

NTP BOARD OF SCIENTIFIC COUNSELORS
Summary Minutes June 29, 2004

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Attachment 1 - Federal Register Notice

Attachment 2 - Agenda

Attachment 3 - Committee Roster

Introductions

The National Toxicology Program (NTP) Board of Scientific Counselors (“the Board”) met on June 29, 2004, at the Marriott Research Triangle Park, Durham, 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. James Popp (Chairperson), Larry Andrews, Diane Birt, Aaron Blair, Kim Boekelheide, Hillary Carpenter, Samuel Cohen, Michael Elwell, John Giesy, James Klaunig, Maria Morandi, Walter Piegorsch, Stephen Roberts, Richard Storer, Mary Anna Thrall, Cheryl Walker and Bruce Weir. The following Board members were absent: Drs. George Bonney, Gail Charnley, Harvey Checkoway, George Daston, Elizabeth Delzell, Howard Frumkin, Thomas Gasiewicz, Irva Hertz-Picciotto, Shuk-Mei Ho, Margaret Karagas, Charlene McQueen, Barbara Pence and Mary Vore.

I. Welcome

Dr. James Popp welcomed everyone to the meeting and asked the Board members and attendees 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. He expressed Dr. Kenneth Olden’s regrets for being unable to attend most of the meeting. He said two members of the Board, Drs. Walter Piegorsch and Samuel Cohen, were retiring this year and acknowledged their service to the NTP. He also noted Dr. Cohen’s contribution as Chair of the Board’s working group for the NTP vision for the 21st century (discussed below) and presented a certificate to him. Dr. Piegorsch arrived later in the day and his certificate was presented to him after lunch.

II. NTP Update

1. Changes in Personnel

Dr. Portier informed the Board that Dr. Olden is stepping down as director of the NIEHS and the NTP as soon as a replacement can be found. He noted the NTP hired a second Executive Secretary, Dr. Kristina Thayer.

2. Meetings held by the NTP

(i) Vision

A meeting was held January 29, 2004, at the Lister Hill Auditorium, National Library of Medicine, National Institutes of Health (NIH) in Bethesda, MD to obtain public input on the NTP vision for the 21st century. A working group consisting of seven Board members [Drs. Hillary Carpenter (chair), Diane Birt, Aaron Blair, Samuel Cohen, George Daston, Charlene McQueen and Steve Roberts] received the public comments. Public and interested stakeholders who provided comments included the American Chemical Council, the International Life Sciences Institute, the Korean National Toxicology Program, the Doris Day Animal League, the Natural Resources Defense Council and the People for the Ethical Treatment of Animals.

The Board’s working group for the NTP vision met on March 25, 2004, following the Society of Toxicology meeting in Baltimore. The working group heard presentations on the future of toxicology and the NTP vision from a number of noted toxicologists, namely, Drs. Linda

Birnbaum from the Environmental Protection Agency (EPA), Jim Bus from Dow Chemical Company, David Eaton from the University of Washington, William Greenlee from the Centers for Health Research, Carol Henry from the American Chemistry Council, Robert Kavlock from EPA, and James Popp from Purdue Pharma.

A NTP retreat for August 10-12, 2004, is planned to discuss the vision and a draft roadmap for its implementation.

(ii) Report on Carcinogens

The NTP held a public meeting January 27, 2004, on the NIH campus in Bethesda, MD to receive public input on the review process and criteria used to evaluate nominations to the Report on Carcinogens. Dr. Portier said Dr. C.W. (Bill) Jameson would provide details on this meeting later in the day.

(iii) ICCVAM/NICEATM

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) met on March 10-11, 2004, in Bethesda, MD. Presentations were made on alternative toxicological methods, an update on the activities of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). NICEATM and ICCVAM published a document on minimum performance standards for *in vitro* dermal corrosivity methods. SACATM was asked for its opinion on the potential use of transgenic mouse models for carcinogenicity studies. SACATM provides advice to the 15 federal agencies represented on the ICCVAM, the Director of the NIEHS, and the NICEATM regarding statutorily mandated duties of the ICCVAM and activities of the NICEATM. This advice addresses priorities and directives related to the development, validation, scientific review, and regulatory acceptance of new or revised toxicological test methods, especially those that reduce, refine, or replace the use of animals in testing.

(iv) Center for the Evaluation of Risk to Human Reproduction (CERHR)

The CERHR conducted expert panel reviews of fluoxetine (March 2-5, 2004) and acrylamide (May 17-19, 2004). Dr. Portier presented the findings from those reviews. The expert panel concluded there is some concern regarding the toxicity of fluoxetine during development. The expert panel concluded that there is sufficient evidence in humans that fluoxetine can produce reproductive toxicity in men and women manifested by reversible, impaired sexual function, specifically orgasm. The panel concluded there are insufficient data on possible drug associations with maternal and/or embryonic/fetal toxicity leading to pregnancy loss.

The expert panel that evaluated acrylamide concluded that there is negligible concern for adverse reproductive and developmental effects for exposures in the general population and minimal concern for acrylamide-induced heritable effects in the general population. However, the expert panel expressed some concern for adverse reproductive and developmental effects, including heritable effects, for exposure in occupational settings. The NTP will develop NTP-CERHR monographs on both chemicals. The CERHR is not scheduling any additional evaluations at this time, but plans to focus on completing NTP-CERHR monographs from previous reviews. A number of compounds are being considered for future evaluation.

3. Other issues

Dr. Portier presented statistics on the status of the testing program.

The next meeting of the Technical Reports Review Subcommittee of the Board is scheduled for December 9-10, 2004, at NIEHS where further studies on polychlorinated biphenyls (PCBs) will be presented.

The NTP exhibited at the Society of Toxicology, Society of Toxicological Pathology, and the American Public Health Association meetings last year.

Dr. Portier noted that there has been considerable discussion at the NIH and at other governmental agencies regarding conflict of interest issues for outside activities; specifically for government employees as well as members of advisory groups. He envisions future changes in NIH policies.

III. NTP Vision for the 21st Century

Dr. Portier said three major groups provided advice to the NTP on the vision: the Board's working group, an interagency subcommittee (IAG) composed of member agencies of the NTP Executive Committee, and an internal working group composed of NIEHS staff. In addition stakeholders and a number of public groups provided advice to the NTP on the vision.

1. Report from the Board of Scientific Counselors

Dr. Samuel Cohen, chairperson of the Board Working Group for the NTP Vision¹, presented the major points outlined in the working group report:

- The NTP is recognized nationally as a testing resource and this activity must be maintained in the future. The NTP's focus should be on risk to humans, not risk to rats, mice, and other species. The NTP should focus on understanding mechanisms and biology related to disease etiology in order to predict adverse effects of chemical and physical exposures for humans. The program must expand beyond merely being a testing program.
- The adoption of "omic" technologies for use in learning about mechanisms must be an evolutionary rather than a revolutionary process. The use of "omic" technologies must be based on testing that is already developed.
- The NTP should consider the incorporation of stop-start studies, exposure during various life stages, and high resolution imaging that will permit longitudinal and noninvasive evaluations of changes in disease etiology, into its testing program.
- The NTP needs to place more emphasis on human disease and risk assessment, hazard identification and mechanism-based assays, and consider genetic variability among the population. The focus on human systems must include *in vitro* assays and epidemiology studies. It will be important to develop assays for detection of early predictive molecular events using "omics" and basic biochemistry and to develop a framework to incorporate these data into risk assessment paradigms. These efforts will require the development of informatics and modeling expertise.

¹ Working group members were Drs. Cohen, Birt, Blair, Daston, Carpenter, McQueen and Roberts

- The NTP should be a more effective communicator to both stakeholders and the public and educate federal agencies and public health officials on how new data can be incorporated into their models.
- It will be necessary to educate NTP scientists and other personnel that will perform studies using the above-mentioned techniques.
- Because of limited resources, it will be necessary to develop partnerships with experts in the new areas of research. The establishment of genomics centers by the NIEHS National Center for Toxicogenomics provides a model for establishing partnerships.
- More emphasis should be placed on the use of noninvasive techniques because society is demanding that animal experimentation be reduced. Non-invasive techniques and mechanism-based approaches could eventually lead to a decrease in the number of animals used in research.

2. Reports from the Interagency and NIEHS Working Groups

The interagency working group (IAG) was composed of agencies represented on the NTP Executive Committee². The NIEHS working group consisted of scientists from the Division of Internal Research (DIR), the Division of External Review and Training (DERT) and the NTP. Dr. Portier commented on the high quality of the document prepared by the NIEHS working group. These reports collectively helped NTP identify four general areas for future discussion: nominations to the program, acquisition of scientific data by the research operations group, scientific review, and NTP liaison between the agencies.

Dr. Portier said for the past 10 years, the NTP has been working on mechanism-based toxicology using mainly mammalian test systems or epidemiological approaches. Based on the findings from these activities, the NTP conducts laboratory studies to identify the mechanisms by which these compounds cause adverse effects. Dr. Portier suggested that the program wants to capitalize on the information available on biological mechanisms and use it to target the development of short-term, mechanism-based assays as screening tools. Data from these assays might reveal a potential for hazard. This activity would allow the program to set priorities for more in-depth testing of the most hazardous compounds. The NTP envisions developing a database based on results from these analyses that might be used to understand the mechanism of action for a specific class of compounds. Dr. Portier asked the Board to advise him on which mechanistic assays to target, the priority of these assays, and how to proceed with their development.

Dr. Portier identified some challenges in getting this new initiative underway: finite available resources, how to determine which compounds should be a priority as they impact public health, how to incorporate these new methods into the program without affecting resources, and how to align this initiative toward the NTP mission. Dr. Portier acknowledged the importance of not over-interpreting initial findings until it is clear how the data can be used to make public health decisions. He added that incorporation of medium-throughput methods such as functional

² Members of the interagency working groups included representatives from the U.S. Consumer Product Safety Commission (CPSC), Food and Drug Administration (FDA), Agency for Toxic Substances and Disease Registry (ATSDR), National Institute of Occupational Safety & Health (NIOSH), Occupational Safety and Health Administration (OSHA), National Center for Environmental Health (NCEH), National Cancer Institute (NIH), National Library of Medicine (NLM), U.S. Environmental Protection Agency (EPA), and National Institute of Environmental Health Sciences (NIEHS).

genomics into the main research endeavors of the program should aid the interpretation of findings from mechanistic assays.

He next summarized the recommendations received from all three reports. These include: strengthening existing initiatives, addressing chemical mixtures, assessing the doses being used in the context of mechanistic studies, testing a broader range of doses especially those closer to human exposures, expanding the use of non-invasive technologies, using predictive tools for toxicokinetic studies, and developing new initiatives to enhance the linkage between basic research scientists, scientists within the NTP, scientists within NTP-member agencies, and the Division of Extramural Research and Training (DERT).

