

**NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS**
May 20, 1999
Summary Minutes

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The National Toxicology Program (NTP) Board of Scientific Counselors (the Board) met on May 20, 1999, at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. (*Attachment 1: Federal Register* meeting announcement; *Attachment 2: Agenda and Roster of Members*.) Members of the Board are Drs. Eula Bingham (Chairperson), George Bailey, Clay Frederick, George Friedman-Jimenez, Kim Hooper, Frank Mirer, John Mulvihill, Richard Peterson, Patricia Rodier, and I. Bernard Weinstein. Expert Consultant to the Board is Dr. Hiroshi Yamasaki. All were present except Drs. Mirer, Peterson and Weinstein. Additionally, there were three *ad hoc* expert consultants present to assist with the initial review of the NTP Center for the Evaluation of Risks to Human Reproduction. They were Dr. Jon Cook, Pfizer Central Research, Dr. Lynn Goldman, Johns Hopkins University School of Hygiene and Public Health, and Dr. Grace Lemasters, Department of Environmental Health, University of Cincinnati.

I. Welcome and Introduction: Dr. J. Carl Barrett, Scientific Director, NIEHS, welcomed the Board members and expert consultants on behalf of himself and Dr. Kenneth Olden, NIEHS and NTP Director, who could not be present. Dr. George Lucier, Director, Environmental Toxicology Program (ETP), NIEHS, briefly outlined the day's agenda, then presented certificates and acknowledged the contributions of retiring members of the Board, Dr. Bingham, Dr. Friedman-Jimenez, and Dr. Mulvihill. Dr. Lucier introduced the major agenda topic for the meeting, the initial review of the recently established NTP Center for the Evaluation of Risks to Human Reproduction in which we hoped to receive input from the Board that will aid in ensuring that the review activities of the Center are objective, use the best and most relevant science available, use a process that will be open and transparent, provide a product that meets the needs of Federal and state agencies and the public, and depict and identify key research areas that scientists here and around the world can use in filling data gaps identified by the Center.

II. Review of the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR):

A. Introduction to the CERHR – Background, Purpose, Status, Activities, and Website Demonstration – Dr. Michael Shelby, NIEHS, Center Director, stated that the facts of human reproductive risks are well known and cited figures to illustrate the magnitude of the problem, including that 10% of couples who desire children experience fertility problems, 50 % of pregnancies are not successfully completed, and there is a 3 to 5 % frequency of birth defects. He cited a number of risk factors and said that a key question is how much do exposures to manmade and natural chemicals contribute to these problems. Dr. Shelby said the purposes of the Center were to (1) provide scientifically rigorous, unbiased, and timely assessments of the available information on reproductive risks, (2) to present the conclusions of the Expert Panels to the scientific community, other government agencies, and the public in clearly understandable terms, and (3) to identify critical data gaps and specific research and testing needs that will allow more effective assessment of risks. The Center's products will be reports that provide consensus opinions on the strength of scientific evidence that a particular exposure poses a hazard to human reproductive health or to the health of children, which

will be published in *Environmental Health Perspectives* and the Center's web site, and will be transmitted to appropriate Federal, state and foreign health and regulatory agencies. Dr. Shelby related the history of the Center culminating in a contract award in June 1998 which became operational in October 1998 for coordinating and conducting activities of the Center. He reported that the Center is composed of scientists including himself and Dr. Gloria Jahnke at NIEHS, Dr. John Moore and Dr. Anthony Scialli at the contractor (Sciences International, Inc.) as well as support staff, a Core Committee made up of the above scientists and scientists from FDA, EPA, and NIOSH, and an expert registry which can be drawn on in forming Expert Panels. Anyone can nominate chemicals to the Center. The NTP Board has oversight responsibility for advising the Center on processes, priorities, and direction. Dr. Shelby summarized the evaluative process which primarily uses a weight of evidence approach involving scientific data and judgement and resulting in a narrative summary reflecting a consensus of the Expert Panel. He listed the diverse areas of expertise encompassed in the approximately 200 names currently found in the Expert Registry. He noted the existence of the CERHR Website (<http://cerhr.niehs.nih.gov>), which provides public access to the Center and its various activities, reports and links to related sites, as well as serving as a means of communication between the Center, Core Committee, and the Expert Panels. Dr. Shelby discussed chemicals/classes initially considered: inorganic arsenic, boric acid, di-(2-ethylhexyl)phthalate and other phthalates, ethylene glycol monomethyl ether, methanol, and nicotine/nicotinic acid. The primary chemical selection criteria for CERHR are: (1) production volume; (2) human exposure – presence in the environment or in products to which people are exposed; (3) data indicating potential reproductive or developmental toxicity; and (4) public concern about chemical/mixture exposure. Dr. Shelby reported that the first Expert Panel would be convened on August 17-19, 1999, in Alexandria, VA, to evaluate the nomination of phthalates. He would discuss this further later in the morning. Dr. Shelby concluded his presentation with a demonstration of the Website and the types of information that could be accessed.

