National Toxicology Program

Technical Report Peer Review Panel Meeting

June 25, 2015

National Institute of Environmental Health Sciences

Research Triangle Park, NC

Peer Review Report

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Summary Minutes

Table of Contents

I. Attendees

Peer Review Panel Members:
Russell Cattley (via WebEx)
Michael Conner (via WebEx)
Willem Faber (via WebEx)
Susan Felter (via WebEx)
Gabriele Ludewig (via WebEx)
Kenneth Portier (panel chair)
Donald Stump (via WebEx)

NTP Board of Scientific Counselors Representative:
Mary Beth Genter (via webcast)

Other Federal Agency Staff:
Paul Howard, FDA (via WebEx)

National Institute of Environmental Health Sciences (NIEHS) Staff:

Mamta Behl	Michelle Hooth	Georgia Roberts
Linda Birnbaum	Angela King-Herbert	Kristen Ryan
Chad Blystone	Grace Kissling	Robert Sills
John Bucher	Robin Mackar	Vicki Sutherland
Natasha Catlin	David Malarkey	Gregory Travlos
Helen Cunny	Barry McIntyre	Molly Vallant
Michael DeVito	Mark Miller	Suramya Waidyanatha
June Dunnick	Dan Morgan	Nigel Walker
Susan Elmore	Esra Mutlu	Kristine Witt
Paul Foster	Tanasa Osborne	Mary Wolfe
Dori Germolec	Arun Pandiri	Yun Xie
Robbin Guy	Cynthia Rider	

Contract Staff to NIEHS
Charles Alden, Kelly Services
Amy Brix, Experimental Pathology Labs, Inc.
Steven Brecher, CSS-Dynamac
Sudha Iyer, CSS-Dynamac
Kyathanahalli Janardhan, Integrated Laboratory Systems
Ramesh Kovi, Experimental Pathology Labs, Inc.
Varghese Tharakan, CSS-Dynamac
Cynthia Willson, Integrated Laboratory Systems

Public Attendees
Kira Bradford, UNC-Chapel Hill
Ernie Hood, Bridport Services

II. Welcome and Introductions

The National Toxicology Program (NTP) Technical Report Peer Review Panel Meeting convened on June 25, 2015, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. Dr. Kenneth Portier served as chair. The other panelists attended via WebEx. Dr. Mary Beth Genter attended by webcast as the NTP Board of Scientific Counselors liaison and Dr. Paul Howard attended via WebEx, representing the FDA.

Dr. Portier welcomed everyone to the meeting and asked all attendees to introduce themselves. Dr. Linda Birnbaum, director of NIEHS/NTP, welcomed everyone attending. Dr. John Bucher, associate director of NTP, welcomed participants and thanked the panel members and staff for their work. Designated Federal Officer Dr. Yun Xie read the conflict of interest policy statement.

III. Peer Review of Draft NTP Technical Report: Charge

Dr. Chad Blystone, toxicologist in the Toxicology Branch of the Division of NTP (DNTP), briefly reviewed the Levels of Evidence of Carcinogenic Activity guidelines used to express the draft NTP conclusions. He also stated the panel's charge.

IV. Incorporation of Perinatal Exposures into NTP Bioassays

Dr. Paul Foster, chief of DNTP Toxicology Branch, briefed the panel on incorporation of perinatal exposures into NTP bioassays.

He reported on the major conclusions and outcomes of several workshops that provided background for the new practices, particularly a 2006 workshop called "Hormonally Induced Reproductive Tumors – Relevance of Rodent Bioassays." As a result of that workshop, NTP moved from the inbred F344 rat to an outbred rat stock, first the Wistar Han and later the Harlan Sprague-Dawley. NTP refined procedures in new versions of the NTP specifications for carcinogenicity and reproductive toxicity testing. NTP also changed the default exposure paradigm to include pregnancy and early life exposures in rat cancer bioassays.

Dr. Foster defined the perinatal bioassay and its differences from the conventional rat cancer bioassay, and provided several reasons for utilizing it, including the ability to better characterize early life exposure and cancer outcome. The default practice for NTP is to conduct perinatal cancer bioassays unless there is a scientific reason not to do so. He noted some preliminary dose-range finding information would be required to determine dose levels. He provided details about the analysis of data from the perinatal studies. Multiple pups are selected from each exposed litter. This raised an issue that needed to be addressed: namely that pups within a litter tend to be more like each other

than pups from another litter, resulting in the need for analysis models to estimate both the litter-to-litter variation and a within-litter variation terms and accounts for these sources of variation in subsequent statistical tests. NTP's approach for analyzing these data is to use mixed effects models, which use data from each pup while accounting for within-litter correlations.

