppm. 1-BP is a mutagen, a neurotoxicant, and a reproductive toxicant. A 2-year bioassay is underway to assess the carcinogenicity of 1-BP. An industry-wide exposure assessment is also being performed by NIOSH to characterize exposure through both inhalation and dermal routes.
Dr. Toraason presented background to the nomination of metal working fluids (MWFs) and proposed studies. The MWF formulations to which workers were exposed 20 years ago are thought to be carcinogenic. Those MWFs are different from MWFs used today because nitrosamines and chlorinated paraffins, anticipated to be human carcinogens, have been removed from the newer products. Neither the fluids used 20 years ago, nor those used today have been adequately tested. Approximately 30 MWF formulations have been identified as products that have significant market share, and by implication, result in significant worker exposures. The formulations will be characterized in order to identify a representative subset for toxicological evaluation.

In 1974, NIOSH recommended that silica sand (or other substances containing more than 1%

free silica) be prohibited as abrasive blasting material and that less hazardous materials be used in blasting operations. While alternatives to silica sand are recommended by NIOSH, these recommendations are based on the presence or absence of known hazards such respirable quartz, arsenic, beryllium, cadmium, lead, chromium, manganese, nickel, titanium silver, and vanadium. Recommendations are not based on potential risks of exposure to specific blasting agents. This is due to a lack of comprehensive studies that have evaluated the health effects of chronic inhalation of most alternative blasting abrasives. NIOSH nominated five alternative blasting materials for testing in order to establish the potential for these agents to induce lung fibrosis as a result of whole body inhalation exposure. Testing data are needed because of the high production volumes of these agents, the large number of workers exposed, and the inadequacy of present toxicity data to determine safe exposure levels.

Welding fumes were nominated for testing because they contain the carcinogenic metals, chromium and nickel. There are over 80 types of welding processes. Three processes have been chosen for testing, namely those that use a gas metal arc with stainless steel or mild steel, and a manual metal arc with stainless steel. NIOSH will devise and construct a device for animal exposure studies to simulate the workplace environment. NIOSH will characterize the physical and chemical properties of the fumes, perform acute studies and provide information and recommendations to NTP regarding future chronic studies.

Board Discussion

Dr. Daston asked whether NIOSH has adopted a strategy for testing complex mixtures that change during use. He asked whether the major ingredients should be tested in isolation or whether the entire complex mixture should be studied. Dr. Toraason responded that while consideration has been given to the changes that occur during use, the first phase of this assessment will examine neat metal working fluids. Testing individual components is considered to be inadequate for assessing the hazards associated with exposure because workers are exposed to the mixture.

Dr. Mattison asked whether a strategy could be developed to study complex mixtures using modeling approaches with exposure scenarios being as close to real world situations as possible and whether NIOSH could serve as the leader within the NTP to manage these types of studies. Dr. Torasson responded that NIOSH is attempting to mimic exposure scenarios that are as close to real world situations. With asphalt fumes, they are trying to recreate the exposure in a laboratory setting. For abrasive blasting material, NIOSH has characterized the dusts that are produced during simulated industrial blasting. This information will be used by the NTP to mimic the exposure conditions. The strategy for the complex mixtures is to assess the hazard associated with the complete mixture. After the toxicity of the mixture is assessed, attempts can be made to identify the contribution of its constituents to the hazard arising from exposure to the mixture.

Dr. Storer asked whether exposure to welding fumes is via inhalation of aerosols or whether dermal exposure is another route. Dr. Toraason responded that inhalation of aerosols is the main

route of exposure although workers do develop skin irritation and hypersensitivity in addition to asthma.

Dr. Blair suggested that epidemiological data might provide some guidance of the risk and mechanism for a disease. For example, workers exposed to metal working fluids have a higher incidence of prostate and esophageal cancer, while those exposed to welding fluids have a higher incidence of lung cancer. Perhaps this data could suggest a mechanism that would obviate the necessity of undertaking a 2-year bioassay.

Dr. Storer asked about the contamination of 1-BP with 2-bromopropane (2-BP) and whether this is a concern in performing an exposure assessment. Dr. Toraason replied that the presence of 2-BP is considered in the exposure assessment, but the contaminant is present at less than 1ppm.

Dr. Portier commented on the issue of the emission of hexavalent chromium (Cr^{6+}) from welding fumes, since the relation of Cr^{6+} to lung cancer is known in humans. He said if Cr^{6+} is the major toxic component of stainless steel welding, then perhaps an exposure assessment is needed rather than a bioassay.

C. Medicinal Herbs and Dietary Supplements

Dr. Burka reported on the extensive program that the NTP has initiated with medicinal herbs and dietary supplements, because interest has been expressed from a number of sectors. In 1994, the Dietary Supplement Health and Education Act were passed which places dietary supplements under the general umbrella of foods, not drugs. No specific health claims can be made for any dietary supplement and FDA cannot regulate them unless they are shown to be a health hazard. In 1998, an international workshop to evaluate research needs on the use and safety of medicinal herbs was held at NIEHS. As a result of the meeting, it was obvious that not much is known about these supplements and studies should be performed. Since most of these supplements are complex mixtures, between 1998-2001 emphasis was placed on assessing the chemical composition of the mixtures. Surprisingly, it was found that most herbs and supplements known by a particular name are similar in composition, even when sold by different companies.

The first toxicology study was performed in 2001 on goldenseal, a crude herb, and in 2003 the first two-year bioassay on milk thistle extract began. Dr. Burka discussed the studies that have started or are complete on kava, ginseng, pulegone (active ingredient of pennyroyal), thujone (active ingredient in wormwood), gingko, black cohosh, senna, bladderwrack, green tea, ephedra and two non-herbal dietary supplements, namely chromium picolinate and androstenedione. Dr. Burka presented information of the status of the medicinal herbs being studied by the NTP. Supplements are being evaluated in 14-day prechronic, 13-week subchronic and 2-year chronic assays. For some substances, special studies were also included.

Dr. Burka highlighted some of the findings from selected studies. The effect of crude herbal extracts on the *in vitro* activities of human cytochrome P450's is being studied. Kava extract was found to inhibit three human cytochrome P450s *in vitro*, namely, CYP2C9, 2C19 and 3A4, which could potentially interfere with the normal metabolism of drugs or endogenous substrates.

