National Toxicology Program
Board of Scientific Counselors
Technical Reports Review Subcommittee

August 28, 2006

NIEHS, Research Triangle Park, NC

Summary Minutes

Contents **Page Number**

Attendees

Members:
Diane Birt, Iowa State University
Prescott Deininger, Tulane University
John Giesy, Michigan State University
Charlene A. McQueen (chair), University of Arizona
Jon Mirsalis, SRI International
Harish Sikka, State University of New York at Buffalo
Keith Soper, Merck Research Laboratories
Vernon Walker, Lovelace Respiratory Institute

NIEHS Attendees:
Charles Alden
Jack Bishop
John Bucher
Rajendra Chhabra
Allen Dearry
June Dunnick
Susan Elmore
Paul Foster
John (Jef) French
Ronald Herbert
William Jameson
Angela King-Herbert
Grace Kissling
David Malarkey
Denise Orzech
Joseph Roycroft
Barbara Shane
Robert Sills
BP Singh
Cynthia Smith
Molly Valant
Samuel Wilson
Kristine Witt
Mary Wolfe
Michael Wyde

Agency Attendees:
Julian Leakey, FDA
Mark Toraason, NIOSH

Public Attendees:
Susan Borghoff, ILS
Louise Fitzgerald, University of Sidney
Diane Gerken, Battelle Science and Technology
Glenda Moser, ILS
John Peckham, Experimental Pathology Laboratories
Kristie Stoick, PCRM
Kimberly Weber, University of Illinois

Transcriptionist:
Kay Rodhe

Peer Review Meeting

The meeting began at 8:30 a.m. on August 28, 2006, in the Rodbell Conference Center of the David P. Rall Building, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. John French, NIEHS, provided an overview of the development of the genetically modified mouse models (Tg.AC, p53 and p16/p19 knockout mice) used in the studies being reported. He outlined the series of criteria that these models should meet to make them useful for short-term studies of about six months. These include decreased latency, low incidence of sporadic tumors, broad range of susceptible tissues but with specific organotrophic responses, a low range of false negative responses, and mechanisms of response similar to those known for human cancer.

Allyl Bromide

Dr. June Dunnick, NIEHS, introduced the studies of allyl bromide in p53 and Tg.AC mice by describing the uses of the chemical, the study rationale, the details of the study design and dose selection, and the results of the histopathologic examination of the animals. The proposed conclusions were:

> Under the conditions of this study, there was *no evidence of carcinogenic activity* in male or female p53 haploinsufficient mice administered allyl bromide at 0.5, 1, 2, 4, or 8 mg/kg per day by corn oil gavage, 5 days a week for 40 weeks.
>
> There was a marginal increase in the incidence of squamous cell papillomas, primarily of the vulva, in female Tg.AC mice administered allyl bromide by corn oil gavage for 40 weeks.

Dr. Giesy, the first principal reviewer, did not have any scientific criticisms and felt the report presented the results clearly, and he agreed with the conclusions. He questioned the statement that allyl bromide was negative in all the studies when it was found to be mutagenic in *Salmonella typhimurium* TA100 and asked for further discussion of this finding. He said the interpretation of the data specific to allyl bromide in the transgenic model is limited because of the small database of chemicals tested in these models.

Dr. Mirsalis, the second principal reviewer, questioned the decision to perform a gavage study in the FVB/N mice at doses that showed no effect in a pilot dermal study. He suggested more explanation of the rationale for the design of that study. He felt the other studies were valid and agreed with the conclusions.

Dr. Sikka, the third principal reviewer, suggested additions to the diagram of the metabolic pathway and asked if an explanation could be given for why the chemical was mutagenic in the absence, but not the presence of metabolic activation. He suggested that

a comparison of the data in transgenic and non-transgenic mice be included in the discussion.

Dr. Dunnick replied that the discussions of mutagenicity and the description of study design would be amplified. She noted that oral gavage was the route of choice for all the genetically modified mouse model studies.

Dr. Mirsalis moved, and Dr. Giesy seconded, that the conclusions be accepted as written. The motion was approved unanimously (7 yes, 0 no, 0 abstention votes).