Dr. Portier suggested that the scope and quality of testing nominations could be improved by broadening the nomination faculty within each of the agencies that interacts with the NTP. The inclusion of basic scientists on study design teams would also strengthen the testing program. He noted that expertise in these new areas at NIEHS, its member agencies and state and federal levels must be developed to incorporate data from these new assays into decision-making. The NTP must be proactive in its approach to training and educating different groups, *for example*, by holding town meetings and interacting frequently with federal agencies. The NTP web site needs to be restructured to integrate information across NTP activities and across the agencies that interact with the NTP in a similar fashion to the single portal approach developed by the National Library of Medicine.

3. Public Comment

Dr. George Clarke, Xenobiotic Detection Systems, presented oral comments to the Board. He focused on how the NTP can interact with small businesses to improve the funding process for companies to validate assays they have developed. He noted that his company submitted information on an *in vitro* screening method for endocrine disrupting chemicals to the NICEATM and ICCVAM for evaluation. Development of the assay was funded through the Small Business Innovative Research (SBIR) mechanism. The first phase of funding is proof of concept (I), and the second is proof of the assay (II). Although funding is not available from the NIEHS for a third phase to validate an assay (III), validation is required before receiving approval by a federal agency for inclusion of an assay into a testing program. He noted the lack of interest in test methods, such as his, by venture capitalists or pharmaceutical companies because there is no market. He asked the Board to consider how small business could interact with the NTP or other sources to obtain funding for Phase III SBIRs.

4. Board Discussion of Dr. Clarke's presentation

Dr. Kim Boekelheide asked whether Phase III SBIR funding is proposed for ICCVAM. Dr. Clarke responded that some NIH institutes have Phase III SBIR grants but not NIEHS. He feels that these grants should be available since the NTP has a mandate for validation of assays. His company is the first to go through this type of review with ICCVAM and NICEATM, but he cannot continue his work since he lacks funding. Dr. Steve Roberts said that there are some commercial products developed to measure *in vitro* endpoints such as corrosivity. He asked whether Dr. Clarke knew how the company that markets those products obtained funding to develop the assay. Dr. Clarke said the Department of Transportation requested the corrosivity assays, so there is a market. He added that the estrogen screen he has developed will never be adopted if it is not validated.

Dr. Popp summarized the discussion noting the need for federal funding for the validation of new methods developed outside the agency. Dr. Hillary Carpenter asked Dr. Portier if there is a mechanism to fund these projects at NIEHS. Dr. Portier responded that he did not know about funding mechanisms through the SBIR program, but the NTP does validate assays through the ICCVAM and NICEATM. He is unsure whether the evaluation process can be expedited. Since NICEATM and ICCVAM provide input into which assays are being validated, he suggested that NICEATM and ICCVAM be apprised of SBIR funding of new relevant assays.

Dr. Maria Morandi said all government agencies have SBIR programs and she is aware of Phase III support by NIOSH. She asked why NIEHS does not have a Phase III. Dr. Portier said NIEHS thought an interested industry group would validate a useful assay after its development. In this case, the estrogen assay developed by Dr. Clarke's company is part of a tiered testing program and the market for it is not clear. In contrast, the dermal toxicity test for corrosivity is a required test, so companies were willing to invest in its development.

Dr. Boekelheide called it a "catch 22" situation: a company develops an assay, has no money for validation, and then the company disappears because of lack of funding while ICCVAM is evaluating the assay. If ICCVAM decides that the assay has merit, the company may no longer exist. He believes funding through Phase III SBIR grants is an important issue since agencies are encouraging the development of new alternative tests through SBIR phases I and II grants. He suggested the Board encourage agencies to resolve this dilemma.

5. Board Discussion on the Vision

The Board discussed a number of issues regarding the working group reports including the use of mechanistic assays, prediction, development and use of assays in non-mammalian species, use of NTP data to develop regulations, communication, and resource allocation and partnering with other entities.

a. Use of mechanistic assays

The Board discussed how reliable a mechanistically based, predictive test needs to be and how much information needs to be collected. The Board working group's report supported the use of a battery of tests. The IAG cautioned against relying on a negative finding to establish the absence of a potential hazard, because this would require that a predictive assay detect all adverse events in all situations.

Dr. Aaron Blair said the Board working group thought a clear advantage of conducting mechanistic assays, once developed, would be the additional information obtained on a chemical for a relatively low cost. The uncertainty would be the number of mechanisms by which the chemical causes an adverse effect and being sure that the absence of an adverse response did not indicate that the wrong end points were chosen for evaluation. A challenge is whether the NTP can have confidence in the short-term assay(s) used to identify compounds that need further testing in the bioassay.

Dr. Samuel Cohen said the only way to be certain there are no false negatives is to classify everything as a hazard. The NTP must be confident that the assay systems used can identify those compounds that are really hazardous. The best way to extrapolate the results in short-term

tests to human risk is to understand the mechanism of the reaction being measured, and whether it is applicable to humans. Dr. James Popp agreed that the NTP needs to determine the level of acceptability of an assay, and the reliability of its predictability based on the mechanism being evaluated. Dr. John Bucher, chair of the IAG, said the working group realized that the best approach would be to develop error rates for the predictability of an assay.

Dr. Richard Storer expressed concern about establishing a false negative rate. Genetic toxicologists have addressed the theory of test redundancy and complementary because they realized that one test does not measure all relevant mechanisms. The reason for false negatives in any predictive test system must be determined, and, once the reason for why a test fails is understood, it will be easier to build redundancy into the testing strategy. Complimentary tests must also be included in a battery of tests.

b. Prediction

Dr. Cheryl Walker thought the NTP is basically addressing whether mechanistic studies will enable the NTP to have input into prediction and she believes it is appropriate for prediction to be incorporated into the NTP's goals for its studies. Dr. Portier responded that the NTP would not set the standard for hazard because other federal agencies have that legal responsibility. However, the NTP is responsible for the Report on Carcinogens and the CERHR monographs which both address some aspects of risk assessment. Dr. Portier added that the NTP will make predictions only in the context of how to prioritize assays or compounds for testing, but not for risk assessment. Dr. Walker said she thinks the NTP should have greater input into the interpretation of mechanistic data and the development of predictive models for those data.

c. Development and use of assays using non-mammalian species

Dr. John Giesy commended the NTP for its vision and the working groups for their documents. He appreciates the conundrum between regulatory requirements and developing new information. He suggested the NTP include additional measurements in the bioassay protocols. He asked how the NTP envisages it will develop assays with invertebrate models. Non-mammalian models are his area of expertise and he adapts techniques and mammalian assays to non-mammalian species.

Dr. Cohen said that the Board working group envisages that models such as the earthworm, yeast, and zebra fish could be used to develop mechanistically based screening methods. He noted that one difficulty in extrapolating from yeast to humans is the evolutionary distance between the two organisms although housekeeping genes and certain cellular pathways are conserved throughout evolution. If lower animal forms are used for these assays, any differences in the mechanism being studied in the test species and man must be understood before any meaningful extrapolations can be made.

Dr. Portier responded that *in vitro* assays using single cell organisms are useful, but the NTP would prefer to use more complex organisms such as *Caenorhabditis elegans* and zebrafish to help set testing priorities. One critical component of the vision is the development of a number of mechanistic-based assays for a small group of compounds. Storing the data obtained from all assays in a reliable database will help to determine the utility of the endpoints. Understanding the usefulness of the data will be an iterative process because it will be difficult to decide which

information is relevant and useful for making decisions whether to proceed with more definitive tests.

Dr. Portier went on to say that an economy of scale would be required in assay development. For some assays, the concept might be tested with 10-20 compounds and the resulting data might suggest that the assay could be adapted, if amenable, to high-throughput screening (HTS). The Board working group suggested that before an assay is developed for HTS, the NTP must decide on the class(es) of substances it wishes to test and find one source for the critical reagents for an HTS assay. They said it would be advantageous if the NTP could engage the extramural community to duplicate the studies to test the reliability of a specific assay.

Dr. Storer said pharmaceutical companies screen one thousand chemicals a week when validating an assay for reproducibility, but reliability testing takes much longer. He wondered whether the NTP has considered forming an advisory board for HTS consisting of one or two experts from pharmaceutical companies. Although companies will not license their technologies, perhaps the NTP can leverage some of this expertise in the development of HTS or develop synergistic interactions with a company.

Dr. James Klaunig suggested the NTP include a large number of compounds already tested by the program when developing the short-term tests. This would allow comparison of the results from the new tests with those from previous studies and allow comparison of their predictability. He favored the NTP partnering with academic scientists.

d. Use of NTP data to develop regulations

Dr. Hillary Carpenter said the NTP is contributing enormously in the regulatory arena, but the program is not doing enough. He said the current testing regimen is not sustainable from a regulatory perspective. The NTP's mandate is to provide information to protect public health and to date, the program has produced excellent data on 500+ chemicals but more is required to protect public health. With the current testing paradigm, the NTP cannot generate sufficient information on all the chemicals that might impact public health; therefore, the program's direction needs to change. The vision and roadmap will provide an opportunity for change in direction and priorities; however, he expressed some concern regarding the shift in priorities toward studying mechanisms because federal and state agencies make decisions based on an adverse effect not on a mechanism. The legal community understands the association of an adverse effect with exposure, but does not understand the implication of a mechanism in decision-making. The only way to change this attitude will be through a strong educational approach in which lawyers are taught the concepts of how a mechanism could be used in decision-making. This change will be difficult to implement and it will not happen immediately. He noted that presently, the legal community is grappling with how to handle genomic data in a risk assessment situation, where a regulatory decision is being made.

e. Communication

Drs. Popp, Carpenter and Larry Andrews said good, open communication is essential to success of the vision and engaging regulators from federal agencies will be an evolutionary process. Communication must progress with the science otherwise the science will not have value. It is important to involve regulators in the planning of studies and the NTP must understand the issues and problems regulators have relative to risk assessment.

f. Resource allocation and partnering with other entities

Dr. Popp noted the NTP's enormous contribution to toxicology testing, but wondered whether the use of resources is appropriate. For example, he wondered whether the balance between conducting chronic assays and undertaking basic studies to understand mechanisms should be changed in the future. Dr. Bucher said a balance is needed between understanding mechanisms and generating data for predictive applications. He understands that the NTP needs to educate regulators on how to use the data collected in the planned short-term assays for regulatory activities.

Dr. Popp said that the NTP would have to develop a strategy for resource allocation and utilization, as the program cannot decrease its present activities in toxicity testing. Dr. Cohen said it is highly unlikely there will be new resources so the question is how to use the resources the program has. He said leveraging resources would be the only method by which the goals of the vision can be achieved. He suggests the NTP partner with academics and other governmental agencies. For example, the 5-6 genomic centers established by NIEHS and the ILSI initiative to study transgenic animals provide a model of leveraging resources. Dr. Cohen said these groups will partner with the NTP because they realize that such an interaction will advance the field more rapidly than if they undertake the studies alone. Dr. Blair is concerned that if there are no additional resources, leveraging alone will not likely provide all the necessary resources needed to implement the vision.

g. Timeline for completion of the Roadmap

Dr. Blair said it would be important to develop a time frame for implementing the vision and to communicate it to the federal agencies. It will be necessary to obtain their acceptance regarding the use of data from mechanistic tests before embarking on an expensive initiative if the data generated will not be useful for risk assessment purposes.