Discussion: Dr. Hooper inquired as to sources of information for the Web and who formats this information. Dr. Shelby replied that information came from various places including the March of Dimes, Cal-EPA, *etc.*, and is prepared or adapted by Center staff. Currently, there are about 400 'hits' daily on the Website. In response to a query about epidemiological expertise, he noted that there were epidemiologists on the Expert Registry and they would be on the Expert Panels. In response to another inquiry, he 'walked' through the evaluative process for a nomination beginning with an initial evaluation by the Center office as to whether it is a valid nomination. If so, the Core Committee then would assign a priority, a brief dossier would be compiled, and if selected for evaluation, an Expert Panel would be assembled and an extensive dossier compiled. Dr. Bingham asked how an obvious reproductive toxin would be handled, eg., lead oxide. Dr. Shelby said resources would have to be expended to document why the chemical should not be studied and the information put on the Website. Dr. Barrett agreed that there would need to be peer review of the decision not to study. Dr. Frederick said that since this is a new endeavour, it would be reasonable to hold a two or three day meeting at some point to affirm all such decisions. Dr. Hooper noted that since Cal-EPA has looked at about 200 chemicals and 37 have gone through their expert peer review, it

would be useful to establish some complementarity with the Center. Dr. Shelby responded that we would hope to have a Cal-EPA representative, especially on the phthalates panel. Dr. Yamasaki stressed the need for epidemiological expertise. There was some discussion about how the Center would handle a nomination of large numbers of chemicals, e.g., 189 Clean Air Chemicals. Dr. Lucier also spoke to the differences between IARC and CERHR, especially noting that IARC reviews result in a categorical assessment while the Center's reviews will result in a narrative assessment, and further, the Center's review meetings will be open to the public. Dr. Lemasters suggested that this Website might serve like a drug or toxic substances 'hot line'. Dr. Hooper commented that there needs to be considerable input from Federal and state regulatory agencies. Dr. Bingham concluded the discussion by asking Board members, expert consultants and staff to write down their comments to aid her in preparation of a report.

B. Value of CERHR to Public Health Issues and Regulatory Agencies – Dr. Bernard Schwetz, FDA, stated that comments he would make will go beyond just the needs of the FDA to the broader field of reproductive and developmental toxicology and the needs of the public and health communities for expert advice. He said the benefits of the Center and this evaluative process fall under four main headings. First, the information conveyed would be organized and prioritized to provide a clear message. Second, the process would help move us beyond the empirical nature of how we have incorporated reproductive and developmental toxicology data in the past. Third, it should help move the whole field forward by better identifying data gaps. Fourth, it gives an example of a transparent process for providing information to the public and the health professionals who need it. Dr. Schwetz briefly commented on the value of the Center, its reviews and its products in that it – provides evaluations of important chemicals, -- provides advice to those who need to know, -- institutionalizes a process based on expert knowledge, similar to the IARC process for cancer, -- represents a benchmark for interpretation of human and animal data, particularly the question of when a subtle effect is adverse, -- will lend attention to chemicals of concern, -- is important to have the ability for identifying data gaps to guide future research, -- will help focus attention on non-cancer health concerns, -- will reinforce the importance of human exposure data, and – will serve as a bridge between the NTP and regulatory, academic and industry scientists in the area of reproductive and developmental toxicology. In conclusion, Dr. Schwetz said this has to be considered as an evolving process.

Discussion: Dr. Frederick inquired about the relationship of the Center to the FDA with regards to pharmacologic agents, in that some of the most clear cut reproductive and developmental toxicants have been therapeutic agents, e.g., DES, retinoic acid, thalidomide. Dr. Schwetz noted that there are many drugs with reproductive toxicity or carcinogenic effects approved for human use because the therapeutic benefits outweigh the risks., and it wouldn't be helpful for the Center to review these. Dr. Hooper wondered why the Center couldn't be an inhouse operation rather than being done on a contract. Dr. Shelby said the contract mechanism is an appropriate way to operate the Center, and the NIEHS does not have the four staff positions required. Intramural NIEHS staff will play a role on the Core Committee and expert panels. Dr. Lucier said

we do not have a lot of flexibility in moving monies around from contracts to inhouse without Congressional approval, and the contract mechanism has worked well in the past.

Dr. William Farland, EPA, said his agency has been supportive from the outset of the establishment of such a center, and several of their scientists have been involved in bringing the concept to fruition. First, he said the Center responds to EPA's needs for comprehensive health hazard assessment for non cancer endpoints, particularly with its focus on a narrative weight of evidence statement and focus on mechanism of action. He said there is public concern about subtle neurobehavioral effects resulting from exposures *in utero* and postnatally. Dr. Farland cited recent concerns about possible endocrine effects that have led to the Food Quality Protection Act and amendments to the Safe Drinking Water Act with specific requirements for assessing risk to the developing fetus and to children. The Center's data collection and evaluations will be helpful to meeting these requirements by producing comprehensive assessments and increasing the experience base, as well as providing a stimulus for research. He commented on the purported focus on the peer review process involving scientists from academia, industry, and public interest groups as well as government. Secondly, the use of a transparent process will be valuable in increasing public confidence in the findings and enhancing their usefulness in the regulatory process. Thirdly, Dr. Farland said EPA thinks the initiative will further both national and international harmonization to dealing with developmental toxicity and reproductive effects, strengthening efforts concerned with science policy issues and assessing risk. The Center concept has already received indications of support by international bodies such as the World Health Organization and the International Program on Chemical Safety where harmonization efforts are underway.

Discussion: Dr. Goldman thought the point on aiding international harmonization efforts to be a good one and wondered how best to promote this, perhaps by having involvement in the Core Committee or expert panels of WHO or international scientists. Dr. Mulvihill suggested that Canada should be involved as they have good data bases in the Mother Risk program and the British Columbia birth defects registry. Dr. Farland responded that members of the Core Committee are involved in harmonization efforts with the WHO, and Canada is very active in the harmonization process with WHO, and agreed that international involvement with the Center would be desirable. Dr. Yamasaki noted that IARC in its monograph meetings has a group looking at reproductive and developmental effects. Dr. Farland agreed the IARC information was useful but the value of the Center's product would be a comprehensive assessment of a limited number of chemicals.

