National Toxicology Program
Board of Scientific Counselors
Technical Reports Review Subcommittee

June 12, 2006

NIEHS, Research Triangle Park, NC

Summary Minutes

Contents **Page Number**

Attendees

Members:
Diane Birt, Iowa State University
Christopher Bradfield, University of Wisconsin
Kenny Crump, Environ International
George Daston, The Procter and Gamble Company
Prescott Deininger, Tulane University
Nancy Kerkvliet, Oregon 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

ad hoc Attendees:
Leena Hilakivi-Clarke, Georgetown University
Paul Cooke, University of Illinois

NIEHS Attendees:
Charles Alden
Gary Boorman
Douglas Bristol
Donna Browning
John Bucher
Rajendra Chhabra
Brad Collins
Michael Cunningham
Allen Dearry
Susan Elmore
Gordon Flake
Paul Foster
Raymond Grissom
Ronald Herbert
William Jameson
Wendy Jefferson
Grace Kissling
Ruth Lunn
David Malarkey
Retha Newbold
Denise Orzech
Shyamal Peddada
Christopher Portier
Barbara Shane
Michael Shelby
Robert Sills
Gregory Travlos
Nigel Walker
Samuel Wilson
Kristine Witt
Mary Wolfe

Agency Attendees:
William Allaben, FDA
Barry Delclos, NCTR
Beoon Seok Han, FDA
Paul Howard, FDA
Greg Olson, FDA
Brent Thorn, FDA
Mark Toraason, NIOSH

Public Attendees:
Andrew Ballard, BNA
Stephen Brecker, Dynamac Corp.
Donna Browning, RTI International
Anne Chappelle, Sunoco
Patricia Crockett, Constella Group
Sanford Garner, Constella Group
Reshan Fernando, RTI International
Jan Holland, Aques New Zealand
Gloria Jahnke, Sciences International
Jessica Matthews, Constella Group
John Peckham, Experimental Pathology Laboratories
Rosalie Schnick, Michigan State University
Gabriel Wilson, Experimental Pathology Laboratories

Transcriptionist:
Kay Rodhe

Peer Review Meeting

The meeting began at 8:30 a.m. on June 12, 2006, in the Rodbell Conference Center, David P. Rall Building, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. Members of the attending subcommittee were Drs. Charlene McQueen (chairperson), Diane Birt, Christopher Bradfield, Kenny Crump, George Daston, Prescott Deininger, Nancy Kerkvliet, Jon Mirsalis, Harish Sikka, Keith Soper, and Vernon Walker, and special *ad hoc* reviewers were Drs. Paul Cooke and Leena Hilakivi-Clarke. For further information, contact Dr. Barbara Shane, Executive Secretary, at 919-541-4253 or *shane1@niehs.nih.gov*.

Multigenerational Study of Genistein
Dr. Barry Delclos, NCTR, introduced the technical report on the multigenerational studies of genistein by providing some background on the joint NIEHS-NCTR series of endocrine disruptor studies. He described the composition of soy products that contain genistin and its aglycone genistein, the latter of which also results from metabolism. He discussed human exposures and the short-term range-finding studies that served as the basis for dose selection for the multigenerational and two-year rodent studies. He then described the exposure regimen for the multigenerational studies and the effects of the chemical on survival, body weight, and reproductive endpoints in exposed animals. The proposed conclusions were:

> Under the conditions of this study, dietary exposure to 500 ppm genistein (approximately 35 mg genistein/kg body weight per day in males and 51 mg/kg per day in females) decreased body weights, accelerated vaginal opening, slightly decreased anogenital distance, and altered estrous cyclicity in females continuously ingesting genistein. Significant decreases in postweaning body weight and decreases in anogenital

> distance in males were confined to the F_1 generation and were not seen in the similarly exposed F_2 generation. In animals exposed to 500 ppm, there was some evidence for reduced litter size in the F_1 and F_2 generations that were continuously exposed to the test chemical. No other impacts on fertility and no histopathologic lesions were observed in females. The male reproductive tract did not show significant alterations, but increased incidences of hyperplasia of the mammary gland and calcification of renal tubules were observed in continuously exposed 100 and 500 ppm males examined at 20 weeks of age. Weaker effects on the incidences of male mammary gland hyperplasia were observed in 500 ppm males exposed only as adults or exposed only *in utero* and through lactation. Other than decreased body weight gains in preweaning pups, there was no evidence for a carryover of genistein effects into unexposed generations.

Dr. Walker, the first principal reviewer, had no substantial scientific criticisms. He noted that the complex multigenerational design was very different from other NTP studies.