Panelist Dr. Russell Cattley asked whether the process of selecting animals from the litters at weaning is random within gender. Dr. Foster replied that it is.

Panelist Dr. Donald Stump asked why postnatal day 12 is used for starting the dosing. Dr. Foster said that PD12 is generally when the pups normally begin to eat diet in a feeding study, thus emulating feeding exposure in a gavage-type study.

V. NTP Toxicology and Carcinogenesis Studies of a Pentabromodiphenyl Ether Mixture [DE-71 (Technical Grade)] NTP (TR 589)

A. Presentations

NTP Study Scientist Dr. June Dunnick briefed the panel on the draft NTP Technical Report on DE-71. The California Office of Environmental Health Hazard Assessment and others nominated pentabromodiphenyl ethers to NTP for study. Pentabromodiphenyl ethers are flame retardants that are bioaccumulative and persistent organic pollutants. DE-71 (technical grade), a mixture of pentabromodiphenyl ethers, was studied because it is what is produced and is representative of exposure to humans, which is widespread.

Gavage studies were conducted in F344/N rats (3-month), Wistar Han rats (2-year), and B6C3F1/N mice (3-month and 2-year).

The 3-month rat study showed that the liver and thyroid are target organs of treatment-related toxicity. Based on the 3-month rat study findings, a top dose of 50 mg/kg was chosen for the 2-year rat study. Based on 3-month mouse study findings, a top dose of 100 mg/kg was chosen for the 2-year mouse study.

Based on the 2-year studies, the draft NTP report's conclusions for DE-71 (technical grade) are:

Male Wistar Han Rats

- ***Clear evidence of carcinogenic activity***
  - Increased incidences of hepatocholangioma, hepatocellular adenoma, or hepatocellular carcinoma (combined)
- Related to exposure (some evidence):
  - Increased incidences of thyroid gland follicular cell adenoma or carcinoma
  - Increased incidences of pituitary gland (pars distalis) adenoma

Female Wistar Han Rats

- ***Clear evidence of carcinogenic activity***
  - Increased incidences of hepatocholangioma, hepatocellular adenoma, and hepatocellular carcinoma.
- Related to exposure (some evidence):
  - Occurrence of cholangiocarcinoma of the liver
- May have been related to exposure (equivocal evidence):
  - Incidences of stromal polyp or stromal sarcoma (combined) of the uterus

Male B6C3F1/N mice

- ***Clear evidence of carcinogenic activity***
  - Increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma

Female B6C3F1/N mice

- ***Clear evidence of carcinogenic activity***:
  - Increased incidences of hepatocellular adenoma and hepatocellular carcinoma

Administration of DE-71 resulted in increased incidences of nonneoplastic lesions in the liver, thyroid gland, kidney, parotid salivary gland, prostate gland, preputial gland, thymus, and forestomach of male rats; liver, thyroid gland, uterus, cervix, kidney, and adrenal cortex of female rats; liver, thyroid gland, forestomach, adrenal cortex, and testes of male mice; and liver, thyroid gland, forestomach, and adrenal cortex of female mice.

Questions for Clarification

Panelist Dr. Susan Felter noted that the dose-selection range-finding study was conducted in the F344/N rat, while the 2-year bioassay was done in the Wistar Han. She asked what kind of experience NTP has had in terms of being able to predict responses between the strains. Dr. Dunnick noted that the same switch had been done in two other NTP studies, including a study of tetrabromobisphenol A. Other scientists, such as those from EPA, have also been working with pentabromodiphenyl ethers in different strains of rats. Other studies have consistently found liver and thyroid toxicity across the different strains and species. Dr. Nigel Walker, DNTP Deputy Division Director for Science, said that during the transition in rat strains, the decision was made not to go back and redo many studies. He also noted that there are considerable data in the literature to support the dose selection for the study.