C. Process for Evaluating Human Reproductive Risks – Dr. John Moore, Sciences International, Inc., said he would focus on the development of the evaluative process, highlight some key features, and discuss some examples. He reported that development of the process represented the effort of 10 scientists, the initial draft was put out for extensive public comment, its utility was leavened through use by experts, and resulted in three published papers in the literature on the process itself, and its use in the assessment of lithium, and boric acid/borax. Dr. Moore listed the 10 process co-authors to illustrate the diversity of expertise including epidemiology, affiliations, and international

representation. He spoke about the key features of the process beginning with its hoped for and achieved transparency. The judgments are expressed in a narrative style. It is an iterative process. It speaks to risk not just hazard, and where the level of concern may be in relation to the level of exposure. It has a summary written so it can be understood by the public, not just scientists. Dr. Moore said that with regard to transparency, the narrative will repeatedly describe what was done and the reasoning behind it, and default assumptions will be used sparingly and openly with full disclosure of the degree of certainty or uncertainty. He gave an illustration of the narrative style. Dr. Moore observed that the iterative process requires that developmental, female reproductive, and male reproductive toxicity be considered separately, and defines two principal segments in the evaluation – activities leading up to determination of relevance of the data to potential human toxicity, and if so, then determination of a quantitative expression of risk. Dr. Moore said that relevance of the data to potential human toxicity proceeds through parallel reviews of the literature and summary conclusions on five areas: (1) human reproductive data; (2) animal reproductive data; (3) general toxicity data; (4) pharmacokinetics; and (5) mechanisms. To assess relevance to human toxicity, one integrates the parallel summaries to obtain a weight-of-evidence speaking to such things as: (1) replication of effect within and across species; (2) routes of exposure; (3) dose-response parameters; (4) relationship of the effective dose to other forms of toxicity; (5) comparative metabolic data; and (6) concordance of biological processes. Dr. Moore discussed the degrees of relevance to humans, and terms associated with determination of a quantitative expression of risk. He concluded his presentation by speaking to critical data needs such that evaluations may identify data as – insufficient for forming judgments, or – compromised leading to uncertainty in judgment. Further, specific data needs are cited if such data are held to materially improve the certainty of an existing judgment, or permit the rendering of an initial judgment.

D. Nominations Considered and Selection of Phthalates – Dr. Shelby said he would discuss further the first group of chemicals selected for evaluation by the Center – seven of the phthalates, noting that the evaluative process described by Dr. Moore would be used by the expert panel in assessing potential human reproductive toxicity. Dr. Shelby noted that the process as described would not necessarily be followed step by step, as the process itself will continue to evolve with use. He acknowledged the considerable efforts of NIEHS scientists in the first two evaluations – lithium and boric acid/borax. Dr. Shelby briefly described the rationale for the seven phthalates: (1) di(2-ethylhexyl) phthalate (DEHP) is a clear reproductive toxicant in rodents and accounts for about 50% of phthalate use in plastics; (2) butyl benzyl phthalate; (3) di-n-butyl phthalate; (4) di-n-hexyl phthalate, (2), (3), and (4) all have some evidence of reproductive and/or developmental toxicity in rodents and are believed to have a similar mode of action as DEHP); (5) di-n-octyl phthalate is included to provide structure-activity comparisons to the other shorter chain or branched chain phthalates; and (6) di-isononyl and (7) di-isodecyl phthalates have widespread use in consumer products, notably in childcare products and toys. Dr. Shelby listed the names, affiliations, and expertise/assignments of the phthalates expert panel which will be chaired by Dr. Robert Kavlock, EPA. He emphasized that there are related activities on health effects of phthalates, and reported that the Consumer Product Safety Commission had recently released a study on the risk

of chronic toxicity associated with exposure to diisononyl phthalate in children's products, and was convening a chronic hazard advisory panel to study chronic toxicity and cancer risk associated with this phthalate in children's products. The American Council on Science and Health has recently convened an expert panel to review the safety of vinyl plastic consumer products and medical devices containing phthalate esters. Further, he said there were similar activities going on in Canada, and they may be able to provide input to the NTP expert panel.

Discussion: Drs. Friedman-Jimenez and Mulvihill commented that there was insufficient epidemiological expertise on the phthalates expert panel – in fact, only one epidemiologist. Dr. Goldman stated that before an expert panel is put in place, there needs to be an alerting of the epidemiology community so that there is an opportunity for epidemiologists to step forward. Dr. Frederick noted that there was only representation by U.S. scientists on the panel, and perhaps foreign participants could be identified. Dr. Shelby responded that additional experts could still be added to the panel.

E. Discussion and Public Comments – Dr. Bingham requested that there be a free wheeling discussion on the Center and especially on the evaluative process. She said she had heard the term “quantitative risk assessment” referred to, and thought this was beyond the purview of the Center. Dr. Barrett said that what had been described was a process but we wanted comments from the Board to help in deciding on the process for assessing human reproductive risk. Dr. Moore emphasized that the process would not categorize but rather provide a narrative statement. Dr. Frederick commented that he was comfortable with Dr. Moore's discussion on quantitative expression including measures of effect or no effect, levels of exposure, etc., but was discomfited by his inclusion of “uncertainty factors”. Dr. Goldman agreed that there was a difficulty within the government among agencies in agreeing on such factors, a recent example being risk evaluation of methyl mercury. Thus, it becomes important to include where possible, bench mark doses (BMD) and/or no adverse effects levels (NOAEL). Dr. Lucier cautioned that it would not be a purpose of the Center to conduct a quantitative risk assessment but it would be important to assess, if not factors, certainly areas or sources of uncertainty, such as was the case with the methyl mercury workshop. Dr. Moore said the Expert Panel's job would be easier if they did not have to grapple with uncertainty or safety factors. Dr. Bingham expressed concern about the use of unlikely effect levels (UEs). Dr. Cook opined that a key to success of the evaluative process hinges on selection of the right experts and areas of expertise for the Expert Panel. Also, the process for outreach to the public needs to be better defined, just having a Website perhaps is not enough. Dr. Mulvihill questioned the transparency of the process in that a number of stakeholders do not seem to be represented on the proposed phthalates Expert Panel, e.g., consumer representatives, President of the Teratology Society. Dr. Friedman-Jimenez noted a lack of community group representation, and suggested that Partnership for Communication grants that have been awarded by the NIEHS for the last several years might draw on community based organizations, research organizations, and practicing physicians to nominate or identify potential reproductive toxicants from an affected community perspective. Dr. Frederick said more intensive use of the Website might reach some of these people that are not reached by the *Federal Register*. Dr.