Dr. Daston, the second principal reviewer, noted that the use of different exposure windows permitted determination of whether responses were primary pharmacologic effects or adaptive responses. He also noted that the control diet and dose selection spanned the varied range of human exposures and suggested that the diet and phytoestrogen levels be specified in more detail in the abstract. He asked for clarification of whether the time in estrus or proestrus was altered by the treatment. He suggested that the known anorectic effect of estrogen be added to the results section. He also noted the limited precision associated with measurement of the phases of the estrous cycle. For the discussion section, he asked for clarification of the doses used compared to human consumption levels. He also thought it worth noting that within the phytoestrogen range of 1 to 100 ppm, the reproductive or developmental parameters remained relatively normal. He added that since this report is one of a series, that the NTP compile a separate report on the lessons learned from these studies, once all the reports are complete.

Dr. Crump, the third principal reviewer, thought the complicated statistical analyses were presented clearly and agreed with the conclusions presented at the end of the discussion section.

The *ad hoc* reviewer, Dr. Cooke, thought the studies were very thorough and well organized and presented. He was pleased that male mammary hyperplasia was considered as an endpoint and commented on the finding of an increase in incidence of this lesion at relatively low concentrations of exposure to genistein. He said a point to be emphasized is that the study design did not parallel the human situation for soy-fed infants. Dr. Walker stated that the model precludes one from delivering the same cumulative dose.

In response, Dr. Delclos agreed that while fetal exposure was significant, post-natal exposure was less, and said he would note those points in the abstract.

Dr. Birt asked for some comparison of the responses in other strains as part of the rationale for selection of the Sprague-Dawley rat and for more detail on the composition and monitoring of the diet. Ms. Retha Newbold, NIEHS, noted that the diets were specially formulated to have low levels of phytoestrogens.

Dr. Kerkvliet inquired about the corresponding times of rodent and human gestational stages. Dr. Delclos responded that postnatal days 1-5 for rodents correspond roughly to the second trimester for humans. Ms. Newbold added that developmental events of various tissues or systems, including the neuroendocrine system, are continuous and not restricted to a particular prenatal window.

Dr. Daston moved, and Dr. Walker seconded, that the conclusions be accepted as written. The motion was passed unanimously with 10 yes votes.

Genistein

Dr. Barry Delclos, introduced the technical report on the 2-year studies of genistein by describing the study design, and the effects of the chemical on body weight, aberrant estrous cyclicity, male mammary gland hyperplasia, female mammary gland fibroadenomas, and pituitary gland adenomas. The proposed conclusions were:

> Under the conditions of this 2-year feed study with continuous exposure to the test compound from conception through termination (F_1C), there was no evidence of carcinogenic activity of genistein in male Sprague-Dawley rats exposed to 5, 100, or 500 ppm. There was some evidence of carcinogenic activity of genistein in female Sprague-Dawley rats based on increased incidences of mammary gland adenoma or adenocarcinoma (combined) and pituitary gland neoplasms. The incidence of benign mammary gland fibroadenoma in female rats was significantly decreased in the 500 ppm group.
>
> Under the conditions of this 2-year feed study with exposure to the test compound from conception through 20 weeks followed by control feed until termination (F_1T140), there was no evidence of carcinogenic activity of genistein in male Sprague-Dawley rats exposed to 5, 100, or 500 ppm. There was equivocal evidence of carcinogenic activity of genistein in female Sprague-Dawley rats based on marginally increased incidences of pituitary gland neoplasms.
>
> Under the conditions of this 2-year feed study with continuous exposure to the test compound from conception through weaning (PND 21) followed by control feed until termination (F_3T21), there was no evidence of carcinogenic activity of genistein in male Sprague-Dawley rats exposed to 5, 100, or 500 ppm. There was equivocal evidence of carcinogenic activity of genistein in female Sprague-Dawley rats based on increased incidences of mammary gland adenoma or adenocarcinoma (combined).

> Exposure to genistein was also shown to accelerate the onset of aberrant estrous cycles in female Sprague-Dawley rats whether exposures were continuous or truncated at PND 140 or at weaning. The effects of genistein on estrous cycling and the incidences of common hormonally related spontaneous neoplasms of female Sprague-Dawley rats are consistent with an estrogenic mechanism of toxicity.

Dr. Mirsalis, the first principal reviewer, said the National Cancer Institute is studying genistein as a potential cancer preventative agent and suggested that some of those studies be mentioned in the background information. He suggested that the sampling of the diet to ensure homogeneity be discussed and added that the increased incidence of pancreatic islet adenomas was worth noting. He thought a comparison of the administered doses with human exposure should be mentioned in the discussion. He questioned whether the report reflected Good Laboratory Practice compliance, particularly as it pertains to administrative detail.

Dr. Bradfield, the second principal reviewer, thought the study was well designed. He thought that the study was more a test of the aglycone than the glucoside, but that the latter might be of greater significance. He also noted that exposure of the neonate was not mimicked in this model.