Kawain, an active ingredient responsible for the calming effect of kava had a lesser effect when tested alone, than in combination with kava extract, because other constituents in the kava extract inhibited metabolism of the kawain. Thus, Dr. Burka said the complex supplement should be tested and not the individual components of an herbal supplement.

Board Discussion

Dr. Allaben said he had bought a copy of FDA's comments on dietary products and ephedra for distribution.

Dr. Birt was pleased that the NTP is focusing on dietary supplements because information is needed. She agreed with Dr. Burka that it is more important to test the dietary supplement consumed by humans and not to attempt to isolate the active ingredient and test it alone. She found an effect similar to that observed with kava and kawain in studies on hypericin, an active ingredient of St. John's wort. In this case, hypericin was less active when tested in combination with St. John's wort than when tested alone. Dr. Birt asked about the rationale for the use of different doses in the studies. Dr. Burka responded that the doses used depended on the maximum tolerated doses for each supplement.

Dr. Mattison asked about the collaboration of the NTP with the National Center for Complementary and Alternative Medicine and Dr. Burka said the NTP is in close contact with this group and has funded the Dietary Supplement Research Centers on Botanicals in Missouri and Iowa.

Dr. Burka asked Dr. Birt about her studies with Echinacea, an herbal supplement that differs in activity from source to source. Dr. Birt said it is important that the chemical and genetic differences in the activity of the three species of Echinacea used medicinally be compared to the remaining six species that are not. Studies suggest that the active compound(s) is only present in the young plant, which supports the folklore adage that aging plants have lower activity.

VIII. NTP Study Nominations and ICCEC Recommendations

Dr. Scott Masten, NIEHS, briefly outlined the nomination, review and selection process for chemicals for future study and noted that this process includes multiple opportunities for public comment. Nominations can be made by anyone. Following the compilation of relevant information on each nomination, the Interagency Committee for Chemical Evaluation and Coordination (ICCEC) makes recommendations on the types of studies appropriate for each nomination. This information is announced in a Federal Register notice asking for public comments. The nominations are next brought to this Board followed by the Executive Committee for their approval. Once agents are selected, studies are initiated as time and resources permit.

Dr. Masten highlighted the questions for the Board's consideration:
1. Does the Board agree with the studies recommended by the ICCEC?

2. Are there other studies that should be conducted on any of these agents?
3. Are there some studies that should have higher priority than others? Which ones and why?

Dr. Masten said the ICCEC reviewed 14 new nominations and recommended 13 for study. He identified the nominations based on their class:

1. Dietary supplements/consumer products – cedarwood oil, chondroitin sulfate, glucosamine and resveratrol
2. Industrial chemicals – antimony trisulfide, cadmium telluride, dimethylethanolamine, tetrabromobisphenol A, and tetrabromobisphenol A bis (2,3-dibromopropyl ether)
3. Therapeutics and other agents – drugs positive for QT interval prolongation or induction of torsade proarrhythmia
4. Environmental contaminants – acrylamide, glycidamide, 4-phenylcyclohexene, tungsten
5. Nanoscale materials – nanocrystalline semiconductors, high aspect ratio carbon nanomaterials, metal oxide nanoparticles

The ICCEC did not recommend the study of 4-phenylcyclohexene.

The International Tungsten Industry Association, which represents 48 companies producing and consuming tungsten submitted public comment on tungsten, including unpublished data on two tungsten compounds.

Board Discussion

Prior to the meeting, certain Board members were asked to serve as lead discussants on each nomination.
Important issues that were raised were as follows.

- **Acrylamide and Glycidamide:** Dr. Storer asked whether the NTP plans to use genetically modified mouse models to test for the carcinogenicity of acrylamide and its metabolite glycidamide, because of the unusual tumors that were found in a previous study with acrylamide. An increase in tumor numbers was found in hormonally responsive organs as well as mesothelioma, and thyroid follicular tumors were observed in male and female rats. He thought that these types of tumors might indicate a genotoxic mode of action. Dr. Bucher responded that the NTP considered using the newborn mouse model, but it has been an insensitive model in previous ILSI studies, thus no decision has been made. At present there are no plans to use transgenic animals, but if the Board considers it important that a transgenic model be used, the NTP will consider it. Dr. Storer said the maximum tolerated dose might be different for glycidamide versus acrylamide. Dr. Bucher agreed that the distribution of a reactive intermediate after direct dosing could be different from what is generated from the parent compound in various tissues. Since acrylamide appears to be a hormonally active compound, Dr. Storer suggested that it be evaluated for endocrine modulation. He also noted that the NTP plans to conduct *in vivo* mutagenicity studies and he mentioned that researchers at NCTR have found the neonatal route of exposure to be more sensitive to *in vivo* mutagenicity studies than chronic studies. Dr. Storer also mentioned that the p53 knockout mouse is sensitive to

diethylstilbestrol in certain tissues and the rasH2 mouse responds to one thyroid carcinogen.

- **Antimony trisulfide**: Dr. Storer mentioned the potential cardiotoxicity of antimony trisulfide in rats. He outlined a report on the death of a group of 6 of 124 workers exposed to antimony trisulfide, in which changes in the T-wave of the heart was observed in many of the workers examined. He suggested that the NTP consider this adverse effect when designing the studies for this chemical. Dr. Masten replied that separate studies to investigate cardiotoxicity were not recommended, but this potential effect will be considered in chronic studies.

- **Cadmium telluride**: Dr. Ho discussed cadmium telluride and suggested that it would be instructive to conduct concurrent comparative studies with a more soluble cadmium compound. Dr. Masten said kinetic studies could be performed with cadmium telluride and compared to those with a more soluble cadmium salt. Oral and inhalation exposure regimens would be considered. Dr. Ho suggested that dermal studies be included because injection of a cadmium salt results in a tumor at the site of injection. Also workers could be exposed by skin contact to the relatively high concentrations of cadmium telluride reported in the workplace. Dr. Bucher said that a pharmacokinetic study would evaluate the different routes of exposure to determine the most appropriate route and dermal exposure would be considered. Dr. Bucher said the NTP tries to consider the most relevant routes of human exposure, but sometimes the chosen route does not result in the highest concentration of the chemical at the target site. Dr. Carpenter stated that people are usually exposed to cadmium via inhalation. Dr. Ho pointed out that the particle size for inhalation studies must be considered because nanoscale cadmium telluride may be used in the future.