Dr. Portier said the NTP will concentrate on balancing its programs so it can build useful databases based on mechanisms for a broad class of compounds, noting it is the agency most suited to accomplishing this.

Dr. Blair requested that Dr. Portier send the vision and roadmap to the entire Board after the retreat for their insight into the document. Dr. Carpenter asked about the schedule for announcement of the roadmap to the public. Dr. Portier replied that after the Board meeting, assuming the working group report is accepted, the NTP will draft a roadmap that outlines changes in the program, defines new NTP activities, and proposes a timeline for each activity. The roadmap will then be discussed at the retreat where expert scientists will provide additional insight into the document and help refine it. It will be made available to the public after review by the Board and NTP Executive Committee. The roadmap will be presented at a public meeting to be held at the New York Academy of Sciences on November 30 - December 1, 2004. Initiatives for new programs will be brought to the Board piecemeal as it will not be possible to address the entire roadmap at one time.

Dr. Popp concluded the discussion by saying the quality of material in the three vision documents was excellent and the individuals involved in their compilation should be commended for their efforts. The Board accepted the working group's report.

IV. Report on Carcinogens (RoC)

Dr. C.W. (Bill) Jameson presented an update on the 11th and 12th RoCs and a summary of the public meeting held in Washington, DC on January 27, 2004, to discuss the process for preparing the RoC.

1. Update on the 11th Report

Dr. Jameson noted the scientific reviews for all nominations to the 11th RoC are complete. He summarized the recommendations of the RG1 (the NIEHS/NTP RoC Review Group), the RG2 (the NTP Executive Committee Interagency Working Group for the RoC), and the NTP Board RoC Subcommittee.

- 1-Amino-2,4-dibromoanthraquinone – the recommendation is to list as *reasonably anticipated to be a human carcinogen*.
- Cobalt sulfate – the recommendation is to list *as reasonably anticipated to be a human carcinogen*.
- Diazoaminobenzene – the recommendation is to list *as reasonably anticipated to be a human carcinogen*.
- Diethanolamine – the recommendation is not to list because the data presented do not meet the listing criteria.
- Hepatitis B virus – the recommendation is to list *as a known human carcinogen*.
- Hepatitis C virus – the recommendation is to list *as a known human carcinogen*.
- Human papilloma viruses: Genital mucosal types – the recommendation is to list *as known human carcinogens*.
- Lead and lead compounds – the recommendation by the RG2 and RoC Subcommittee is to list *as reasonably anticipated to be human carcinogens*. The RG1 recommended lead and lead compounds be listed *as known human carcinogens*.
- Naphthalene – the recommendation by the RG1 and RoC Subcommittee is to list *as reasonably anticipated to be a human carcinogen*. The RG2 could not make a recommendation for either listing or not listing naphthalene in the RoC.
- Neutrons – the recommendation is to list *as a known human carcinogen*.
- Nitrobenzene – the recommendation is to list *as reasonably anticipated to be a human carcinogen*.
- Nitromethane – the recommendation is to list *as reasonably anticipated to be a human carcinogen*.
- 4,4'-Thiodianiline – the recommendation is to list *as reasonably anticipated to be a human carcinogen*.
- Three heterocyclic amines 2-Amino--methyl-6-phenylimidazo[4,5-*b*] pyridine (PhIP), 2-Amino-3,4-dimethylimidazo[4,5-*f*] quinoline (MeIQ), and 2-Amino-3,8-dimethylimidazo[4,5-*f*] quinoxaline (MeIQx) – the recommendation is to list *as reasonably anticipated to be human carcinogens*.
- X-radiation and Gamma radiation – the recommendation is to list *as known human carcinogens*.

The NTP Executive Committee received the review package for each nomination to the 11th RoC and the recommendations from the three RoC review committees. The NTP Executive

Committee concurred with the recommendations. Dr. Olden received the recommendations for his consideration in reaching a recommendation on each nomination to propose to the Secretary, Health and Human Services. The final draft of the 11th RoC is in preparation for submission to the Secretary by the end of summer 2004. The 11th RoC is required to be submitted to the Congress by the end of this year.

Board Discussion

Dr. Andrews asked about the RG2's concerns for listing naphthalene. Dr. Jameson replied that the RG2 questioned whether the animal data meet the criteria for listing. He indicated the recommendation for listing is based on an NTP bioassay where olfactory neuroblastomas, a rare neurological tumor type, were found in rats.

Dr. Walker asked why the RG1 recommended listing lead and lead compounds as known human carcinogens. Dr. Jameson replied that the RG1 opined the data from the human epidemiology studies are sufficient to support listing lead and lead compounds as known human carcinogens. The RG2 voted 4 yes and 3 no to list lead and lead compounds as reasonably anticipated to be human carcinogens. The three dissenting members within RG2 thought the human data are sufficient to list as known human carcinogens. The RoC Subcommittee agreed unanimously that the human epidemiology data are limited because of potential confounding factors especially in worker cohorts co-exposed to arsenic and other compounds. The RoC Subcommittee recommended listing as reasonably anticipated to be human carcinogens. Dr. Walker then asked whether the RG1 had similar epidemiology expertise as the other two groups, and Dr. Jameson responded the epidemiology expertise in the three groups was similar. Dr Popp recalled that the RoC Subcommittee agreed the human studies are positive, but thought that the data could not be linked to lead alone, but rather to lead plus other compounds.

2. Nominations for the 12th RoC

Dr. Jameson outlined the list of nominations for the 12th RoC. The NTP published the list in a Federal Register notice dated May 19, 2004 and asked for public comment on the nominations, and specifically for information on their production, use, toxicity, and for the identification of any issues relevant to the carcinogenicity of any nomination that should be considered during its review. He noted the NTP might modify the definition of a nomination based on either information from the literature and/or information received from the public. The nominations include:

- aristolochic acid and aristolochic-related herbal remedies
- asphalt fumes
- atrazine
- benzofuran
- captafol
- cobalt / tungsten-carbide hard metal manufacturing
- di-2-ethylhexyl phthalate (DEHP),
- etoposide, teniposide and etoposide in combination with cis-platin and bleomycin
- respirable size glass wool (may be divided into two nominations: insulation glass wool fibers and special purpose glass wool fibers)
- metal working fluids
- *o*-nitrotoluene
- oxazepam

- riddelliine
- styrene
- talc (the talc nomination may be divided into two nominations: cosmetic talc and occupational exposure to talc)
- vinyl monohalides as a class (fluoride, bromide and chloride mono-halides are listed separately, but based upon recent, additional, human *in vivo* information, it might be more appropriate to list the monohalides as a class).

Board Discussion

Dr. Andrews asked if the list is complete or if additional substances would be added. Dr. Jameson replied that additional nominations for the 12th report are possible.

Dr. Blair asked about the rationale for listing the vinyl monohalides separately in the RoC since it is known that vinyl chloride is a human carcinogen. Dr. Jameson replied that the majority of the RoC Subcommittee thought that the mechanism of tumor formation by vinyl fluoride and vinyl bromide is similar to that of vinyl chloride in animals, and these two mono-halides should be listed as *known human carcinogens* rather than the current listing of *reasonably anticipated to be a human carcinogen*. However, he noted that there are no adequate human data for vinyl bromide and vinyl fluoride to support this proposal. Dr. William Allaben, FDA, asked about human studies with the monohalides and Dr. Portier said the RoC Subcommittee recommended the conduct of *in vitro* human cell studies to determine whether vinyl bromide and vinyl fluoride produce the same metabolite profile as vinyl chloride. Data from these studies will be presented to the Board for review, in the future.

Dr. Walker applauded the nomination of DEHP based on its mechanism of action. Dr. Diane Birt asked for clarification on the evaluation of DEHP since IARC reclassified DEHP as Group 3 (not classifiable) based on mechanistic considerations. Dr. Portier said a nomination is reviewed for listing or delisting when new information is available. Dr. Boekelheide asked whether the NTP would evaluate other diethylhexyl phthalates besides DEHP. Dr. Portier replied the NTP would evaluate the data available for compounds with similar structures to determine if they should be nominated for consideration.

Dr. Mark Torasson, NIOSH, asked whether glass wool or one of its products would be delisted. Dr. Jameson responded that the nomination requests a reevaluation of the listing of respirable size glass wool because IARC reevaluated manmade vitreous fibers and classified insulation glass wool as Group 3 (not classifiable). The nomination of respirable size glass wool will be divided into two nominations namely, insulation glass wool and special purpose glass fibers.

Dr. Allaben asked how many of the nominations are for delisting. Dr. Jameson answered that DEHP and glass wool were nominated for delisting.

3. Report of Public Meeting to Discuss the Process for the RoC

Dr. Jameson presented information about the public meeting held at the National Library of Medicine on January 27, 2004, to discuss the review process and criteria for the Report on Carcinogens. Dr. Lynn Goldman from the Johns Hopkins School of Public Health chaired the meeting. She was assisted by Drs. Carpenter and Elizabeth Delzell from the NTP Board of Scientific Counselors RoC Subcommittee, Dr. Rafael Moure-Eraso, a former member of the RoC

Subcommittee, Dr. Toraason representing the RG2, and Dr. Bucher representing the RG1. The NTP received a number of written comments and seven people registered to give oral comments. Dr. Bernard Goldstein, who chaired a similar meeting in 1999, outlined the highlights from the 1999 meeting and the changes that have been implemented since that meeting.

Dr. Jameson presented proposed changes to the process for review of nominations to the RoC and preparation of the background documents. These changes include the following.

- Establishment of the NIEHS/NTP Nomination Committee for the RoC in order to make the initial identification/selection of nominations for review independent of the review process for listing. This committee will be comprised of senior NIEHS/NTP staff who review the information provided for each nomination and make a recommendation for going forward with its formal review and preparation of a background document or not pursuing the nomination at the time. Previously, the RG1 evaluated the preliminary information for nominations to the RoC and recommended which nominations should go forward for formal review.
- Increased use of experts with knowledge of specific nominations to write and/or review the background documents on nominations as a means to continue to improve their quality.
- Placing background documents accepted as the “documents of record” for nominations to the RoC on the NTP web site at least 30 days prior to initiation of the scientific review process for possible listing in or removal from the RoC. This change is being proposed in response to requests for earlier public accessibility of the background documents.

Dr. Jameson reported that the majority of the comments received focused on a more transparent review process and more opportunity for public involvement in that process as early and as often as possible. Some comments identified specific suggestions regarding changes, ranging from modifying or adding additional steps to the existing RoC review process to completely revising it. Other comments focused on the role of the NTP Executive Committee in the RoC review process, the revision of background documents, the publication of the RoC, and the listing criteria.