Dicyclohexylcarbodiimide

Dr. Rajendra Chhabra, NIEHS, introduced the studies of dicyclohexylcarbodiimide by describing the uses of the chemical, its nomination, and the previous NTP studies on related carbodiimides, the protocol and dose selection for the studies of dicyclohexylcarbodiimide in genetically modified mice; the survival, clinical pathology, and reproductive and histopathology findings in the 3-month studies in the standard rodent models; the 6-month studies in p53 haploinsufficient mice; and the 20-week studies in Tg.AC mice. One notable finding was the formation of the highest proportion of papillomas at 26 weeks in p53 mice after exposure for only eight days to the highest dose of dicyclohexylcarbodiimide.

The proposed conclusions were:

> Under the conditions of this 26-week dermal study, there was *no evidence of carcinogenic activity* of dicyclohexylcarbodiimide in female p53 haploinsufficient mice administered 0.75, 1.5, 3, 6, or 12 mg/kg in ethanol.
>
> Female Tg.AC hemizygous mice dermally dosed with dicyclohexylcarbodiimide for 20 weeks had significantly increased incidences of squamous cell papilloma of the skin at the site of application.
> Nonneoplastic lesions noted at the site of application included chronic active inflammation and epidermal hyperplasia in female p53 haploinsufficient mice and female Tg.AC hemizygous mice.

Dr. Walker, the first principal reviewer, noted that in the Tg.AC mice forestomach papillomas occurred in every treated group but not in the controls. He added that even if this finding did not achieve statistical significance, it was worthy of mention in the body of the report and possibly in the abstract because of the dermal application of the chemical. He also suggested a discussion of the liver lesions and thymic atrophy be added.

Dr. Birt, the second principal reviewer, asked for clarification about the potential impact of administering lower concentrations of dicyclohexylcarbodiimide at some times during

the study and whether this would alter the study interpretation. She also asked for some information in the introduction about the potential human exposure levels. She asked about the range of expected survival of mice at 20 weeks based on previous NTP studies, as the survival rates in this study were not particularly good.
Dr. Soper, the third principal reviewer, agreed with the conclusions. He noted the contrast in the response in skin papillomas between Tg.AC and p53 mice and wondered if this difference might be due to the different length of the exposure in the two mice strains.

Dr. Chhabra said text would be added to explain the reasons for discounting the forestomach papillomas and liver and thymus lesions. He also noted that initially the dosing formulations were stored at room temperature, and the occasional loss of chemical by evaporation was remedied when the formulations were refrigerated. This loss occurred for about six weeks in the 26-week study and this information would be added to the report. He said while no quantitative measures of workplace exposure are in the literature, the chemical is a strong irritant and there have been a number of incidents of severe dermatitis resulting from exposure. In mice, skin irritation results from concentrations as low as 0.006%. Regarding the survival of the mice, he said this study is no different from others and this information would be added to the report. Dr. Chhabra said a longer period of exposure does not necessarily mean that preneoplastic lesions will progress to tumors,

Dr. Birt moved, and Dr. Walker seconded, that the conclusions be accepted as written. The motion was approved unanimously (7 yes, 0 no, 0 abstention votes).

Benzene

Dr. June Dunnick, NIEHS, introduced the study of benzene in haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice by reviewing the derivation of the mouse strain and describing the uses and previous carcinogenicity studies of benzene, the dose selection and protocol for the present study, and the nonneoplastic and neoplastic lesions, hematologic changes, and micronucleus formation observed in the 27-week study. The proposed conclusions were:

> Under the condition of this 27-week gavage study, there was *clear evidence of carcinogenic activity* of benzene in male haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice based on the occurrence of malignant lymphoma. There was *no evidence of carcinogenic activity* of benzene in female haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice administered 25, 50, 100, or 200 mg/kg.
>
> Treatment of male and female haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice with benzene was associated with toxicity to the hematopoietic system, lymphoid atrophy, and the accumulation of pigment in the extremities.