- **Cedarwood oil:** Dr. Storer agreed that Virginia (as opposed to Texas) cedarwood oil appeared to be the more appropriate oil to study because of the higher concentration of some of the putative reactive components in the Virginia oil compared to the Texas oil. He also asked whether the individual components of cedarwood oil would be tested. Since herbal products vary in their composition, it was suggested that the type of cedarwood oil to which humans are exposed be studied. Dr. Masten mentioned that as a first step the NTP would likely study cedarwood oil itself rather than any one of its components.

- **Chondroitin sulfate and Glucosamine:** Dr. Ho agreed that studies co-administering chondroitin sulfate and glucosamine were appropriate since both compounds are ingested together by humans. She asked whether the pure compounds would be tested or whether commercial products would also be included in the studies. She expressed concern about the use of commercially available chondroitin sulfate, which is isolated from the bovine nasal septum, since the septum could be contaminated with prions. Since the commercially available products vary in composition, she suggested that both the pure compounds and two or three of the commonly consumed products be tested because of their widespread use and to assess the possible variability in response between different brands.

- **Dimethylethanolamine**: Dr. Elizabeth Delzell agreed that the dimethylethanolamine studies should focus on pharmacokinetics and metabolism. Dr. Blair asked why the ICCEC had

only recommended metabolism studies and not a broader array of tests. Dr. Masten responded that given the NTPs previous studies with other ethanolamines, studies to determine whether dimethylethanolamine is metabolized to nitrosamine and incorporated into phospholipids would aid in understanding potential toxicity and the need for more extensive studies. If further testing is warranted, the chemical will be taken back to the ICCEC for further evaluation.

- **Nanoscale materials**: Dr. Boekelheide said the testing of nanoscale materials for toxicity is very important. The NTP must decide on which materials to focus and significant efforts should be devoted to determining the composition of the materials. He said the NTP should consult with the experts at Rice University and hold a workshop to obtain additional information from interested stakeholders. Although the focus seemed to be on the phototoxicology of metal oxides, the pharmacokinetics of metal oxides might be more important as they are likely to be more toxic than the carbon particles. Dr. Morandi said some nanoparticles have been classified as high aspect ratio fibers but because of their size, they may be translocated throughout the organism if they are inhaled. Dr. Gasiewicz said it would be difficult to obtain particles of the same size and composition and Dr. Masten responded that the NTP is aware of these difficulties. The NTP intends to acquire these particles from a source that has generated, characterized and sized them. The Board also commented on the importance of carefully selecting materials for study. The Board agreed that a workshop would be an important mechanism to obtain advice on nanoscale materials. Dr. Mattison summarized the discussion by saying that the Board is enthusiastic about these studies, but that a series of questions should be addressed at a workshop.

- **Torsade proarrhythmia**: Dr. Boekelheide discussed the importance of developing methods to measure torsade proarrhythmia and stated that there are *in vitro* and *in vivo* methods under development. The FDA is asking the NTP for help in developing the *in vivo* model. One of the difficulties is the disparate effort by different groups, and the NTP is the ideal program to coordinate the activity across agencies. Despite the difficulty of this research project, Dr. Boekelheide supported it. Dr. Carpenter was concerned that the ICCEC did not give specific study recommendations regarding this nomination and Dr. Portier responded that the Board is perhaps better suited to discuss this as a broader research issue. The NTP is asking whether the program should be involved in the development of the *in vivo* model. Dr. Boekelheide said the research program is likely to succeed and proarrhythmia is a public health issue that has not been well addressed. Dr. Mattison stated that the study of torsade proarrhythmia is important, as seven of ten recent with drawls of drugs from the market have been due to this phenomenon. Even though NTP does not usually study drugs it will be important to develop the *in vivo* assay. Dr. Bucher said once the method is developed, the FDA might require its use in the screening of new drugs.

- **4-Phenylcyclohexene**: Dr. Delzell discussed 4-phenylcyclohexene despite it not being recommended by the ICCEC for testing. She said the major exposure is via emissions from new indoor carpets. She agreed that the data suggests it is less toxic than other compounds emitted from carpets and supported the decision not to test it even though toxicology studies of the compound are limited. Dr. Masten addressed a question by Dr. Blair about whether the

structure of 4-phenylcyclohexene suggests a potential hazard. He said that 4-phenylcyclohexene lacks functional groups known to be associated with toxicity.

- **Resveratrol**: Dr. Ho supported the testing of resveratrol because it is a component of natural food products such as red wine, but more importantly, it is being used in high doses in dietary supplements. Although it has been shown to be beneficial as a cardioprotective agent and an anti-carcinogen in certain animal models, it has been shown to be genotoxic at high doses and is a mixed estrogen agonist and antagonist. Since it is an antagonist when tested with estrogen and is structurally similar to diethylstilbestrol, Dr. Ho recommended that it be tested alone and in combination with estrogen. Dr. Gasiewicz expressed his concern that resveratrol might have neurobehavioral effects and this possibility should be investigated. Although red wine contains two mg of resveratrol per glass, some of the dietary supplements on the market contain 1 g of resveratrol per pill.

- **Tetrabromobisphenol A**: Dr.Boekelheide said that tetrabromobisphenol A is relatively well studied. It binds to the estrogen receptor and competes with 3,5,3',5'-tetraiodothyronine for the thyroxine receptor, and thus should be tested in reproductive and developmental toxicity studies. The NTP should also consider testing it in the *in vitro* endocrine disruptor battery of studies.

- **Tetrabromobisphenol A bis (2,3-dibromopropyl ether):** Dr. Boekelheide had similar concerns for tetrabromobisphenol A bis (2,3-dibromopropyl ether) because other halogenated propanes are both carcinogens and reproductive toxicants. As discussed for tetrabromobisphenol A, it should be included in the *in vitro* estrogen receptor assays being proposed by ICCVAM and tested for its potential reproductive hazards.

