National Toxicology Program

Peer Review of the Draft NTP Technical Reports on Cell Phone Radiofrequency Radiation

March 26–28, 2018

National Institute of Environmental Health Sciences
Research Triangle Park, NC

Peer-Review Report

Table of Contents

I. Attendees

Peer-Review Panel Chair
David Eaton, University of Washington

Peer-Review Panel 1
Provided consultation on the reverberation chamber exposure system
Frank Barnes, University of Colorado (retired)
Asimina Kiourti, The Ohio State University (present for Days 1 and 2)
James Lin, University of Illinois at Chicago (retired)

Peer-Review Panel 2
Provided input on study findings and voted on NTP's draft conclusions
Rick Adler, GlaxoSmithKline
Lydia Andrews-Jones, Allergan, Inc.
J. Mark Cline, Wake Forest School of Medicine
George Corcoran, Wayne State University
Susan Felter, Procter & Gamble
Jack Harkema, Michigan State University
Wolfgang Kaufmann, Merck (retired)
Tyler Malys, Data Management Services
Kamala Pant, BioReliance
Matthias Rinke, Bayer Pharma AG (retired)
Laurence Whiteley, Pfizer

Technical Experts
Myles Capstick, IT'IS Foundation
Niels Kuster, IT'IS Foundation
John Ladbury, National Institute of Standards and Technology

NTP Board of Scientific Counselors Representative
Donald Stump, Charles River Laboratories

National Institute of Environmental Health Sciences Staff
Edward Adams
Chad Blystone
John Bucher
Mark Cesta
Michelle Cora
Helen Cunny
Mike DeVito
Darlene Dixon
June Dunnick
Susan Elmore
Gordon Flake
Christine Flowers
Dori Germolec
Virginia Guidry
Janice Harvey
Ron Herbert
Michelle Hooth
Troy Hubbard
Daven Jackson-Humbles
Gloria Jahnke
Angela King-Herbert
Ramesh Kovi
Grace Kissling (retired)
Gregory Krane
Kelly Lenox
Ruth Lunn
Debabrata Mahapatra
David Malarkey
Suril Mehta
Alex Merrick
Arun Pandiri
Fred Parham
Rick Paules
Georgia Roberts

Andy Shapiro
Keith Shockley
Robert Sills
Matt Stout
Vicki Sutherland
Molly Vallant
Andrea Vornoli
Nigel Walker
Amy Wang
Atlee Watson
Donna Webb
Kristine Witt
Mary Wolfe
Michael Wyde

Federal Agencies
Goncalo Gamboa da Costa, Food and Drug Administration
Galen Koepke, National Institute of Standards and Technology (retired)
Russell Owen, U.S. Environmental Protection Agency
Ed Mantiply, Federal Communications Commission
Ed Margerrison, Food and Drug Administration

Contract Staff to NIEHS
Terry Adams, ILS
Susan Blaine, ICF
Steven Brecher, CSS Inc.
Amy Brix, EPL
Canden Byrd, ICF
Sheba Churchill, Charles River Laboratories
Margarita Gruebbel, EPL
Kate Helmick, ICF
Georgette Hill, ILS
Kyathanahalli Janardhan, ILS
Peter Little, EPL
Jeanne Luh, ICF
Kelly Shipkowski, ICF
Marjo Smith, SSS
Tom Steinbach, EPL
Gabrielle Willson, EPL
Cynthia Wilson, ILS

Public Attendees
Young Hwan Ahn, Ajou University, South Korea (by phone)
Dave Anderson, ABC11
Marc Arazi, Phonegate Alert Association
Carl Blackman, Wake Forest University
Andrea Blanford, ABC11
Devra Davis, Environmental Health Trust and The Hebrew University
Joe Elder, consultant
Paul Heroux, McGill University
Ernie Hood, Bridport Services
Ron Melnick, Ron Melnick Consulting, LLC (NIEHS/NTP retired)
Kevin Mottus, California Brain Tumor Association
John Murawski, News & Observer
Hiroaki Myagi, consultant
Olga Naidenko, Environmental Working Group
Robert Richardson, CBS17
Annie Sasco, Inserm (retired)
Theodora Scarato
Louis Slesin, Microwave News
Kristopher Vorren, Duke University

Day 1: March 26, 2018

II. Welcome and Introductions

The peer review of the Draft NTP Technical Reports on Cell Phone Radiofrequency Radiation was convened March 26–28, 2018 in Rodbell Auditorium, Rall Building, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. Dr. David Eaton served as chair. Other peer-review panel members in attendance were Drs. Rick Adler, Lydia Andrews-Jones, Frank Barnes, J. Mark Cline, George Corcoran, Susan Felter, Jack Harkema, Wolfgang Kaufmann, Asimina Kiourti, James Lin, Tyler Malys, Matthias Rinke, and Laurence Whiteley, and Ms. Kamala Pant. Dr. Donald Stump attended as the NTP Board of Scientific Counselors liaison. Interested members of the public attended the meeting in person or watched the proceedings via webcast.

Dr. Eaton welcomed everyone to the meeting and asked all in-person attendees to introduce themselves. Dr. John Bucher welcomed participants, thanked the panel, and provided an orientation to the 3-day meeting. Designated Federal Official Dr. Mary Wolfe read the conflict of interest statement and asked panel members to sign updated conflict of interest forms. Dr. Eaton presented the meeting format, with Day 1 devoted to the technical aspects of the radiofrequency radiation (RFR) exposure facility, Day 2 addressing the mouse studies, and Day 3 covering the rat studies. Slide presentations for the meeting are available on the NTP website (https://ntp.niehs.nih.gov/go/Presentations_RFR).

III. Panel 1: Peer Review of Exposure System for NTP Studies on Cell Phone RFR

III.A. Charge

Dr. Chad Blystone presented the Day 1 charge to the panel: to assess the reverberation chamber technology for evaluating the effects of cell phone RFR exposure in rats and mice.

III.B. Nomination, NTP's Considerations for Toxicological Evaluation of Radiofrequency Radiation Exposure in Rodents, and Background on Exposure System Selection

Dr. Michael Wyde described the NTP nomination of cell phone RFR exposure by the U.S. Food and Drug Administration (FDA) in 1999. The nomination was based on widespread and expanding human exposure, with little known about potential long-term health effects and insufficient data to assess risk to human health. The FDA and the Federal Communications Commission (FCC) share regulatory responsibility for RFR.

Dr. Wyde provided information about the background of the program, including establishment of research collaborations with RFR experts at the National Institute of Standards and Technology (NIST) and the IT'IS Foundation in Zurich, Switzerland. The IIT Research Institute (IITRI) in Chicago was chosen as the study laboratory. He discussed previous RFR toxicology studies and the selection of the exposure system for the NTP studies: frequencies of 900 MHz (rat) and 1900 MHz (mouse) with both Global System for Mobile communications (GSM) and Code Division Multiple Access (CDMA) modulations, reflecting the standards in use when the study began. He described the reverberation chamber exposure system designed for the initiative.

Twenty-one reverberation chambers were constructed in Switzerland: seven each for mice, male rats, and female rats; male and female rats were separated due to weight differences

between the sexes. For mice, male rats, and female rats, each group had separate low, medium, and high dosage chambers for the GSM and CDMA modulations, plus one common control chamber. Dosage for RFR is measured as specific absorption rate (SAR).

The toxicology and carcinogenicity studies, consisting of three phases, were conducted on B6C3F1/N mice and Hsd:Harlan Sprague Dawley rats.

- 5-day thermal pilot studies at SARs of 4–12 Watts/kilogram (W/kg) in young and aged mice and rats and pregnant rats (10 studies) – presented on Day 1
- 28-day prechronic toxicology studies – presented on Days 2 (mice) and 3 (rats)
- 2-year toxicology and carcinogenicity studies – presented on Days 2 (mice) and 3 (rats)

In all studies, daily exposure to RFR in the reverberation chambers totaled 9 hours, 10 minutes per day—18 hours, 20 minutes per day in 10-minute on-off cycles. The system generating the signals ran continuously, alternating exposure to the GSM and CDMA groups.

III.B.1. Questions for Clarification

Dr. Harkema asked whether the study design had been flexible, given the project would be lengthy and inevitably the technology would change. Dr. Wyde said the program was locked into the technologies in use at the time, because switching during the course of the studies would have been very expensive.

Dr. Cline asked about the provenance of the cell phone usage information presented in Dr. Wyde's slides. Dr. Wyde said that most of the information had come from surveys. Dr. Cline also asked if the animals could perceive whether the machine was on or off and what kind of emissions were perceptible with the exposure. Dr. Wyde deferred this question for discussion during the toxicology portion of the studies.

Dr. Eaton asked about the involvement of light-cycle circadian rhythms in the exposure schedules, noting that mice and rats are nocturnal animals. Dr. Wyde described the two husbandry periods: one in the early morning and one in the afternoon. The exposures continued throughout the night, and circadian rhythms were not taken into account.

Dr. Lin asked about the presence of mechanical noise, particularly as related to stirrers or paddles. He asked if the stirrers were turned on in the control chambers. Dr. Wyde confirmed the stirrers were turned on in the control chambers. Dr. Lin asked about the sequence of the exposures. Dr. Wyde explained that the system that generated the signals alternated between GSM and CDMA, but all animals were exposed to only one of the modulations.

Dr. Barnes asked about the statistical variation of rodent exposure between the chambers. Dr. Wyde deferred the answer to Dr. Myles Capstick's talk.

III.C. Reverberation Chamber System for RFR Exposures

Dr. Capstick from the IT'IS Foundation briefed the panel on the physical and environmental design of the reverberation chambers. Requirements included:

- Ability to expose large numbers of rodents
- Ability to expose to a high SAR up to 20 hours per day
- Animals to be unconstrained and housed in standard laboratory cages
- Food and water to be available on demand
- Excellent field and SAR homogeneity

- Detailed dosimetry (numerical and experimental)
- Ability to discern a possible dose response
- Third-party verification of the correct operation of the system

Several elements were involved in the rationale for the selection of the exposure, including frequency, modulation, and extremely low frequency envelope. Dr. Capstick described the GSM and CDMA modulation methods. The reverberation chambers were described, including:

- Two mode stirrers per chamber to achieve high field homogeneity and isotropy (including stirrer speeds)
- Standard gain antennas
- Air flow system
- Chamber design
- Lighting (per specific NTP requirements)
- Chamber field uniformity
- Exposure field uncertainty
- Noise
- Air handling
- Drinking water provision/Automatic watering system
- Stirrers and sensors
- Control equipment and amplifiers
- Data acquisition

Details on aspects of the reverberation chamber listed above are included in Dr. Capstick's online presentation.[1] The constructed chambers were shipped from Switzerland to Chicago, where they were installed in a specially designed facility.

III.C.1. Questions for Clarification

Dr. Whiteley asked whether the animals were rotated in the caging. Dr. Capstick said that, as the animals moved around the cages, any inhomogeneity was evened out. The cages were rotated twice per week. Dr. Whiteley asked whether the 10 minutes on, 10 minutes off approach was used for a biological reason. Dr. Capstick said previous studies had shown the intermittency of exposure was an important factor biologically. Dr. Kuster elaborated on the prior studies.

Dr. Lin asked for more information regarding the exposure alternation. Dr. Capstick explained that, for 10 minutes, the energy was sent to the GSM chambers, and in the following 10 minutes, it was sent to the CDMA chambers. The chambers and their exposures were separate.

Dr. Lin noted that the historical data had been gathered in conditions using fluorescent lighting, as opposed to the incandescent lighting chosen for the NTP experiments. He considered the different lighting sources weakened the comparison of this study with historical studies. Dr. Bucher responded that the issue highlights a perplexing aspect of the study when trying to bring a historical perspective to interpreting the tumor data. He noted several of the differences between the current study and previous studies, including lighting, food, housing, and exposure methods.

[1]The slides and video of Dr. Capstick's presentation on the reverberation chamber system for RFR exposures are available at https://ntp.niehs.nih.gov/go/Presentations_RFR (slides) and https://doi.org/10.22427/NTP-VIDEO-47 (video).

Dr. Harkema asked about the phantoms and activity of the animals affecting the dose they received. Dr. Capstick deferred the answer to the dosimetry talk. Dr. Harkema also commented about the lighting, noting that lighting studies on plants by other researchers are ongoing.