Dr. Soper, the third principal reviewer, felt the studies were well designed and agreed with the conclusions presented. He suggested that the decrease in mammary gland fibroadenoma in the group receiving 500 ppm genistein could have been due to a decrease in body weight.

Dr. Kerkvliet suggested that more about the rationale for dose selection and exposure periods should be carried from the range-finding study into the text of this report. She questioned the use of terms such as 'slightly' or 'marginally' increased or 'generally similar' in descriptions of lesion incidences. She also questioned use of the term 'carcinogenic' to describe the action of a chemical that elevated the incidence of tumors, which occurred spontaneously with high frequency, and inquired if the reduced incidences of tumors would be attributed to 'anticarcinogenic' properties of the chemical.

Dr. Hilakivi-Clarke suggested that not all the observed effects should be described entirely as estrogenic, but that some might also have a genotoxic component. She inquired why hormone levels were not measured and also why the rats were housed singly.

In response, Dr. Delclos said discussion of the pancreatic islet tumors would be expanded. He explained that the full laboratory report, which includes all the administrative and procedural details, was prepared and audited for GLP compliance at the NCTR prior to the preparation of the technical report. He agreed to expand the references on the beneficial effects of genistein in the introduction, discuss why the rats were housed separately, and enhance the discussion about the distinction between the

aglycone and glucoside conjugate. He explained that limitations of study size precluded including extra animals for hormone measurements.

Dr. Kerkvliet inquired about the immunotoxicity data for these studies, and Dr. Delclos explained that they are presented in the report on the range-finding studies.

Dr. Sikka also thought that statements about genistein acting through an estrogenic mechanism should be modified to include the possibility of a genotoxic mechanism, and that more emphasis should be placed on the chemopreventative as well as carcinogenic effects of the compound. Dr. Daston noted that the high rate of false positives in the *in vitro* genotoxicity tests suggest that genistein is not likely to be a genotoxic agent, and he thought the overall study results outweighed this *in vitro* data. He inquired whether the human epidemiology literature might help interpret the results from the present rodent study. He noted that not all estrogen-receptor tissues would be expected to respond similarly; for example, the uterus contains predominantly the estrogen receptor alpha, while genistein is predominantly an estrogen receptor beta interacting ligand.

Dr. John Bucher, NIEHS, said caution must be exercised in applying human data to interpretation of the animal studies. The primary purpose of the current review is to evaluate the animal data by themselves and extrapolation of the findings to (or from) human health effects would be the purview of another NTP program, the Center for the Evaluation of Risks to Human Reproduction.

Dr. Walker also noted that all the tissues affected were hormonally related and favored retaining a statement suggested by Dr. Hilakivi-Clarke that they were consistent with an estrogenic effect without making conclusions about genotoxicity.

For consideration of the conclusions, Dr. McQueen suggested they be addressed paragraph by paragraph. Dr. Daston inquired whether the conclusions could include the dose levels at which a particular effect was seen. Dr. Bucher replied that was not the normal practice, as not all possible doses were used. Dr. Walker asked if it were possible in the conclusions to mention that the incidence of pancreatic tumors was increased in the 500 ppm male rat group, but to explain why it was not considered related to genistein exposure. Dr. Bucher suggested it might be sufficient to mention this information in the body of the abstract and to make a note of it in the summary table and Dr. Walker agreed.

Dr. Daston moved and Dr. Mirsalis seconded a motion to include in the first paragraph the concentrations at which the increases in mammary gland and pituitary gland adenomas were seen. Dr. Christopher Portier, NIEHS, argued that including those numbers might be interpreted as implying a threshold for response. Drs. Walker and Birt spoke against including specific dose levels in the conclusions as they might oversimplify more complex patterns described in the results section. Dr. Bucher noted that in some cases there were statistically significant trends that included increases in tumors in lower dose groups that were not significant by pairwise comparisons. Drs. Kerkvliet, Soper, and Crump cited examples of complications that might arise from stating specific dose levels for a carcinogenic effect. The motion was defeated with one yes vote (Dr. Daston)

and nine no votes. Dr. Birt then moved, and Dr. Soper seconded, to approve the first two paragraphs of the conclusions as written. The motion was approved unanimously with ten yes votes.

For the remaining conclusions, Dr. Daston moved that the following text be added to the end of the last sentence of the final paragraph, "are consistent with an estrogenic mechanism of toxicity," and that the spontaneous neoplasms be referred to as "hormonally related" spontaneous neoplasms. Dr. Walker seconded the motion, which was approved unanimously with ten yes votes.