Rodier observed that the panels are formed on the basis of information available about a nomination and not on the basis of what is not known, thus this latter aspect should enter into selection of members. Dr. Barrett pointed out that the core group picks the members. Dr. Hooper wondered if this first panel could serve like a pilot project for assessing whether the expertise involved and the public input are adequate and diverse enough. Dr. Lucier emphasized that these Expert Panel meetings are open, space permitting, and written comments can be submitted prior to the meeting. He sees this as an evolving process and stated that NTP would come back to the Board next year to report on how the process is working.

Public Comments: Dr. Raymond David, Eastman Kodak, representing the Chemical Manufacturers Association Phthalate Esters Panel (PE Panel), reported that coming from over 25 years of research on phthalate esters, the PE Panel had provided unpublished and published data to the Center in belief that there would be an open dialogue. He said they had three specific concerns: (1) too many substances are under review – inadequate time is allocated for thorough review of seven esters, and esters with known reproductive/developmental effect are lumped with those lacking such effects; (2) the conclusions should be clearly dictated by sound science and not influenced by perceived political expectations; and (3) the process should be opened to allow for scientific dialogue including opportunities to provide input on the monograph before publication.

Dr. Phillip Leber, Goodyear Tire and Rubber Company, concurred with previous discussion that some of the most knowledgeable scientists regarding phthalates research and testing are in industry and this expertise should have a place on the Expert Panel. He said that the CMA could recommend an appropriate scientist. Dr. Hudson Bates, Nickel Producers Environmental Research Association (NiPERA), wanted to address the issue of transparency, which needs to be a give and take rather than a one way process whereby scientifically qualified individuals can participate in the process.

Further Discussion: Dr. Frederick wondered why there could not be one or two non-voting representatives on the Panel. Dr. Lucier responded that at this point in time most anything reasonable is possible, and certainly, petitions could be accepted for additions to the group. Dr. Friedman-Jimenez spoke to the concern that having too many phthalates to review might blur distinctions among them., but rather it would be a useful exercise to enable clarifying the distinctions. Dr. Farland commented on the issue of transparency by sharing EPA's experiences with expert panels in drawing on public input early in the review process. Dr. Goldman stated that it is essential that both industry and public interest groups have input but expressed reservations about the IARC process where she felt industry has too strong a role making it difficult for other nongovernmental groups to be a part. Dr. Lemasters said she would like to see in the evaluative process patterns of exposure associated with disposal of products that contain phthalates and whether there were links with EPA that could be exploited. She thought persons with expertise in environmental/occupational exposures should be considered for the Panel. Dr. Farland reported that an exposure expert from EPA had been involved in a pilot evaluation process. He commented that people may be exposed to more than one phthalate at a time so mechanistic studies looking at possible additive or synergistic effects could be

important. Dr. Frederick spoke to the need for industry representation from the standpoint of drawing on toxicological/exposure assessment expertise that is there and not political or legal types of representation. Dr. Bingham said there needed to be an avenue for community input regarding personal exposures, and this could be as testimony before the Panel. Dr. Bingham summarized the discussion by stating that she would prepare a report to the NTP following the meeting incorporating written and verbal critiques from Board members and expert consultants. Further, she thought it would be appropriate for the Board to move a statement expressing support for the Center. Dr. Hooper moved that the NTP Board of Scientific Counselors approve the continuation of the NTP Center for the Evaluation of Risks to Human Reproduction and applauds the effort. Dr. Frederick seconded the motion, which was accepted unanimously by the Board.

In further discussion, Dr. Hooper handed out a lengthy listing of chemicals classified since 1986 by the State of California as developmental toxins, and male and female reproductive toxins. Dr. Goldman noted that she was with the state of California when many of the chemicals were listed, and pointed out that pharmacologic agents dominate the list as there was so much toxicologic information available to aid in listing, much coming from the FDA. Dr. William Allaben, NCTR/FDA, said the FDA had some regulatory responsibility for phthalates and proposed that a regulatory agency scientist be added to the Panel. There was some further discussion about the contract mechanism and possible role of contractor scientists with regard to science policy issues. Dr. Lucier stated that it was the NTP's responsibility for the evaluations that are derived by the Center, and for any policy recommendations. Dr. Mulvihill recommended that there be a brief update on the Center and the progress of its evaluations at the next Board meeting. Dr. Lucier responded that there would be more than that since a responsibility of the Board would be ongoing oversight of the Center.

III. Process for Development of a Year 2000 White Paper on Toxicology and the NTP:

Dr. Lucier said there has been considerable thought and discussion within and without the Program as to where the NTP should be going and what should be its priorities in the new millenium that is fast approaching. He said that we are in the early stages of developing a White Paper, with nothing drafted yet, and need input from the Board and others to help us. Much of the current activities and initiatives are summarized in a program booklet sent to members prior to the meeting. The Center for the Evaluation of Risks to Human Reproduction is one of these initiatives. To provide a framework for the discussion, Dr. Lucier summarized and gave examples of the four primary goals of the NTP, being (1) to provide toxicological evaluation on substances of public health concern, (2) to develop and validate improved methods, (3) to develop methods, approaches and generate data to strengthen the science base for risk assessment, and (4) to communicate with all stakeholders. Dr. Lucier noted that the NTP was an interagency program headquartered at NIEHS with policy oversight provided through the NTP Executive Committee, comprised of the heads of the various Federal health research and regulatory agencies or their designates. He reviewed the provision of scientific oversight by the Division of Intramural Research Board of Scientific Counselors and the NTP Board and its two subcommittees, as well as the recently established Advisory Committee for Alternative