- **Tungsten:** The main reason for the nomination of tungsten is the finding of unusually high levels of tungsten in the urine of residents in a community in Nevada where epidemiological evidence of a cluster of childhood cancer was found. Dr. Masten said that the NTP is considering chronic toxicity studies of tungsten beginning with gestational or perinatal exposure. Dr. Morandi was concerned tungsten had been nominated for in-depth study simply because CDC found high levels in urine and thought that there are perhaps more important compounds than tungsten that should be tested for their perinatal effects. Dr. Checkoway remarked that investigators had not found that the high urinary tungsten levels indicated that it is an etiological factor for leukemia. There was some disagreement about whether tungsten should be studied at all but Dr. Carpenter was in favor of the nomination because of the public health concern. He was enthusiastic about a program to address neonatal and perinatal exposures because he said there is a dearth of information on early life exposures. Dr. Blair concurred with Dr. Carpenter even though the epidemiological evidence is weak. Dr. McQueen mentioned that she lives in Tucson near a community where tungsten has been implicated in a childhood cancer cohort and this was an extremely important issue for these constituents; it should be studied. From a public health perspective, people are agitated and she thought that it is the NTP's role to consider public health concerns when making decisions. Dr. Morandi asked about the prioritization of compounds that could be tested for perinatal effects, since she imagined that

resources are limited for these types of studies.

Dr. Portier interpreted this discussion on tungsten as a mixed response. He asked the members whether it is the NTP's role to stimulate further epidemiological investigations from weak associations if NTP should find leukemia in mice during neonatal and perinatal exposure. Dr. Carpenter stated that it is unlikely that a cause and effect relationship between tungsten and leukemia would be found, but in the public health arena, often it is not the science that is considered.

Dr. Steve Roberts stated that EPA is struggling with cancer risk assessments in relation to early life exposures. More information needs to be generated and the NTP should develop a strategy to assist in the process. He suggested that the NTP brief the Board at a future meeting on the inclusion of early life exposures in bioassays.

Dr. John Bucher stated that in the early 1980s perinatal exposures were considered with the adult exposures in the carcinogenicity bioassays, but the results of these studies did not appear to generate additional useful data and they were discontinued. He stated that the NTP should revisit this issue as it is being raised more frequently. He said perinatal exposure regimens have been incorporated into the preliminary design for the tungsten studies and they might be appropriate for additional studies.

The Board agreed with the NTP going forward with the design and conduct of the proposed studies with the understanding that the NTP consider the comments and suggestions they provided.

Dr. Portier expressed his appreciation for the extensive review and noted that he would report on the progress of the studies to the Board at the next meeting. Dr. Walker asked about the next stage of testing. Dr. Portier responded that generally the NTP undertakes those studies recommended by the ICCEC and approved by the Board and the NTP Executive Committee that are technically feasible and within budget constraints. Dr. Walker was concerned about the dose setting for dietary supplements, particularly as it pertains to doses to which humans might be exposed. Dr. Portier said general issues regarding dose setting and study design could be discussed at a future Board meeting. He said that more pharmacokinetic models are being incorporated into the bioassays to help understand the relevance of experimental animal doses in relation to human exposure. Dr. Gasiewicz stated that not only is the mechanism of action of a compound dependant on the dose, but also the study's interpretation.

IX. NTP U.S. Geographical Survey (USGS) Collaboration to Map Mercury levels in Fish on a National Scale

Dr. Paul Hearn, USGS presented information on a joint NIEHS/USGS Project to correlate location and analysis of environmental contaminants in general, and specifically mercury (Hg) in the pilot. He introduced Dr. Stephen Wente, an aquatic biologist and Dr. Dave Donado, a computer scientist. For the past 20 years, research has indicated that the principal pathway of

exposure of humans to Hg is through methylmercury in fish.

The pathway of entry of Hg into the environment is not completely known, although emissions of elemental Hg from coal-fired power plants is believed to be a major source. Other sources include volcanic ash and mineralized deposits of cinnabar, a common constituent of gold mining operations. Elemental Hg is reduced by sulfate reducing bacteria in the soil or in aquatic environments to methylmercury, making it more bio-available.

The objectives of this particular study are (1) the compilation of a national database on the levels of Hg in fish tissues and other media, (2) the modeling of the fish datasets to factor out effects of dissimilar samples and (3) efforts to make this data accessible to the public over the Internet with background maps and analytical tools.

Presently, USGS has 36,000 tissue samples from various sources, close to 100,00 records of Hg concentrations in sediments, 28,000 records from coal, and close to 200,000 records from mines and ore deposits. The reason for collecting this information is to predict Hg concentration in fish, so that states can issue appropriate fish consumption advisories.

One of the disadvantages of the study is the variability in fish species at the different sampling sites and the different sampling protocols used to collect the data at the different sites. The USGS team is developing an empirical model to compare Hg concentrations in different fish species at various sampling sites across the country. The objective of the model is to establish relationships and make inferences about fish in a particular area, so that zones can be set for consumption advisories and spatial trends can be examined over large areas. Presently, a state spends about $1,500,000 to obtain relevant data required to issue an advisory. Use of this model will cut these costs by one order of magnitude.

The development of the database will make the data more accessible to the public who will be able to query the database by area of interest. The user will be able to view the records, examine the maps showing the location of fish and the concentration of Hg in their tissues and determine areas of concern. The data will be entered into a national digital map that will be linked to high resolution background aerial photographs to provide geographic content.

In the future, the USGS hopes to build on the consortium with NIEHS to determine spatial correlation with disease, map temporal trends in Hg concentration in fish, identify additional geological sources of mercury, extend the model to other lipophilic contaminants, optimize sampling, and determine the total maximum load issues.

Board Discussion

Dr. Morandi asked about the extensiveness of the database and the variability in the analytical methods and detection limits of Hg in samples over time. Dr. Wente responded that EPA collected most of the data from 1990 to 1995, but some data were derived from information from different states going back to the late 1970's. A potential concern is the accuracy of the data, but

scientists have been able to make predictions about observations from the past based on the model, so this does not seem to be an issue. Dr. Morandi was concerned that an advisory may not be issued when it is needed. Dr. Wente responded that EPA is planning on establishing protocols, rather than advisories, on where it is safe to fish and the agency is developing guidance documents as to how many samples are needed to develop an advisory.

Dr. Storer asked about similar studies with saltwater species, such as tuna and swordfish, and whether there is any collaboration with NOAA in studying marine species. He said striped bass is both a fresh and saltwater fish, marketed nationally, and therefore one could develop an integrated exposure assessment. Dr. Portier responded that this question is beyond the scope of the project, but the U.S. government does have an interagency task force on Hg in marine fish in the Gulf of Mexico.