α-Methylstyrene

Dr. Michael Wyde, NIEHS, introduced the toxicology and carcinogenicity studies of α-methylstyrene by describing the uses of the chemical, the study design for the short- and long-term studies, the effects of the chemical on the kidney and liver in the short term studies, and the effects on the kidney, liver, and nose in the long term studies. The proposed conclusions were:

> Under the conditions of this 2-year inhalation study, there was some evidence of carcinogenic activity of α-methylstyrene in male F344/N rats based on increased incidences of renal tubule adenomas and carcinomas (combined). The increased incidences of mononuclear cell leukemia in 1,000 ppm male F344/N rats may have been related to α-methylstyrene exposure. There was no evidence of carcinogenic activity of α-methylstyrene in female F344/N rats exposed to 100, 300, or 1,000 ppm. There was equivocal evidence of carcinogenic activity of α-methylstyrene in male $B6C3F_1$ mice based on marginally increased incidences of hepatocellular adenoma or carcinoma (combined). There was clear evidence of carcinogenic activity of α-methylstyrene in female $B6C3F_1$ mice based on increased incidences of hepatocellular adenomas and carcinomas.
>
> Exposure of rats to α-methylstyrene resulted in kidney toxicity, which in males exhibited some features of α2u-globulin nephropathy. Exposure to α-methylstyrene resulted in nonneoplastic lesions of the nose in male and female rats and mice and of the liver and kidney in female mice.

Dr. Birt, the first principal reviewer, thought the study was performed and reported carefully and she agreed with the conclusions. She suggested adding more text about the ataxia in the 3-month studies, the buildup and decay of the chemical in the chamber, and the body weight effects.

Dr. Kerkvliet, the second principal reviewer, said she would like to have seen measurements of hepatic cytochrome P-450 activity included in the report given styrene's known mode of action. She suggested that the whole-body route of exposure by inhalation rather than the nose-only route be mentioned more prominently in the Materials and Methods section, and asked if the forestomach lesions could have had any

other effects on the animals' health. She also thought that it would be useful to discuss the differences in the mode of action between styrene and α-methylstyrene, and asked for more details on the procedures for vaginal cytology.

Dr. Deininger, the third principal reviewer, thought the report was well written and noted the difficulty in drawing conclusions for mononuclear cell leukemia, because of the reported high background incidences and variability in the responsiveness among the treated animals.

Dr. Wyde replied that details about body weights, chamber conditions, and vaginal cytology would be amplified, and noted that ataxia was not observed in the 2-year studies. He also agreed to expand the discussion on the comparison of the metabolic pathways of styrene and α-methylstyrene. Dr. Robert Sills, NIEHS, said the forestomach lesions were focal and mild in severity and likely did not affect the eating or digestion of the animals.

Dr. Sikka said a discussion on the structure-activity relationship between styrene and α-methylstyrene would be useful particularly in relation to the potency of the two chemicals.

Dr. Daston asked if the conclusion statements regarding the kidney tumors in rats might carry some qualifying statement about a possible relationship with accumulation of α2u-globulin.

Public Comment

Dr. Anne Chappelle, representing Sunoco Corporation, said the results of the 3-month and 2-year studies supported an α2u-globulin nephropathy-mediated mechanism for the induction of kidney tumors in the male rats. She also thought the increase in liver tumors in female mice was due to a lower than normal incidence in the control group. She also asserted that a maximum tolerated dose (MTD) was exceeded in some animal groups.

Dr. Walker noted the erythrocyte micronucleus data for mice indicated that the chemical had a clastogenic effect; therefore, its mechanism of action in rats was not solely due to α2u-globulin. Regarding liver tumors in female mice, he also noted that there was a clear difference in the increase in tumors in the treated mice compared with concurrent controls. Even though these control values were low, they were not the lowest values seen among the historical control database.

In discussing the conclusions, Dr. Daston proposed that the sentence: "This effect was seen in association with α2u-globulin accumulation" be moved to the first paragraph after the text about the kidney tumors in male rats. Dr. Robert Sills presented an overview of the spectrum of kidney lesions that were observed, some of which might be associated with α2u-globulin, while others, such as the cytotoxic effects, might be due to the chemical. Dr. John Bucher said there was not enough evidence to support a statement that all the male kidney tumors were due to α2u-globulin and not to a direct effect of the chemical.

Dr. Daston maintained that some suggestion of the possibility of a contribution by α2u-globulin in the conclusion would be useful. Dr. Sills replied that while some aspects of the classic α2u-globulin syndrome were seen, others, such as cell proliferation, single cell necrosis, and granular casts were not. He also noted a recent study of *p*-nitrobenzoic acid in which α2u-globulin accumulation and cell proliferation were seen, but no kidney tumors were found.

Dr. Daston moved and Dr. Kerkvliet seconded a motion to add the statement: "This effect was seen in association with α2u-globulin accumulation" to the first paragraph of the conclusions. Drs. Bucher and Wyde noted that the α2u-globulin is typically observed in the 3-month studies but not in 2-year studies. The motion was defeated with one yes vote (Dr. Daston), eight no votes, and one abstention (Dr. Deininger).