Dr. Soper, the first principal reviewer, felt the study was well conducted and agreed with the conclusion regarding carcinogenicity. He noted that the majority of animals with tumors occurred in the top dose that may have equaled the maximum tolerated dose and, thus, the dose selection for these models might be more important than in 2-year bioassays. He suggested that reducing the number of dose groups, but increasing the number of animals per group, might increase the study's sensitivity.
Dr. Walker, the second principal reviewer, also agreed with the conclusions. He suggested more discussion of the possible role of genotoxicity in benzene carcinogenesis because the mechanism of benzene-induced chromosomal damage is not understood despite the large number of studies with this chemical. He noted some unpublished dissertation research indicating that benzene could induce point mutations and suggested that a reference to this new finding be included in the report as it would suggest another possible mechanism for benzene induced carcinogenicity.

Dr. Birt, the third principal reviewer, also agreed with the conclusions and had no major scientific criticisms.

Dr. Dunnick replied that she would be willing to add the information on point mutations to the report, but Dr. Deininger said this information would need to be qualified since the work is not yet been published in the peer-reviewed literature.

Dr. John Bucher, NIEHS, noted that in a previous NTP study involving this model that showed no neoplastic response, a statement was added to the conclusion indicating that the sensitivity of the model is still uncertain. Dr. Walker said such a qualifier might not be needed in the present benzene study where there was a clear neoplastic response.

Dr. Soper moved, and Dr. Mirsalis seconded, that the conclusions be accepted as written. The motion was approved unanimously (7 yes, 0 no, 0 abstention votes).

Glycidol

Dr. June Dunnick, NIEHS, introduced the study of glycidol in haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice by reviewing the uses of the chemical, the previous NTP carcinogenicity findings for glycidol, the design and dose selection for the genetically modified mouse model studies, and the nonneoplastic and neoplastic lesions observed in the present study. The proposed conclusions were:

> Under the conditions of this 40-week gavage study there was *clear evidence of carcinogenic activity* of glycidol in male haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice based on the occurrence of histocytic sarcomas. The increased incidences of alveolar/bronchiolar adenomas in male mice were also considered to be related to glycidol administration. There was *some evidence of carcinogenic activity* of glycidol in female haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice based on the occurrence of alveolar/bronchiolar

adenoma. The occurrence of forestomach papillomas in female mice may also have been related to glycidol administration.

Treatment of male and female haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice with glycidol was associated with nonneoplastic lesions in the forestomach and brain.

Dr. Mirsalis, the first principal reviewer, felt the study was well conducted and agreed with the conclusions. He asked for the addition of a section on rationale for dose selection to be consistent with other NTP reports in this series, and for an explanation of the survival statistics used.

Dr. Giesy, the second principal reviewer, had no further comments.

Dr. Deininger, the third principal reviewer, noted that the main evidence for this study came from histiocytic sarcomas, which have a naturally high background rate.

Dr. Dunnick noted that an explanation about the dose selection was included in the review of prior studies and would be more clearly identified. Dr. Grace Kissling, NIEHS, said the survival statistics were based on the total survival time for all the animals in a group rather than on the number of animals surviving to study termination.

Dr. Sikka asked if a mechanism or metabolite is known to be responsible for the carcinogenic activity of glycidol. Dr. Walker answered that the expoxide of glycidol reacts directly with DNA. Dr. Walker cautioned about use of the term "potent" in citing literature statements about the carcinogenicity and mutagenicity of glycidol.

Dr. Mirsalis moved, and Dr. Deininger seconded, that the conclusions be accepted as written. The motion was approved unanimously (7 yes, 0 no, 0 abstention votes).

Phenolphthalein

Dr. June Dunnick, NIEHS, introduced the study of phenolphthalein in haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice by reviewing the uses of the chemical as a laxative, the previous NTP carcinogenicity findings, the design and dose selection for the genetically modified mouse model studies, and the nonneoplastic lesions observed in the present study. The proposed conclusions were:

Under the conditions of this 27-week feed study, there was *no evidence of carcinogenic activity* of phenolphthalein in male or female haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice exposed to 200, 375, 750, 3,000, or 12,000 ppm.
Phenolphthalein induced atypical hyperplasia, a preneoplastic lesion of the thymus in male and female mice, hematopoietic cell proliferation of the

> spleen in male and female mice, and toxicity to the kidney and reproductive system in male mice.

Dr. Deininger, the first principal reviewer, noted that the dose selection was based on the 2-year study and suggested that possibly doses could have been higher in this study. He suggested that the disclaimer that this is a new model be added to the conclusions.