Board Discussion

A member asked Dr. Jameson to expand on the question regarding the role of the NTP Executive Committee in reviewing the nominations for the RoC and why this committee’s deliberations are not public. Dr. Portier reiterated that federal agencies reserve the right to discuss the implications of reports in closed session as part of the need for governmental agencies to make decisions on reports after receiving public comments. Therefore, the meetings of this group are closed and the minutes are not published. The process of review of the 12th RoC will be extended to allow comments from the public at various time points.

4. Public comments

(i). Machine working fluids (MWF)

Dr. Richard Kraska, a toxicologist from the Lubrizol Corporation, made a statement on machine working fluids (MWF) on behalf of the Independent Lubricant Manufacturers Association (ILMA). He said ILMA is a national trade organization of 145 North American companies that manufacture 80% of MWF in the United States. ILMA entered into an alliance with the

Occupational Safety and Health Administration (OSHA) to promote the safe use of lubricants and provide MWF users with educational and outreach information.

He said MWF are diverse, complex products designed for a multitude of specific applications in the machining environment. The MWF formulations have changed over time because of changes in usage and the possibility of adverse effects of their specific components e.g., nitrites, polynuclear aromatic hydrocarbons and diethanolamine. Many of these components are no longer in the formulations. Four major classes of MWF are recognized, but there are thousands of formulations within each class, each of which may contain 20 different components. In addition, more than 700 unique components, none of which are carcinogenic, are intentionally added to MWF making them even more complex. Each of these additives is assessed for its suitability under OSHA's hazard communications standard and principles for products steward. Some components, such as antimicrobials are highly regulated and millions of dollars have been spent on risk assessment of these components. The fluids themselves change over time during use in the manufacturing facility; therefore, exposure may be to different components than those in the original formulation. ILMA believes that it is scientifically incorrect to list all these fluids under one listing for the RoC because of the wide variability in their composition.

Dr. Kraska said scientists agree that the epidemiological association between MWF and cancer is weak and the courts found the studies "equivocal." MWF workers are exposed to a number of other compounds during their daily routine. Using epidemiological studies performed more than 20 years ago to represent present day exposures seem inappropriate for any proposed listing of the MWF. He mentioned that the few animal studies performed prior to 1990 probably exposed animals to fluids that do not resemble the MWF to which workers are exposed today. In conclusion, he said ILMA believes that the association between MWF and cancer is weak, thus, an inclusive listing of currently used MWF in the RoC as reasonably anticipated to be human carcinogens is not justified.

Board Discussion

Dr Maria Morandi asked how closely industry works with the NTP to provide information on the composition of the MWF and Dr Kraska responded that the industry is highly competitive and formulations are proprietary. ILMA has not conducted an exhaustive survey of the composition of MWF, but has information on components used in the fluids.

Dr. Allaben asked Dr. Kraska how he could determine which MWF might be toxic since the composition changes continuously. Dr. Kraska replied that presently the fluids do not contain any toxic components. He added there is no mechanistic data to explain the epidemiology studies in which diverse tumors were noted. He believes the association to be weak and reasons other than exposure to MWF can explain why some cohorts developed cancer. He believes the industry has acted responsibly to remove any suspicious components.

Dr. Roberts asked how the NTP proposes to choose one representative metal working fluid and extrapolate this data to the class in general especially since MWF are a heterogeneous group of materials. Dr. Portier asked for suggestions on what approach the NTP should take. Dr. Andrews asked whether there is a way to partition out MWF into broad families to address this dilemma. Dr. Jameson responded that the NTP is gathering preliminary information on MWF and will decide the best way to define the nomination once it has this data,

(ii) Talc

Mr. Scott Slaughter representing the Center for Regulatory Effectiveness (CRE) said he does not believe there is any justification for the re-nomination and listing of talc. One difficulty is that a specific Chemical Access Registry Number (CASRN) does not define talc scientifically. The inclusion of the CASRN is necessary for any nomination so it is clear which substance is being listed and the nature of its exposure. He asked the Board to recommend to the NTP that talc reviewed for the 12th RoC be defined by its CASRN. He noted the RoC Subcommittee considered talc, in its pure form, for listing in the 10th RoC, but voted 7 to 3 to recommend not to list. In his opinion, there appears to be no new scientific evidence to support a listing. Several new studies exonerate the listing of talc rather than supporting the nomination based on occupational exposure.

Board Discussion

Dr. Storer said he believes some types of cosmetic talc contain asbestiform fibers and suggested the nomination be divided into three nominations: pure talc, cosmetic talc and occupational exposure to talc. Dr. Blair asked why the CASRN would not be used to define the talc nomination and Dr. Jameson responded that it would limit the information used in the evaluation to only data on talc as defined by the CASRN. The initial review of epidemiology studies on talc indicates that the talc to which people were exposed is not pure talc as defined by the CASRN; thus, to evaluate talc as defined only by its CASRN would be misleading. The purpose of the Federal Register notice is to obtain relevant information to help the NTP define the nomination. Dr. Blair suggested the listing have multiple categories, one of which is defined by the CASRN and the remainder listed as discussed above. Dr. Portier said the NTP would consider this suggestion. He wants the definition to be clear and concise so the information is scientifically defensible.

(iii) Atrazine

Mr. Jere Weide, Executive Director, Kansas Corn Growers Association (KCGA), said his constituents farm 6 million acres of farmland in Kansas. The KCGA disagrees, from a scientific perspective, on the nomination of atrazine. They have retained an outside source, Cantox Environmental Services, to undertake a human health evaluation of atrazine. Apparently, the rationale for listing atrazine is based on an IARC evaluation performed in 1999, which classified atrazine as a Group 3 carcinogen (not classifiable). IARC reached this decision despite an increase in mammary tumors in Sprague Dawley rats, because the working group concluded that the mechanism for formation of the tumors in rats is not relevant to humans. He added that he is confused why some compounds, listed as Group 3 carcinogens, would be nominated to the RoC for delisting, while atrazine, a Group 3 carcinogen, is recommended for listing. He believes the IARC classification has been misinterpreted. The EPA has reviewed atrazine aggressively since 1994 and it concluded that atrazine is unlikely to be a human carcinogen. A 2001 EPA Scientific Advisory Panel (SAP) concurred. He does not believe there is additional, published data since the 2001 SAP review, although Dr. Blair mentioned a negative epidemiology study published since the 2001 review.

Dr. James Swenberg, from the University of North Carolina and a member of the SAP, spoke on atrazine. He said numerous groups have evaluated atrazine and concluded it is not a human

carcinogen based on its well-understood mechanism of action in rodents. Atrazine interferes with the hypothalamic axis by decreasing the surge of luteinizing hormone required for rats to cycle out of estrus and ovulate. Female Sprague Dawley rats exposed to atrazine are unique because they become senescent resulting in sustained estrus whereas Fischer rats become pseudo pregnant. This effect is not because atrazine is estrogenic, as it has no hormonal activity, but because of its interaction with the hypothalamus. All of the scientific panels that have reviewed atrazine for the EPA agree that this mechanism is not relevant to humans. The human epidemiological studies have been inconclusive and inadequate. Dr. Swenberg referred to the study mentioned by Dr. Blair that found an apparent increase in prostate cancer in an occupational setting, although the increase may have been due to the detection of a rise in prostate specific antigen (PSA). The EPA concluded it is unlikely that an association exists between exposure to atrazine and prostate cancer in this study based on the concentration to which workers were exposed and the duration of exposure. He said atrazine has been reviewed thoroughly by numerous governmental agencies and there are no new human data that raise concerns regarding its safety. Reevaluation of atrazine will result in an unnecessary drain on resources. He concluded by saying that atrazine is the most widely used herbicide in the world and as a result, its toxicity is continuously monitored. Should its toxicity change, he is confident that any concern would be brought to the NTP's attention.

Board Discussion

Dr. Diane Birt asked how the NIEHS interprets the IARC Group 3 classification. She wanted clarification regarding why the NIEHS is using a Group 3 classification as a basis to delist several nominations, but to list atrazine. Dr. Portier said the IARC finding of sufficient evidence of carcinogenicity of atrazine in animals is the reason for concern, even though the human epidemiology evidence is weak. Also, atrazine is used widely and globally and the controversy governing its potential toxicity is not yet settled. The process used by EPA in its evaluation of atrazine is broad and transparent, while IARC's process is less transparent. The NTP review of atrazine for the RoC will follow an established, open process.

Dr. Roberts clarified the SAP's review of the epidemiology data in 2003. He recalled that the SAP was concerned that only prostate cancer was evaluated in the occupational cohort mentioned above by Dr. Swenberg.

(iv) Nomination Review Procedure for 12th RoC

Mr. Slaughter representing CRE commented on the nomination review procedures for the 12th RoC. He said the problem with the process for the 12th RoC is that the public does not know which procedure will be used because the Federal Register notice published on May 19, 2004, conflicts with the procedures outlined on the RoC web site. The CRE and the Kansas Corn Growers Association filed a data quality request asking for withdrawal of the Federal Register notice until the NTP informs the public of its procedure for the 12th RoC. He understands that the current RoC process on the NTP web site applies to the 12th RoC. One difference with the previous review procedures is that under the new procedures, the RG1 can stop the review of a nomination. If this should occur, neither RG2 nor the RoC Subcommittee reviews the nomination.

Board Discussion

Dr. Walker asked for clarification on how nominations are made and at what point a decision is made to move forward on specific compounds. Dr. Portier responded that this decision is made after the information submitted with the nomination and the results from a preliminary literature search is reviewed, and it is determined that there is sufficient preliminary information available to warrant a formal review by the NTP. The NIEHS/NTP RoC Nomination Committee reviews the preliminary information and makes a recommendation to the NTP Director to proceed or not proceed with a formal review of a nomination. The NTP Director has final approval for reviewing nominations.

Dr. Walker asked how the NTP handles the nomination of a class of compounds, such as metal working fluids and talc, and whether mechanistic data are used in deciding not to complete a review. Dr. Portier said he is seeking advice from the Board regarding how the NTP should approach the review of the above-mentioned nominations. Regarding the use of mechanistic data, he said there is no fixed algorithm whether a nomination will be listed or delisted; it depends on the strength of evidence of the available data.

Dr. Popp reiterated Dr. Walker's question regarding the decision not to continue with the review of a nomination because of mechanistic evidence that suggests the nomination is not a human carcinogen. Dr. Portier responded that the NTP has reviewed nominations based on mechanism and has listed or delisted them when appropriate. He said it is the program's responsibility to decide whether there is enough evidence for a review. He said the issues raised during this discussion are valid including whether the definition of a nomination is clear, whether a nomination is likely to be listed, whether resources are being used effectively, and whether a review should be delayed when publication of new relevant data is expected in the near future. Following this discussion, Dr. Walker reiterated her statement to use mechanism as a means of continuing the review process.