Dr. Birt then moved and Dr. Bradfield seconded that the conclusions be accepted as originally written. Dr. Walker proposed changing the word "accumulation" to "nephropathy" in the second paragraph and Dr. Birt modified her motion. The motion was passed unanimously with ten yes votes.

Methylene Blue Trihydrate

Dr. Douglas Bristol, NIEHS, introduced the toxicology and carcinogenicity studies of methylene blue trihydrate by describing the uses and hematotoxicity of the chemical, the experimental design and dose selection for the 1-month, 3-month, and 2-year studies, the survival and body weight profiles for those studies, and the nonneoplastic and neoplastic lesions observed in the 2-year study. The proposed conclusions were:

> Under the conditions of these 2-year gavage studies, there was some evidence of carcinogenic activity of methylene blue trihydrate in male F344/N rats based on increased incidences of pancreatic islet cell adenoma and adenoma or carcinoma (combined). There was no evidence of carcinogenic activity in female F344/N rats administered 5, 25, or 50 mg/kg. There was some evidence of carcinogenic activity in male $B6C3F_1$ mice based on increased incidences of carcinoma and of adenoma or carcinoma (combined) in the small intestine. The increased incidence of malignant lymphoma in 25 mg/kg males may have been related to the administration of methylene blue trihydrate. There was equivocal evidence of carcinogenic activity in female $B6C3F_1$ mice based on marginally increased incidences of malignant lymphoma.
>
> Methylene blue trihydrate administration caused methemoglobinemia and a regenerative Heinz body anemia with secondary injury to other organs in rats and mice

Dr. Sikka, the first principal reviewer, agreed with the conclusions. He suggested discussing in the report the potential mutagenicity of the metabolites of methylene blue.

Dr. Crump, the second principal reviewer, felt that while the lymphoma response in male mice was weak, it was supported by an increase in females. He also thought that the increase in pancreatic islet tumors in male rats was relatively weak, but the statistical trend in the increase in lung tumors might be considered equivocal. He said a statistical test for formally incorporating historical controls in the analysis would be published soon, and he asked for a presentation of this approach with examples at a future meeting.

In response to the subcommittee's comments, Dr. Bristol said a discussion of the mutagenicity of methylene blue metabolites would be added to the report. Dr. David Malarkey, NIEHS, reported that the average historical control rate for male rat lung tumors was higher than the control rate seen in the present study. Dr. Grace Kissling, NIEHS, said there are plans to present the method for statistical analysis of historical controls to the panel after it is published, and the NTP would ask the subcommittee to consider whether it should be included in future reports. Dr. Birt asked if mentioning the lung tumors in male mice would strengthen the *some evidence* call. Dr. Bucher replied that if the incidence were considered equivocal it would be phrased as "may have been related" to chemical administration.

Dr. Daston mentioned that a number of negative trends in tumor incidence also occurred. Dr. Bristol replied that methylene blue has some paradoxical properties. For example, it is used as a treatment for methemoglobinemia at low doses, but causes methemoglobinemia at higher doses.

Dr. Sikka asked about mentioning the possible influence of methylene blue's mutagenicity in the conclusions, and Dr. Bucher responded that such an addition has not been done in the past. Dr. Kerkvliet asked why the report did not mention the significant decrease in mononuclear cell leukemia in the rats. Dr. Bucher replied that although the incidence was decreased, the inclusion of this finding in the conclusions might be misleading, because the effect was secondary to the primary toxicity and is rather specific to the F-344/N model. A decrease in mononuclear cell leukemia in this strain of rats is expected in instances where splenic toxicity is observed. The NTP agreed to explain this finding more fully in the discussion section of the report.

Dr. Soper moved and Dr. Walker seconded that the conclusions be accepted as written. The motion was passed unanimously with ten yes votes.

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS

Technical Reports Review Subcommittee Meeting
Agenda

June 12, 2006
8:30 a.m – 5:00 p.m.

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

June 12 8:30 a.m.	Welcome	Dr. Allen Dearry, NIEHS and Dr. Charlene McQueen, University of Arizona, Chair

Chemical, CASRN	**Report Number**	**Primary Use, Route and Species**	**Staff Scientist and Pathologist**	**Principal Reviewers**
Genistein - Multigenerational Study, 446-72-0	TR 539	Naturally occurring phytoestrogen, found in soy products; feed, male and female rats	Dr. Barry Delclos Dr. Greg Olson	Dr. Walker Dr. Daston Dr. Crump Dr. Cooke (*ad hoc*)
Genistein – Bioassay, 446-72-0	TR 545	Naturally occurring phytoestrogen, found in soy products; feed, male and female rats	Dr. Barry Delclos Dr. Greg Olson	Dr. Mirsalis Dr. Bradfield Dr. Soper Dr. Nancy Kerkvliet Dr. Hilakivi-Clarke (*ad hoc*)
α-Methylstyrene, 98-83-9	TR 543	Used in the production of resins and polymers; inhalation, male and female rats and mice	Dr. Michael Wyde Dr. Robert Sills	Dr. Birt Dr. Kerkvliet Dr. Deininger
Methylene Blue Trihydrate, 7220-79-3	TR 540	Dye used to stain tissues and bacteriological samples for microscopy, antidote for methemoglobinemia, used formerly as a hair colorant; gavage studies in male and female rats and mice	Dr. Douglas Bristol Dr. John Peckham	Dr. Sikka Dr. Crump Dr. Giesy