Dr. Walker, the second principal reviewer, had no additional comments.
Dr. Sikka, the third principal reviewer, suggested that in the discussion of the role of p53, apoptosis as well as cell cycle arrest should be mentioned.

Dr. Walker suggested that the following statement be added to the conclusion, because no neoplastic effects were seen in this study:

> Because this is a new model, there is uncertainty whether this study possessed sufficient sensitivity to detect a carcinogenic effect.

Dr. Deininger moved, and Dr. Soper seconded, that the conclusions be accepted with this addition. The motion was approved unanimously (7 yes, 0 no, 0 abstention) votes.

Utility of Genetically Modified Models in NTP Cancer Hazard Identification

Dr. John Bucher, NIEHS, reviewed the history of the development, experience, and interpretation of studies with genetically modified models (GMMs) by the NTP over the previous decade and examined the sensitivity and specificity of the various models against other results for rodents and humans. He said the scientific community accepts the p53 model because the role that the p53 protein plays in carcinogenesis is understood, but the relevance of the Tg.AC model to humans is questioned. He described other ongoing studies and some perspectives about the uncertainties that need to be resolved to permit the use of results from GMM studies in hazard identification or risk assessment. These issues include the doses used for 6 or 9-month studies, the insensitivity of the GMMs to known rodent carcinogens, the high false negative rate, the effect of the background strain, and cost benefit analysis. Dr. Bucher presented the rationale for the testing of the 13 chemicals, which the NTP studied using different GMMs. He mentioned that FDA accepts data generated using the p53 and Tg.AC (dermal only) models as replacements for the mouse 2-year bioassay.

Dr. Bucher then presented for the subcommittee's consideration some proposals regarding the utility of GMM models in hazard identification, their future development, and conditions under which they might and might not be considered for use by the NTP. The subcommittee had an extended discussion regarding the applicability of GMMs to hazard identification, risk assessment, and regulatory guidance and the development of future models. Dr. Birt asked if there has been any effort to improve the models for detection of carcinogens and Dr. French replied that a number of other models have been constructed through a Request for Applications (RFA), but to the best of his knowledge

no subchronic tests have been performed using these models. Dr. Mirsalis cautioned the NTP that breeders do not always check the genotype of transgenic animals before shipping and investigators should be careful to verify genotypes before initiating studies. In addition, he noted that just as in vitro genetoxicity assays never replaced animal carcinogenicity studies, likewise GMMs may be useful as additional sources of mechanistic data, but should not be expected to replace more traditional assays such as chronic carcinogenicity studies. Dr. Walker was concerned that the NTP would abandon the GMMs in the testing program and Dr. Bucher replied that that is not the NTP's intent. Rather the NTP might use short-term tests to understand the mechanism of action of a chemical and then use a GMM, if available, to test a specific hypothesis. Dr. French said perhaps the NTP was too optimistic that GMMs with one alteration in a specific gene would respond to chemicals from many different classes. Dr. Walker encouraged the NTP not to discontinue the use of these models, but rather to consider the use of GMMs when there are appropriate mechanistic data on a chemical. Dr. Mirsalis agreed with Dr. Walker and said the NTP has a better understanding of the strengths and weaknesses of the models. There was consensus that GMMs should not replace the mouse 2-year bioassay. The panel redrafted the proposals, and after further discussion, Dr. Birt moved, and Dr. Mirsalis seconded, that the following recommendations be submitted to the NTP Board of Scientific Counselors. The motion was approved unanimously (7 yes, 0 no, 0 abstention votes).

Proposal for Use of Genetically Modified Models (GMMs) in NTP Cancer Hazard Identification

The NTP proposes to utilize GMMs as needed, for example:

- when there is compelling prior evidence that suggests that a particular agent or class of agents could be adequately studied in a particular model, or
- when there is insufficient test agent available to employ conventional 2-year or lifetime exposure cancer models, or
- when studying the effects of mixtures of agents if the response of the particular model chosen is known for at least one component of the mixture.

The NTP proposes to continue to develop and/or refine GMMs for the study of agents when appropriate.

The NTP concludes that there is insufficient evidence to support the routine replacement of the 2-year mouse bioassay with GMMs.