Toxicological Methods (ACATM), noting that there would be progress reports from the subcommittees and the ACATM later in the day. Dr. Lucier described some of the current activities and initiatives, noting that the centerpiece was mechanism-based toxicology, and gave examples. He emphasized the continuing effort pertaining to human studies with two recent hires, one an epidemiologist to assist with the *Report on Carcinogens* and study design teams, and the other a toxicologist to coordinate exposure assessment activities. He spoke of activities in risk assessment methodology under the direction of Dr. Christopher Portier with a focus on development of biologically-based models. Dr. Lucier said that a newer thrust has to do with ecological effects and the human common ground, noting that toxicity in wildlife may have implications for human health, e.g., malformed frogs, pfiesteria, and endocrine disruptors. He reviewed high priority agents under study, including drinking water disinfectants, herbal medicines, natural products, electric and magnetic fields (EMF) (with a final report to Congress forthcoming), environmental estrogens, dioxins and dioxin-like compounds, cosmetics, and mixtures. Dr. Lucier mentioned recently established NTP centers including the Center for the Evaluation of Risks to Human Reproduction, the Center for the Evaluation of Alternative Toxicological Methods, and most recently a phototoxicity center at NCTR which will allow evaluation of cosmetics and other substances where phototoxicity may be relevant. He reported on our activities related to the *Report on Carcinogens*, partnerships with stakeholders, the use of RO3 grants, and numerous conferences and workshops.

Dr. Lucier turned to a discussion of the proposed process for development of a White Paper on NTP priorities and strategies in the new millennium. He said the first step would be today's discussion with the Board. Then an announcement will be put out asking for public comments on the process. Dr. Lucier said he envisioned a series of meetings where there could be dialogue with various stakeholders that would include NIEHS grantees, industry, public and professional organizations, labor, state public health and environmental officials, the Society of Toxicology and perhaps the American Public Health Association, and the NTP Executive Committee and other Federal agencies. Following these meetings, a draft White Paper would be prepared, and further review and comment would be sought from stakeholders and the public. Then, the Board would receive the draft along with public comments for review. Finally, the final White Paper would be prepared, published and disseminated.

Discussion: Dr. Goldman suggested that one or two public workshops also be considered. Dr. Lucier noted the series of NIEHS town meetings around the country and thought these might be a possible venue. Dr. Bingham agreed and wondered how NTP would proceed. Dr. Lucier responded that we needed advice about this and whom to invite from various stakeholder groups from those around the table and others with whom we work. One aim would be to identify possible areas of overlap and duplication. Dr. Hooper said he hoped there would be input sought from within NIEHS and other NTP agencies as to what priorities should be. Dr. Lucier agreed and asked Dr. Hooper's advice on how best to engage state health officials. Dr. William Allaben, NCTR/FDA, pointed out that there are mechanisms within the agencies for discussion and input to be received, such as the NTP Steering and Executive Committees. Dr. Mulvihill, referring more specifically to the CERHR, suggested the National Institute of Child Health and Human

Development (NICHD) be considered as a partner. Dr. Mulvihill commented that other types of grants besides RO3s might be considered and also some thought needed to be given to training.

IV. Concept Reviews:

Rodent Disease Diagnostic Laboratory -- (Attachment 3) Dr.G. N. Rao, , NIEHS, presented the concept, and Dr.Frederick, Board Member, served as principal reviewer. Dr. Rao said that this was a support service for which we do not have a laboratory or other inhouse resources so the Program has to depend on a contract to provide information for control and prevention of disease in NTP studies. The purpose of this contract is monitor the microbial status and health status of the animals, investigating any disease conditions that might appear in production colonies and animals we supply, and monitoring ongoing studies through use of sentinel animals for viral and bacterial infections and other diseases. This resource has been in place since 1984, and has helped control and prevent viral infections in the NTP studies. By 1992, all of the NTP studies were free of known infections. Dr. Rao said that through this contract we do comprehensive health evaluations of all the animals produced in the colonies, which gives us a handle on types of opportunistic infections we may need to follow and control, e.g., *Helicobacter* species. The current contract has a small component for improving the reagents and diagnostic procedures. Dr.Rao concluded that this resource is necessary not only to identify and document disease status of NTP rodent studies but also to prevent infections in the future. Dr. Frederick spoke to concerns about studies for which interpretation was compromised by *Helicobacter*. Dr. Rao said there were two studies in 1988 and several in 1990 that were affected, but since 1991 all colonies have been free of *Helicobacter* infections. In response to a question by Dr. Frederick, Dr. Rao gave assurance that the newest diagnostic methodologies are being used. Dr. Frederick moved that the concept proposal be approved. Dr. Bailey seconded the motion, which was approved unanimously by the Board.

Genetic Monitoring of Inbred Rodents -- (Attachment 3) Dr. Rao presented the contract, and Dr. Frederick served as principal reviewer. Dr. Rao said this resource was established in 1983 to provide genetic monitoring of inbred stocks at the rodent production centers, and is necessary to maintain the genetic integrity of the rodent production colonies as well as animals supplied for toxicity and carcinogenicity studies. The NIEHS does not have inhouse capabilities. Dr. Rao related the history and early problems with genetic variants. The genetic integrity of inbred rodents are evaluated by skin grafting to detect genetic drift due to fixed mutations, and strain homogeneity is assured through biochemical markers. Dr. Rao reported that we are evaluating DNA-based markers for complementing biochemical and immunologic markers. Dr. Frederick observed that monitoring was for a very rare event, and few if any of the biochemical markers used related to chemical carcinogenesis, the toxicological endpoint of concern. He was concerned that the most current technology was not being used. Drs. Yamasaki and Mulvihill supported the use of DNA-based (microsatellite) technology. Further, Dr. Mulvihill proposed convening a one-day workshop involving other major breeders to resolve the efficacy of the various methodologies. Dr. Jeffrey Everitt, Chemical Industry Institute of Toxicology (CIIT), opined in response to Dr. Frederick that microsatellite