Chester, OH 45069. Officers: John J. Plnes, CEO, (Qualifying Individual).
Guaranteed International Freight and Trade, Inc., dba International Freight and Trading, 239–241 Kingston Ave., Brooklyn, NY 11213. Officers: Lawrence Medas, Sr., President, (Qualifying Individual), Cornelius Medas, CEO.
Florida Freight Forwarders, LLC, 2041 NW 12th Ave., Miami, FL 33127. Officer: Jose Maria Rivas, Vice President, (Qualifying Individual).
Sunset Transportation, Inc., 11406 Gravois Road, St. Louis, MO 63126. Officers: Deborah L. Kopeny, Director, (Qualifying Individual), James A. Williams.
D.M.C. Logistics Incorporated, 207 Meadow Road, Edison, NJ 08817. Officers: Julia Ertler, Vice President, (Qualifying Individual), Francis S. Molfetta, President.
Cargo Shipping Expedition International Inc., 6 Sandow Court, Fair Lawn, NJ 07410. Officers: Gerry Lysogorsky, Vice President, (Qualifying Individual), Alexander Zilberman, President.

Ocean Freight Forwarder—Ocean Transportation Intermediary Applicants

Hal-Mari International Logistics, Inc., 935 Knotty Elmwood Trail, Houston, TX 77062. Officer: Ilkka Halmari, President, (Qualifying Individual).
Matt Global Freight Co. LLC, 3517 Langrehr Road, Suite 102, Baltimore, MD 21244. Officers: Mathew T. Chacko, President, (Qualifying Individual), Ann T. Mathews, Vice President.
Allfreight Worldwide Cargo, Inc., dba Allfreight, 4810 Beauregard Street, Suite 100, Alexandria, VA 22312. Officers: Demeke Meri, CEO/ President, (Qualifying Individual), Abel Meri, Director.

Dated: March 3, 2006.

Karen V. Gregory,

Assistant Secretary.

[FR Doc. E6–3315 Filed 3–8–06; 8:45 am]

BILLING CODE 6730–01–P

FEDERAL RETIREMENT THRIFT INVESTMENT BOARD

Sunshine Act; Notice

TIME AND DATE: 9 a.m. (est); March 20, 2006.

PLACE: 4th Floor Conference Room, 1250 H Street, NW., Washington, DC.

STATUS: Open.

MATTERS TO BE CONSIDERED:

1. Approval of the minutes of the February 21, 2006, Board Member meeting.
2. Thrift Savings Plan activity report by the Executive Director.

CONTACT PERSON FOR MORE INFORMATION: Thomas J. Trabucco, Director, Office of External Affairs, (202) 942–1640.

Dated: March 6, 2006.

Thomas K. Emswiler,

Acting General Counsel, Federal Retirement Thrift Investment Board.

[FR Doc. 06–2325 Filed 3–7–06; 1:01 pm]

BILLING CODE 6760–01–P

GOVERNMENT ACCOUNTABILITY OFFICE

Publication of Volume II of GAO's Principles of Federal Appropriations

AGENCY: Government Accountability Office.

ACTION: Notice of publication.

SUMMARY: The third edition of Volume II of GAO's *Principles of Federal Appropriations Law* is being prepared for publication by the Government Printing Office (GPO). Government departments, agencies, and other federal organizations that normally require more than one copy have been given an opportunity to request them through their agencies' account representatives at pre-publication rate. This notice is intended for other parties who might be interested in purchasing the book.

SUPPLEMENTARY INFORMATION: The Government Accountability Office (GAO) will shortly publish Volume II of *Principles of Federal Appropriations Law*, third edition—also known as "The Red Book" This publication is part of a multi-volume set intended to present a basic reference covering those areas of law in which the Comptroller General renders decisions. Our approach is to lay a foundation with text discussion, using specific legal authorities to illustrate the principles discussed, their application, and exceptions. These authorities include GAO decisions and opinions, judicial decisions, statutory provisions, and other relevant sources.

GAO will provide copies of this volume to the heads of Federal agencies, and agencies have already been given an opportunity to place advance (rider) orders for additional copies of this volume with their account representatives at the Government Printing Office (GPO).