Dr. Felter asked about the basis for choosing the different radiofrequencies for mice versus rats. She asked how frequency selection applied to animals of different sizes. Dr. Capstick deferred the answer to the dosimetry talk.

Dr. Kiourti asked about the statistical variation of animal sizes and weights. Dr. Capstick deferred the answer to the dosimetry talk.

Dr. Cline asked Dr. Capstick to elaborate on the ambient noise within the rats' hearing range. Dr. Capstick said that the GSM noise was measured, and no components were above 14 kHz. He said that high-frequency noise emanating from the air conditioning equipment was not measured. Efforts were made to keep the stirrers well lubricated to minimize potential noise.

Dr. Lin asked about the GSM noise, and how it was transmitted into the chambers. Dr. Capstick replied the GSM noise was generated inside the chamber, but its origin was unclear, and efforts to dampen it were unsuccessful. Dr. Lin wondered if the noise was instead introduced from the electronics and power-transfer systems.

III.D. Dosimetric Considerations for Rodents Exposed in Reverberation Chambers

Dr. Capstick briefed the panel on dosimetry used in the cell phone RFR studies.

Dosimetry in the fields of health physics and radiation protection is the measurement, calculation, and assessment of the internal exposure to the body, expressed in Watts per kilogram (W/kg). Directly measuring SAR in a subject, human or animal, is not possible, so SAR is calculated using numerical simulations and is validated in homogenous experimental phantoms. High-resolution, anatomical models were used to determine numerical dosimetry, with tissue parameters based on published databases. Ultimately, the appropriate frequencies were determined to be 1900 MHz for mice and 900 MHz for rats to obtain a more uniform SAR distribution. Dosimetry in the reverberation chambers was calculated based on generation of a homogeneous, isotropic field, using Rayleigh-distributed, temporal variations. Exposure-environment measures used representations employing the random plane-wave method and the 12 plane-wave method.

An automated watering system was designed to ensure that no energy was absorbed by water, which would cause a dose-dependent elevation in drinking water temperature. Also, the system was designed to avoid increased SAR or RF burns to the animals, which could deter them from drinking.

The isotropic field employed ensured minimum variation in whole-body SAR with posture. Variation in organ-specific SAR was also taken into account. Dr. Capstick also presented details regarding uncertainty and variability estimates. Full details on the dosimetric considerations are included in Dr. Capstick's online presentation.[2]

[2]The slides and video of Dr. Capstick's presentation on the dosimetric considerations are available at https://ntp.niehs.nih.gov/go/Presentations_RFR (slides) and https://doi.org/10.22427/NTP-VIDEO-48 (video).

III.D.1. Questions for Clarification

Dr. Eaton expressed continued confusion about the units of SARs. Dr. Capstick explained that SAR is measured in watts per kilogram (W/kg) and that the limit for human exposure is SAR averaged over a 1-g or 10-g cube. He described how SAR was calculated in mice and rats over smaller cubes scaled to the relative adult weights. He explained that the measures in decibels (dB) used is a logarithmic ratio that can be related to either the whole-body average or the peak SAR. He explained how SAR sensitivity, the SAR per unit of electric field strength, is calculated.

Dr. Eaton said that although not the focus of the current studies, the data would be used for risk assessment at some point. He asked if anyone had derived modeled dosimetry in humans based on behaviors. Dr. Capstick said much work was ongoing in that area, particularly on exposures in children and device placement on the body.

Dr. Felter asked for clarification about how mass affects the measurement of SAR and if surface area has an effect. Dr. Capstick explained the concept of whole-body average SAR as an average over the mass. So, the larger the animal, for a given whole-body SAR, the more power is absorbed. He described the difference between organ-based SAR and whole-body SAR. His answer to the question about surface area explained that the ratio of surface area to total mass affects an animal's thermal regulation—a larger ratio means the animal can cool itself more quickly.

Dr. Kuster remarked that the study was run under the assumption that the fields locally induced in the tissue are the biologically relevant parameters, not the total absorbed power or whole-body averaged exposure. He noted that SAR and the square of the E-field are directly related, whereas the square of the local H-field (magnetic field) is sufficiently related for uniform exposures. As little is known about the radiofrequency sensitivity of specific tissues, the exposure was optimized for maximally uniform local E-field and H-field exposures.

Dr. Lin asked for more detail on organ-based SAR and whole-body-based SAR as it related to the figures Dr. Capstick presented on individual organ SAR differentials from whole body.

Dr. Melnick, retired NIEHS/NTP scientist and public attendee, was recognized by the chair for a question. He was concerned about the exposure of some of the sub-tissues in the heart. Dr. Kuster explained that the anatomical models provided a good proxy of exposure for different body regions and tissues, but no effort was made in this study to examine sub-tissues.

Dr. Felter asked about the pups, which were housed with the mother until weaning. She indicated her understanding was, when pups are clumped, their SAR can be increased, but when pups are apart, their exposure is similar to that of the dam. She asked why their estimated exposures would not be higher, given their much smaller body weight. Dr. Capstick explained that in terms of body weight and length, the pups are on an upward curve and the dams are on a downward curve, ending up at approximately the same SAR sensitivity.

III.E. Reverberation Chamber System Validation and Verification

John Ladbury from NIST briefed the panel on validation and verification of the reverberation chamber system. He provided background information on NIST and described the ideal characteristics of a reverberation chamber. The validation and verification plan emphasized uniformity of temperature in the phantoms, probe field, and antenna power. Validations were performed in 2007, 2012, and 2015. The standard deviation for the loaded chamber field uniformity was 1.3 dB. Calibration was performed with radiofrequency field probes. Signal quality was within standard parameters for communications standards. Full details on the

reverberation chamber system validation and verification are included in Mr. Ladbury's online presentation.[3]

III.E.1. Questions for Clarification

After remarking about the robustness of reverberation chambers, Dr. Lin asked why the reverberation chambers had not been built in Chicago. Dr. Bucher explained that the system was assembled through contractual arrangements with various organizations, including IT'IS. Mr. Ladbury noted, although commercial reverberation chambers are available, they are designed primarily for electronics testing, and at the time, none were available for biological testing.

Dr. Cline asked if he was correct that no measurements were taken in the control chambers. Mr. Ladbury confirmed that no measurements were made in the control chambers. Dr. Capstick noted field probes were placed inside the control chambers and noise levels of the measurement system were recorded throughout the study.

III.F. Thermal Pilot Studies of Cell Phone Radiofrequency Radiation

Dr. Wyde presented information about the 5-day thermal pilot studies at SARs of 4–12 W/kg in mice, young and aged rats, and pregnant rats—10 studies. The studies were designed to evaluate a wide range of SARs to determine the threshold for potential thermal effects of cell phone RFR, the impact of animal size and pregnancy on body temperature, and the potential effects of RFR exposure on pregnancy in rats. Body temperatures were collected via implanted microchips at multiple time points over 5 days.

In the mouse studies:

- No thermal effects were observed at SARs up to 12 W/kg regardless of age, sex, or modulation.
- 5, 10, and 15 W/kg were selected for 28-day studies.

In the rat studies:

- Lethal effects and excessive increases in body temperatures were observed at 10 and 12 W/kg.
- Increased early resorptions and decreased body-weight gain in pregnant dams were observed at 12 W/kg GSM.
- Based on those data, SARs of ≥10 W/kg were not recommended for further study in rats.
- 3, 6, and 9 W/kg were selected for 28-day studies.

III.F.1. Questions for Clarification

Dr. Adler asked whether body temperatures were measured at night, when rodents are eating, metabolically more active, and likely to have diurnal variation in body temperature, or only during the light cycle. Dr. Wyde said they were measured only during the day, and all measurements were made within 2–3 minutes of system shutdown to minimize the effect of heat loss. The temperature decay rate of an animal with elevated temperature was not independently measured, although some preliminary studies with the thermal sensors were done. Dr. Adler asked if any other physical parameters were measured, such as respiratory

[3]The slides and video of Mr. Ladbury's presentation on the validation and verification of the reverberation chamber system are available at https://ntp.niehs.nih.gov/go/Presentations_RFR (slides) and https://doi.org/10.22427/NTP-VIDEO-49 (video).

rate. Dr. Wyde said the goal was to examine only gross effects in body temperature, body weight, and survival, with no provision for histopathology. Some additional measures were performed in the 28-day studies. Dr. Adler pointed out that rodents acclimate quickly to environmental changes so that differences occurring at 5 days might not be detected at 28 days. The pharmaceutical industry prefers these measurements be done in 5-day studies because they can understand what additional systems are perturbed by the external influence before the animals reach steady state.

Dr. Felter asked why the 10 minutes on, 10 minutes off standard was chosen, and whether any experiments had been conducted with longer exposures. Dr. Wyde said that no other exposure lengths had been explored. Ten minutes was considered sufficient to allow for thermal regulation. The intermittent exposure was considered important to determining response to the RFR exposure, while the 10-minute exposure was somewhat arbitrary.

Dr. Kiourti asked about the implanted temperature sensors and how they communicated with the reader. Dr. Capstick confirmed that the system was radio-frequency identification.

Dr. Lin asked what other temperatures would be monitored if the experiment were to be repeated. Dr. Wyde said that NTP is considering some follow-up studies using data loggers to collect information in real time during the exposures.

Dr. Barnes asked if distortion of the fields with the sensor under the skin were possible. Dr. Kuster said that had been evaluated, and no distortion or interference with the measurements was apparent.

Dr. Rinke asked if the same rodent strains were used in all studies. Dr. Wyde said yes.

Dr. Gamboa da Costa from FDA asked whether some important information regarding the temperature of the main organs might have been missed. Dr. Wyde replied that was possible. Dr. Lin pointed out that the hottest spot was at the tail, so anatomy should be considered when determining where to implant the temperature sensor. Dr. Capstick noted that in his previous presentation showing the tail as a hot spot, it was the SAR distribution that had been modeled, which is not necessarily directly related to temperature distribution in the animal.

Dr. Barnes asked if use of an infrared camera had been considered. Dr. Kuster said that some investigators had tried to use thermal cameras in dosimetry, but they lacked the needed sensitivity.

III.G. Oral Public Comments on Technical Aspects of the NTP Exposure System

Dr. Eaton identified the written public comments received and presented a list of those public commenters. He described the format for presenting the oral public comments; five public commenters made oral comments on the exposure system.

Theodora Scarato, a private citizen, addressed the unique vulnerability of children to RFR, and the ever-increasing combined RFR exposures to the public. Cell phone use is now widespread, and they and other wireless devices are often used near the body. Pregnant women and children are exposed at much higher levels. Children, with thinner skulls and smaller heads, are much more vulnerable to RFR energy deposition. Published research modeling children's exposure shows that children's heads and brains are proportionally more exposed compared to adults. The use of multiple devices can increase SAR, as does the presence of metal inside or outside the body. The public is unaware that phones and wireless devices emit radiation, or that health concerns are associated with the exposures.

Dr. Olga Naidenko presented comments on behalf of the Environmental Working Group (EWG). She expressed EWG's support for NTP and NIEHS for having embarked on the absolutely essential cell phone RFR study and its appreciation that the first part of the study had been completed. EWG believes the exposures are relevant to people and to the exposures people are facing today. The study was conducted in 2G technology, whereas today 3G and 4G are in use, with 5G being rolled out. EWG's position is that the science currently in hand must prevail. EWG believes the next generation of exposure studies should increase emphasis on biological factors. The recent National Institute on Drug Abuse's study is a good example of research designed to elucidate short-term, immediate, and subtle effects such as changes in metabolism and in calcium-channel transmission and impacts on blood-glucose metabolism.

Dr. Devra Davis presented comments on behalf of the Environmental Health Trust (EHT). The exposure system is an important, positive study that was well executed under difficult conditions. She noted, however, that the exposure system used does not reflect current exposures. Historical controls are not relevant in the study; the only relevant controls are those from the study, and using historical controls from other NTP studies for comparison is a mistake. With respect to SAR values, basing guideline limits on average tissue volume data is inaccurate, as body parts are not cubes. She pointed out several issues for disagreement with NTP's study: The NTP study does not account for the multiple exposures experienced every day and cannot clarify what is happening in the occupational workforce, where RFR levels are much higher. The NTP study will not be relevant to 5G. She believes the whole-body approach taken in the NTP study is appropriate. French studies of exposures related to phones placed beside the body have shown much higher levels than those permitted by the FCC.