Dr. Felter asked whether the maximum tolerated dose (MTD) was exceeded in the male rats based on survival data. Dr. Dunnick said that the MTD was not exceeded because the decrease in survival in male rats at the high dose is due to the development of pituitary adenomas. Dr. Felter asked why the pituitary tumors were used as evidence that the MTD was not exceeded. She indicated that because they are benign tumors they are allowed no weight in assessing the conclusion of clear evidence of cancer. Dr.

Dunnick said that the pituitary adenomas were considered “some evidence” for a carcinogenic effect. The mid-dose findings in the uterus is characterized as “may have been related to exposure” because these are primarily benign tumors and are not significantly different from controls at the high dose by pair wise comparison. Dr. Ludewig asked whether the conclusion would be different if the high dose results are removed in the analysis and only the data from the other lower doses are used in the analysis. Dr. Grace Kissling, NIEHS statistician, replied that such an analysis would probably result in a finding of marginally statistically significant increase.

B. Public comments

Dr. Portier confirmed that no written public comments were sent to NTP and no one had registered to provide oral comments by phone. He asked for oral public comments from those in the room; there were none.

C. Peer reviewer comments

Dr. Cattley, the first reviewer, asked for clarification on which specific endpoints were considered to reflect “minimal liver toxicity” for the lowest dose levels with respect to the various changes in organ weight, enzyme induction, histological lesions, or clinical pathology findings. He asked for the diagnostic criteria used with the hepatocholangiomas, and how they were distinguished from a “hepatocellular adenoma with some dilated, non-neoplastic bile ducts”. He asked about distinguishing cholangiocarcinoma from cholangiofibrosis and suggested that if there is a published criterion for that differentiation, it should be included and cited. For the description of the mechanism of action, Dr. Cattley suggested adding a table listing evidence for the activation of different nuclear receptors by components of DE-71.

Regarding the conclusion that the occurrence of cholangiocarcinoma of the liver in female rats is related to exposure, Dr. Cattley noted the lack of historical controls. While he agreed with the overall conclusion that there is “clear evidence of carcinogenic activity” in the female rat, he asked whether the evidence concerning cholangiocarcinoma should be considered “equivocal” rather than “some evidence.” In male rats, for the conclusion that increased incidences of thyroid gland follicular cell adenoma or carcinoma is related to exposure, Dr. Cattley noted there were no carcinomas in the high dose group. There is a limited number of historical controls for gavage studies in this strain and he suggested limiting the conclusion to adenomas alone.

Panelist Dr. Michael Conner, the second reviewer, agreed with Dr. Cattley’s suggestion to reword the conclusion to reflect increased incidences of thyroid gland follicular cell adenoma alone. He noted that the report should state explicitly the significance level, which appears to be 0.05. For the conclusion of a carcinogenic effect based on hepatic tumors in male rats, he asked if the conclusion was referring to the combined

incidences of “hepatocholangioma, hepatocellular adenoma, and hepatocellular carcinoma”.

Regarding dose selection for the 2-year study, Dr. Dunnick said that the lower doses were chosen to give a broader range of doses.

Study pathologist Dr. Amy Brix responded to Dr. Cattley’s comments about the hepatocholangiomas. She said that they (hepatocholangiomas) are thought to arise from cells that can differentiate into both hepatocytes and biliary cells. In this study, they were distinguished from hepatocellular adenomas with dilated, nonneoplastic bile ducts by the increased number of bile ducts within hepatocholangiomas. Hepatocellular adenomas typically lack bile ducts. In addition, the epithelium of the biliary component of the hepatocholangiomas was cuboidal, in contrast to the typically flattened epithelium found in biliary cysts. Regarding the cholangiocarcinomas, she said that distinguishing between cholangiofibrosis and cholangiocarcinoma is difficult to do, and is primarily based on the extent of liver invasion. Dr. Brix noted that after extensive discussion within the NTP Pathology Working Group, some of the lesions were determined to be cholangiocarcinomas.

Regarding the thyroid, Dr. Brix said that progression from follicular cell adenomas to carcinomas, as with many endocrine proliferative lesions, is commonly seen in laboratory rodents. Thus, it made sense when interpreting the results from this study to consider those lesions together, even if it does not change the statistical conclusions.

Regarding Dr. Cattley’s comment about the mechanism of action, Dr. Dunnick said that it was not possible to determine which component of the mixture might contribute to a particular effect. Many of the components have not been tested alone because it is difficult to acquire sufficient amounts of purified agents.