This notice is intended to tell the general public that they will be able to place pre-issue orders for this publication through GPO's new online bookstore, at *http://bookstore.gpo.gov/collections/gao_appropriation.jsp.* Otherwise, we expect this publication will be available for purchase from the Superintendent of Documents, United States Government Printing Office, P.O. Box 371954, Pittsburgh, PA 15250–7954, by April 2006. The price is $69.

Orders for Volume II should specify GPO Stock No. 020–000–00287–5 or the ISBN 0–16–0075602–2. Through periodic training courses on federal appropriations law, GAO believes that this publication might be useful in particular to law offices, to accounting firms, to the financial, budget, or accounting officers of government contractors, to university and state law libraries, to corporate chief financial officers, and to people who follow Federal financial management, contracts, grants, and loans.

As with the second edition of Principles, we are publishing the third edition in loose-leaf format but will include a CD–ROM as well. Volume II covers chapters 6 through 11: *availability of appropriations, amount; obligation of appropriations; continuing resolutions; liability and relief of accountable officers; Federal assistance, grants and cooperative agreements; and Federal assistance, guaranteed and insured loans.* We plan three volumes with annual updates. The updates will only be published electronically. Users should retain copies of the remaining volumes of the second edition until each volume is revised. Volume III of the second edition addresses functions that the GAO Act of 1996 transferred to the Executive Branch and will not be updated. The first annual update of Volume I is currently available online at *http://www.gao.gov/legal.htm.*

Authority: 31 U.S.C. 712, 717, 719, 3511, 3526–29.

Susan Poling,

Managing Associate General Counsel, Government Accountability Office.

[FR Doc. 06–2235 Filed 3–8–06; 8:45 am]

BILLING CODE 1610–02–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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 four draft NTP Technical Reports of rodent toxicology and carcinogenicity studies 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 (NTP Board) at a future date.

DATES: The TRR Subcommittee meeting will be held on June 12, 2006. All individuals who plan to attend are encouraged to register online by May 30, 2006, at the NTP Web site (*http://ntp.niehs.nih.gov/* select "Advisory Boards & Committees"). 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 May 30, 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 May 30, 2006, to enable review by the TRR Subcommittee and NIEHS/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 "Advisory Boards and Committees") and 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 four draft NTP Technical Reports of rodent toxicology and carcinogenicity studies conducted by the NTP (see Preliminary Agenda below) on studies with conventional strains of rats and mice.

Attendance and Registration

The meeting is scheduled for June 12, 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 Web site by May 30, 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 "Advisory Boards and Committees") or may be requested in hardcopy from the NTP (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 May 30, 2006, to enable review by the TRR Subcommittee and NIEHS/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 NIEHS/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 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 NTP Board advises the NTP on matters of scientific program content, both present and future, and conducts periodic review of the program for the purposes of determining and advising on the scientific merit of its activities and their overall scientific quality. The TRR Subcommittee is a standing subcommittee of the NTP Board. NTP Board 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. NTP Board meetings are held annually or biannually.

Dated: February 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

June 12, 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

- TR 539 Genistein (CASNR 446–72–0)—Multigenerational Study.

Naturally occurring phytoestrogen, found in soy products.

- TR 545: Genistein (CASNR 446–72–0)—2-year Bioassay.
  Naturally occurring phytoestrogen, found in soy products.
- TR 543: α-Methylstyrene (CASNR 98–83–9).
  - Used in the production of resins and polymers.
- TR 540: Methylene blue trihydrate (CAS No. 7220–79–3).
  - Dye used to stain tissues and bacteriological samples for microscopy and an antidote for methemoglobinemia; previously used as a hair colorant.

[FR Doc. E6–3317 Filed 3–8–06; 8:45 am]
BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

Disease, Disability, and Injury Prevention and Control Special Emphasis Panel: National Institute for Occupational Safety and Health (NIOSH) Support for Conferences and Scientific Meetings, Request for Applications PAR 06–014

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), the Centers for Disease Control and Prevention (CDC) announces the following meeting:

Name: Disease, Disability, and Injury Prevention and Control Special Emphasis Panel (SEP): NIOSH Support for Conferences and Scientific Meetings, Request for Applications PAR 06–014.

Time and Date: 1 p.m.–4 p.m., March 29, 2006 (Closed).

Place: Teleconference.

Status: The meeting will be closed to the public in accordance with provisions set forth in section 552b(c)(4) and (6), Title 5 U.S.C., and the Determination of the Director, Management Analysis and Services Office, CDC, pursuant to Public Law 92–463.

Matters to Be Discussed: The meeting will include the review, discussion, and evaluation of applications received in response to NIOSH Support for Conferences and Scientific Meetings, Request for Applications PAR 06–014.