Mr. Slaughter asked the NTP to address Dr. Kraska's request for clarification of the process for review of nominations to the 12th RoC and the timeline for convening the RG1. Dr. Portier said he would ensure that the web page is accurate with regard to the process. He reiterated that the NTP has not changed the process for reviewing nominations to the 12th RoC except to allow more time for public input. The NTP changed a few technical issues regarding the assembly of the background documents. Historically, the background documents were compiled differently and now the documents are being prepared with the use of more outside experts than previously. In the past, the background documents were initially reviewed by the RG1, who then immediately proceeded to review the nomination and make a recommendation for listing in the RoC. Now the RG1 must first evaluate the adequacy of the background document for use in reviewing the nomination and applying the criteria for listing in the RoC. Once approved, the background document is considered the "document of record" and placed on the NTP RoC web site. A notice is then published on the NTP list-serv and the NTP web site announcing the availability of the background document for a nomination. The formal, scientific review of a nomination by any of the RoC review groups will not begin for at least 30 days after announcement of the availability of the background document for that nomination. Comments received on the background document prior to review of the nomination will become part of the public record and distributed to the review committees. The sequence for voting by the review committees will remain the same. Dr. Bucher stated that the background documents for nominations to the 12th RoC are being prepared; therefore, the schedule for RG1's reviews is not

yet set. Dr. Jameson said the public comment period on the nominations closes in the middle of July. A schedule will be finalized once the background documents are final.

Dr. Kraska appreciated Dr. Portier's clear explanation. He commented on the difficulty of timelines for the public. He said the NTP takes all the time it needs at each step in the process, but the allotted time of 30 to 60 days for the public comment is often burdensome. He asked for more advanced notice, if possible, with publication of timelines and projected dates to aid in planning.

Dr. Portier summarized the discussion. A few, additional nominations may be added for review for the 12th RoC, and if so, the NTP will publish a Federal Register notice announcing them. He thanked the public commentators and the Board for their input and said the program would consider the excellent suggestions. Finally, he commented on Dr. Swenberg's plea to not waste resources, and said it would be cost effective to include the recent reviews of atrazine in its background document.

V. Report on the Technical Reports Review Subcommittee (TRR Subcommittee) Meeting

Dr. Hailey summarized the meeting held on February 17-18, 2004. Four studies reviewed at the meeting related to the toxic equivalency factor (TEF) initiative involving polychlorinated biphenyls (PCBs), which are dioxin-like compounds, and polychlorinated dibenzofurans (PeCDFs). The validity of the use of TEFs for cancer risk assessment is uncertain. The objective of these studies is to determine the toxicity and carcinogenicity of individual PCBs, dioxin (TCDD), and mixtures of these compounds by (1) determining the potency of the dioxin-like compounds, (2) testing the validity of the TEF method for predicting carcinogenicity of a simple mixture, and (3) determining if non-dioxin like PCBs antagonize the carcinogenicity of dioxin-like PCBs.

The first four reports in the TEF project evaluated 3,3',4,4',5-pentachlorobiphenyl (PCB 126), TCDD, 3,3',4,4',5-pentachlorodibenzofuran (PeCDF), and a mixture of the PCB 126, and PeCDF. Three reports on PCBs will follow in Fall 2004 and one in the future. All the studies reported on at the meeting in February were conducted in female Sprague Dawley rats. Dr. Hailey summarized the findings from these studies. There was *clear evidence of carcinogenicity* of TCDD and PCB 126 based on hepatocellular adenomas and cholangiocarcinomas of the liver, benign lung tumors, and squamous carcinomas of the oral cavity. Tumors were also found in the uterus of female rats exposed to TCDD. There was *some evidence of carcinogenicity* of PeCDF based on liver and oral cavity tumors in female rats. There was *clear evidence* of carcinogenicity in rats fed the PCB126/ PeCDF mixture. The TRR Subcommittee approved the findings from each report and further analysis is underway to assess the TEF concept.

The data from the studies on malachite green and its reduced metabolite, leucomalachite green, a dye used in fish farming as an antifungal agent, followed the TEF studies. Malachite green and leucomalachite green were administered in feed to F344 rats and B6C3F1 mice. Malachite green was not tested in males. There was *equivocal evidence of carcinogenicity* based on neoplasms of the thyroid gland, liver and mammary gland of female rats. There was *no evidence* in female

mice that malachite green is carcinogenic. Data were *equivocal* for leucomalachite green in rats based on thyroid and testis neoplasm in males and there was *some evidence of carcinogenicity* in female mice based on liver neoplasms.

The report on the carcinogenicity of anthraquinone was re-evaluated in light of comments received from industry suggesting that the presence of a contaminant in the anthraquinone tested may have affected the results of the study. The TRR Subcommittee accepted the report and conclusions as valid for the substance tested; however, there was a tie vote broken by the chair that the title be changed to “anthracene-derived anthraquinone” instead of simply anthraquinone. The TRR Subcommittee asked that the Board revisit the issue of contaminants in NTP study materials.

The NTP conducted studies in two small fish species, the Guppy and Medaka, to evaluate the use of a fish as a model for carcinogenicity. The NTP tested three compounds, two mutagens and one non-mutagen, which had been tested previously in mice and rats. Because tumors in fish species are found primarily in the liver, the NTP chose carcinogenic chemicals that affect multiple tissues in rodents to determine whether other sites were responsive in the fish. The loss of fish due to early death and their subsequent cannibalization by live fish were problems that interfered with interpretation of the studies in some cases. The results of the fish studies were:

- 2,2, bisbromoethyl-1, 3-propanediol resulted in tumors in multiple tissues when fed to male and female rats and mice. The results were positive in the male Guppy and male Medaka based on liver tumors, but negative in female Medaka. Results were inadequate in female Guppy due to reduced survival.
- The multi-site rodent carcinogen 1,2,3-trichloropropane was positive in both sexes of both species of fish with liver tumors in all species as well as gallbladder tumors in male and female Medaka.
- Nitromethane, when inhaled, was carcinogenic in male and female mice and female rats, but not male rats. The data were inadequate in the male Guppy (due to survival), and negative in the Medaka and female Guppy.

Dr. Hailey said the NTP was disappointed with the outcome of the fish studies, but added that these assays, limited to three chemicals, may not necessarily be a good assessment of the fish models. He indicated that early death and subsequent cannibalism were problems; the studies were not as inexpensive or as short as originally estimated, and that cost savings in pathology was less than anticipated. In most cases tumors were only found after 12 to 16 months of exposure. Both the Guppy and the Medaka seem less sensitive than rodents although the Medaka appear to be more sensitive than the Guppy. The liver was the only target organ in which tumors were found in the fish, except for one case of gall bladder tumors.

Reviews of the following reports will take place at the upcoming December peer review: three TEF studies: 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153), a mixture of 3,3',4,4',5-pentachlorobiphenyl (PCB 126) and PCB 153, a mixture of 2,3,4,4',5, pentachlorobiphenyl (PCB 118) and PCB 126, sodium chlorate, benzophenone, bromodichloromethane, a transplacental azidothymidine (AZT) study, and a genistein dose range finding study.

1. Public Comment on Anthraquinone

Mrs. Linda Beckett, a private citizen, discussed the use of two preparations of goose repellents that contained 50% 9,10-anthraquinone in her neighborhood in Warrington, VA. Arkion and Airopel, a subsidiary of Arkion, market these preparations known as Flight Control Plus and Avipel. School playgrounds and lakesides in their area are overrun with Canadian geese. Homeowners in the area do not want to build fences or allow grass to grow because these activities reduce property values and esthetics. The chemical repellent has been successful in controlling the numbers of geese that congregate in their development. However, the downside to spraying these repellents is exposure of the public to these preparations. She is concerned about the safety of these preparations and does not understand why Flight Control Plus is restricted for sale and can only be applied by licensed applicators whereas Avipel sales are unrestricted and unregulated, although the active ingredient is the same in both preparations. She read the original NTP technical report on anthraquinone (TR-494) showing clear evidence of carcinogenicity in mice and rats. However, the revised technical report appears to only address anthraquinone manufactured from anthracene. She obtained a copy of the New York State Department of Environmental Conservation registration disallowing the use of anthraquinone in public areas where people could be exposed by absorption of anthraquinone through the skin. In February 2004, she contacted a representative of Arkion who said that there is clear evidence of carcinogenicity of anthraquinone in mice and rats and her concern about exposure was well grounded. Since the NTP report now limits the conclusion of its study to “anthracene-derived anthraquinone,” the company has changed its mind about the toxicity of its product. Now, the company says that only “anthracene-derived anthraquinone” may be carcinogenic, but their product, Flight Control Plus, that contains a plant-derived anthraquinone, is completely safe. She is confused and asked whether Arkion is correct, whether New York State is overacting, and whether this chemical is safe. She questioned whether the company changed the name of their products and distribution to skirt EPA regulations. She said Arkion asked EPA to relax their restrictions, but EPA denied the request until the company produces evidence showing that its chemical is not carcinogenic. She wants to know if these repellents are safe for frequent use and whether children are at risk.

Board Discussion

Dr. Roberts, a member the TRR Subcommittee, summarized the discussion that ensued at the February meeting. He said the anthraquinone used in the 2-year bioassay contained a contaminant, 9-nitroanthracene that is mutagenic. According to Arkion when 9-nitroanthracene is extracted from anthraquinone, the residual anthraquinone is no longer mutagenic. Apparently, 9-nitroanthracene is produced during the manufacture of anthraquinone when anthracene is the starting material. The company maintains that mutagenicity is not observed with the anthraquinone they sell, as it is manufactured by a different process. The TRR Subcommittee had extensive discussion about how to handle the report and whether different sources of anthraquinone should be discussed in the report. A potential solution was to designate the starting material in the manufacturing process of anthraquinone in the name of the report. The recommendation to rename the report to “anthracene-derived anthraquinone” passed by the chair, breaking a tie. He said the TRR Subcommittee did not realize the ramifications of its decision to rename the technical report, which apparently has resulted in the study being marginalized as discussed by Mrs. Beckett. At the end of the meeting, members of the TRR Subcommittee asked that the issue of contaminants be revisited, especially in relation to the possibility that a

contaminant, and not the chemical being tested, is responsible for carcinogenicity. Dr. Roberts asked the members of the TRR Subcommittee at the Board meeting to comment on its decision regarding the report's title.

Dr. Klaunig said he attended the meeting and voted to change the title of the report but now he has second thoughts. The results of the bioassay are based on anthracene-derived anthraquinone, which contains 9-nitroanthracene, a mutagenic contaminant. Evidence presented at the public meeting by Arkion suggested that this contaminant might be responsible for the carcinogenicity. However, no carcinogenicity studies have been performed with 9-nitroanthracene. Dr. Klaunig said he is hesitant now about maintaining the title change for the report. He believes the bioassay was conducted correctly.