methods were the wave of the future and saw skin grafting as a backup or second tier confirmation. Dr. Everitt noted that a commercial organization presented methods for sale for microsatellite markers at the 1998 AALAS annual meeting. Dr. Rao stated that in discussions with Jackson Laboratories they had agreed that skin grafting was still the best method for detecting genetic inhomogeneity, and he anticipated further discussions with Jackson Laboratories and the NCI. He commented that the microsatellite markers are from sequences of the genome not coding for any biologically significant molecules. Dr. Frederick moved to approve and support the concept with the provision that the Program actively pursue genomic methods as substitutes for biochemical methods. Dr. Mulvihill seconded the motion, which was accepted unanimously by the Board.

V. Investigation of Causes for Amphibian Malformations:

Dr. James Burkhart, NIEHS, stated that when we first learned of the problem there was an awareness that multiple factors could be involved including UV radiation, disease, predation, etc. Therefore, there were three questions to be resolved: (1) is the anecdotal evidence for an increased incidence of frog malformations scientifically valid?; (2) are there factors that cause the malformations in the aquatic environment?; and (3) can causal factors be identified and what is their hazard to human and environmental health? Dr. Burkhart said the first step was to verify the anecdotal findings, the second to make best use possible of diagnostics on the animals taken from the field, the third was to determine whether there was an association between water and a marker for developmental abnormalities, the fourth was characterization of anything identified as an association, the fifth was to try and identify specific agents, and sixth whether we could reconstruct anything that could be compared with the diagnostics. Dr. Burkhart reported that field verification studies indicate: -- there has been a dramatic increase in frequency of abnormal frogs, -- there are differences in malformation rates between sites in Vermont and Minnesota, -- there are differences in malformation rates between species within sites, -- malformation rates can change for individual sites, and -- malformed frogs are almost exclusively first year metamorphs. He noted that diagnostic studies indicate that multiple limbs are a minor proportion of the malformations, trematode cysts are distributed between normal and abnormal frogs, malformations are observed in early life stages before trematodes enter, and there can be multiple and disrupted limb buds. With regard to association, he pointed out that many water and sediment samples from affected sites can malform *Xenopus* and *Rana* embryos in the absence of UV and microorganisms. Dr. Burkhart reported that the characterization studies indicate: -- toxicity can be extracted and recovered by solid phase chromatography, -- there is likely disruption of the thyroid axis and neural patterning, -- activity of toxic fractions can be potentiated by non toxic fractions from affected and unaffected sites, and -- the water matrix may influence, but is not sufficient to account for malformations seen in the lab or field. Dr. Burkhart stated that attempts to identify specific agents suggest that: -- there is no striking common chemical or metal contaminant, -- specific agents can be associated with affected sites when compared to reference sites, -- factors with similar activities may be interacting with complex mixtures, and -- native water conditions may alter toxicity of compounds. With regard to reconstruction, he said that abnormalities similar to that seen in field samples have been induced in adult frogs using fractions and compounds identified in field samples. Dr. Burkhart said that current conclusions are that: (1)

chemical agents in the aquatic environment are contributing to amphibian malformation and decline; (2) endocrine/retinoid/thyroid activities contribute to developmental disruption; (3) toxicity is enhanced by mixtures of manmade and natural compounds; and (4) although risk is uncertain, similar effects may be possible in higher animals or humans. He ended by acknowledging the importance of the interactions among state and Federal agencies and industry.

VI. Center for the Evaluation of Alternative Toxicological Methods -- Update:

Dr. William Stokes, NIEHS, said the Interagency Center was an initiative that began just over a year ago. He described the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), established in May 1997 and representing 14 Federal regulatory and research agencies, whose purpose is to coordinate issues on development, validation, acceptance and harmonization of test methods, communicate with test developers, review test methods of multi-agency interest, and provide recommendations to agencies. The Center serves to provide operational/technical support for ICCVAM and ICCVAM-related activities, administer test method peer reviews and workshops, disseminate information, and communicate with stakeholders. Dr. Stokes said the goal of ICCVAM and the Center is to promote the scientific validation and regulatory acceptance of new test methods that (1) are more predictive of human and ecological effects than current methods, and (2) refine, reduce, and replace animal use where scientifically feasible. Using a flow diagram, he went over the ICCVAM test method review process, noting that two methods have been reviewed during the past year. Within this process, the Center office serves to prescreen nominations before forwarding to ICCVAM. Dr. Stokes discussed the first method evaluated by this process, the Murine Local Lymph Node Assay (LLNA), for which recommendations have been sent to the agencies. The LLNA is a mouse-based method for determining allergic contact dermatitis potential of chemicals. It was developed by a scientist at Zeneca, and further developed with scientists at Unilever and Procter and Gamble. The method was evaluated by an ICCVAM Peer Review Panel in September 1998 and the final report was released in February 1999. The Peer Review Panel evaluated the extent to which the submission addressed validation and acceptance criteria, and developed a consensus on the usefulness and limitations of the LLNA as a stand-alone alternative to current assays for allergic contact dermatitis. The consensus was the LLNA was useful as a stand-alone assay with the exception of a few types of chemicals. The advantages were cost-effectiveness, time savings, readily transferable between laboratories, and future improvements were possible. Further, from an animal welfare viewpoint, the assay uses fewer animals, does not use irritating adjuvants, and does not involve the elicitation of clinical signs that may cause discomfort. Due to time constraints, Dr. Stokes deferred discussion of Corrositex®, an *in vitro* method for assessing dermal corrosivity, that is currently under review.