Regarding Dr. Conner’s question about P-values, Dr. Kissling said that statistical results are one piece of evidence the team examines when interpreting results. Although P-values are calculated, there is not a strict decision to accept or reject hypotheses, and P-values are considered in the wider context of the biological issues. Dr. Dunnick added that cholangiocarcinomas were not seen in any of the previous studies using the Wistar Han rat. Dr. Walker noted that cholangiocarcinomas were quite rare in this study and were considered related to treatment, leading to the conclusion of “some evidence of carcinogenic activity”.

Dr. Conner asked whether the hepatocholangiomas alone were being considered as evidence of carcinogenicity. Dr. Dunnick said that the conclusion is based on combined occurrence of “hepatocholangioma, hepatocellular adenoma, or hepatocellular

carcinoma". He suggested including the term "combined" early in the report to clarify that point.

Dr. Cattley asked whether the conclusion regarding the liver cholangiocarcinomas should be "some evidence," as written, or " equivocal." Dr. David Malarkey, pathology group leader of DNTP's Cellular and Molecular Pathology Branch, noted that in the report, those tumors are "also considered related," which would mean the category of some evidence. Dr. Cattley drew a distinction between "may have been related" and "considered related." Dr. Malarkey said that the tumor has not been seen previously in NTP studies in thousands of animals in multiple strains, which adds to the conclusion of "some evidence." Dr. Cattley asked if there were any data on this strain and the incidence of the lesion. Dr. Malarkey said there are six studies, and the lesion is not seen in related controls. Dr. Cattley noted that two of those were gavage studies, and observed that "equivocal" does not mean not related. Dr. Walker confirmed that the cholangiocarcinomas are not combined with the hepatocellular tumors, which is why they stand alone in the conclusions. They were also considered related to treatment, leading to the "some evidence" conclusion.

Dr. Felter, the next reviewer, noted that the text indicated a positive trend for cholangiocarcinomas in the female rats, but this tumor was not listed in Table B2. She asked about dosing in the rats and whether the MTD was exceeded. She noted that many of the effects are only seen at the highest dose. She suggested that additional information be added to the section on survival.

Panelist Dr. Gabriele Ludewig provided her review comments. She asked why the NTP-2000 diet was used for all studies and NIH-07 was used during pregnancy. She noted there can be strong effects based on diet. With respect to blood cells, she noted that there are decreases in reticulocytes and the ratio of polychromatic erythrocytes to micronucleated normochromatic erythrocytes; lower leucocytes, lymphocytes, neutrophils, and eosinophils; and more lymphomas. The report states that there is no bone marrow toxicity and hemotoxicity. She asked for further discussion in the report. She noted that there is an increase in liver lipids in the F1 rats, which should be added to Results. She did not find the citation of the studies of polybrominated diphenyl ether congeners that is mentioned. She also suggested adding several citations regarding AhR activation and inhibition, impurities in DE-71 as AhR agonists, and β-catenin in tumors.

Dr. Dunnick said that the cholangiocarcinoma would be added to table B2 as recommended by Dr. Felter. Regarding Dr. Ludewig's question about diet, she explained that the NIH-07 diet is used during lactation and development to provide adequate nutrition during those phases of the study, and the NIH-2000 diet is used as the maintenance diet in adult animals because of reduced proteins levels to reduce

incidences of chronic nephropathy. Regarding blood cells, she said there is a downward trend in the ratio of polychromatic erythrocytes to micronucleated normochromatic erythrocytes; however, none of the dose groups differed significantly from the control group. The conclusion is that the small alteration is not biologically significant. Decreases in leukocyte and lymphocyte levels are considered to be stress-related. She briefly explained the approach for measuring polybrominated diphenyl ether levels in tissues, noting that polybrominated diphenyl ether congeners are used as standards. She noted more information would be added regarding the standards and their purity. She thanked Dr. Ludewig for the suggested references.

Panelist Dr. Willem Faber was the next reviewer. He asked for greater detail regarding the necropsy schedule and schedule for obtaining the blood samples for thyroid hormone and thyroid stimulating hormone levels, as those values can change depending on time of day. He pointed out the use of the term “perinatal” period for when the F0 dams were in quarantine and suggested that “preimplantation” period was intended. He asked for clarification on descriptions of dose administration, which should have been continuous, rather than on a five-day-per-week schedule reported. He said the report should state clearly that the body weight values were collected daily on the dams during gestation and lactation and should specify what body weight values were used to determine dosing volume. The same should be done for the pups.