Dr. Boekeheide said he was present at the meeting and voted against changing the title. He pointed out that there was no clear resolution whether carcinogenicity was due to the contaminant that arose from the manufacturing process, or alternatively was from a metabolite of anthraquinone that had been isolated from the urine of rats fed anthraquinone. He said there was confusion as to the concentration of 9-nitroanthracene in the anthraquinone tested in the bioassay. 9-Nitroanthracene is a bacterial mutagen, but not a known carcinogen in mammals. In addition, he noted that the anthraquinone metabolite found in the urine was found to be several fold more mutagenic than the 9-nitroanthracene found at a concentration of 0.1% in the material tested. For these reasons, he did not vote for a change in name of the report. Dr. Birt said she voted against changing the title of the report for reasons discussed at the meeting and because she thought the report on the carcinogenicity of anthraquinone would be ignored.

Dr. Storer stated that he had originally suggested a change in title of the report because the Subcommittee was at an impasse. The scientific presentation had not proven the source of the carcinogenic activity. He had naively thought that responsible agencies would correctly interpret the information, but he realizes the translation to users has been misused and information has been taken out of context. Regulators and the public have erred on the intent of the name change. He still thinks it is appropriate to characterize and identify correctly what was tested. Dr. Storer said that the information presented at the TRR Subcommittee meeting was complex, but at the time the information was compelling that highly mutagenic contaminants could be reproducibly isolated from anthraquinone manufactured from anthracene. Dr. Andrews voted for the name change and he agreed with the points Dr. Storer made. Dr. Piegorsch voted in favor of a name change because Dr. Storer's suggestion was the best recommendation presented at the meeting; however, he now realizes that the consequences seem to be more far reaching than he expected.

Dr. Mary Anna Thrall who chaired the meeting and broke the tie said she voted for a name change because she thought this would be a special name change only.

Dr. Popp said one has to consider the generic issue of impurities and the generic issue of metabolites make the problem even more complex. He asked for clarification on the degree of contamination and the amount of the major metabolite produced. Dr. Bucher responded that the major metabolite, 2-hydroxyanthraquinone, comprises 40-50% of the metabolites and it is mutagenic. The anthraquinone used in the bioassay was 99.9% pure and it had less than 0.1% of

9-nitroanthracene. The NTP used this particular anthraquinone because technical grade anthraquinone is only 80-85% pure and the NTP wanted to use a purer material.

Dr. Morandi asked whether the amount of the impurity and its potency could explain the number and type of tumors. She suggested that if the tumors could not be attributed to the impurity then it could not be the cause of the tumors. Dr. Bucher responded that the impurity has been tested only in mutagenicity studies and not in carcinogenicity studies; therefore, this determination cannot be made.

Dr. Popp said the presence of impurities is not unique at all and many chemicals studied in the bioassay have higher levels of impurities. Dr. Bucher said the NTP is satisfied if they can find a chemical that is 99.9% pure and the program attempts to identify any impurity that is present at a level of 0.1% or higher. Dr. Popp reiterated that this issue is generic and wondered why the naming of the anthraquinone report should be handled any differently from any other chemical with impurities that has been tested.

Dr. Cohen said nitro aromatic compounds are frequently highly mutagenic in the Ames test and other genotoxicity assays, but there is no correlation of bacterial mutagenicity with mammalian carcinogenicity by these compounds. He would be surprised if the 9-nitroanthracene explained the carcinogenicity of the anthraquinone, since there was clear evidence of carcinogenicity and not a marginal response. Dr. Popp agreed with Dr. Cohen especially since the level of the contaminant is so low.

Dr. Walker asked whether the Board is being asked to approve the recommendation and Dr. Portier responded that the NTP is seeking the Board's advice. It appears to him that the Board is suggesting that this issue of contaminants should be discussed in greater depth with the TRR Subcommittee.

Dr. Klaunig agreed with Dr. Portier and said he would feel more comfortable if the issue of contaminants was discussed further by the Subcommittee. This will be an important consideration when the NTP begins to investigate and define mixtures. Dr. Roberts agreed with Dr. Klaunig and Dr. Popp. The TRR Subcommittee should discuss at what level a contaminant might affect the results of a study and whether that could substantially affect the interpretation of a report. Dr. Popp suggested that the example of anthraquinone could be taken as a basis to look at the broader issue of the interpretation of studies with impurities. He previously served on the Subcommittee and although contaminants have been mentioned in relation to other study chemicals, this issue was not discussed further.

Dr. Storer said it is also an issue of communication and interpretation because regardless of whether the report is entitled anthraquinone or "anthracene derived anthraquinone" the supporters of the safety of non-anthracene derived anthraquinone are stating that the carcinogenicity of anthraquinone is associated with these mutagenic contaminants. This is important for interpretation by state agencies, and the NTP report should be more explicit in discussing the implications of these findings with anthracene-derived anthraquinone. The burden of proof should be on industry to show that other sources of anthraquinone are safe rather than the NTP having to prove that other sources of anthraquinone are also carcinogenic.

Dr. Carpenter stated that from a regulatory standpoint if he is presented with information on a bioassay in which a compound tested positive, he has to assume that carcinogenicity or toxicity will occur even if the commercial product is only 85% pure.

VI. NTP Studies on Trimethylolpropane Triacrylate (TMPTA)

Dr. Bucher outlined the historical background to this agenda item. He said the background material demonstrates the close interaction between industry and the NTP. The NTP studied pentaerythritol triacrylate (PETA) and TMPTA, two compounds nominated by the NCI in 1987. The NTP designed prechronic studies as well as dermal absorption studies that were completed in 1996. The NTP chose to evaluate both chemicals in the Tg.AC transgenic mouse model, which was thought useful for evaluating skin carcinogenesis, because exposure is via the dermal route. The study was completed in 1999 and the report reviewed by the TRR Subcommittee in September 2002. The NTP withdrew the conclusions for evaluation by the TRR Subcommittee and asked them to provide input on the utility of this model for evaluating carcinogenicity. The subcommittee did not consider the Tg.AC mouse a suitable model for carcinogenicity but said that transgenic models might be useful for testing within a battery of assays. Based upon this input from the Board, the NTP decided to conduct traditional 2-year bioassays on PETA and TMPTA. In March 2004, the NTP asked the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) to comment on the validation of transgenic animals. The SACATM did not think transgenic models suitable substitutes for traditional rodent models in evaluating carcinogenicity but said these models may be useful for certain applications.

1. Presentation by Dr. Rajenda Chhabra

Dr. Chhabra said PETA and TMPTA are multifunctional monomers used as cross-linking agents in the formulation of UVR curable inks, in the manufacture of acrylic glues, adhesives and sealants and in resins for specialty plastics, surface coatings, emulsion polymers and latex coatings. NCI nominated TMPTA and PETA in 1987 as representatives of multifunctional acrylates because of an increase in production volume and use, the potential for occupational exposure, and the lack of data on chronic toxicity or carcinogenicity. Dr. Chhabra noted the interactions between the NTP and industry regarding studies on these products. Members and consultants to the Specialty Acrylates and Methacrylates (SAM) Panel have made presentations to the NTP about these acrylates and discussed dose selection of the compounds for a 2-year bioassay. To date, TMPTA and PETA have been tested in genetic toxicology assays, in *in vitro* toxicity and contact hypersensitivity assays, in 2- and 13-week dermal studies, and in chronic studies with the Tg. AC mouse. The NTP plans to test TMPTA in a chronic 2-year bioassay. He noted there has been discussion regarding the inclusion of TMPTA at the maximum tolerated dose (MTD) for this study. The study on PETA was dropped because of the inability to secure sufficient test material.

Dr. Chhabra summarized the data on the dermal histopathologic lesions at the site of contact in rats and mice exposed for 90 days to TMPTA. Hyperplasia was observed in all the male rats receiving 3 mg/kg while degeneration, inflammation, hyperkeratosis, and sebaceous gland hyperplasia were observed in all male rats receiving 6 mg/kg. Similar results were recorded in female rats, but fewer animals had lesions compared to the males. He said the effect in male and female mice was similar to female rats, but necrosis was less prevalent. In the Tg. AC mice, hyperkeratosis was observed in all animals at 3 mg/kg, but the other lesions were recorded only

in a few mice. Female transgenic mice were less sensitive. At 6 mg/kg, all the male and female Tg.AC mice lesions were similar to those seen in male rats, but in addition, squamous cell papillomas were observed in about 75% of the mice. Despite the pathological changes at 6 mg/kg, the NTP decided to include this dose in the bioassay, since it is the dose in the Tg. AC mice where carcinogenicity was reported. Dr. Chhabra said the doses chosen for the bioassays are 0, 0.75, 1.5 and 3.0 mg/kg in male rats; 0, 1.5, 3.0 and 6.0 mg/kg in female rats; and 0, 0.75, 1.5, 3.0 and 6.0 mg/kg for male and female mice.

2. Presentation by Dr. James R. Hailey

Dr. Hailey outlined the rationale for dose selection generically in dermal studies and showed slides of the histopathologic lesions from mice receiving TMPTA for 90 days. He said dose selection for the bioassay is based on the data from the 90 day study. The low dose would have virtually no effect while the high dose would indicate a challenge to the skin. The mid-dose would be intermediate between the high and low dose. He said the NTP would avoid using doses that cause ulceration, necrosis, fibrosis, chronic inflammation, hyperplasia, hyperkeratosis, and sebaceous gland hyperplasia. He noted that if the severity of the lesion caused by a dose is greater than the mild classification in the 90 day study which is a 2 on a scale of 1-4, that dose is avoided in the 2-year study. Lesions are aggregated, and the character of the dose-response curve at 90 days is also considered. Dr. Hailey showed a few histopathology slides to demonstrate the type of lesions seen with TMPTA.

3. Public Comments

(i) Specialty Acrylates and Methacrylates (SAM) Panel

Dr. J. P. Van Miller, representing the SAM panel, commented on the studies with the Tg.AC mouse and the proposed bioassay planned with TMPTA. He said human exposure to the acrylates is limited and industry has reduced exposure levels in the workplace. He said testing at high concentrations is undesirable especially since high concentrations cause cell proliferation and irritation, effects that may confound the interpretation of the study. The SAM panel reported their findings on another acrylate, triethylene glycol diacrylate (TREGDA), in a 2-year bioassay to the Environmental Protection Agency (EPA). They used concentrations of TREGDA that did not cause skin irritation or cell proliferation and found no tumors. He believes that EPA does not have a concern regarding the triacrylates. Since the Tg.AC model has not been validated for carcinogenicity of skin irritants, he does not consider the study with TMPTA in this model to be valid. Furthermore, the bioassay cannot validate the Tg.AC model. He opined that the doses selected for the bioassay with TMPTA are inappropriate, because they exceed the dose for irritation and because the NTP has altered its approach to dose selection. He stated there is significant skin irritation at 3 mg/kg/day based on the data presented by Dr. Hailey. Previously, the NTP used lower doses of benzothionium chloride, an irritant that is similar to TMPTA and he proposed the highest dose be below 3 mg/kg/day. He suggested that additional preliminary studies on cell proliferation be performed. He added that there is a need for a pathology-working group to compare the results of the SAM panel studies with those performed by the NTP. The SAM panel would be willing to provide data and histology slides from their studies for such an evaluation.