Dr. Portier stated that the NTP has become involved in this study with Hg because it is an agent of national concern and it is important to communicate to researchers what is known and link hazard identification information with national exposure assessment. He asked the Board if they thought this study is appropriate and worthwhile. Dr Boekelheide responded in the affirmative to Dr. Portier's question. He said that the proposed spatial mapping might expand the availability of epidemiological data that could increase the understanding regarding whether Hg in fish affects human health. Dr Hearn said one of the difficulties for USGS is the development of a partnership with the appropriate agency to identify populations that may be exposed. Dr. Morandi stated that an effort to find relationships and then make predictions would be useful. However, she said that it is important to outline the limitations of the database, because scientists may not be aware of them.

Dr. Blair asked how this initiative fits into the NTP mandate and whether it detracted from other activities. He said EPA should be involved in these studies. Dr. Portier responded that this is a good point and he is hopeful that FDA and CDC would be interested in the data, CDC because it is related to the exposure report card where Hg could be measured in human blood samples and FDA should be interested in the levels of Hg in fish. Dr. Carpenter stated that this study is in the methods development arena and EPA and FDA have different responsibilities. FDA is responsible for marine fishing and the states are responsible for sport fishing. The amount of data that each state has is an indication of the quality of the programs in that state to monitor Hg concentrations in fish.

X. Other NTP Activities

A. Statistical Issues in Phototoxicology Studies

Phototoxicology studies are in progress at the National Center for Phototoxicology, NCTR, on topically applied chemo-exfoliating acids (alpha- and beta-hydroxy acid) and aloe vera, components of many cosmetics. The impact from their continuous use in combination with exposure to sunlight on the possible development of skin cancer is not known. Studies are also being designed to evaluate the phototoxicity and photocarcinogenicity of topically applied retinyl palmitate, a Vitamin A derivative, tattoo ink chemicals, and fluorescein-based dyes. Since there

has been concern regarding the statistical analysis that is being used to analyze these data, Dr. Portier asked the Board whether they are agreeable that a working group be organized to evaluate the statistical methods presently being used and to suggest whether different approaches should be used in the future. The Board agreed, and Dr. Portier said he would ask Dr. Piegorsch, a statistician on the Board, to chair the working group. The working group would compile a report and report on the meeting to the Board at their next meeting.

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

Dr. Shelby gave a short overview of the activities of the CERHR. He said that a new contract was awarded recently to the incumbent, Sciences International. In February, ethylene glycol (EG) and propylene glycol (PG) were reviewed for their reproductive and developmental effects. Although EG caused developmental effects in rodents and humans, the concentration at which this effect was reported is much higher than the concentration to which humans are exposed, and thus the panel concluded that there is little concern for hazard to humans. There are no reproductive toxicity effects of EG in humans. Propylene glycol is not a reproductive or developmental toxicant in several rodent species and, the panel concluded that there was negligible concern for this chemical for humans.

Dr. Shelby said the Center was started in 1998. He presented information about NTP-CERHR monographs and how they are prepared. The Center follows a similar procedure to that used by IARC. The Center convenes panels of experts who evaluate all the literature on a particular compound and come to a conclusion as to whether a substance is a reproductive and/or developmental hazard. The public is given the opportunity to comment on the expert panel report and the NTP prepares the monograph. Dr. Shelby said that the monographs on diethylhexyl phthalate and methanol should be available soon followed shortly by the monographs on 1- and 2-bromopropane.

He summarized the outcome of a workshop held in October 2002 to discuss chemical-induced thyroid dysfunction and its potential impact on reproduction and development. A background document was prepared before the meeting on the role of the thyroid gland in reproduction in rodents and humans. This review has been accepted for publication in Birth Defects Research and a summary of the meeting report has been submitted to Environmental Health Perspectives. The expert panel recommended that various endpoints relating to thyroid function should be measured in reproductive and developmental toxicity tests. These include gland weight, histopathology, and serum levels of triiodothyronine, 3,5,3',5'-tetraiodothyronine and thyroid stimulating hormone. Postnatal neurotoxicity tests such as acoustic startle reflex and body temperature regulation might be included in the evaluations of pups.

Two expert meetings will be held during 2004; one to discuss fluoxetine (Prozac) and a second to evaluate acrylamide. The number of people exposed to Prozac is likely to increase in the near future because the drug has been approved for use in pre-menstrual dysphoric disorder and also for 7-17 year olds. Thus, children and women of reproductive age are likely to be exposed to the drug. He said the FDA has been helpful in obtaining information regarding prescriptions for the

drug and any reported adverse effects. The expert panel to review fluoxetine will be comprised of a number of representatives from the medical community.

Board Discussion

Dr. Boekelheide said the activities of the Center are important but he is concerned about the pace at which the nominated chemicals are reviewed. Dr. Shelby agreed that the pace has been slower than anticipated although the 2-3 reviews held each year met the Center's projected target. He is hopeful that initiating a "fast-track" truncated process to review more compounds each year can shorten the review process. The downside to such an approach is the possibility that the process may not be as rigorous as the procedure presently being used.

Dr Blair asked about the role of the contractor and Dr. Shelby responded that the contractor prepares dossiers on chemicals nominated for evaluation. A committee consisting of representatives of federal agencies reviews the dossiers using four criteria, namely, production volume, database of information, extent of human exposure and level of public concern. If the committee votes for an in-depth review, the nomination is sent to Drs. Portier and Olden for their approval. For approved chemicals, the contractor assists in identifying expert panel members, makes travel and meeting arrangements and prepares the first draft of sections 1-4 of the expert panel report. The contractor incorporates the panel's comments and prepares the document for public comment. After a public meeting, the final expert panel report is prepared by contractor for submission to the NTP.

Dr. Blair asked about the method for nominating compounds and how many nominations the Center received since its inception. Dr. Shelby responded by saying that the nomination process is an open nonsolicited process. The Center has received 350 nominations in 5 years, but many of the compounds did not warrant a review or could not be reviewed because there is insufficient toxicity information on the compound.
Dr. Mattison ended the discussion by stating that he enjoyed the presentation and the Board endorses the continuance of the program.