VII. NTP Board Subcommittee Updates:

A. Report on Carcinogens Subcommittee -- Dr. C. W. Jameson, NIEHS, provided an update on the review of 11 nominations for the 9th *Report on Carcinogens* (RoC) by the Board's RoC Subcommittee on December 2-3, 1998. The nominations and Subcommittee recommendations are as follows: (1) Alcoholic Beverage Consumption

was recommended for listing as a *known to be human carcinogen*; (2) Boot and Shoe Manufacture and Repair was recommended for deferral of action because of the lack of exposure assessment information; (3) Diesel Exhaust Particulates were recommended for listing as *reasonably anticipated to be a human carcinogen*; (4) Environmental Tobacco Smoke was recommended for listing as a *known to be human carcinogen*; (5) Ethyl Acrylate was recommended for delisting from the Report based on mechanistic considerations; (6) Ethylene Oxide was recommended for upgrading to a *known to be human carcinogen*; (7) Isoprene was recommended for listing as *reasonably anticipated to be a human carcinogen*; (8) Methyl-t-Butyl Ether was recommended not to be listed in the Report as *reasonably anticipated to be a human carcinogen*; (9) Nickel Compounds were recommended for upgrading to *known to be human carcinogens*; (10) Silica, Crystalline (Respirable Size) was recommended for upgrading to a *known to be human carcinogen*; and (11) 2, 3, 7, 8-Tetrachlorodibenzo-p-Dioxin (TCDD) was recommended not to be upgraded to a *known to be human carcinogen*. These 11 along with 13 nominations that completed scientific review by the Subcommittee in October 1997 constitute the 24 nominations reviewed for possible listing in or delisting from the 9th RoC. These nominations were also reviewed by the NTP Executive Committee and are awaiting final decisions by Dr. Olden, NTP Director, prior to submitting the 9th RoC to Secretary Shalala, later in the summer. Dr. Jameson reported that the NTP has 11 nominations for review by the Subcommittee in December 1999 for possible inclusion in the 10th RoC, projected for publication in 2001. The nominations are: Beryllium and Beryllium Compounds; 2,2-Bis-(Bromomethyl)-1,3-Propanediol (technical grade); 2,3-Dibromo-1-Propanol; Dyes Metabolized to Dimethoxybenzidine; Dyes Metabolized to Dimethylbenzidine; IQ (2-Amino-3-Methylimidazo[4,5-f] quinoline); Styrene-7.8-Oxide; Toluene Diisocyanate (~~delist~~); UV Radiation (UVA, UVB, UVC); Vinyl Bromide; and Vinyl Fluoride. Dr. Jameson said that a *Federal Register* announcement had been published asking for public comments on these nominations.

Discussion: Dr. Hooper, a member of the Subcommittee, stated that the workload prior to the meeting was somewhat overwhelming especially with the number of difficult and complex nominations, and wondered if this would be the case with the next round of nominations. Dr. Jameson said they hoped to balance the complex nominations over the two rounds of review for the 10th RoC, and thought there were only two difficult/complex nominations for the December meeting. Dr. Hooper asked if more thought had been given to obtaining more balanced public input. Dr. Jameson commented that the aim was to get the background documents sent out to the Subcommittee and public six weeks ahead of the meeting and to then cut off written public comments two weeks prior to the meeting. Dr. Lucier added that to allow more opportunity for comments on process and other issues concerning the RoC, the NTP is considering holding a stakeholders meeting in Washington, D.C. in mid-September 1999.

B. Technical Reports Review Subcommittee -- Dr. John Bucher, NIEHS, reported that two meetings of the Subcommittee had taken place since the last Board meeting, and one meeting would take place tomorrow (May 21). The Subcommittee met on March 11, 1998, to review long-term rodent studies on electric and magnetic fields (EMF) at 50 and 60-Hertz and several gauss levels, and 13- and 26-week mammary gland

initiation/promotion studies of EMF with DMBA. With the exception of *equivocal evidence of carcinogenic activity* in male rats, there was *no evidence of carcinogenic activity* in the long-term studies, and there was no evidence that magnetic fields promoted development of mammary gland neoplasms.

The Subcommittee met on October 30, 1998, to review 2-year bioassays on five chemicals. Inhalation studies with 2-butoxyethanol resulted in *equivocal evidence* in female rats, and *some evidence* in male mice (liver) and female mice (forestomach). Inhalation studies of glutaraldehyde at quite low doses resulted in *no evidence* in rats and mice. Gavage studies of methyleugenol resulted in *clear evidence* in male rats (liver, glandular stomach, and several other sites), in female rats (liver, glandular stomach), in male mice (liver, glandular stomach), and in female mice (liver). Gavage studies with oxymetholone gave *equivocal evidence* in male rats and *clear evidence* in female rats (liver, lung, skin). Dermal studies with triethanolamine had been peer reviewed previously but due to its being the first study shown to be contaminated with *Helicobacter* it was rereviewed.

Dr. Bucher reported on the four reports to be peer reviewed the next day. Anthraquinone, the parent for seven compounds that have gone through bioassays, is proposed to be a potent carcinogen, while emodin, an anthraquinone derivative, is proposed to be weakly or not carcinogenic at all. Fumonisin B, a mycotoxin found in corn, was the first chemical to be reported under the NIEHS/FDA Interagency Agreement and studied at NCTR, and gave *clear evidence* in male rats (kidney) and female mice (liver). Gallium arsenide by inhalation resulted in *clear evidence* in female rats (lung, adrenal medulla, mononuclear cell leukemia) but *no evidence* in male rats and male and female mice.