(ii) RadTech

Dr. James MacGregor spoke on behalf of RadTech, a nonprofit organization comprising 800 affiliated corporations involved in UV and electron beam coating technologies. He said acrylates are critical components of numerous coatings and have health and environmental benefits. Although EPA regulates acrylates as a class, a negative finding on a single member of the class will impact the class. Thus, he hopes the NTP will ensure that future studies are performed correctly. He is concerned with results from the genetically promoted Tg.AC model because tumors are produced on the skin by wounding alone. Because EPA currently recognizes the importance of cell proliferation elicited by this class, he believes that this end point should be measured throughout the NTP study and not inferred from histopathology at the end of the study. The role of inflammation and cell proliferation in initiation and/or promotion of the tumorigenic process are known, and as the acrylates are irritating substances, he considers it important that these endpoints be considered in relation to threshold events. In his opinion, the upper dose should not be set too high, because EPA assumes the default assumption of linearity over the entire dose range. The recommendations of RadTech were similar to those of the SAM panel and included the expansion of the dose range, the review of the slides of both the Van Miller study and the NTP pilot studies by recognized experts, the determination of the threshold for cell proliferation and inflammation, and the monitoring of these endpoints throughout the study. He suggested that bromodeoxyuridine (BrdU) staining be used to measure cell turnover directly rather than staining for proliferating cell nuclear antigen (PCNA) at the end of the study. Finally, he stated that it is important that dose of TMPTA, which elicits minimal inflammation, be used for the upper dose and that sufficient doses be included in the lower dose range.

Board Discussion

Dr. Popp asked about the objective of the pathology review and whether anything would be learned that would make a difference to the experimental design. Dr. MacGregor responded that such an evaluation would allow a direct calibration between the van Miller studies in C3H mice and the pilot studies in B6C3F1 mice and cell proliferation monitored directly in the Van Miller study.

Dr. Michael Elwell the first primary reviewer stated that the NTP has conducted numerous short- and long-term studies on skin carcinogenicity. The doses proposed for this study are based on prechronic studies plus experience from previous studies. It appears to him that the results presented by Dr. Hailey indicate a “no effect” level at low doses that increased quantitatively but not qualitatively in the high dose range in one sex of mice, while in rats there was a minimal response. He reviewed the previous acrylate studies where pathological approaches were used to assess cell proliferation and the presence of inflammatory cells. In his opinion, the addition of special stains for cell proliferation is not justified. He said although Drs. Van Miller and MacGregor suggest that the NTP use doses that elicit a clear minimal response, it is not clear to him what a “clear minimal response” is. In the study by Dr. Van Miller, cell proliferation was observed in 30% of the cells in control mice and in 60% of treated groups, but this parameter did not correlate with neoplasia. Thus, he questioned whether the measurement of cell proliferation would help explain the outcome. He said Dr. Van Miller did not use inflammation to establish the doses for the long-term study by the SAM panel. He agreed that B6C3F1 mice might respond differently than C3H mice, but the final dose selection should depend on the 90-day study in B6C3F1 mice and F344 rats. The design appears to follow NTP scientific practices applied previously in dermal studies.

Dr. Storer, the second reviewer, agreed with Dr. Elwell's assessment. When he reviewed the Van Miller paper he noted that the grading system for responses in the initial short-term 14-day study was mild, moderate and severe. However, doses that caused a severe response at 14 days were used in the 78-week study. In the 90-day and the 78-week studies where the authors used a grading system of 1-5, it seemed the results were concordant, *that is*, the 13-week or 3-month range finding study seemed to be predictive of the degree of inflammation at 78 weeks. Thus, it seemed reasonable for the NTP to base the dose selection on the 13-week study in the B6C3F1 mouse. He questioned the use of additional resources to measure cell proliferation at intervening time points, as he did not expect the results to differ markedly from those published. He added that the NTP's purpose for the studies must be clear, whether it is a health concern for human exposure to acrylates as a class or to understand the response observed in Tg.AC mice.

Dr. Chhabra responded that the primary purpose of the study is to evaluate the carcinogenicity of TMPTA and not to validate the transgenic mouse model. The results of the transgenic assays strongly suggest that these acrylates might be carcinogens and exposure to humans is significant because dermatitis has been reported in workers in occupational settings. The NTP also sees this study as an additional opportunity to compare the results with those observed in the Tg.AC model and for that reason proposed the 6 mg/kg dose.

Dr. Birt asked whether the inclusion of a dose of 6 mg/kg in mice would have a regulatory implication if a response were found at this dose. Dr. Chhabra replied that if a response is only seen at 6mg/kg the TRR Subcommittee would likely conclude that the MTD was exceeded.

Dr. Klaunig said he did not understand the rationale of first determining the MTD, and then including a dose of 6 mg/kg/day that exceeds the MTD. He thought the inclusion of this high dose should be reconsidered.

Dr. Andrews was concerned about EPA's regulation of acrylates and the agency's significant new use rule. He thought the EPA would want information on cell turnover and markers of inflammation to aid in its understanding of the data from the bioassay. He felt the NTP should get input from the EPA about the doses for the study. He said the hypothesis that irritation leads to cell proliferation resulting in tumorigenesis is simplistic; Van Miller showed a 17-fold increase in cell proliferation without tumorigenesis. None of the 4-5 skin irritants tested previously by the NTP, which caused cell proliferation, were tumorigenic. The NTP is always willing to include mechanistic studies that will aid in the interpretation of an outcome, but in this case he does not believe such studies are warranted.

Dr. Piegorsch asked whether the NTP could add a dose that is 1/8 the MTD. Dr. Bucher commented that the NTP would consider all options for dose setting in designing the best study. The acrylates were tested in the Tg. AC mouse because they are not considered high priority chemicals. The additional suggested studies could be done, but resources are limited and the program must prioritize expenditures.

Dr. Portier asked Drs. Piegorsch and Klaunig for clarification on their comments regarding dose. It appears that they are not comfortable with the addition of the 6 mg/kg dose, but seem satisfied

with the inclusion of a fourth dose at a lower concentration. He said the NTP would add additional doses because of its uncertainty regarding how the 6 mg/kg dose might affect the overall interpretation of the data. Dr. Piegorsch said he is not convinced that a 6 mg/kg dose is too high; however, he did think that expanding the number of doses should be considered and might provide important information for regulatory agencies. Dr. Klaunig again expressed concern about using the 6 mg/kg dose and questioned the criteria for exceeding the MTD. He said Dr. Hailey's presentation alluded to some degeneration in the tissues of animals receiving a dose of 6 mg/kg and he thought the NTP would avoid using a dose that causes degeneration. He said the NTP should be consistent in dose setting and carefully explain its criteria for choosing to exceed the MTD. Dr. Chhabra responded that the NTP would consider the Board's advice carefully.

Dr. Allaben asked whether the end users of the study's results had been consulted about dose selection. Dr. Bucher said the NTP is in a quandary because the program is attempting to accommodate the NCI's nomination of acrylates but it is unclear whether the EPA would be interested in additional data.

Dr. Popp summarized the discussion and included his own thoughts. He said the dose spread needs to be considered; the high dose appears to be too high and the low dose is also of concern because it is near the "no observed affect level" (NOEL). He thinks one dose below the NOEL should be included. He did not think another dose needs to be added, but the dose spread should be increased. He did believe that a comparison of the pathology data from the SAM studies and those from the 90-day study conducted by the NTP would be useful. However, obtaining cell proliferation data during the bioassay, but not during the short-term testing might be helpful for interpreting the results. In summary, he would change the dose range and collect data on cell proliferation and inflammation under conditions of the bioassay.

VII. Review of Statistical Methods to Analyze Photocarcinogenicity Studies

Dr. Piegorsch (chair), University of South Carolina, of the NTP Board of Scientific Counselors Working Group on Statistical Methods presented a summary of the meeting held on March 9, 2004, in Columbia, SC. This meeting's purpose was to review the statistical methods being used to analyze tumorigenicity outcomes from photocarcinogenicity studies and to provide guidance on the most appropriate methods to analyze tumor multiplicity. Members of the working group included: Dr. Thomas Fears -NIH, Dr. Greg Carr -Proctor and Gamble and Dr. Nancy Flournoy - University of Missouri, Dr. Barbara Pence -University of Texas, and Dr. Bruce Turnbull - Cornell University. Dr. Paul Howard from NCTR who conducted these studies and Dr. Barbara Shane - NIEHS, Executive Secretary were present.

The two primary issues for discussion were tumor multiplicity and dependent censoring. The working group concluded that the statistical methods currently used by the NTP are appropriate for analyzing data from these studies, but their analysis did not consider tumor multiplicity and dependent censoring. The working group recommended a semi-parametric point process regression model for analyzing tumor multiplicity with proper statistical adjustment for the censoring effect. Also, the group said appropriate statistical methods should be used to analyze possible interactions between multiple exposures, such as sunscreens and ultraviolet light.

Prior to the Board meeting, Dr. Portier asked scientists and statisticians from NCTR to respond to the working group's report. Dr. Piegorsch said NCTR had decided to use the log rank test and Kaplan-Meier plots of time to first tumor. Dr. Piegorsch said these were reasonable methodologies, although generally descriptive. He added that the choice of the Andersen-Gill regression model to analyze multiple tumors is appropriate and is in concert with the working group's recommendation. He was pleased that FDA planned to adopt many of the recommendations proposed by the working group.

Board Discussion

Dr. Portier said the analysis of the first studies conducted with solar energy would incorporate these two tests. He added that the NTP would consider inclusion of other suggested analytical methods in the future.

Dr. Andrews asked whether these tests address the censoring of data. Dr. Piegorsch responded that dependent censoring considers the removal of an animal from the study when it develops a tumor that is 10 mm in size. This parameter must be built into the test to avoid biases or the assignment of an incorrect p value that could interfere with interpretation. Dr. Piegorsch said the working group recommended ways by which this censoring could be built into the Andersen-Gill model.

Dr. Popp asked whether the Board accepted the Working Group Report. Hearing no objection, he accepted the report on behalf of the Board.

Dr. Portier thanked the Board for their thoughtfulness on behalf of all the federal agencies, and the public meeting was adjourned. The Board reconvened in closed session after the break.

DEPARTMENT OF HEALTH AND HUMAN SERVICES**National Institutes of Health****Prospective Grant of Exclusive License: Human-Bovine Reassortant Rotavirus Vaccine**

AGENCY: National Institutes of Health, Public Health Service, DHHS.

ACTION: Notice.

SUMMARY: This is notice, in accordance with 35 U.S.C. 209(c)(1) and 37 CFR 404.7(a)(1)(i), that the National Institutes of Health (NIH), Department of Health and Human Services, is contemplating the grant of an exclusive license in the U.S., Europe, and Canada only to practice the invention embodied in U.S. Serial Number 60/094,425, filed July 28, 1998, PCT filed (PCT/US99/17036) on July 27, 1999, and National Stage filed in China, India, Korea, Australia, Canada, Europe, Japan, Brazil and the U.S., entitled "Multivalent Human-Bovine Rotavirus Vaccine" (DHHS ref. E-015-1998/0) to Aridis, LLC, having a place of business in Portola Valley, California. The patent rights in these inventions have been assigned to the United States of America.