Dr. Toraason asked if a pamphlet is being prepared by the Center on each chemical reviewed. Dr, Shelby responded that this information is summarized in the NTP briefs in the monographs. He said that each monograph is made up of three components: an NTP brief, the complete expert panel report, and all the public comments received on the panel report.

C. NTP Board of Scientific Counselors Technical Reports Review Subcommittee

Due to time constraints Dr. Hailey was unable to discuss the latest information from the Technical Reports Review Subcommittee. Dr. Mattison asked the Board members if they had any questions on the material in the notebooks. No questions were posed.

D. NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

Due to time constraints Dr. Jameson was unable to discuss the latest information from the Report on Carcinogens Subcommittee. Dr. Mattison asked the Board members if they had any questions on the material in the notebooks. No questions were posed.

Diseases Special Emphasis Panel, Biomarkers Review for Co-op Projects.

Date: August 29, 2003.

Time: 8:30 a.m. to 2:30 p.m.

Agenda: To review and evaluate grant applications.

Place: Double Tree Rockville, 1750 Rockville Pike, Rockville, MD 20852.

Contact Person: Aftab A Ansari, PhD, Health Science Administrator, National Institute of Arthritis and Musculoskeletel and Skin Diseases, 6701 Democracy Plaza, Suite 800, Bethesda, MD 20892, (301) 594–4952.

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and fundying cycle.

(Catalogue of Federal Domestic Assistance Program Nos. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research, National Institutes of Health, HHS)

Dated: August 14, 2003.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 03–21714 Filed 8–25–03; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Allergy and Infectious Diseases; Notice of Meeting

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of a meeting of the AIDS Research Advisory Committee, NIAID.

The meeting will be open to the public, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.

Name of Committee: AIDS Research Advisory Committee, NIAID.

Date: September 29–30, 2003.

Time: September 29, 2003, 1 p.m. to 5 p.m.

Agenda: The Committee will provide advice on scientific priorities, policy, and program balance at the Division level. The Committee will review the progress and productivity of ongoing efforts, and identify critical gaps and/or obstacles to progress.

Place: National Institutes of Health, Natcher Building, 45 Center Drive, Conference Room E1/E2, Bethesda, MD 20892.

Time: September 30, 2003, 8:30 a.m. to adjournment.

Agenda: The Committee will provide advice on scientific priorities, policy, and program balance at the Division level. The Committee will review the progress and productivity of ongoing efforts, and identify critical gaps and/or obstacles to progress.

Place: National Institutes of Health, Natcher Building, 45 Center Drive, Conference Room E1/E2, Bethesda, MD 20892.

Contact Person: Rona L. Siskind, Executive Secretary, AIDS Research Advisory Committee, Division of AIDS, NIAID/NIH, Room 4139, 6700–B Rockledge Drive, MSC 7610, Bethesda, MD 20892–7601, 301–435–3732.

In the interest of security, NIH has instituted stringent procedures for entrance into the building by non-government employees. Persons without a government I.D. will need to show a photo I.D. and sign-in at the security desk upon entering the building.

(Catalogue of Federal Domestic Assistance Program Nos. 93.855, Allergy, Immunology, and Transplantation Research; 93.856, Microbiology and Infectious Diseases Research, National Institutes of Health, HHS)

Dated: August 19, 2003.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 03–21832 Filed 8–25–03; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Center for Scientific Review; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: Center for Scientific Review Special Emphasis Panel, ZRG1 VACC 15: Small Business: Vaccine delivery systems.

Date: August 19, 2003.

Time: 2 P.M. to 4 P.M.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892, (Telephone Conference Call).

Contact Person: Mary Clare Walker, PhD, Scientific Review Administrator, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 5104, MSC 7852, Bethesda, MD 20892, (301) 435–1165.

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

Name of Committee: Center for Scientific Review Special Emphasis Panel, Signaling.

Date: August 20, 2003.

Time: 2 P.M. to 3 P.M.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892, (Telephone Conference Call).

Contact Person: Marcia Litwack, PhD, Scientific Review Administrator, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 6206, MSC 7804, Bethesda, MD 20892, (301) 435–1719.

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

(Catalogue of Federal Domestic Assistance Program Nos. 93.306, Comparative Medicine; 93.333, Clinical Research, 93.306, 93.333, 93.337, 93.393–93.396, 93.837–93.844, 93.846–93.878, 93.892, 93.893, National Institutes of Health, HHS)

Dated: August 14, 2003.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 03–21705 Filed 8–25–03; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program (NTP); Notice of a Meeting of the NTP Board of Scientific Counselors

Pursuant to Pub. L. 92–463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors on September 10–11, 2003, in the Rodbell Auditorium, Rall Building at the National Institute of Environmental Health Sciences, 111 T. W. Alexander Drive, Research Triangle Park, NC 27709.

The NTP Board of Scientific Counselors (''the Board'') is composed of scientists from the public and private sector and provides primary scientific oversight to the NTP.

Agenda

The meeting being held on September 10–11, 2003, begins each day at 8:30 a.m. and is open to the public from 8:30 a.m. to adjournment with attendance limited only by the space available. Persons needing special assistance should contact the Executive Secretary (contact information below) at least

seven business days in advance of the meeting. A draft agenda with a tentative schedule is provided below. Primary agenda topics include: (1) A vision for the NTP that includes its concept and projection of new areas into which toxicology will develop in the next 5–10 years; (2) a presentation on the development of new, publicly accessible, electronic databases for NTP studies; (3) a demonstration of an interactive, web-based, 2-D-imaging system to evaluate the pathological outcomes of NTP studies; and (4) updates on the NTP testing program including the design of studies on radio-frequency radiation from cellular phone devices, collaborations with the National Institute of Occupational Safety and Health, studies on medicinal herbs and dietary supplements and the recommendations of the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) for substances nominated to the NTP for study. There will also be updates on the NTP Board of Scientific Counselors Technical Reports Peer Review Meeting held on May 22, 2003, the status of the 11th Edition of the Report on Carcinogens and the NTP Center for the Evaluation of Risks to Human Reproduction. Time is allotted during the meeting for the public to present comments to the Board and NTP staff on agenda topics.