Dr. Kuster asked Dr. Davis why she believes the NTP study did not cover multiple exposures, noting that the local exposure levels used were higher than actual exposures from multiple exposure sources, even higher than occupational exposures. Dr. Davis said that current smartphones can have as many as four different antennas operating simultaneously, and that the synergy that occurs when electric and magnetic fields are combined with radiofrequencies or chemicals cannot be evaluated in a study like the NTP study. The real world is complicated, and studies such as the NTP study cannot capture that complexity. She stated the use of the technology has exploded and the capacity within experimental models to fully approximate human exposures is not available, noting little information is available about the impact on human health today and in the future. Children are routinely exposed to RFR devices in close proximity.

Kevin Mottus spoke for the California Brain Tumor Association, which supports individuals who have developed brain tumors from cell phone radiation. NTP is to be thanked for embarking on the study and following it through so conscientiously. The study reflects what is being seen in the real world, particularly DNA damage related to the carcinogenic effect. The association works not only with brain tumor sufferers, but also with people who have become sick from RFR and microwave exposures. The NTP study and the Ramazzini study offer biological confirmation of the cellular effects observed in human studies for years. Wireless should be reclassified as a Class 1 human carcinogen. The NTP study shows a clear increase in brain tumors in the areas that get the most cell phone use—the frontal lobe, cerebellum, and temporal lobe. Brain cancer is now the number one cancer in children 15–19 years old and is one of the top three cancers up to age 39 years, reflecting an epidemic. Mr. Mottus was critical of FDA's critiques of the NTP study. Addition of 5G high-frequency transmission on top of low-frequency 3G and 4G will result in more disease. The use of multiple devices and frequencies will result in a microwaving of the U.S. population. He stated the FCC is hiding health effects of exposures and exempting new technologies from environmental review. He believes FCC is an industry-compromised

organization and that NTP should take a stand against such compromise and insulate itself from industry influence.

Dr. Paul Heroux from McGill University was the final public commenter. He believes the NTP reverberation chamber delivered the test animals a stable challenge over a specific, integrated time frame. The variation of ±2.5 dB quoted in the report, although excellent performance, could have been reduced by using larger chambers, so that the objects would occupy less of the total chamber volume. The study shows its age by its overemphasis on heat. The finding of lower survival in the non-exposed animals is not simply an artifact and has been borne out in other large animal studies. Another interesting aspect is that the survival advantage effects are stronger in males than in females. The NTP studies do not mention control of the background extremely low frequency environment. The effects of GSM and CDMA differ, so the details of the exposure are significant and important.

III.H. Peer-Review Comments on the Reverberation Chamber Exposure System

Dr. Barnes, the first peer reviewer, felt the study was very well done in terms of accomplishing what it set out to do. With SAR as the critical parameter to define, NTP did a very good job of determining the exposure distributions and confirming the average values were as stated. Those elements were well tested and monitored throughout the studies. If the studies were designed today, however, Dr. Barnes said a variety of additional experiments could be conducted and additional parameters could be controlled. For example, translations from physics to chemistry and chemistry to biology could be built into future studies. Examining problems of feed-forward and feedback loops in more detail should be incorporated. Overall, NTP is to be complimented on a very thorough study. Dr. Bucher asked Dr. Barnes to elaborate on the concept of feed-forward, as NTP is interested in improving its studies. Dr. Barnes said feed-forward is related to elaborate communication systems inside the body, such as acupuncture points. An exciting development is the opportunity to convert electric and magnetic signals to biological signals in the chemical realm that the body already knows how to use.

Dr. Lin, the second peer reviewer, applauded NTP and NIEHS for having conducted the cell phone RFR studies because for the U.S. government to conduct such research and not leave it entirely to industry is important. He noted we are exposed to more and more RFR every day. The NTP study was the largest of its kind, was expensive, and took a long time to complete. The study showed that prolonged exposure to RFR levels, roughly three times current RFR exposure guidelines, could lead to tumor development, particularly schwannomas in the heart tissue of rats, and to some degree gliomas in the brain. He said the reverberation chamber (RC) apparently was selected *a priori* for the project and whether it is the optimal technology for the project or alternative, competing technologies were considered is unclear.

Descriptions in the report of what was implemented are clear and measurement techniques are accurate, within limitations. Although RCs are generally acknowledged to provide substantially uniform, average-field distributions in the absence of a test object, the bodies of rats and mice would be major radiofrequency energy absorbers, resulting in a very different interaction mechanism for fields inside the RCs. Free-roaming animals inside the cages would make the exposure field substantially less uniform compared to an empty RC. Although much effort was expended to achieve RF-field homogeneity and so-called “isotropy,” whether the RC approach had any advantage over simpler approaches is unclear.

He voiced concerns that mixing dB and linear scales is confusing and felt that describing uniformity using average-field distribution would have been more appropriate. He pointed out that field distortions introduced by the watering system do not appear to have been quantified.

Dr. Lin believes the use of liquid-filled, round, plastic bottles for the measures of uniformities in the RCs does not provide realistic simulations of animals' body shapes, resulting in inaccurate measures of SAR variations. He speculated that differences in resonant absorption might account for the different observed biological responses in the rats and mice, and wondered what influence, if any, the differential wbSAR, psSAR or oSAR could have had on observed cancer incidence.

He believes the methodologies, paradigms, and protocols used in the studies were reasonable, but whether the studies are intended for cell phone or base-station RF exposures, and whether they represent near-field or far-field exposure scenarios, is unclear. The use of temporal and spatial averaging ignores anatomy-related responses of the animal as functions of time or age to RF SAR and SAR distribution. He noted the apparent lack of provision for physiological monitoring or animal behavioral observation during the 2-year studies. He raised concerns about the sonic noise in the chambers. Ear or tympanic temperature should have been measured periodically throughout the study to monitor core temperature. Seeing the SAR-dependent reports of schwannomas in rats is perplexing. The experiments specified whole-body exposure, and wbSAR was the key metric for exposure, but a correlation study of pSAR or oSAR with total observed primary tumors should be included in the report.

Dr. Bucher noted that one objective of the peer review is to identify how the report could be improved in communicating several of the issues Dr. Lin had raised. He said that some of the information Dr. Lin suggests has been in the day's presentations, although not currently in the report, and welcomed suggestions for how best to encapsulate some of that information, particularly with respect to psSARs.

Dr. Kiourti, the third peer reviewer, congratulated NTP on a very thorough study. She had no major comments regarding technical aspects of the study. She asked how NTP could catch up with the technology, in general. Although the study delivers 100% of what had been promised, 2G is not even used today. She noted that the report should clarify that "exposures cycled between modulations every 10 minutes" means the cycling was between on and off for a given modulation, not cycling between the different modulations. She asked for more details about where the RF sensors were placed and why those locations were selected. She asked how the specific environmental conditions had been chosen and whether any differences would have affected the study's results. Although the animals were freely moving, they were still caged for 2 years, and she wondered whether that could have compounded stress. She asked for more details on the design of the antennas used, cage rotation, and how the NIST and IT'IS phantom studies compared.

III.I. Panel Discussion and Recommendations for Reporting of Chamber Design and Performance and Dosimetry Considerations

Dr. Eaton introduced the panel discussion section of the session. He said that, as a biologist, he appreciated the presentations detailing how the exposures were conducted. With the technologies having changed considerably since the studies were conducted, he asked whether the biological effects are likely to be better or worse now. Dr. Barnes replied that how the power is distributed as a function of frequency differs between the older technologies used in the study and the upcoming 5G. How to go from the physics to the chemistry to the biology can change, but there could be common responses, and elucidating the exact mechanisms affecting biology is very challenging.

Dr. Kuster addressed the question regarding bottles versus more anatomical phantoms. He stated that the numerical study provides the dosimetry and the purpose of the experimental

study with the bottle phantoms was to validate the numerical dosimetry. First, the presence of any coupling between phantoms had been carefully evaluated, and based on that information, the cages were separated to exclude coupling. Thus, how the energy was scattered did not matter; the only concern was how the energy was absorbed. The bottle phantoms were optimized to absorb the same amount of energy as the rats absorbed. Dr. Kuster said that the dosimetry information has only recently been published. Dr. Lin noted that the animals' posture made a difference in dosimetry, and therefore a round bottle was not an animal-shaped body. Dr. Kuster explained the bottles were used to validate the numerical dosimetry and the uniformity of exposure throughout the chamber, and were not affected by the presence of the animals. The differences caused by the postures of the anatomical phantoms are addressed in the numerical dosimetry. Dr. Lin noted additional field measurements after installation of the watering system were not indicated. Dr. Kuster replied that the measurements were made at the end of the process, after everything had been installed. Dr. Lin said that the field inside the animal would depend on posture and geometry. Dr. Kuster agreed that that needed to be better explained in the report.

Dr. Cline mentioned that "dosimetry" is used incorrectly in the discussion. Dosimetry is the measurement of the dose, not a mathematical model of what the dose might be. Dr. Lin disagreed with that statement, noting the differences between ionizing and non-ionizing radiation. Drs. Lin and Cline exchanged several comments on the point.

Dr. Lin added that, despite that 5G technology is being rolled out, 3G is still most relevant, as it remains what most people have in their pockets. He also discussed what the fundamental purpose and impacts of this study should be and the validity of this study.

Dr. Harkema asked if the design of the study (in 2007) was influenced or hindered in some way by constraining the timeline to a 2-year bioassay. Dr. Eaton added that NTP had been rather clairvoyant in the design of the study, as starting studies in utero was unheard of at the time, and now the importance of early-life exposures is recognized. Dr. Bucher pointed out that NTP tried to set the number of animals used to achieve maximum efficiency, with minimal animal use versus costs involved in increasing statistical power by adding population. He described some of the challenges associated with that approach.

Dr. Eaton recognized two public attendees: Dr. Davis from Environmental Health Trust and Dr. Melnick, retired NIEHS/NTP scientist. Dr. Davis commented on the issue of the relatively lower power of 5G, and whether it would result in fewer biological effects. She cited a study that reported the opposite effect—the weaker power but higher frequency was more biologically potent. Dr. Melnick noted that the objective of the NTP study, like all toxicology studies, was to test the null hypothesis. People were saying, "this is non-ionizing radiation, there's no possibility of adverse biological effect," and therefore the study was designed to challenge that hypothesis. The assumption that no biological effect occurs holds for consideration of 5G technologies. With the current study having disproved the null hypothesis, testing the newer technology would be wise to determine if any health effects on the general population occur.

Dr. Eaton returned the discussion to consideration of the draft NTP reports. His sense was that the panel offered strong praise for the NTP program and for its designers and consultants for having constructed a very challenging exposure situation. He perceived no "fatal flaws" in terms of the exposures.

The panelists discussed uncertainties in the dose metric used in the studies. Dr. Felter alluded to the concept that the male rats experienced more effects because they are larger and pointed out that that should have resulted in lower exposure due to a larger body surface area. Dr.

Barnes elaborated on the SAR dose metric and added that some additional properties were taken into account during dose measurement. Dr. Kuster noted the goal in the studies was to achieve uniform exposures of all tissues, to the extent possible. Dr. Felter said that the complicated nature of the dosing and dose metrics should be described in more detail in the reports.

Dr. Lin speculated about the best path forward in future studies. He noted that investing in a repeatable experiment might be appropriate before shifting the investigation to new technologies such as 5G.

The panelists and other experts discussed the issue of thermal versus non-thermal effects. Dr. Gamboa da Costa from the FDA urged caution about ascribing effects observed in the studies as non-thermal because monitoring temperature with fine granularity is difficult. Other panelists agreed that information to specifically rule out a thermal or non-thermal effect was insufficient. Dr. Barnes commented that a non-thermal effect is fairly ill defined.

Mr. Ladbury commented on the difficulty of moving the inquiry from reactive to predictive in terms of assessing the impact of newer technologies. He felt that the field would remain reactive to changing technologies for many years to come.

Dr. Whiteley stated that before studying 5G, gaining a better understanding of the dose-response biology of effects observed in the current studies, in the specific cell types that were affected, would be advisable.

Although panelists referred to the Ramazzini Institute study, Dr. Bucher cautioned that this meeting's intent is to peer review the NTP studies, so comparison to another study is probably not appropriate at the time. Again, an emphasis on clearly explaining dosimetry was brought up because the exposure system for the Ramazzini study was different. Concern was expressed that the broader field would make incorrect comparisons to this study if exposure were not clearly defined.