Dr. Bucher thanked the subcommittee for their helpful discussion on the use of the GMMs.

Attachment 1

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS

Technical Reports Review Subcommittee Meeting
Agenda

August 28, 2006
8:30 a.m. – 5:00 p.m.

National Institute of Environmental Health Sciences
Rodbell Auditorium, Rall Building
111 TW Alexander Dr.
Research Triangle Park, NC

Welcome			Dr. Allen Dearry, NIEHS Dr. Charlene McQueen, University of Arizona, Chair	
Chemical (CASRN)	**Report Number**	**Route Species**	**Staff Scientist Staff Pathologist**	**Principal Reviewers**
Overview of genetically modified models (GMM)			Dr. Jef French, NIEHS	
Allyl Bromide (106-95-6)	GMM 07	Gavage Male and female Tg.AC and $p53^{+/-}$ mice	Dr. June Dunnick Dr. David Malarkey	Dr. John Giesy Dr. Jon Mirsalis Dr. Harish Sikka
Dicyclohexylcarbodiimide (538-75-0)	GMM 09	Dermal Male and female Tg.AC and $p53^{+/-}$mice	Dr. Rajendra Chhabra Dr. Susan Elmore	Dr. Vernon Walker Dr. Diane Birt Dr. Keith Soper
Benzene (71-43-2)	GMM 08	Gavage Male and female $p16/p19^{+/-}$ mice	Dr. June Dunnick Dr. David Malarkey	Dr. Keith Soper Dr. Vernon Walker Dr. Diane Birt
Glycidol (556-52-5)	GMM 13	Gavage Male and female $p16/p19^{+/-}$mice	Dr. June Dunnick Dr. David Malarkey	Dr. Jon Mirsalis Dr. John Giesy Dr. Prescott Deininger
Phenolphthalein (77-09-8)	GMM 12	Feed Female $p53^{+/-}$ and male and female $p16/p19^{+/-}$ mice	Dr. June Dunnick Dr. David Malarkey	Dr. Prescott Deininger Dr. Vernon Walker Dr. Harish Sikka
Discussion on the utility of genetically modified models (GMM) for cancer hazard identification (**ACTION**)			Dr. John Bucher, NIEHS	

The Department specifically requests comments on: (a) Whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility; (b) the accuracy of the agency's estimate of the burden of the proposed collection of information; (c) the quality, utility, and clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques or other forms of information technology. Consideration will be given to comments and suggestions submitted within 60 days of this publication.

Dated: July 8, 2006.

Robert Sargis,

Reports Clearance Officer.

[FR Doc. 06–6079 Filed 7–7–06; 8:45 am]

BILLING CODE 4184–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Proposed Collection; Comment Request; NIH Leadership Development Programs Evaluation

SUMMARY: In compliance with the requirement of section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, for opportunity for public comment on proposed data collection projects, the Office of the Director (OD), National Institutes of Health (NIH) will publish periodic summaries of proposed projects to be submitted to the Office of Management and Budget (OMB) for review and approval.

PROPOSED COLLECTION: *Title:* NIH Leadership Development Programs Evaluation. *Type of Information Collection Request*: NEW. *Need and Use of Information Collection*: This evaluation will focus on Leadership Development Programs that are administered at NIH. These programs are integral components in the NIH Human Capital Strategy, submitted to the HHS/Office of the Secretary. NIH has committed to an evaluation of all leadership development programs as part of the Human Capital Strategy. The overarching purpose of evaluating the NIH Leadership Development Programs is to assess the effectiveness of existing programs as analyzed against the needs of the NIH community. The findings of this study will be used to: (1) Implement recommendations for program: Realignment, modification, retirement, and/or development; (2) assess the investments in the programs as they relate to the NIH Human Capital Strategy and NIH budget priorities; (3) improve communication of the programs and promote awareness throughout the NIH community; (4) identify opportunities for sharing best practices, reducing redundancies, and emphasize trans-NIH and/or IC program impacts; (5) conduct more effective succession planning to strategically optimize the leadership pipeline; and (6) integrate recommendations with the current NIH workforce planning initiative. The findings of this study will be used to ensure that programs meet the NIH Human Capital Strategy goals. *Frequency of Response*: On occasion. *Affected Public*: Individuals. *Types of Respondents*: Past program participants, program managers, officials who have selected both graduates and non-graduates from leadership development programs, and key administrative and scientific leaders across a diverse representation of the NIH's 27 Institutes/Centers. The annual reporting burden is as follows: *Estimated Number of Respondents*: 100; *Estimated Number of Responses per Respondent*: 1; and *Average Burden Hours Per Response*: 1. There are no Capital Costs to report. There are no Operating or Maintenance Costs to report.