Dr. Stump was the final peer reviewer. He asked for an explanation in the Methods section for why dosing began in the pups on postnatal day 12; this design is different than what NTP has used in the past. He noted the pregnancy rate seemed quite low in the study. The pregnancy rate looked to be about 85 percent, and he expected the rate to be at least 90 percent.

Dr. Dunnick said that blood was collected and the necropsies were conducted over approximately a two-hour period in the morning from 8-10am. The animals were necropsied by a randomized schedule across doses. Dams were quarantined throughout the perinatal period, which was upon arrival up to the end of lactation. The dams were dosed and weighed daily, and the weight from the previous day was used to calculate the dose on the following day. Regarding reproductive endpoints, she said that NTP specifications were followed for sperm analysis and noted the small decrease in sperm motility was treatment-related. She added that the Wistar Han strain did not have as high a pregnancy rate as the Sprague Dawley, which was one of the reasons for switching to the Sprague Dawley. She explained that dosing began at postnatal day 12 because that is when the pups begin to eat. NTP tried to make the exposures consistent with their natural physiology and behavioral patterns.

D. Panel discussion and votes

Dr. Portier requested a motion and second on the draft conclusions to initiate the panel discussion. Dr. Portier asked to move the discussion one species and one sex at a time. He asked for a motion to accept the conclusions on the male Wistar Han rats. Dr. Conner moved to accept the conclusions as written. Dr. Felter seconded the motion. Dr. Portier opened the panel discussion on those conclusions.

Dr. Cattley recommended deleting the words “or carcinoma” in the second bullet point (regarding thyroid tumors) under conclusions for the male Wistar Han rat. Dr. Conner agreed. Dr. Walker said that the carcinomas were included because it was a plausible mechanism due to a decrease in thyroid T4, increase in thyroid stimulating hormone levels, and occurrences of thyroid nonneoplastic lesions. Including them fit in with the whole mechanism of thyroid carcinogenesis, with the carcinomas in the lower dose group almost certainly related to treatment.

Dr. Cattley said that dropping the “or carcinoma” phrase would not take away from the mechanism described by Dr. Walker. Dr. Conner said that the data associated with the carcinomas do not seem to be treatment-related. Dr. Walker noted that no follicular cell carcinomas were seen in the 295 historical controls assessed across all routes of exposure. The combination of mechanism and the historical control data led to the conclusion as written.

Dr. Felter asked whether the evidence for carcinoma is strong enough that the conclusion would be the same without reference to the adenomas. If not, she agreed that it should be deleted from the conclusion. Dr. Blystone said that the carcinomas alone would not rise to an evidence category. Dr. Brix pointed out that there is decreased survival in the high dose.

Dr. Malarkey pointed out that a progression from adenoma to carcinoma is often seen. Also, a substantial percentage of animals had hypertrophy, so the thyroid gland follicular cell is a target. Dr. Stump suggested including an explanation that a potential reason the carcinomas were not seen in the high dose group is due to reduced survival, which would make a stronger case for including the carcinoma in the conclusion statement.

Dr. Ludewig said that the fact that the carcinoma is an extremely rare cancer in the control animals should be weighted heavily. Thus, there is evidence that the occurrence in the study animals was related to exposure. Different activation and antagonistic effects with respect to receptor action could be a mechanism to explain why no carcinomas were seen in the high doses. She would keep the conclusion as written.

Dr. Conner said that in the absence of a dose response, it is less plausible that the carcinoma is a treatment-related effect. As a non-genotoxic mechanism, a dose-related increase in tumors would be expected.

There was further discussion on the meaning of "or" in the phrase "or carcinoma" and if adding "(combined)" at the end of the sentence would be better. The language for explaining the levels of evidence categories was also discussed.

Dr. Portier called for a vote on the original motion, which was to agree with the conclusions as written on male Wistar Han rats. There was one vote in favor of the motion and five votes against. Rather than ask for explanations of the no votes, Dr. Portier elected to ask for an alternative motion.