Day 1 of the proceedings was adjourned at 5:05 p.m.

Day 2: March 27, 2018

IV. Welcome and Introductions

Dr. Eaton welcomed everyone to Day 2 of the meeting and asked all attendees to introduce themselves. Designated Federal Official Dr. Mary Wolfe read the conflict of interest statement. Dr. Eaton presented the meeting format for Days 2 and 3.

V. Panel 2: Peer Review of Draft NTP Technical Reports on Cell Phone RFR

V.A. NTP's Toxicology and Carcinogenesis Studies: Experimental Design, Statistical Analyses, Genetic Toxicology Testing, and Hazard Determinations

Dr. Blystone provided an overview of the methodologies and approaches used in standard NTP chronic studies and in the cell phone RFR studies, including design considerations, and the animal models and numbers used: Hsd:Sprague Dawley SD rats and B6C3F1/N mice, 90 animals per sex per group. For these RFR studies, the exposure language differed from that for typical toxicology studies. He described several elements of the statistical analyses used in the

studies, including the historical controls. He informed the panel about the NTP Levels of Evidence of Carcinogenic Activity, which form the basis for conclusions.

V.A.1. Questions for Clarification

Dr. Harkema asked if historical control data are available from the contractor, IITRI. Dr. Blystone said no. Dr. Harkema asked about the low and medium doses and what "additional lower doses were spaced accordingly" meant—according to what, he inquired. Dr. Blystone explained the variety of factors taken into account, including capturing a wide dose range, appropriately evaluating hazard identification, and considering route of exposure. Dr. Harkema asked how the low and medium doses were scientifically determined. Dr. Wyde explained that, due to system feasibility, only three exposure groups were an option. Extending the exposure range to 6 W/kg enabled NTP to challenge animals on a thermal basis, and extending the range to 1.5 W/kg brought the exposures to a relevant level near the FCC regulatory limit. Dr. Bucher followed by explaining that dropping the exposure range to even lower levels would have diminished the likelihood of detecting effects.

Dr. Harkema asked for clarification on the difference between "some" and "equivocal" in the levels of evidence. Dr. Blystone addressed the issue, noting that the "bright line" between the two was whether an observed effect was considered associated with the exposure. Responding to a question from Dr. Eaton, he added that historical control data and discussions among staff are used when making those decisions, but the determination ultimately relies on discerning positive versus negative effects.

Beginning with a question from Dr. Felter, a discussion ensued regarding the historical controls, particularly for the rats, which consisted of four studies, and including the concurrent controls in the overall historical control incidences. Dr. Felter felt that the historical controls should have been kept separate from the concurrent controls. Dr. Blystone stated that including the concurrent controls heavily weighted the historical control data for these studies, but both options were examined. Dr. Keith Shockley from NIEHS noted that the concurrent controls were used as part of the statistical testing, but the historical controls were not. Dr. Bucher said that in the next version of the reports, an appendix will delineate the studies included in the historical controls. The panel also posed questions regarding the use of a common control for the studies, which Dr. Wyde explained was due to space constraints and the cost of additional chambers. Dr. Bucher followed by saying that, if the studies were done again, a second control group would probably be included.

Dr. Harkema asked for more detail on the historical controls used in the mouse studies. Dr. Blystone said 11 studies, including the concurrent controls, were included. Dr. Lin said the historical controls were not relevant to the current studies due to differences in exposure, such as different lighting and different study designs. Dr. Harkema stated that, although the historical controls might not have been the most appropriate, they are still informative. Dr. Barnes pointed out that the assumption is that we are looking at a linear system with regard to dose response, but, in some sense, the historical controls are not free of exposure to RFR. He cautioned against treating historical controls as unexposed, as RFR probably was not measured and, therefore, they might not be true controls for comparison in these studies. Dr. Felter also cautioned against disregarding the historical control data, as they provide a wealth of information on variability in tumor response.

Dr. Rinke asked if the rodents used were from the same breeder or supplier as the historical controls were from. Dr. Bucher said that the rats were, and he believed that the mice were from the same breeder, although he was not certain.

Dr. Kaufmann asked what elements of neurobehavioral observations had been considered in the design of the studies. Dr. Blystone explained that, due to the constraints posed by the closed exposure chambers, detailed clinical observations were not possible. The nervous system was pathologically examined, with increased sectioning of the brain from three to seven slices.

V.B. Genetic Toxicology Studies in Mice and Rats Exposed to Radiofrequency Radiation

Ms. Kristine Witt briefed the panel on the genetic toxicology studies, describing the rationale for selecting the assays, the assay protocols (erythrocyte micronucleus assay, comet assay), the data analysis used, and how the data were interpreted. Subsets of mice and rats were assessed for genetic damage after 14 weeks (mice) or 19 weeks (rats) of exposure.

V.B.1. Questions for Clarification

Dr. Cline asked if comet assays had been performed on brain tissue. Ms. Witt replied that they had. Dr. Cline asked how the brain cell types were selected. Ms. Witt said that they selected the hippocampus, cerebellum, and frontal cortex, with no microscopic selection of particular cell types. Dr. Cline noted that several types of micronucleus tests are available and recommended that the assay be called the erythrocyte micronucleus assay in the report to avoid potential confusion.

Dr. Harkema asked how the brain sites for the comet assay were determined and how they were handled statistically. Ms. Witt said that each tissue type was considered independently and they were not combined for statistical analysis. She explained that the frontal cortex was selected because of the possibility of brain tumors, and the hippocampus and cerebellum were selected because they comprise large portions of the brain and cover a wide space for analysis. Dr. Harkema followed by asking if the comet assay was the most appropriate for comparisons to histopathology. Dr. Malarkey described the standard neurohistopathological evaluations and stated that there are no findings that correlate with the genetic toxicological findings. Dr. Bucher clarified that the animals taken for the comet assay were different from the animals used for interim histopathology.

Dr. Adler asked if the comet assay has a positive/negative threshold and whether a positive control was run. Ms. Witt said NTP animal studies do not have a positive control, but positive control slides with human cells exposed to a known genotoxic agent are run as an internal technical control. She added that the software does not delineate between positive and negative. No historical controls for the comet assay for these studies were included.

Dr. Lin asked whether other parts of the animals were assayed in addition to the neurological tissues. Ms. Witt said the liver and peripheral blood leukocytes also were assayed.

Relating to the positive predictive value of the erythrocyte micronucleus test, Dr. Eaton asked about the occurrence of false positives. Ms. Witt said that the last time a systematic review of the test was compared with a bioassay was 2000, which showed a 95–98% rate of positive predictivity. She noted the test has low sensitivity, but a positive response is meaningful, in both rats and mice. Ms. Witt is unaware of any chemical that induced micronuclei *in vitro* and does not induce carcinogenicity *in vivo* in 2-year studies.

Dr. Felter asked how the results from the comet assays were reported, in terms of positive, equivocal, and negative findings. She wondered what would be done if the data supported a trend in the opposite direction. She cited the example of a statistically significant decrease in the

comet tail in the females in both modulations in the frontal cortex. Ms. Witt said that 2-sided trend tests are not conducted, so whether it was a statistically significant decrease could not be stated, although it might appear to be.

V.C. Pathology Peer-Review Process for 2-Year Studies of Cell Phone Radiofrequency Radiation

Dr. Amy Brix briefed the panel on the pathology peer-review process used in the 2-year studies. She described the role of the study pathologist and outlined the steps in the pathology peer-review process, including the Pathology Data Review (PDR), the audit of pathology specimens, the pathology quality assessment slide review, the Pathology Working Group (PWG), and the final steps to complete the process.

V.C.1. Questions for Clarification

Dr. Harkema noted that no place conducts the pathology process better than NTP, which sets the gold standard. He asked Dr. Brix to summarize the review process used with the lymphomas. She said that the study pathologist initially noted them in the report. During the PDR, items were flagged for review including the statistical tables, incidence tables, and anything unusually high or low in the controls. All lymphomas diagnosed in the mice were reviewed, and all tissues with neoplasms were automatically reviewed. That information was then given to the PWG. She said the conclusion did not change throughout the study. Dr. Harkema said it seems unusual to have two pathologists, one looking at males, one looking at females. Dr. Brix agreed, although it was necessary because of the size of this project. Dr. Harkema also asked where the study pathologist was located for these studies. Dr. Brix replied that IITRI used a subcontractor as a pathologist and did not have one on site.

Dr. Lin asked about blinding at the study pathologist and pathology review levels. Dr. Brix said that slides are not blinded at the study laboratory, because it is not considered as sensitive a read if something is seen when blinded. Slides are also not blinded during the quality assurance (QA) review. At the PWG level, blinding is used and PWG participants are unaware of the study or QA pathologist calls. Dr. Lin noted that at the study pathology level, the pathologist would have known whether a tissue came from exposed or control animals. Dr. Brix confirmed that impression and added that NTP follows the industry standard for such studies, and non-blinding is the most scientifically appropriate method. She said that the pathologists are evaluating a biologically complex system, and they must be able to compare treatment-related findings to control incidences to distinguish which findings actually differ. Dr. Lin and Dr. Brix exchanged several comments on the issue. Dr. Bucher noted that the argument is not unique to NTP, having persisted among pathologists for a long time. Dr. Harkema said that even pathologists do not take the issue lightly and the entire process has been rigorously reviewed. He believes that in this case, the peer review, which is the most unbiased, is at the correct level in the process. If any study pathologist bias were to occur, it would be caught at the peer-review level.

Dr. Cline asked how the rest of the head, aside from the brain, was assessed. In particular, he wanted to know if the vestibular system and auditory nerve were included. Dr. Malarkey said they were not assessed in the mouse, but some exploration in the rat was conducted.

VI. Peer Review of NTP Studies in Mice of Cell Phone RFR

VI.A. Charge to the Panel

Dr. Blystone presented the charge to Panel 2, addressing the draft *NTP Technical Report TR-596, Toxicology and Carcinogenicity Studies in B6C3F1/N Mice Exposed to Whole-Body*

Radiofrequency Radiation at a Frequency (1,900 MHz) and Modulations (GSM and CDMA) Used by Cell Phones. The panel was charged to:

- Review and evaluate the scientific and technical elements of the study and its presentation
- Determine whether the study's experimental design, conduct, and findings support the NTP's conclusions regarding the carcinogenic activity and toxicity of the test agent

VI.B. Oral Public Comments on Technical Aspects of NTP Studies in Rats and Mice

Dr. Eaton acknowledged the written public comments received and presented a list of those public commenters. He described the format for the oral public comments to be delivered. In the second session, nine oral public commenters on the NTP studies in rats and mice were accommodated.

Ms. Scarato drew a distinction between FCC human exposure limits and safety guidelines. Proper safety testing has never been completed on chronic, low-level exposure. The NTP findings of increased cancerous and pre-cancerous lesions confirm that the FCC limits are non-protective. The technical reports should include the regulatory limits of other countries and summarize that the FCC limits are far higher. Co-exposures should also be taken into account, with studies showing synergies included in the reports. The reports also should refer to studies addressing changes in the permeability of the blood-brain barrier related to cell phone use, decreases in brain cells resulting from prenatal exposures, and behavioral issues related to prenatal exposures. The reports should include information on worldwide governmental actions to reduce RF exposure. Maryland and California have acted to reduce RF exposures. The mouse technical report omitted NTP data presented in 2016 regarding DNA damage analysis and this data should be added back in. Similarly, reference to the conclusion by the World Health Organization's International Agency for Research on Cancer was included in the 2016 report but not in the 2018 draft technical report, and it should be added. Discussion of the Ramazzini studies should be added to the technical reports, as should the concordance of the observations of schwannoma in rats and lymphoma in mice, considering that we live in a world of multiple exposures. The U.S. government should act to limit public exposures.

Dr. Naidenko from the Environmental Working Group stated that NTP is in a unique position to study the biological effects of cell phone RFR exposures. She alluded to a company, Novocure, which has FDA approval to use electromagnetic fields (EMF) for treatment of glioblastoma. She described how EMF can impact biological systems, showcasing the extremely complex biology involved, including the effects investigated by NTP and considered by the peer-review panel.