The agenda and background materials on agenda topics, as available, will be posted on the NTP Web site (*http://ntp-server.niehs.nih.gov, see* What's New) or available upon request to the Executive Secretary (contact information below). Following the meeting, summary minutes will be prepared and available through the NTP web site and upon request to Central Data Management, NIEHS, P.O. Box 12233, MD E1–02, Research Triangle Park, NC 27709; telephone: 919–541–3419, fax: 919–541–3687, and e-mail: *CDM@niehs.nih.gov.*

ICCEC Recommendations for Substances Nominated for Future NTP Studies

Information about substances nominated to the NTP for toxicology and carcinogenesis studies and the ICCEC's recommendations were published in the **Federal Register** on July 16, 2003 (Vol. 68, No. 136, p. 42068–71). This notice is available on the Web (*http://ntp-server.niehs.nih.gov/htdocs/Liason/ICCECFinal02JuneFR.html*) along with supporting documents for each nomination (*http://ntp-server.niehs.nih.gov/htdocs/liason/BkgrSum02June.html*) or by contacting the NTP Executive Secretary (contact information below). This meeting provides an additional opportunity for the public to provide comment on these nominations and study recommendations to the Board and NTP staff. Comments submitted to the NTP in response to the July 2003 **Federal Register** notice are under consideration and do not need to be resubmitted or readdressed.

Public Comment Encouraged

Public input at this meeting is invited and time is set aside for the presentation of public comments on any agenda topic. At least 7 minutes will be allotted to each speaker, and if time permits, may be extended to 10 minutes. Each organization is allowed one time slot per agenda topic. Persons registering to make oral comments are asked to provide their name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any). To facilitate planning for the meeting, persons interested in providing formal oral comments are asked to notify Dr. Barbara Shane, NTP Executive Secretary, NIEHS, P.O. Box 12233, MD A3–01, Research Triangle Park, NC 27709; telephone: 919–541–0530; and e-mail: *shane@niehs.nih.gov* by September 2, 2003. Persons may also submit written comments *in lieu* of making oral comments. Written comments should be sent to the Executive Secretary and must be received by September 2, 2003, to enable review by the Board and NTP staff prior to the meeting. Persons submitting written comments should include their name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any) with the document.

Individuals will also be able to register to give oral public comments on-site at the meeting. However, if registering on-site and reading from written text, please bring 30 copies of the statement for distribution to the Board and NTP staff and to supplement the record.

Registration

The NTP Board of Scientific Counselors meeting is open to the public. Attendance at this meeting is limited only by the space available. Due to changes in security policies at the NIEHS, individuals who plan to attend are asked to pre-register with the Executive Secretary (contact information above). The names of those registered will be given to the NIEHS Security Office in order to gain access to the campus. Persons attending who have not pre-registered may be asked to provide pertinent information about the meeting, *i.e.*, title or host of meeting before gaining access to the campus. All visitors (whether or not you are pre-registered) will need to be prepared to show 2 forms of identification (ID), *i.e.*, driver's license and one other form of ID, such as company ID, government ID, or university ID.

NTP Board of Scientific Counselors

The Board is a technical advisory body comprised of scientists from the public and private sectors who provide primary scientific oversight to the overall program and its centers. Specifically, the Board advises the NTP on matters of scientific program content, both present and future, and conducts periodic review of the program for the purposes of determining and advising on the scientific merit of its activities and their overall scientific quality. Its members are selected from recognized authorities knowledgeable in fields, such as toxicology, pharmacology, pathology, biochemistry, epidemiology, risk assessment, carcinogenesis, mutagenesis, molecular biology, behavioral toxicology and neurotoxicology, immunotoxicology, reproductive toxicology or teratology, and biostatistics. The NTP strives for equitable geographic distribution and minority and female representation on the Board. Its members are invited to serve overlapping terms of up to four years and meetings are held once or twice annually for the Board and its two standing subcommittees (the Report on Carcinogens Subcommittee and the Technical Reports Review Subcommittee).

Dated: August 12, 2003.

Kenneth Olden,

Director, National Toxicology Program.

Preliminary Agenda: National Toxicology Program (NTP) Board of Scientific Counselors: September 10–11, 2003

National Institute of Environmental Health Sciences, Rodbell Auditorium, Rall Building, 111 T.W. Alexander Drive, Research Triangle Park, NC.

September 10, 2003

8:30 a.m.—Welcome and Opening Comments.
NTP Update.
A Vision for the NTP.
NTP Databases.
11:45 a.m.—Lunch.
1 p.m.—Imaging Technology for Pathological Evaluations.
Research Highlights
- Carbonyl Sulfide;
- Endocrine Disrupting Agents.

NTP Study Updates
- Design of Study on Radio-frequency Radiation Emissions;
- NTP–NIOSH Collaborations;
- Medicinal Herbs and Dietary Supplements.

5 p.m.—Adjourn

September 11, 2003

8:30 a.m.—Welcome and Introductions.
NTP Testing Program Study Nominations.
NTP–USGS Collaboration to Map Mercury Levels in Fish on a National Scale.
NTP Updates.
- Statistical Issues in Phototoxicology Studies;
- Technical Reports Peer Review Meeting on May 22, 2003;
- Report on Carcinogens;
- NTP Center for the Evaluation of Risks to Human Reproduction.

Other Business.
11:30 a.m.—Adjourn.

[FR Doc. 03–21697 Filed 8–25–03; 8:45 am]
BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

[CFDA #: 93.676]

Office of Refugee Resettlement Grant to Lutheran Immigration and Refugee Service for the Unaccompanied Alien Children's Program

AGENCY: Office of Refugee Resettlement, HHS.

ACTION: Grant award announcement.

SUMMARY: This notice is hereby given that an award is being made to Lutheran Immigration and Refugee Service (LIRS), 700 Light Street, Baltimore, MD, in the amount of $367,575 in FY03 due to urgent and compelling circumstances. The award will be used to assess and develop a capacity plan for unaccompanied alien minors transferred into the custody of the Office of Refugee Resettlement (ORR) from the Department of Homeland Security by reason of their immigration status. The program providing such services shall hereafter be referred to as the Unaccompanied Alien Children's Program (UAC).

The specific goal of the program is to facilitate the provision of family reunification and/or long-term foster care services to unaccompanied alien minors referred to LIRS by ORR and currently held in the legal custody of the ORR. The provisions of services will include child welfare related services, including family reunification and foster care placement, to alien unaccompanied minors who have been approved for such services by the appropriate entities. LIRS has extensive experience in this area drawing from the Unaccompanied Refugee Minors Program. In addition, they have one of the largest affiliate networks, allowing them to easily facilitate capacity development and establish a much needed presence in major apprehension centers.