For More Information Contact: George Bockosh, MS, Scientific Review Administrator, National Institute for Occupational Safety and Health, CDC, 626 Cochran Mill Road, MS PO–5, Pittsburgh, PA 15236, Telephone 412–386–6465. The Director, Management Analysis and Services Office, has been delegated the authority to sign **Federal Register** notices pertaining to announcements of meetings and other committee management activities, for both the CDC and the Agency for Toxic Substances and Disease Registry.

Dated: March 3, 2006.

Alvin Hall,

Director, Management Analysis and Services Office, Centers for Disease Control and Prevention.

[FR Doc. E6–3354 Filed 3–8–06; 8:45 am]
BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

National Center for Injury Prevention and Control Initial Review Group

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), the Centers for Disease Control and Prevention (CDC) announce the following meeting:

Name: National Center for Injury Prevention and Control (NCIPC) Initial Review Group (IRG).

Times and Dates: 6:30 p.m.–10 p.m., April 10, 2006. 8:30 a.m.–6 p.m., April 11, 2006. 8 a.m.–5:30 p.m., April 12, 2006.

Place: Hilton Atlanta Airport and Towers, 1031 Virginia Avenue, Atlanta, Georgia 30354.

Status: Open: 6:30 p.m.–7:15 p.m., April 10, 2006.

Closed: 7:15 p.m. to 10 p.m., April 10, 2006. 8:30 a.m. to 6 p.m., April 11, 2006. 8 a.m. to 5:30 p.m., April 12, 2006.

Purpose: This group is charged with providing advice and guidance to the Secretary, Department of Health and Human Services (HHS) and the Director, CDC, concerning the scientific and technical merit of grant and cooperative agreement applications received from academic institutions and other public and private profit and nonprofit organizations, including state and local government agencies, to conduct specific injury research that focuses on injury prevention and control.

Matters to be Discussed: Agenda items include an overview of the injury program, discussion of the review process and panelists responsibilities, and the review of, and vote on, applications. Beginning at 7:15 p.m., April 10, through 5:30 p.m., April 12, the Group will review individual research grant and cooperative agreement applications submitted in response to six Fiscal Year 2006 Requests for Applications (RFAs) related to the following individual research announcements: #06001, Research Grants to Prevent Unintentional Injuries; #06002, Dissertation Grant Awards for Violence-Related Injury Prevention Research in Minority Communities; #06003, Research Grants to Describe Traumatic Brain Injury Consequences; #06004, Grants for Violence-Related Injury Prevention Research: Youth Violence, Suicidal Behavior, Child Maltreatment, Intimate Partner Violence, and Sexual Violence; #06005, Research Grants for the Care of the Acutely Injured; #06007, Evaluation of Community-based Approaches to Increasing Seat Belt Use Among Adolescent Drivers and Their Passengers.

This portion of the meeting will be closed to the public in accordance with provisions set forth in section 552b(c)(4) and (6), Title 5, U.S.C., and the Determination of the Director, Management Analysis and Services Office, CDC, pursuant to section 10(d) of Public Law 92–463.

Agenda items are subject to change as priorities dictate.

For Further Information Contact: Gwendolyn H. Cattledge, Ph.D., M.S.E.H., Executive Secretary, NCIPC IRG, CDC, 4770 Buford Highway, NE, M/S K02, Atlanta, Georgia 30341–3724, telephone 770/488–4655.

The Director, Management Analysis and Services Office has been delegated the authority to sign **Federal Register** Notices pertaining to announcements of meetings and other committee management activities for both CDC and the Agency for Toxic Substances and Disease Registry.

Dated: March 3, 2006.

Alvin Hall,

Director, Management Analysis and Services Office, Centers for Disease Control and Prevention.

[FR Doc. E6–3346 Filed 3–8–06; 8:45 am]
BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

National Institute for Occupational Safety and Health Advisory Board on Radiation and Worker Health

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), the Centers for Disease Control and Prevention (CDC) announces the following committee meeting:

Name: Advisory Board on Radiation and Worker Health (ABRWH), National Institute for Occupational Safety and Health (NIOSH).

Time and Date: 10 a.m.–4 p.m., EST, Tuesday, March 14, 2006.

Place: Audio Conference Call via FTS Conferencing. The USA toll free dial in number is 1–866–643–6504, pass code of 9448550.

Status: Open to the public, but without a public comment period.

Background: The ABRWH was established under the Energy Employees Occupational Illness Compensation Program Act (EEOICPA) of 2000 to advise the President, delegated to the Secretary of Health and Human Services (HHS), on a variety of policy and technical functions required to implement and effectively manage the new compensation program. Key functions of the Board include providing advice on the development of probability of causation guidelines which have been promulgated by HHS as a final rule, advice on methods of dose reconstruction which have also been promulgated by HHS as a final rule, advice on the scientific validity and quality of dose

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
Technical Reports Review Subcommittee Meeting
June 12, 2006

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*** Not in attendance