Dr. Davis spoke on behalf of colleagues at Hebrew University. She noted that this 3-day review was unprecedented. She appreciated the explication of the blinded pathology review. The NTP study is not a lifetime study, ending at 2 years, and 60% of all cancers in humans occur after age 60. The rodent studies end at the equivalent of age 60. She recommended using the NTP study's controls and not historical controls. She noted that the baseline rate of cardiac schwannoma was quite low, even in historical controls. She recommended reexamining the data on reproductive endpoints and birth weight impacts. She added several other detailed recommendations. She further discussed the Ramazzini study and presented relevant conclusions from the study. She presented data from several other recent studies, suggesting reproductive endpoint effects of RFR exposures and increasing rates of brain tumors in the United States.

Dr. Kuster said that Dr. Davis' comparison of exposures was "apples and bananas," and that the NTP study is conservative with respect to simulating the exposure, independent of usage. She agreed, but pointed out that phone testing methods vary, with many agencies testing them in a holster away from the body, which would reduce exposures and is an out-of-date method. The French, she observed, test phones in close proximity to the body.

The next oral public commenter was Dr. Marc Arazi from the Phonegate Alert Association in France, an organization devoted to sharing technical and scientific information on cell phone radiation and formulating safety recommendations. He commended NTP for using high SAR levels in its studies and found the results in several organs particularly important to understanding the risks associated with RFR on the whole body, not just the brain. He described a 2016 report on tests by the French government called *Exposure to Radiofrequency and Child Health*. Data showed that many of the most popular phones in the European market exceed regulatory RFR limits. Another new report showed that RFR sensitivity is a real and widespread illness. He emphasized that focusing on realistic use of cell phones by users and implementing simple measures to protect the billions of users in the world are necessary.

Dr. Annie Sasco is a former Unit Chief at the World Health Organization's International Agency for Research on Cancer and retired director of research at INSERM (Institut national de la santé et de la recherche médicale, the French National Institute of Health and Medical Research). At this review, she spoke on her own behalf. She described her background and education as a cancer epidemiologist. She said that over her 35-year career, the situation with regard to cancer had not really improved. She noted that today hardly anyone on the planet has not been exposed to EMF radiation, making the demonstration that EMF exposure is a carcinogen difficult. Focusing research on those most heavily exposed and exposed for long duration will be important. Most case-control studies of that nature have found increased risk. With the challenges to epidemiology in the area, experimental studies such as those undertaken by NTP will be important going forward. She suggested using a larger unexposed group to avoid the need to use historical controls. With the need to rely on experimental studies in the future, the research needs to accelerate to keep up with introduction of new technologies. She commended the NTP studies, which she described as large, well conducted, and methodologically sound, providing more evidence of RFR carcinogenicity. She said the situation has evolved from precaution to prevention, as evidence has accumulated.

Dr. Lin reiterated his assertion that there are no unexposed animals.

Kevin Mottus from the California Brain Tumor Association wished to highlight the comments of Dr. Lennart Hardell, an oncologist and leading authority on wireless radiation and cancer. His comments pertained to the NTP studies and others. He cited clear evidence of several cancers including glioma and some evidence of other cancers, and the International Agency for Research on Cancer recommendation that RFR be classified as a Group One carcinogen to humans. Mr. Mottus then added his own comments. He said the mechanism behind RFR and cancer is now known, and that evidence is mounting of brain cancers in the frontal lobe, the cerebellum, and the temporal lobe—the brain regions that receive the most cell phone radiation. He believes FDA should take quick action to rein in FCC, which is dominated by industry, especially with the rollout of 5G and its thousands of transmitters. He said everyone should be alarmed, because the situation is not a public health crisis in the making, but is going on currently, and could become horrific in the near future.

Dr. Young Hwan Ahn from the EMF Research Committee of the Korean Institute of Electromagnetic Engineering and Science spoke by phone from Korea. He briefly introduced himself and described his background as a neurosurgeon. He described classification of tumors

of the nervous system, such as glioblastomas and schwannomas, which comprise about 8% of brain tumors. Cardiac schwannomas are extremely rare. Despite that fact, the NTP study reports have drawn special attention to tumors of the nervous system. If life-span RF exposure can cause increased incidence of tumors of the nervous system, regardless of statistical significance, attention must be paid to the carcinogenic potential of RFR in humans. He stated the NTP study was well organized, with the survival of the sham-exposed group the most significant drawback.

Dr. Heroux from McGill University suggested that page 13 of the rat document be reworked to group the results according to tissue types, which would highlight that brain and nervous tissues showed carcinogenic action at various stages and in various locations in the body. He felt that health effects in rodents would emerge later in life, past the 2-year bioassay point. If bandwidth is increased, the chances of interferences and consequences to biological systems also increase. He concurred with Dr. Lin's point that there are no controls, in that the rats thought of as controls have in fact been exposed to extremely low frequency radiation. Genetic drift caused by exposure is also a problem, with potentially serious consequences that are not discussed in the literature.

Dr. Ronald Melnick, a retired NIEHS/NTP toxicologist and one of the original scientists associated with the NTP cell phone RFR studies, spoke on the utility of the NTP data on cell phone RFR for assessing human health risks. He provided background information about the history of the project, which began with the original nomination in 1999. The initial objectives were to test the null hypothesis—that cell phone RFR at non-thermal exposure intensities is incapable of inducing adverse health effects—and to provide dose-response data that could be used to assess potential human health risks for any detected adverse effects. The results described in the technical reports "show quite clearly" that the null hypothesis has been disproven, with many adverse effects identified. Dr. Melnick delineated the adverse effects observed and described their levels of evidence of carcinogenicity. He pointed out that even a small increase in cancer risk could have a serious public health impact due to the widespread use of cell phones.

Dr. Lin asked Dr. Melnick to discuss how the decision was made to use one common control in the studies. Dr. Melnick said that comparing exposure groups to sham controls was ideal for space constraints and feasibility. In hindsight, he said, including additional control groups might have been better. With the provision of 90 animals per group, NTP felt sufficient power was achieved with the common controls. He acknowledged the historical controls were difficult to work with due to differences in housing and the exposure system; however, they were used to demonstrate how rare a particular event was in the NTP database, not for direct comparisons.

VI.C. Results of the NTP Studies of Cell Phone Radiofrequency Radiation in B6C3F1/N Mice

Dr. Wyde briefed the panel on the results of the 28-day prechronic toxicology studies and the 2-year toxicology and carcinogenicity studies in mice, which included 14-week interim evaluations of histopathology, genetic toxicity, and hematology.

The draft report's preliminary conclusions (subject to peer-review modification) were as follows:

- In the male mice exposed to GSM-modulated cell phone RFR at 1,900 MHz, there was *equivocal evidence of carcinogenic activity*, based on combined incidence of fibrosarcoma, sarcoma, or malignant fibrous histiocytoma in the skin, and incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in the lung.

- In the female mice exposed to GSM-modulated cell phone RFR at 1,900 MHz, there was *equivocal evidence of carcinogenic activity*, based on incidences of malignant lymphoma (all organs).
- Exposure to GSM-modulated cell phone RFR at 1,900 MHz did not increase the incidence of any nonneoplastic lesions in male or female B6C3F1/N mice.
- In the male mice exposed to CDMA-modulated cell phone RFR at 1,900 MHz, there was *equivocal evidence of carcinogenic activity*, based on incidences of hepatoblastoma of the liver.
- In the female mice exposed to CDMA-modulated cell phone RFR at 1,900 MHz, there was *equivocal evidence of carcinogenic activity*, based on incidences of malignant lymphoma (all organs).
- Exposure to CDMA-modulated cell phone RFR at 1,900 MHz did not increase the incidence of any nonneoplastic lesions in male or female B6C3F1/N mice.

VI.C.1. Questions for Clarification

Dr. Andrews-Jones asked for clarification about the incidence of malignant fibrous histiocytoma, first regarding the historical control incidence in the female mice and the locations involved. She noted that the incidences were primarily on the tail, with one on the pinna, and commented that those were areas of the mouse that received the most exposure. Dr. Brix said that she reviewed five previous studies with incidences of that particular tumor, and found 13 animals with malignant fibrous histiocytomas, with a total of 14 tumors. Of the 14, 10 were on the tail and 1 was on the ear pinna. In the current study, only one tumor not on the skin occurred, which had metastasized throughout the mesentery (a control animal). The rest were on the pinna or the tail in exposed animals, none of which had metastasized.

Dr. Rinke asked Dr. Brix where the tail tumors were located. Dr. Brix said that she saw pigment in the lesion of several of the tumors, indicating that they were near the tattoo, which would be in the proximal half of the tail.

Dr. Andrews-Jones asked whether the tail was examined only if a gross lesion was present. Dr. Brix said the lesions were mostly gross lesions. Although the tail is not collected as part of the standard protocol for histological examination, it was examined in every animal, grossly.

Dr. Kaufmann asked if the histopathology sectioning of the brain differed between rats and mice. Dr. Brix said that seven sections were taken from both rats and mice, so they were comparable.

Regarding the GSM female mice with a dose-dependent increase in malignant lymphomas, Dr. Lin felt that the statistics were fairly clear and wondered how the decision was made to classify the findings as equivocal. Dr. Wyde said the statistically significant increase had been seen only in the low- and mid-dose groups, with no significant trend test, so no SAR-dependent trend was observed. The top dose group showed no statistically significant increase, and the incidences fell within the historical control range. Thus, the findings were classified as equivocal.

Dr. Corcoran asked whether, in past NTP chemical studies, instances had been observed of statistically increased incidences of tumors in low- and mid-dose groups, but not in the high-dose group, and a conclusion was reached that was not equivocal. Dr. Wyde said that in over 500 NTP Technical Reports, he was sure that had been done, although he could think of no specific examples. Dr. Blystone said there were such cases, and added that the calls depend on several factors, such as survival. Dr. Corcoran said he would return to the topic of linearity versus nonlinearity in his later comments.

Noting that the comet assay was positive for the frontal cortex at 14 weeks in the mice, although evidence of brain tumors at 2 years was absent, Dr. Adler asked about the latency for DNA damage-induced brain tumors in mice. He asked whether the study was adequate to show it, or whether there was another explanation for why a clear genetic damage signal did not have an outcome of positive brain tumors. Dr. Wyde said that a positive comet assay finding did not guarantee an increase in tumor incidence following 2 years of exposure. The comet assay is a snapshot in time and would not take into account DNA repair and other such processes. He reiterated that findings are rendered "under the conditions of this study." Dr. Eaton clarified that the micronucleus test was negative, although the comet assay was positive.

Dr. Rinke said he would have found it advantageous if the preneoplastic lesions had also been considered for the lymphomas. Dr. Brix said that lymphoid hyperplasias in the spleen were similar in the controls and dose groups, so abnormality was not indicated.

Dr. Barnes commented that his group's data indicate that nonlinearity is important, and provided examples.

Dr. Felter asked if time to first tumor is part of NTP's considerations for making carcinogenicity calls and recommended that it should at least be included in the discussion. She said that tumors were observed earlier in control animals relative to exposed animals in this study. Dr. Wyde cautioned against using latency period as a deciding factor, as tumors are generally not noted until an animal is necropsied; therefore, the tumor could have developed before that. Dr. Felter asked if that held true for skin tumors as observed in the study, which might have been grossly visible. Dr. Brix added that the tumors were probably not the cause of the animals' death and clarified that NTP only reports tumor incidence at study termination unless an early death occurs.

Dr. Harkema asked Dr. Brix for her reaction to the low lymphoma rate in controls. Dr. Brix replied that a second control group would have helped. Dr. Harkema asked what the second control group would have looked like, and whether any considerations would be made about the potential protective effect of the chambers in regard to controls. Dr. Brix replied that they could not address whether that was a factor. They agreed that a control group outside of the reverberation chamber would have answered some of the associated questions.

Dr. Andrews-Jones asked whether any consideration was given to going back and trimming in the tails from all animals in the area where gross lesions had been seen, to increase confidence that no microscopic lesions were missed. Dr. Brix said they had not done so, but all tails were looked at grossly, although not microscopically.