DATES: Only written comments and/or application for a license which are received by the NIH Office of Technology Transfer on or before September 7, 2004 will be considered.

ADDRESSES: Requests for a copy of the patent application, inquiries, comments and other materials relating to the contemplated license should be directed to: Susan Ano, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852-3804; Email: anos@od.nih.gov; Telephone: (301) 435-5515; Facsimile: (301) 402-0220.

SUPPLEMENTARY INFORMATION: The prospective exclusive license will be royalty bearing and will comply with the terms and conditions of 35 U.S.C. 209 and 37 CFR 404.7. The prospective exclusive license may be granted unless, within 60 days from the date of this published Notice, NIH receives written evidence and argument that establishes that the grant of the license would not be consistent with the requirements of 35 U.S.C. 209 and 37 CFR 404.7.

This technology describes multivalent immunogenic compositions comprising at least four human-bovine reassortant rotaviruses, where the gene encoding VP7 protein from G1, G2, G3, or G4 human rotavirus strain is inserted into a bovine rotavirus backbone. These VP7 serotypes represent the clinically most

important human rotavirus serotypes, which depends on VP4 and VP7 proteins, both found in the viral capsid and both of which independently induce neutralizing antibodies. Additionally, human-bovine reassortants for VP7 serotypes G5 and G9 and a bovine-bovine reassortant for VP7 G10 serotype are mentioned. Each of these reassortants is monovalent, and administered as a multivalent mixture. Compared to other human-bovine rotavirus reassortants, the compositions described in this technology induce an immunological response at significantly lower dosage than other human-bovine rotavirus reassortants (which required 10-100 times the dose of human-rhesus reassortants) and does not result in a low-grade, transient fever.

The field of use may be limited to development of human-bovine reassortant rotavirus vaccines.

The licensed territory will be exclusive in the U.S., Canada, and Europe.

Properly filed competing applications for a license filed in response to this notice will be treated as objections to the contemplated license. Comments and objections submitted in response to this notice will not be made available for public inspection, and, to the extent permitted by law, will not be released under the Freedom of Information Act, 5 U.S.C. 552.

Dated: May 28, 2004.

Steven M. Ferguson,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. 04-12860 Filed 6-7-04; 8:45 am]

BILLING CODE 4140-01-P

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 Public Law 92-463, notice is hereby given of a meeting of the National Toxicology Program (NTP) Board of Scientific Counselors on June 29, 2004, at the Marriott at Research Triangle Park, 4700 Guardian Drive, Durham, NC 27703.

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 and Registration

The meeting on June 29, 2004 begins at 8:30 a.m. and is open to the public from 8:30 a.m. to approximately 3:30 p.m., when it will be closed to the public until adjournment. The closure is in accordance with the provisions set forth in section 552b(c)(4) "disclosure of commercial or financial information," (c)(6) "disclosure of information of personal nature where disclosure would constitute a clearly unwarranted invasion of personal privacy" and (c)(9) "disclosure of information of a premature nature which would significantly frustrate implementation of a proposed agency action" of Title 5 U.S.C. for the review and evaluation of the Carcinogenic Potency Database.

Attendance at the public meeting will be limited only by the space available. Persons needing special assistance should contact the Executive Secretary (contact information below) at least 7 business days in advance of the meeting.

A draft agenda with a tentative schedule is provided below. Primary agenda topics include: (1) NTP activities for development of a roadmap (or framework) for implementation of the NTP Vision for the 21st Century (<http://ntp-server.niehs.nih.gov>), (2) report from the Board's Working Group on the review of statistical methods to analyze photocarcinogenicity studies, (3) planned NTP Studies on trimethylolpropane triacrylate (TMPTA), (4) activities of the NTP Board's Technical Reports Review Subcommittee, and (5) an update on the Report on Carcinogens, including the status of the Eleventh Edition, and on the public meeting held January 27, 2004, to receive comment on the review process and criteria used to evaluate nominations to the Report on Carcinogens.

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, 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.

Public Comments Welcome

Time is allotted during the meeting for the public to present comments to the Board and NTP staff on any agenda topic. This meeting provides another

opportunity for the public to provide input to the NTP on its vision and important elements for the roadmap. 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 contact 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 June 21, 2004, and provide their name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any). 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.

Persons may also submit written comments in lieu of making oral comments and these comments should be sent to the Executive Secretary and received by June 21, 2004, to enable review by the Board and NTP staff prior to the meeting. Written comments received in response to this notice will be posted on the NTP Web site along with other meeting information. Persons submitting written comments should include their contact information (name, affiliation, mailing address, phone, fax, e-mail) and sponsoring organization (if any) with the document.

NTP Board of Scientific Counselors

The Board is a federally chartered advisory committee comprised of scientists from the public and private sectors who provide primary scientific oversight to the NTP on its overall program and 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. The Secretary of Health and Human Services appoints members to

the Board and they are invited to serve overlapping terms of up to four years. 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: May 28, 2004.

Samuel H. Wilson,

Deputy Director, National Toxicology Program.

Preliminary Agenda: National Toxicology Program (NTP) Board of Scientific Counselors

June 29, 2004

Marriott at Research Triangle Park, 4700
Guardian Drive, Durham, NC 27703,
Hotel Telephone: 919-941-6200.

June 29, 2004

8:30 a.m. Welcome and Opening

Comments

NTP Update

NTP Vision for the 21st Century

Working Group Report on Statistical

Methods to Analyze

Photocarcinogenicity Studies

11:45 a.m. Lunch

1 p.m. Updates

NTP Studies on Trimethylolpropane

Triacrylate (TMPTA)

NTP Board's Technical Reports

Subcommittee Meeting on February

17-18, 2004

Report on Carcinogens

3:30 p.m. Closed Session*

Review and Evaluation of the

Carcinogenic Potency Database

5 p.m. Adjourn

[FR Doc. 04-12853 Filed 6-7-04; 8:45 am]

BILLING CODE 4140-01-P

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. FR-4903-N-39]

Notice of Submission of Proposed Information Collection to OMB; LOCCS Voice Response System Payment Vouchers for Public and Indian Housing Programs

AGENCY: Office of the Chief Information Officer.

ACTION: Notice.

SUMMARY: The proposed information collection requirement described below

*The closure is in accordance with the provisions set forth in section 552b(c)(4) "disclosure of commercial or financial information," (c)(6) "disclosure of information of personal nature where disclosure would constitute a clearly unwarranted invasion of personal privacy" and (c)(9) "disclosure of information of a premature nature which would significantly frustrate implementation of a proposed agency action" of Title 5 U.S.C.

has been submitted to the Office of Management and Budget (OMB) for review, as required by the Paperwork Reduction Act. The Department is soliciting public comments on the subject proposal.

HUD is requesting extension of OMB approval for the application for grant funds disbursement through the LOCCS Voice Response System.

DATES: Comments Due Date: July 8, 2004.

ADDRESSES: Interested persons are invited to submit comments regarding this proposal. Comments should refer to the proposal by name and/or OMB approval Number (2577-0166) and should be sent to: HUD Desk Officer, Office of Management and Budget, New Executive Office Building, Washington, DC 20503; fax: 202-395-6974.

FOR FURTHER INFORMATION CONTACT:

Wayne Eddins, Reports Management Officer, AYO, Department of Housing and Urban Development, 451 Seventh Street, SW., Washington, DC 20410; e-mail Wayne_Eddins@HUD.gov; telephone (202) 708-2374. This is not a toll-free number. Copies of available documents submitted to OMB may be obtained from Mr. Eddins and at HUD's Web site at <http://www5.hud.gov:63001/po/i/icbts/collectionsearch.cfm>.

SUPPLEMENTARY INFORMATION: This notice informs the public that the U.S. Department of Housing and Urban Development (HUD) has submitted to OMB, for emergency processing, a survey instrument to obtain information from faith based and community organizations on their likelihood and success at applying for various funding programs. This notice is soliciting comments from members of the public and affecting agencies concerning the proposed collection of information to: (1) Evaluate whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; (2) evaluate the accuracy of the agency's estimate of the burden of the proposed collection of information; (3) enhance the quality, utility, and clarity of the information to be collected; and (4) minimize the burden of the collection of information on those who are to respond; including through the use of appropriate automated collection techniques or other forms of information technology, e.g., permitting electronic submission of responses.

This notice also lists the following information:

**NTP Board of Scientific Counselors Meeting
June 29, 2004
Marriott at Research Triangle Park
4700 Guardian Drive, Durham, NC 27703**

8:30 AM	Introductions and Welcome	Dr. James Popp, Purdue Pharma L.P., Chair
8:40 AM	Recognition of Retiring Members	Dr. Kenneth Olden, NIEHS
9:00 AM	NTP Update	Dr. Christopher Portier, NIEHS
9:20 AM	NTP Vision for the 21 st Century <ul style="list-style-type: none"> • Board Presentation • NIEHS and Agency Presentation • Public Comments • Board Discussion 	Dr. Samuel Cohen, University of Nebraska Medical Center Dr. Christopher Portier
10:30 AM	BREAK	
10:45 AM	<ul style="list-style-type: none"> • Board Discussion 	
11:30 AM	Report on Carcinogens <ul style="list-style-type: none"> • Update on 11th Report • Nominations to 12th Report • Public Meeting January 27, 2004 • Public Comments • Board Discussion 	Dr. C. W. Jameson, NIEHS
12:15 PM	LUNCH	
1:00 PM	Technical Reports Review Subcommittee <ul style="list-style-type: none"> • Report on February 17-18 2004 Meeting • Upcoming Peer Review • Public Comments • Board Discussion 	Dr. James R. Hailey, NIEHS
1:45 PM	NTP Studies on Trimethylolpropane Triacrylate (TMPTA) <ul style="list-style-type: none"> • Public Comments • Board Discussion 	Dr. Rajendra Chhabra, NIEHS Dr. James R. Hailey, NIEHS
2:30 PM	Working Group Report on Statistical Methods for Photocarcinogenicity Studies <ul style="list-style-type: none"> • Public Comments • Board Discussion (Action) 	Dr. Walter Piegorsch, University of South Carolina

3:00 PM BREAK

3:30 PM CLOSED SESSION*
Report on Review of Carcinogenic Potency Databases
• Board Discussion

Dr. Christopher Portier

5:00 PM ADJOURN

*The closure is in accordance with the provisions set forth in section 552b(c)(4) "disclosure of commercial or financial information," (c)(6) "disclosure of information of personal nature where disclosure would constitute a clearly unwarranted invasion of personal privacy" and (c)(9) "disclosure of information of a premature nature which would significantly frustrate implementation of a proposed agency action" of Title 5 U.S.C.

NATIONAL TOXICOLOGY PROGRAM
Board of Scientific Counselors Meeting
June 29, 2004

Attachment 3

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NATIONAL TOXICOLOGY PROGRAM
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