Request for Comments: Written comments and/or suggestions from the public and affected agencies should address one or more of the following points: (1) Whether the proposed collection of information is necessary for the proper performance of the function of the agency, including whether the information will have practical utility; (2) The accuracy of the agency's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) Ways to enhance the quality, utility, and clarity of the information to be collected; and (4) Ways to minimize the burden of the collection of information on those who are to respond, including the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology.

FOR FURTHER INFORMATION CONTACT: To request more information on the proposed project or to obtain a copy of the data collection plans and instruments, contact Debbie Butcher, Acting Director, NIH Training Center, WSDD, OD, NIH, Suite 100, 6120 Executive Blvd., Rockville, MD 20852, or call non-toll-free number 301–435–6755 or E-mail your request, including your address to: *butcherd@od.nih.gov.*

Comments Due Date: Comments regarding this information collection are best assured of having their full effect if received within 60 days of the date of this publication.

Dated: June 28, 2006.

Debbie Butcher,

Acting Director, NIH Training Center, OD, National Institutes of Health.

[FR Doc. E6–10726 Filed 7–7–06; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Toxicology Program (NTP); Liaison and Scientific Review Office; Meeting of the NTP Board of Scientific Counselors Technical Reports Review Subcommittee

AGENCY: National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH).

ACTION: Meeting announcement and request for comments.

SUMMARY: Pursuant to Public Law 92–463, notice is hereby given of a meeting of the NTP Board of Scientific Counselors Technical Reports Review Subcommittee (TRR Subcommittee). The primary agenda topic is the peer review of the findings and conclusions presented in five draft NTP Technical Reports of rodent toxicology and carcinogenicity studies in genetically modified mice conducted by the NTP (see Preliminary Agenda below). The TRR Subcommittee meeting is open to the public with time scheduled for oral public comment. The NTP also invites written comments on any draft technical report discussed at the meeting. The TRR Subcommittee deliberations on the draft technical reports will be reported to the NTP Board of Scientific Counselors (BSC) at a future date.

DATES: The TRR Subcommittee meeting will be held on August 28, 2006. All individuals who plan to attend are encouraged to register online by August 14, 2006, at the NTP Web site (*http://ntp.niehs.nih.gov/* select "Calendar of Upcoming Events"). In order to facilitate planning for this meeting, persons wishing to make an oral presentation are asked to notify Dr. Barbara Shane via online registration, phone, or e-mail (see **ADDRESSES** below) by August 14, 2006, and if possible, to send a copy of the statement or talking points at that time. Written comments on the draft reports are also welcome and should also be received by August 14, 2006, to enable

review by the TRR Subcommittee and NTP staff prior to the meeting. Persons needing special assistance, such as sign language interpretation or other reasonable accommodation in order to attend, should contact 919–541–2475 (voice), 919–541–4644 TTY (text telephone), through the Federal TTY Relay System at 800–877–8339, or by e-mail to *niehsoeeo@niehs.nih.gov*. Requests should be made at least 7 days in advance of the event.

ADDRESSES: The TRR Subcommittee meeting will be held in the Rodbell Auditorium, Rall Building at the NIEHS, 111 T. W. Alexander Drive, Research Triangle Park, NC 27709. A copy of the preliminary agenda, committee roster, and any additional information, when available, will be posted on the NTP Web site (*http://ntp.niehs.nih.gov/* select "Calendar of Upcoming Events") or provided upon request. Public comments and any other correspondence should be submitted to Dr. Barbara Shane, Executive Secretary for the NTP Board (NTP Liaison and Scientific Review Office, NIEHS, P.O. Box 12233, MD A3–01, Research Triangle Park, NC 27709; telephone: 919–541–4253, fax: 919–541–0295; or e-mail: *shane@niehs.nih.gov*).