VI.D. Presentation of Peer-Review Comments

Dr. Harkema, the first peer reviewer, stated the studies were well designed, justified, and executed. He suggested elements for looking at exposures beyond 2 years could have been added due to the potential for later appearance of tumors. Much has been learned from the presentations, and the additional information in them should be added to the report. He asked for a clearer and more concise description of the historical control data, including information on the 5-year window and specific comments on the studies that currently comprise the historical control database. He requested more details about noise levels and measurements, more information about time of day the mice were exposed and the lighting used during exposure, and more discussion of the strengths and limitations of the studies and remaining data gaps. Discussion of the practice of putting lesions in "bins" also would improve the report. Although Dr. Harkema agreed with the conclusions of equivocal evidence in the 2-year study, he requested

better explanation of the rationale behind the equivocal call and why it did not rise to the higher category of some evidence. He recommended adding a section comparing the mouse and rat studies and asked for more clarity in the report on the justification for all doses, beyond just the high doses.

Dr. Wyde mentioned the statistical issues surrounding the distinction between 2-year and lifetime studies and pointed out that extending the study would naturally result in more common tumors arising. Dr. Harkema said that, in his experience with inhalation toxicology studies, a dramatic increase in tumors would have been missed if the studies had been cut off after 2 years.

Dr. Wyde said he would follow Dr. Harkema's recommendation regarding the historical controls. Regarding the noise, lighting, and activity issues, more information will be added to the report as suggested, as will more discussion of the equivocal findings and why they did not rise to a higher level. In terms of comparison between the rats and mice, Dr. Wyde said he envisioned a follow-up manuscript on that topic.

Dr. Corcoran, the second peer reviewer, commended NTP for conducting a one-of-a-kind study. Several key factors distinguish the NTP studies from previous studies of RFR radiation and rodents. He said that the study design was comprehensive and robust, with sound rationales for each factor selected, including the exposure system, chambers, animals, and parameters evaluated. He recommended the reports include a section on the strengths and weaknesses of the reverberation chamber model. The innovation of the exposure model demonstrates important advancements in the ability to study RFR. A review of the conduct of the study, which required a very large number of observations and measurements, yielded no apparent evidence to suggest that the study findings had been compromised—no significant issues were found with the conduct of the study.

He objected to use of the word "similar" in reference to body weights of male and female mice exposed to RFR for 2 years and sham controls. He questioned the standard error values of 0.00 in the results reported in Table G1 and elsewhere. The report would be strengthened by more discussion of why the occurrence of lesions in sham controls fell at or below the low end of the historical control range, as well as discussion of how cumulative Type 1 error associated with the large numbers of comparisons was maintained at $p < 0.05$. He urged more discussion of linear and nonlinear causation of cancer, and how it relates to RFR. He called for a more analytical approach to the equivocal level of evidence call, with a rubric of 10–20 factors and a weighting for each factor, which would lead to a weight-of-evidence determination. He questioned the use of historical control data and linearity of the dose response when making the level-of-evidence call.

Dr. Corcoran noted that Dr. Brix's presentation added important details about the pathology review process and recommended additions to the report. He felt the report would be strengthened by including instances in which significantly different pathology assessments were encountered. He said the report was parsimonious in acknowledging published findings and meeting quality standards and should expand discussion of selected published findings, some of which were noted in the public comments. Although not perfect, the study has enormous strengths, along with some challenges, and brings very high probative value, contributing a great deal to the existing body of literature.

Dr. Wyde noted that body weights are considered similar when they are within 10% of controls. He agreed to rework Table G1 to reflect actual values; the 0.00 values occurred due to

rounding. Regarding historical versus concurrent controls, he said that all panel comments would be considered as the report is finalized.

Dr. Shockley responded to Dr. Corcoran's comment on the Type 1 error, specifically pointing out the use of Dunnett's test for non-tumor data. He acknowledged that, when making hundreds of comparisons, some error is expected. NTP does not adjust for multiple comparisons with tumor analysis. He noted that NTP uses a weight-of-evidence approach in reaching its hazard conclusions, not a strict statistical decision rule. He said that several studies have examined false positive rates in NTP studies using all relevant information in reaching conclusions, and the results were equivalent to a $p < 0.05$–0.07 level. Even though NTP is testing at the 0.05 level, the actual false positive rate—if the background tumor rate is low enough—would be lower than 0.05. He said he would try and address the issue in more detail in the report.

In response to Dr. Corcoran's comment on linear and nonlinear causation of cancer, Dr. Wyde said that, although there is an expectation of linearity, nonlinear effects do occur with some agents. Regarding the pathology, Dr. Brix noted no differences in conclusions between the study pathologist and NTP pathologists, and the majority of the differences were in terminology. Dr. Wyde said NTP would evaluate the more recent literature and would incorporate the material as appropriate, including the Ramazzini study.

Dr. Andrews-Jones, the third peer reviewer, also commended NTP for the design and execution of the study and for the rigor with which the pathology data were reviewed, which is the industry gold standard. She said she was struggling with the malignant fibrous histiocytomas in the skin, a rare tumor with a total incidence, including both GSM and CDMA exposures, of 11 in the male mice and 6 in the females in the treated groups, with 1 in the controls. She was still unclear about the historical control incidence in female mice. She appreciated the clarification about the location of where the tumor occurred in previous studies. The point that the tails were examined only if they had a gross lesion should be brought forward in the description of the lesion. The tumor incidence did not show a dose response, leading to the equivocal conclusion, but the incidences were higher than the historical control range, potentially elevating it to the level of *some evidence*. She noted that the report ultimately would be written not just for the technical and scientific community but for the public as a whole. Therefore, explanation of the methods and language should be more robust, with addition of a dictionary that would be hyperlinked. The challenge would be that it would need to be written in a format that a lay person could understand, with visual and graphic support.

Dr. Wolfe mentioned that a lay summary is prepared as part of the final report. Dr. Wyde thanked Dr. Andrews-Jones for her advice, particularly the idea of a glossary, which he suggested could be included as an appendix. He said the issue of the tail tumors being observed grossly would be elaborated further in the report.

Dr. Rinke, the fourth peer reviewer, also said that the study was very well done. He suggested more explanation of the 1999 nomination by FDA to put the ensuing years in more context. Regarding the malignant lymphomas, they were not deemed the cause of early death in the control group, and he wondered what the cause of death was and whether that could be elaborated. Regarding the historical controls, the procedures should be updated in the report, particularly with the 5-year range explained further. He also would have liked to see additional control groups in the study. He said the malignant fibrous histiocytomas also raised a concern with him because they are such a rare tumor. More information on their location would be advisable, as they might have been more significant if they had been located closer to the body. He noted other rare tumors were not discussed in the report, and suggested a table of

uncommon, rare tumors. He said that the hepatoblastoma is a very rare lesion, but the criteria employed might differ from his customary ones. He added several editorial comments.

Dr. Brix said she would rewrite the paragraph on the malignant fibrous histiocytomas based on Dr. Rinke's editorial comments. Regarding the areas on the tail, in several of the tumors, she noted the pigment could actually be seen. The other rare tumors, while deserving mention in the results, did not rise to the level of biological significance and thus were not brought forward to the discussion; however, they could be put in a table, as Dr. Rinke suggested. Dr. Wyde pledged to add to the discussion of the 1999 nomination and the ensuing timeline.

Ms. Pant, the fifth peer reviewer, as a genetic toxicologist, addressed those elements in the report in her review. She felt the study was well designed and conducted under robust conditions. She agreed an additional control group should have been included. The comet assay and the micronucleus assay are short-term studies, and the effects are not cumulative. As such, she wondered why sacrifice was delayed until 14 weeks after dosing began. The genetic toxicology studies were well done, following guidelines. She suggested that the comet assay results should simply be stated as "positive in comet assay," as opposed to breaking out according to organs. Regarding the historical data, she believed the concurrent controls were a better comparison for this study. She said that normally the genetic toxicology assays are conducted in 6- to 8-week-old animals, 10 weeks at the most, but in this study, they were conducted at 14 weeks, which could have an effect.

Ms. Witt explained that the reason for the 14-week time frame for the micronucleus studies was that the micronucleus assessments are routinely integrated into the 14-week toxicity studies, a standard practice that avoids the need to use additional animals. Length of time does not appear to influence the assay outcomes. She said that the overall call for the comet assay is positive in both males and females, with the location of response indicated.

Dr. Eaton noted that Ms. Witt showed a quantitative measure of degree of change in the comet assay, from marginal to the "hedgehog." The call, however, is yes or no. He wondered if it would be useful to comment on the degree of positivity in the positive assays. Ms. Witt replied that the strength of response is captured along the way, and NTP could review the p-value applied to the data. Dr. Eaton observed that having more information about a positive response beyond the yes/no would be helpful. Ms. Pant added that the negative control also would play a role.

Dr. Malys, the sixth peer reviewer, found the study extremely well done and thorough, and from a data perspective (his specialty), accommodated many statistical effects. That the goal of the exposure system was to normalize to the amount absorbed per body weight should be stated up front and clearly. That SAR is tissue-based should be emphasized. He was glad to see the level of care taken in the tests chosen for the many traits assessed throughout the study. He approved of the statistical methods used to account for litter effects. He agreed with Dr. Corcoran on the Type I error concerns (individual control versus global control) and requested clarification of the multiple-hypothesis testing correction and clarification that the multiple-source comparison system kept p-values at the appropriate level. He appreciated Dr. Shockley's explanation of the issue and said it should be added to the report. He approved of including the historical controls. As NTP moves to design future studies, everything is becoming progressively more data driven, so as plans for new studies are made, the anticipation of weak effects should be taken into account. NTP should consider whether additional evidence can be used to support findings that are statistically, but not biologically, significant.

Dr. Shockley appreciated Dr. Malys' suggestions about controlling Type 1 error rates and taking litter effect into account.

In terms of statistical power, Dr. Malys asked if a better control could be included in the design, could power calculations be considered, and could a margin be added to turn the power calculation into a real result. He noted the mice that were not exposed to RFR experienced lower survival. He said that result stood and felt that it was important and warranted further discussion in relation to the level-of-evidence call. He believes the survival curve carries a lot of weight in these longer-term studies.

VI.E. Panel Discussion and Recommendations

The chair introduced the session, noting that at the end of the discussion, Panel 2 members would vote on the conclusions for the draft mouse NTP Technical Report. Panel 1 members would not vote, but were available for technical consultation.

Dr. Eaton acknowledged the widespread praise among the panel for the basic design and validity of the studies. Considerable discussion was held about the role of historical controls and how they were used in the report. The nature of the dose-response relationship was another issue of concern, with some evidence of strong response at the lower doses and no response at the higher doses. He described the voting procedure:

- He would accept a motion and second to accept the draft report's conclusions as written.
- If there is a motion and no second, or if the motion is voted down, each conclusion would be considered and voted on individually.
- If the motion carried, the draft report's conclusions would be accepted as written, with no further action necessary.
- Panel members who vote no or abstain would be asked to explain their reasons for doing so.
- The chair would vote only in the event of a tie.

Dr. Eaton permitted an ad hoc comment from the audience. Dr. Heroux from McGill University said lumping all exposures, including GSM and CDMA exposures, would be allowable. He added that having no extremely low frequency magnetic field measurements is not acceptable because it was a real confounder in the data. Determining where the rats came from would be worthwhile so their exposures prior to the experiments could be estimated.

Dr. Eaton, Dr. Wolfe, and Dr. Bucher further explained the voting procedure.

Dr. Wolfe displayed the initial conclusions for the panel's consideration.

Dr. Cline commented on the nonlinear dose-response curves, citing two examples of the phenomenon. The mechanism for RFR is not necessarily known, but it is clear that linearity is not always the case.

Dr. Harkema asked that NTP staff summarize the factors behind each conclusion. Dr. Eaton said that would be appropriate, if voting on each conclusion individually were undertaken.

Regarding the skin fibrosarcomas, Dr. Whiteley said the classification had been challenged, and if NTP were to change it based on the panel's feedback, would it change NTP's conclusions? Dr. Blystone reiterated that the NTP recommendation was *equivocal evidence*. Dr. Whiteley said he was reacting to NTP's saying earlier that it would "take it under advisement," and asked whether that meant the treatment of the issue would be changed. Dr. Wyde said the statement meant the report would be added to. Dr. Wolfe further explained what the panel would be voting on.

Dr. Felter asked Dr. Brix about the relationship between the hepatoblastomas and the hepatoadenomas and hepatocarcinomas, and whether they are considered to be on a continuum. Dr. Brix replied that the liver tumors are considered individually and in combination. Hepatoadenomas and hepatocarcinomas arise from the same cell type, and hepatoblastomas can arise within a hepatocellular adenoma or carcinoma. The cell of origin is unclear, so there is a reason for combining them.