Dr. Conner moved to accept the conclusions with "or carcinoma" being struck. Dr. Cattley seconded the motion. Dr. Malarkey asked whether the conclusion regarding carcinoma should be changed from "some evidence" to "equivocal evidence" after being removed from the conclusion. Dr. Conner supported that change.

Dr. Portier called for a vote on the motion. The panel voted (4 yes, 2 no, 0 abstentions) to accept the motion. Drs. Ludewig and Stump voted against the motion. Both explained that they preferred to keep the "adenomas or carcinomas" statement. Thus, the panel recommended the following amended conclusions for male Wistar Han rats:

Male Wistar Han Rats

- ***Clear evidence of carcinogenic activity***
  - Increased incidences of hepatocholangioma, hepatocellular adenoma, or hepatocellular carcinoma (combined)
- Related to exposure (some evidence):
  - Increased incidences of thyroid gland follicular cell adenoma
  - Increased incidences of pituitary gland (pars distalis) adenoma

Dr. Portier called for a motion on the female Wistar Han rat conclusions. Dr. Conner moved to accept the conclusions as written. Dr. Ludewig seconded the motion. The panel voted (5 yes, 1 no, 0 abstentions) to accept and the motion. Dr. Cattley explained he voted no because the evidence regarding cholangiocarcinoma fits an equivocal call.

Dr. Portier called for a motion on the male mice conclusion. Dr. Stump moved to accept the conclusions as written. Dr. Cattley seconded the motion. The panel voted unanimously (6 yes, 0 no, 0 abstentions) to accept the motion.

Dr. Portier called for a motion on the female mouse conclusion. Dr. Faber moved to accept the draft language as written. Dr. Conner seconded the motion. Dr. Felter noted that the use of "and" versus "or" in the language of the conclusions should be clearer. He called for the vote. The panel voted unanimously (6 yes, 0 no, and 0 abstentions) to accept the motion.

Dr. Portier asked the panel members if they had any final comments. Dr. Conner noted that the NTP technical reports are used a lot and are frequently read. He said that in recent years they have been getting better, in terms of being more comprehensive and clearly written.

The following are the amended conclusions for a pentabromodiphenyl ether mixture [DE-71 (Technical Grade)] recommended by the panel:

Male Wistar Han Rats

- ***Clear evidence of carcinogenic activity***
  - Increased incidences of hepatocholangioma, hepatocellular adenoma, or hepatocellular carcinoma (combined)
- Related to exposure (some evidence):
  - Increased incidences of thyroid gland follicular cell adenoma
  - Increased incidences of pituitary gland (pars distalis) adenoma

Female Wistar Han Rats

- ***Clear evidence of carcinogenic activity***
  - Increased incidences of hepatocholangioma, hepatocellular adenoma, and hepatocellular carcinoma.
- Related to exposure (some evidence):
  - Occurrence of cholangiocarcinoma of the liver
- May have been related to exposure (equivocal evidence):
  - Incidences of stromal polyp or stromal sarcoma (combined) of the uterus

Male B6C3F1/N mice

- ***Clear evidence of carcinogenic activity***
  - Increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma

Female B6C3F1/N mice

- ***Clear evidence of carcinogenic activity***:
  - Increased incidences of hepatocellular adenoma and hepatocellular carcinoma

Administration of DE-71 resulted in increased incidences of nonneoplastic lesions in the liver, thyroid gland, kidney, parotid salivary gland, prostate gland, preputial gland, thymus, and forestomach of male rats; liver, thyroid gland, uterus, cervix, kidney, and adrenal cortex of female rats; liver, thyroid gland, forestomach, adrenal cortex, and testes of male mice; and liver, thyroid gland, forestomach, and adrenal cortex of female mice.

Dr. Bucher thanked everyone who prepared for the peer review, and thanked the panel members for their hard work at the meeting. Given that the format of the meeting is new, he asked the panel to provide feedback about the format to NTP staff after the meeting. Dr. Portier also thanked the panel and adjourned the proceedings at 4:30 PM, June 25, 2015.

This peer review report has been read and approved by the Chair of the June 25, 2015, National Toxicology Program Technical Report Peer Review Panel.

[Signature Redacted]

Kenneth M. Portier, Ph.D.

Chair, NTP Technical Report Peer Review Panel

Date: 9/10/2015