Per the *Flores* v. *Reno* settlement agreement, no child apprehended by the Department of Homeland Security can remain in a secure detention setting for longer than 72 hours, unless warranted. Given the recent influx of apprehensions along the southwest border and southern border, ORR has the urgent need to assess and develop a capacity plan for the program.

Grant and Cooperative Agreement Program Authority for this activity is contained in the Refugee Education Assistance Act of 1980, Title V, Section 501(c) Pub. L. 94 Stat.1799, 1809–1810, Executive Order 12341, the Immigration and Naturalization Act, and Section 462 of the Homeland Security Act.

The Recipient will:

1. Assess and develop a capacity plan;
2. Identify agencies and sites for reception and assessment centers in major apprehension locations throughout the United States;
3. Develop residential, therapeutic and foster care programs;
4. Assist with developing a long-term care program;
5. Develop a system for family reunification assessment including support systems;
6. Participate in the development of a universal assessment placement plan under the direction of ORR;
7. Coordinate placement plan recommendations; and
8. Develop an assessment training manual of protocols and procedures.

Other services for these minors may be provided if ORR determines in advance that the service is reasonable and necessary for a particular minor.

LIRS will ensure services comply with State child welfare statutes and generally accepted child welfare standards, practices, principles, and procedures, and the *Flores* v. *Reno* settlement agreement. Services offered provide for the safety and security of each child.

After the appropriate reviews, it has been determined that the need to assess and develop a capacity plan is compelling. The project period is July 1, 2003 to September 30, 2006.

FOR FURTHER INFORMATION CONTACT: Theresa Bell, Office of Refugee Resettlement, Administration for Children and Families, 370 L'Enfant Promenade, SW., Washington, DC 20447, telephone (202) 401–4863.

Dated: July 3, 2003.

Nguyen Van Hanh,

Director, Office of Refugee Resettlement.

[FR Doc. 03–21784 Filed 8–25–03; 8:45 am]
BILLING CODE 4184–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

[CFDA# 93.676]

Office of Refugee Resettlement Grant to Southwest Initiative Group for the Unaccompanied Alien Children's Program

AGENCY: Office of Refugee Resettlement, HHS.

ACTION: Grant award announcement.

SUMMARY: This notice is hereby given that a urgent grant award is being made to Southwest Initiatives Group, Nixon, TX in the amount of $797,152 in FY03, to provide shelter care and child welfare services to alien minors transferred into the custody of the Office of Refugee Resettlement (ORR) from the Department of Homeland Security by reason of their immigration status. The programs providing such services shall hereafter be referred to as the Unaccompanied Alien Children's Program (UAC).

The specific goal of the program is to provide residential shelter care and other related child welfare services to male and female alien children under 18 years of age who are in the custody of the ORR. The provision of services will include: a structured, safe and productive environment which meets or exceeds respective state guidelines and ORR minimum standards for services designed to serve minors in UAC care and custody. This announcement provides for the delivery of services to a population of at least 16 children. The program is licensed for up to 36 children. This grant is being made to Southwest Initiatives Group due to its strategic location in a major apprehension area, ability to expeditiously meet state licensing and ORR requirements to accommodate the current need for shelter care, emergency influx expansion potential and high quality of care.

Shelter care services will be provided for the interim period beginning when

Agenda
NTP Board of Scientific Counselors Meeting

Rodbell Auditorium, Rall Building
National Institute of Environmental Health Sciences
Research Triangle Park, NC
September 10-11, 2003

September 10, 2003

8:30 AM	Introductions and Welcome	Dr. Donald Mattison, (NICHD), Chair
8:40	Recognition of Retiring Members	Dr. Christopher Portier, NIEHS
8:45	Update on the NTP	Dr. Christopher Portier, NIEHS
9:00	A Vision for the NTP	Dr. Christopher Portier, NIEHS
9:15	○ Board discussion	
10:00	**BREAK**	
10:20	○ Board discussion	
	NTP databases	Dr. William Eastin, NIEHS (15')
10:45	○ Board discussion	
11:45	**LUNCH**	
1:00 PM	2-D Imaging Technology for Pathological Evaluations	Dr. Robert Maronpot, NIEHS (15')
	○ Board reaction	
	Research Highlights	
1:30	- Carbonyl Sulfide	Dr. Robert Sills, NIEHS (20')
	○ Board reaction	
2:10	- Endocrine Disrupting Agents	Ms. Retha Newbold, NIEHS (20')
	○ Board reaction	
2:50	Future Research Highlights	Dr. Christopher Portier, NIEHS (10')
3:00	**BREAK**	

September 10, 2003 (continued)

3:15	NTP Study Updates - Experimental Design of Studies on Radio-frequency Radiation Emissions from Cellular Phone Devices o Public comments o Board reaction	Dr. Ronald Melnick, NIEHS (15')
3:50	- NTP-NIOSH Collaborations o Board reaction	Dr. Mark Toraason, NIOSH (15')
4:25	- Medicinal Herbs and Dietary Supplements o Board reaction	Dr. Thomas Burka, NIEHS (15')
5:00 PM	**ADJOURN**	

September 11, 2003

8:30 AM	Introductions	Dr. Donald Mattison, (NICHD), chair,
8:40	NTP Study Nominations and ICCEC Recommendations o Public comments o Board discussion	Dr. Scott Masten, NIEHS (15')
9:30	NTP-USGS Collaboration to Map Mercury Levels in Fish on a National Scale o Board reaction	Dr. Paul Hearn, USGS (15')
10:00	**BREAK**	
10:15	Other NTP Activities - Statistical Issues in Phototoxicology Studies - Technical Reports Peer Review May 22, 2003 - Report on Carcinogens - NTP Center for the Evaluation of Risks to Human Reproduction	Dr. Christopher Portier, NIEHS (10') Dr. James Hailey, NIEHS (10') Dr. C.W. Jameson, NIEHS (15') Dr. Michael Shelby, NIEHS (10')
11:00	- Other Business	Dr. Donald Mattison, (NICHD), chair
11:15	**ADJOURN**	

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