Dr. Andrews-Jones noted that nonlinear dose response in the mice could change the interpretation of the malignant fibrous histiocytomas and other tumors such as pituitary adenomas and carcinomas, for which a nonlinear dose response occurred. Dr. Barnes reiterated the dose response here clearly is nonlinear.

Dr. Eaton asked what the process would be to elevate tumors mentioned in the report and not included in conclusions. Dr. Bucher said it would be accomplished by motion.

Dr. Adler asked whether the statistical analysis for nonlinear response is different. Dr. Bucher cited pairwise comparisons and trend tests. He said that linearity of response is not always assumed in chemical findings. Dr. Adler asked if nonlinearity of response is taken into account in the NTP conclusions framework. Dr. Blystone replied that the conclusions are not necessarily designed to address nonlinearity, depending on other factors. Dr. Barnes added that, in addition to experimental data, at least two theoretical approaches can lead to the kind of nonlinear responses observed.

Dr. Eaton called for a motion to accept the recommendations in full as written in the draft report. Dr. Harkema so moved. No second was made, the motion failed, and consideration moved to the individual conclusions.

VI.E.1. GSM-Exposed Males

The first conclusion was for the first bullet point under GSM modulation in the male mice, "*equivocal evidence of carcinogenic activity* based on combined incidences of fibrosarcoma, sarcoma, or malignant fibrous histiocytoma in the skin." Dr. Wyde explained that, although the incidences were outside the historical control range, no statistically significant increase occurred and no SAR-dependent increase in response was noted. This led to the *equivocal evidence* conclusion.

Dr. Andrews-Jones pointed out two incidences in the CDMA males were observed. Dr. Brix explained that the staff felt those incidences did not rise to the level of *equivocal evidence*. Dr. Rinke said he had been convinced that *equivocal* was appropriate for the tail tumors. Dr. Kaufmann agreed the evidence for a *some evidence* call was not sufficient.

Dr. Eaton called for a motion. Dr. Rinke moved to approve the conclusion as written; Dr. Corcoran seconded. The vote was 8 yes, 3 no, so the motion passed. Drs. Andrews-Jones, Felter, and Adler were the "no" votes. Dr. Andrews-Jones explained that she voted as she had because of the sheer number of tumors compared to so few in the historical control database. She felt the conclusion should have been *some evidence*. Dr. Felter said her reasoning was much the same and agreed the area between equivocal and some was very gray. Dr. Adler said he could not call it *equivocal* due to how much the historical control range had been exceeded.

The panel proceeded to the second bullet point under GSM modulation in the males, "*equivocal evidence of carcinogenicity* based on incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in the lung." No discussion took place, so Dr. Eaton called for a motion. Dr.

Andrews-Jones moved to accept the conclusion as written; Dr. Felter seconded. The vote was 11 yes, 0 no, so the motion carried.

Dr. Andrews-Jones moved to include hibernomas as *equivocal evidence of carcinogenicity*. Dr. Wyde delineated the incidence and stated none occurred in the historical controls. Dr. Harkema observed that the SAR was low in fat. Dr. Kuster clarified that the SAR might not be the correct unit of merit. For example, the induced E-fields in fat are similar to the E-fields induced in other tissues. Dr. Rinke asked where the hibernomas were located. Dr. Brix believed they were mesenteric but was not completely sure. Dr. Lin asked that tumor incidences be projected to aid memory, so that votes could be taken on quantitative data. Dr. Eaton said that was why staff were being asked to review the evidence in each instance. Dr. Lin was concerned that the conclusions were biased toward a linear-only response. Dr. Eaton disagreed with that assertion. Dr. Rinke pointed out a number of uncommon tumors had been observed, including teratomas and pituitary tumors. The panel examined the incidences of those tumors. Dr. Brix pointed out that the only tumor being discussed in the GSM males was the hibernomas. Dr. Eaton called for a second to the motion; there was no second, so the motion did not carry.

Dr. Felter noted that in some instances no tumors occurred in the treated animals but did occur in the controls. Dr. Eaton said that point was legitimate, but that the *equivocal evidence* conclusion would address the point. Dr. Malarkey pointed out that a vote for *equivocal* does not differentiate between linear or nonlinear responses.

VI.E.2. GSM-Exposed Females

Dr. Eaton moved to the next conclusion, for GSM-exposed females, which was "*equivocal evidence of carcinogenic activity* based on incidences of malignant lymphoma (all organs)." Dr. Wyde described the incidences of malignant lymphomas and stated that, although all exposed groups were outside of the historical control range, no SAR-dependent increase in response occurred. He said that the control group was below the historical control range and all exposed groups were similar within the historical range, even those that were statistically significant. These together led to the *equivocal evidence* conclusion. Dr. Eaton noted the very low tumor incidence rate in the controls and that the historical control incidence was highly variable; he expressed concern over whether this control was adequate due to such low background levels.

Dr. Eaton called for a motion. Dr. Andrews-Jones moved to accept the conclusion as written; Dr. Harkema seconded. The vote was 9 yes, 2 no, so the motion carried. Drs. Corcoran and Cline were the "no" votes. Dr. Corcoran explained his "no" vote as this is a unique case in which the historical controls might not be very informative and also cited the lack of linearity in dose response. He asked Dr. Brix why the call had not been *some evidence*. She explained that no abnormal pattern had been seen; all incidences were similar across exposure groups and all were within expectations. Dr. Cline explained that his "no" vote was based on the parallel control. He believed the response at the low- and mid-exposure groups was a real effect and was also confident in the statistics.

VI.E.3. CDMA-Exposed Males

The panel next considered the CDMA modulation conclusions for the male mice. The call was "*equivocal evidence of carcinogenicity* based on incidences of hepatoblastoma of the liver." Dr. Wyde related the incidences and explained that no SAR-dependent increase and no positive trend were observed, and the control incidences were at the high end of the historical control range. Dr. Felter said the relevance of hepatoblastomas has changed over the years; therefore, the entire spectrum of liver tumors should be considered. Given the variability and high

background incidence, she asked for clarification as to why the call was *equivocal evidence* and not *no evidence.* Dr. Brix said the call was made because the incidence in exposed groups was two-fold higher than controls. Dr. Harkema agreed that the *equivocal* call was the most conservative approach.

Dr. Eaton called for a motion on the conclusion. Dr. Andrews-Jones moved to accept the conclusion; Dr. Adler seconded. The vote was 10 yes, 1 no. The "no" vote was Dr. Felter. Dr. Felter reiterated the points she had made in the discussion to justify her "no" vote.

Dr. Andrews-Jones moved to add pituitary tumors in the mid-dose group as *equivocal evidence*, the incidence of which was two adenomas and one carcinoma, which were considered rare. There was no second, so the motion did not carry.

VI.E.4. CDMA-Exposed Females

The panel proceeded to the conclusion for CDMA-exposed female mice. Dr. Wyde explained the incidence and rationale for the call, which was "*equivocal evidence of carcinogenic activity* based on incidences of malignant lymphomas (all organs)." Dr. Wyde stated that the incidences were statistically significant only at 2.5 W/kg, which differed from the GSM modulation. There was no discussion. Dr. Andrews-Jones moved to accept the conclusion as written; Dr. Felter seconded. The vote was 11 yes, 0 no, so the motion carried unanimously. There was no motion to add additional tumors.

VI.E.5. Nonneoplastic Lesions

The panel moved on to consider the nonneoplastic lesions, which were GSM and CDMA combined. The conclusions were that neither modulation increased the incidence of nonneoplastic lesions in male or female mice. The panel discussed whether considering the modulations together was appropriate, based on the fact that the frequencies actually differed, along with some other elements. Ultimately, they agreed the conclusion was acceptable when evaluating weight of evidence and biological relevance; however, the data should not be combined for statistical analysis. Dr. Eaton called for a motion to accept the conclusions as written. Dr. Adler so moved, and Dr. Felter seconded. The vote was 11 yes, 0 no, so the motion carried unanimously.

VI.F. Final Conclusions

The final list of conclusions for the RFR studies in mice follows:

Technical Report TR 596: Cell Phone Radiofrequency Radiation Studies in Mice

<u>GSM Modulation</u>

Male B6C3F1/N mice, exposed to GSM-modulated cell phone RFR at 1,900 MHz

- ***Equivocal evidence of carcinogenic activity***
  - Combined incidences of fibrosarcoma, sarcoma, or malignant fibrous histiocytoma in the skin
  - Incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in the lung

Female B6C3F1/N mice, exposed to GSM-modulated cell phone RFR at 1,900 MHz

- ***Equivocal evidence of carcinogenic activity***

- Incidences of malignant lymphoma (all organs)

Exposure to GSM-modulated cell phone RFR at 1,900 MHz did not increase the incidence of any nonneoplastic lesions in male or female B6C3F1/N mice.

CDMA Modulation

Male B6C3F1/N mice, exposed to CDMA-modulated cell phone RFR at 1,900 MHz

- ***Equivocal evidence of carcinogenic activity***
  - Incidences of hepatoblastoma of the liver

Female B6C3F1/N mice, exposed to CDMA-modulated cell phone RFR at 1,900 MHz

- ***Equivocal evidence of carcinogenic activity***
  - Incidences of malignant lymphoma (all organs)

Exposure to CDMA-modulated cell phone RFR at 1,900 MHz did not increase the incidence of any nonneoplastic lesions in male or female B6C3F1/N mice.

Day 2 of the proceedings was adjourned at 4:31 p.m.

Day 3: March 28, 2018

VII. Welcome and Introductions

Dr. Eaton welcomed everyone to Day 3 of the meeting and asked all attendees to introduce themselves. Designated Federal Official Dr. Mary Wolfe read the conflict of interest statement.

VIII. Peer Review of NTP Studies in Rats of Cell Phone RFR

VIII.A. Charge to the Panel

Dr. Blystone presented the charge to Panel 2, addressing the draft *NTP Technical Report TR-595, Toxicology and Carcinogenicity Studies in Hsd:Sprague Dawley SD Rats Exposed to Whole-Body Radiofrequency Radiation at a Frequency (900 MHz) and Modulations (GSM and CDMA) Used by Cell Phones*. The panel was charged to:

- Review and evaluate the scientific and technical elements of the study and its presentation
- Determine whether the study's experimental design, conduct, and findings support the NTP's conclusions regarding the carcinogenic activity and toxicity of the test agent

VIII.B. Results of the NTP Studies of Cell Phone Radiofrequency Radiation in Hsd:Sprague Dawley Rats

Dr. Wyde briefed the panel on the partial findings, the results of the 28-day prechronic toxicology studies, and the 2-year toxicology and carcinogenicity studies in rats, which included 14-week interim evaluations of histopathology, genetic toxicity, and hematology.

In December 2015, the final report was received from the study lab, in which concern was raised regarding the findings in the brain and the heart. That led to a complete review of the

brain and heart lesions, and preparation of the partial findings report, which was released in May 2016, following external peer review.

The draft report's preliminary conclusions (subject to peer-review modification) were as follows:

In male rats exposed to GSM-modulated cell phone RFR at 900 MHz, there was *some evidence of carcinogenic activity*, based on incidences of malignant schwannoma in the heart. Lesions that *may have been related to cell phone RFR exposure (equivocal evidence)* included:

- Incidences of adenoma or carcinoma (combined) in the prostate gland
- Incidences of malignant glioma and benign or malignant granular cell tumors in the brain
- Incidences of adenoma of the pars distalis in the pituitary gland
- Incidences of pheochromocytoma (benign, malignant, or complex combined) in the adrenal medulla
- Incidences of pancreatic islet cell adenoma or carcinoma (combined)

Nonneoplastic lesions occurred in the heart, brain, and prostate gland.

In female rats exposed to GSM-modulated cell phone RFR at 900 MHz, there was *no evidence of carcinogenic activity*. Nonneoplastic lesions occurred in the heart, thyroid gland, and adrenal gland.

In male rats exposed to CDMA-modulated cell phone RFR at 900 MHz, there was *some evidence of carcinogenic activity*, based on incidences of malignant schwannoma in the heart. Lesions that *may have been related to cell phone RFR exposure (equivocal evidence)* included:

- Incidences of malignant glioma in the brain
- Incidences of adenoma of the pars distalis in the pituitary gland
- Incidences of adenoma or carcinoma (combined) of the liver

Nonneoplastic lesions occurred in the heart, brain, and prostate gland.