AGENDA
NATIONAL TOXICOLOGY PROGRAM (NTP)
BOARD OF SCIENTIFIC COUNSELORS

May 20, 1999

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

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

8:45 – 9:15 a.m.	Welcome and Introduction	Dr. C. Barrett, NIEHS Dr. G. Lucier, NIEHS
9:15 – 10:00 a.m.	Introduction to the CERHR – Background, Purpose, Status, Activities, and Website Demonstration	Dr. M. Shelby, NIEHS
10:00 – 10:30 a.m.	Value of CERHR to Public Health Issues and Regulatory Agencies	Dr. B. Schwetz, FDA Dr. W. Farland, EPA
10:30 – 10:45 a.m.	<i>Break</i>	
10:45 – 11:15 a.m.	Process for Evaluating Human Reproductive Risks	Dr. J. Moore, Sciences International, Inc.
11:15 – 12:00 p.m.	Nominations Considered and Selection of Phthalates	Dr. M. Shelby
12:00 – 12:45 p.m.	Discussion and Public Comments	The Board
12:45 – 1:30 p.m.	<i>Lunch</i>	
1:30 – 2:15 p.m.	Process for Development of a Year 2000 White Paper on Toxicology and the NTP	Dr. G. Lucier
2:15 – 2:40 p.m.	Concept Reviews: -- Rodent Disease Diagnostic Laboratories -- Genetic Monitoring of Inbred Rodents	Dr. G. Rao, NIEHS
2:40 – 3:00 p.m.	<i>Break</i>	
3:00 – 3:20 p.m.	Investigation of Causes for Amphibian Malformations -- Update	Dr. J. Burkhardt, NIEHS
3:20 – 3:40 p.m.	Center for the Evaluation of Alternative Toxicological Methods – Update	Dr. W. Stokes, NIEHS
3:40 – 4:15 p.m.	NTP Board Subcommittee Updates -- Report on Carcinogens Subcommittee	Dr. C. W. Jameson,
NIEHS		
	-- Technical Reports Review Subcommittee	Dr. J. Bucher, NIEHS
Adjourn		

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Environmental Toxicology Program
Division of Intramural Research
National Institute of Environmental Health Sciences

CONCEPT REVIEWS

Prepared for:

National Toxicology Program
Board of Scientific Counselors

May 20, 1999

CONCEPT REVIEWS

National Toxicology Program
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BACKGROUND ON CONCEPT REVIEWS

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

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

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

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

- a. scientific, technical or program significance of the proposed activity;
- b. availability of the technology and other resources necessary to achieve required goals;
- c. extent to which there are identified, practical scientific or clinical uses for the anticipated results; and
- d. where pertinent, adequacy of the methodology to be used in performing the activity.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONTRACT TITLE: Rodent Disease Diagnostic Laboratory

PROJECT OFFICER: Ghanta N. Rao, (919) 541-7899

OBJECTIVE: To continue to provide rodent disease diagnostic services to the rodent production colonies and the toxicity and carcinogenicity studies. This Project/Contract is necessary 1) to maintain the microbial quality of animals supplied for the studies, 2) to document the infection and disease status of the animals during the course of the studies, and 3) to implement procedures to control and prevent infections and diseases in the production colonies and the toxicity and carcinogenicity studies.

CONCEPT STATEMENT: Centralized colonies of rodents with homogeneous genetic properties and defined health profiles ensure an adequate and continuous supply of defined quality animals for the toxicity and carcinogenicity studies. It is necessary to perform rodent disease diagnostic procedures to characterize infection and disease status of animals prior to and during the toxicity and carcinogenicity studies. Infection and disease status information is necessary for interpretation of studies and to implement control and preventive measures for future studies.

This contract/project will provide rodent disease diagnostic laboratory services for monitoring the microbial status and health status of the animals and for investigating any disease conditions that might appear. Animals from the production colonies are examined for pathogenic microorganisms and parasites. These evaluations include pathologic examination of selected tissues for microbial and parasitic lesions. Serum samples from sentinel animals in the toxicology studies are evaluated for viral antibody profiles. In addition, sentinel animals and tissues from animals on studies are evaluated for microbial or parasitic disease conditions. This program is necessary to ensure the production of disease-and-infection free rodents and to maintain the toxicity and carcinogenicity studies free of infections and diseases.

PROPOSED CHANGES TO THE CURRENT STATEMENT OF WORK: There are no substantial changes to the Statement of Work. However, the Statement of Work is revised to update the pathogenic agents and diagnostic procedures for some agents.

NATIONAL TOXICOLOGY PROGRAM CONCEPT REVIEW

CONTRACT TITLE: Genetic Monitoring of Rodents
PROJECT OFFICER: Ghanta N. Rao, (919) 541-7899

OBJECTIVE: To continue to provide genetic monitoring of inbred stocks at the rodent production centers. This contract is necessary to maintain the genetic integrity of the rodent production colonies as well as the animals supplied for toxicity and carcinogenicity studies.

CONCEPT STATEMENT: This project provides genetic monitoring to assure the genetic integrity of inbred F344/N rats, B6C3F1 hybrid mice and other strains of rodents produced for the NTP studies. Genetic loci are being monitored by electrophoresis of erythrocyte lysates, kidney homogenates and serum proteins to detect contamination, back-crossing and mutations. The genetic integrity of inbred rodents is also being evaluated by skin grafting to detect genetic drift due to fixed mutations. In addition, kidneys from B6C3F1 hybrid mice received at the study laboratories are being evaluated for biochemical markers by electrophoresis to assure that the mice used for the NTP studies are B6C3F1 hybrid. Constant monitoring for biochemical genetic variants and fixed mutations of foundation and production stock and test animals will ensure that data from NTP animal studies are collected from genetically homogeneous rats and mice.

PROPOSED CHANGES TO THE CURRENT STATEMENT OF WORK: **None.** However, when procedures are established to monitor a large number of DNA based markers by RFLP, SSLP, etc..., such procedures may be added instead of or in addition to biochemical markers and skin grafting procedure to detect fixed mutations.