SUPPLEMENTARY INFORMATION:

Background

The primary agenda topic is the peer review of the findings and conclusions of five draft NTP Technical Reports of rodent toxicology and carcinogenicity studies conducted by the NTP (see Preliminary Agenda below) in genetically modified mouse models. The TRR Subcommittee will also provide advice to the NTP on the utility of GMM models for cancer hazard identification.

Attendance and Registration

The meeting is scheduled for August 28, 2006, from 8:30 a.m. to adjournment and is open to the public with attendance limited only by the space available. Individuals who plan to attend are encouraged to register online at the NTP website by August 14, 2006, at *http://ntp.niehs.nih.gov/* select "Advisory Boards and Committees" to facilitate access to the NIEHS campus. Please note that a photo ID is required to access the NIEHS campus. The NTP is making plans to videocast the meeting through the Internet at *http://www.niehs.nih.gov/external/video.htm*.

Availability of Meeting Materials

A copy of the preliminary agenda, committee roster, and any additional information, when available, will be posted on the NTP Web site (*http://ntp.niehs.nih.gov/* select "Calendar of Upcoming Events") or may be requested in hardcopy from the Executive Secretary (see **"ADDRESSES** above). Following the meeting, summary minutes will be prepared and made available on the NTP Web site.

Request for Comments

Public input at this meeting is invited and time is set aside for the presentation of public comments on any draft technical report. Each organization is allowed one time slot per agenda topic. At least 7 minutes will be allotted to each speaker, and if time permits, may be extended to 10 minutes. Registration for oral comments will also be available on-site, although time allowed for presentation by on-site registrants may be less than that for pre-registered speakers and will be determined by the number of persons who register at the meeting.

Persons registering to make oral comments are asked, if possible, to send a copy of their statement to Dr. Shane (see **ADDRESSES** above) by August 14, 2006, to enable review by the TRR Subcommittee and NTP staff prior to the meeting. Written statements can supplement and may expand the oral presentation. If registering on-site and reading from written text, please bring 40 copies of the statement for distribution to the TRR Subcommittee and NTP staff and to supplement the record. Written comments received in response to this notice will be posted on the NTP Web site. Persons submitting written comments should include their name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization (if any) with the document.

Background Information on the NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC) is a technical advisory body comprised of scientists from the public and private sectors who provide primary scientific oversight to the overall program and its centers. Specifically, the BSC 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. The TRR Subcommittee is a standing subcommittee of the BSC. BSC 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. Its members are invited to serve overlapping terms of up to four years. BSC and TRR Subcommittee meetings are held annually or biannually.

Dated: June 27, 2006.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences and the National Toxicology Program.

Preliminary Agenda; National Toxicology Program (NTP) Board of Scientific Counselors Technical Reports Review Subcommittee Meeting; August 28, 2006; Rodbell Auditorium, Rall Building, National Institute of Environmental Health Sciences, 111 TW Alexander Drive, Research Triangle Park, NC

NTP Technical Reports (TR) Scheduled for Review

- GMM 07: Allyl Bromide (CASNR 106–95–6).
  - Chemical intermediate in the manufacture of polymers, pharmaceuticals, and agricultural products.
- GMM 09: Dicyclohexylcarbodiimide (CASNR 538–75–0).
  - Reagent in the chemical and pharmaceutical industries; stabilizing agent in elastomers, synthetic rubber, and other types of resins.
- GMM 08: Benzene (CASNR 71–43–2).
  - Used in the manufacture of medicinal chemicals, dyes, oil, varnishes, and lacquers.
- GMM 13: Glycidol (CASNR 556–52–5).
  - Stabilizer in the manufacture of vinyl polymers; additive for oil and synthetic hydraulic fluids.
- GMM 12: Phenolphthalein (CASNR 77–09–8).
  - Laboratory reagent; cathartic drug in laxatives.
- The utility of genetically modified models for cancer hazard identification.

[FR Doc. E6–10728 Filed 7–7–06; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Prospective Grant of Exclusive License: (N)-Methanocarba Adenosine Derivative as A3 Receptor Agonists

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

ACTION: Notice.

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
Technical Reports Review Subcommittee Meeting
August 28, 2006

Diane F. Birt, Ph.D.
Professor and Director
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