In female rats exposed to CDMA-modulated RFR at 900 MHz, there was *equivocal evidence of carcinogenic activity*, based on incidences of malignant glioma in the brain and incidences of pheochromocytoma (benign, malignant, or complex combined) in the adrenal medulla. Nonneoplastic lesions occurred in the brain.

VIII.B.1. Questions for Clarification

Dr. Andrews-Jones asked in which sub-anatomic area of the brain the lesions occurred. Dr. Wyde said he was not sure they were limited to one anatomic region, and Dr. Cesta confirmed they were scattered.

Dr. Felter asked about the impact of the CDMA modulation on the pups in terms of survival and decreased body weight, and whether that would meet the bar for exceeding a maximum tolerated dose in an NTP bioassay. Dr. Wyde said that, although the body weight decreases in the 28-day study in the 9 W/kg group were quite significant, they were not as severe in the 2-year study in the 6 W/kg group, and neither group exceeded a maximum tolerated dose. Dr. Blystone said the decreases were considered delays, and the pups caught up eventually, constituting a transitory effect. Dr. Felter asked about the decreased pup survival at postnatal day 4 in the high-dose group. Dr. Blystone said that NTP believes the decrease in survival was a real effect, but was not significant enough to exceed the maximum tolerated dose.

Dr. Felter asked about the GSM females, with the three different tumor types in the heart. If they occurred in separate animals, would they not be combined to give an incidence? Dr. Cesta said that for the analysis, the myocardial and endocardial lesions were combined, but nonneoplastic lesions were not combined with neoplastic lesions, so the hyperplasias were not combined with the schwannomas. Dr. Malarkey noted that the paragangliomas would not have been combined with the schwannomas due to the different cell origins. Dr. Felter asked for confirmation that in the GSM females, the incidence in the mid-dose for related heart tumors was 3 in 90. Dr. Cesta confirmed that.

Dr. Kaufmann asked about litter size and its effect on growth rate, and how the pups were distributed to the dose groups. Dr. Wyde said that three pups from each litter were included in the 2-year study, but as all but the control pups came from exposure chambers, they were already exposed. Dr. Blystone noted pup distribution was randomized.

Dr. Andrews-Jones asked whether dam lactation had been considered as a possible source of the decreased pup weights. Dr. Blystone said that had not been evaluated.

Dr. Cline asked for confirmation that the ears were not trimmed in this study. Dr. Wyde said they were not. Dr. Cline asked if gynecomastia was present in any male animals, to which Dr. Wyde replied, no. Dr. Cline asked about adrenal weights in the animals with pituitary tumors, and whether the tumors were derived from lactotrophs or corticotroph tumors. Dr. Wyde said that had not been explored. Dr. Cline asked about the association between lymphoid organ atrophy and chronic progressive nephropathy, and whether there was a rationale for the association. Dr. Cesta explained the atrophy was due to decreased blood flow because of exacerbated polyarteritis nodosa.

Regarding the body weight issue, Dr. Lin asked for confirmation that food and water consumption were not monitored, which Dr. Wyde said was true.

Dr. Felter asked about the mammary tumors observed in the 14-week interim evaluation—whether that finding was unusual, or such tumors are sometimes seen that early. Dr. Cesta said that some mammary tumors can occur earlier, but the adenocarcinoma was surprising.

Dr. Whiteley asked Dr. Cesta about assessment of reproductive cyclicity with vaginal swabs and whether, during the histopathology evaluation, ovarian and vaginal morphologies were evaluated to assess cyclicity. Dr. Cesta said that cyclicity data cannot be determined from the histopathology evaluation, but the ovaries and vagina can be evaluated to determine if there is discordance or evidence that they are not cycling.

Dr. Whiteley asked why no functional observational battery assessments were done, particularly because concerns for central nervous system toxicity were present. Dr. Wyde said they were not part of the study design, and animals could not be observed during the exposures.

Dr. Andrews-Jones asked Dr. Cesta what the typical severity expectation would be for chronic progressive nephropathy (CPN) in this age of rats at 2 years, noting the 4-point severity scale. Dr. Cesta said many grade 4s had been observed, especially in the controls, which was unusual.

VIII.C. Pathology Peer-Review Process and Selected Lesions for the 2-Year Study of Cell Phone Radiofrequency Radiation in Rats

Dr. Cesta briefed the panel on the pathology peer-review process for the rat study, and described and depicted heart, brain, and kidney lesions observed in the 2-year study.

He delineated the standard NTP pathology peer-review process. With the release of the partial report, some adjustments were required. Potential treatment-related proliferative heart and brain lesions were initially selected for early reporting in the partial report. Four Pathology Working Groups (PWGs) were convened—the two initial PWGs and two additional PWGs composed of specialists in neuro- and cardiovascular pathology.

Dr. Cesta provided more details about the heart, brain, and kidney (CPN) lesions observed, including diagnostic criteria and visual depictions.

VIII.C.1. Questions for Clarification

Dr. Kaufmann questioned the diagnostic criteria for the brain lesions. He made a distinction between a tumor-like hyperplasia and a true hyperplasia. The similarity to a glioma is an important finding and should be in the report, he noted. He asked about the basis of the diagnostic term, glial cell hyperplasia. Dr. Cesta said he was unsure of the term's origin, but that the PWG agreed with the study pathologist diagnosis. Dr. Kaufmann asked if any special staining had been considered to differentiate between neoplastic and non-neoplastic changes. Dr. Cesta said staining had been discussed, with plans to investigate the issue further. Dr. Malarkey said that NTP agrees with Dr. Kaufmann's concerns about differentiation of the tumors, and studies are underway to look at immunohistochemical staining of the lesions.

Dr. Lin asked if one or more of the sections taken from the brain were through the auditory nerve or the cranial nerve, and whether any special attention had been paid to any sections where the auditory nerve was visible. Dr. Cesta replied that none of the sections had gone through the auditory nerve. He said no lesions in the brain having morphology of a schwannoma had been observed. Dr. Lin said, without a section through the auditory nerve, observing any pathologies in that region would have been difficult. He added that the team, having *a priori* knowledge that acoustic neuroma or vestibular schwannoma were part of the findings in humans, should have investigated the issue. Dr. Sills, NTP Chief of Pathology, provided further clarification and explained that a comprehensive evaluation of the nervous system (i.e., central nervous system, peripheral nervous system, all the nerves within the animal) is performed with all studies. He said that as such, if involvement of the nerves of the brain, including cranial nerves or nerves that deal with the auditory system, were indicated, it would have been detected at that point. Dr. Sills stated that Dr. Cesta did perform a comprehensive reevaluation of the whole neck area because of the issue of acoustic neuromas.

Dr. Adler was concerned about the incidence of right ventricular cardiomyopathy. He asked, in NTP's experience, if the left ventricle is more often the site of spontaneous cardiomyopathy. Dr. Cesta said spontaneous cardiomyopathy was certainly more prevalent and more obvious in the left ventricle. Dr. Adler asked if concluding that RFR was related to the lesions on the right side would be fair. Dr. Cesta replied that if the criteria were applied to nonneoplastic lesions, it would be equivocal; it was a minor component of the overall cardiomyopathy. Dr. Adler noted that he would like additional references to examples in which spatial associations were not found. Dr. Adler asked whether there was an effect compared to the historical data. Dr. Cesta replied that NTP does not have historical control data on this issue. Dr. Malarkey added that more data should be available for the Hsd:Sprague Dawley SD rats soon. Dr. Adler asked if any correlation was observed between the malignant schwannomas and the ventricular cardiomyopathy. Dr. Cesta said not that NTP could discern.

Dr. Rinke supported Dr. Adler's point about the right ventricular cardiomyopathies and asked about their distribution, along with the distribution of the endocardial schwannomas or hyperplasias, which are not frequently observed in the right ventricle. He asked Dr. Cesta if

immunohistochemistry was performed on the schwannomas. Dr. Cesta said plans are to explore that further, but NTP has done nothing to this point.

Dr. Whiteley asked if anything was unique about the schwannomas—any features more prominent in those observed in the animals relative to the textbook descriptions. Dr. Cesta said that he noticed nothing unusual about the schwannomas; they were relatively standard.

Dr. Andrews-Jones asked if a spatial irregularity in the right ventricular schwannoma had been shown. Dr. Cesta said some, but not all, lesions tended to occur more toward the apex. Dr. Andrews-Jones asked Dr. Sills to confirm that glioblastoma multiforme is a term used only in humans. He replied that in this study, the lesions were called malignant gliomas based on peer-review agreement. He noted that more information is emerging about the molecular nature of the tumors in humans and rodents.

Dr. Harkema asked for more information about the variability of the right ventricular lesions, and whether they were more epicardial. Dr. Cesta said they tended to be focused in the subepicardial region, while more severe cases extended somewhat into the myocardium. Such lesions are quite rare, Dr. Cesta confirmed.

Dr. Cline asked whether a hyperthermia effect, independent of the radiation effect, had been considered relative to the CPN. Dr. Cesta replied that had not been examined. He noted that no thermal effect was observed on the testes, which are sensitive to heat and were examined for that reason. Dr. Cline asked if heat shock proteins were evaluated. Dr. Cesta said no, and agreed that that would be an interesting area to investigate. Dr. Lin noted that a 1°C variation in body temperature is within a normal physiological range, should not per se be a matter of concern, and would not trigger heat shock proteins.

Dr. Barnes noted some data in the literature indicate that a very small increase in temperature could trigger heat shock proteins. Dr. Harkema said that different organs respond differently to heat increases, such as the skin and testes. Dr. Lin agreed, but clarified that temperature variations are not always deleterious. Dr. Kuster added that only the whole body temperature change was determined, not tissue-specific temperatures, and cautioned against putting too much weight in the temperature data. Dr. Gamboa da Costa from FDA clarified that only subcutaneous temperatures were measured, not internal temperatures, and also cautioned against making claims about tissue-specific temperature effects.

The chair permitted ad hoc comments from some public attendees. Mr. Mottus from the California Brain Tumor Association questioned why no EMF experts were included on the peer-review panel. As a result, he asked that the panel recuse itself and reconvene with EMF scientists. Dr. Eaton responded that the studies are pathology studies and the panel has some of the best animal pathologists in the country.

Dr. Melnick, retired NIEHS/NTP scientist and public attendee, noted that the hyperplasia severity varied among the rats, and asked Dr. Cesta to show a severity grade 4 instead of a 2, as he had, so that the lesion would be evident. He also observed that, although the right ventricular cardiomyopathy had been characterized as not being very severe, it had been listed as the cause of death on some of the individual animal pathology reports. Having detected a schwannoma at necropsy, he asked why additional sections were not cut to see if any schwannomas in the heart had been missed. Dr. Cesta replied that he could not show a grade 4 hyperplasia because he did not have one available. He said some debate had occurred among the pathologists about the right ventricular cardiomyopathy as the cause of death, so confidence

in that very subjective assessment was not high. He noted that additional sections of the heart are not typically taken to avoid bias and maintain consistency.

Regarding the 28-day studies, Dr. Davis from Environmental Health Trust asked Dr. Cesta if perinatal effects might have been consistent. She pointed specifically to Table H2 in the report, which summarizes the epididymal spermatozoa measurements. She said there appeared to have been a significant pathological impact and statistically significant declines, and wondered why a Williams' trend test had not been conducted. She noted the lack of linearity in the response. Dr. Shockley said the tests had been conducted, and the trend was not significant. The 6 W/kg group showed a large uncertainty and did not pass the statistical filter. Dr. Davis said that, in many cases, statistical significance might not be the same as public health importance.

VIII.D. Presentation of Peer-Review Comments

Dr. Felter, the first peer reviewer, felt that it would be important for the report to contain an in-depth discussion of dose metrics that a layperson could understand, particularly SAR sensitivity. She was concerned that discussion of SAR sensitivity in the report as it relates to humans could be misinterpreted, especially the comparison of the low dose in rats, 1.5 W/kg, to the FCC limit of 1.6 W/kg. She suggested more discussion of the increased pup mortality and survival at high doses. Regarding interpretation of the tumor findings, the evidence should be considered in totality. Regardless of the lack of statistical significance in the females, the findings in the heart and brain of that group should be discussed due to biological evidence of an effect. She commended NTP for taking on such a challenging project, and suggested including all information that might be illustrative, or if not considered helpful, expressing why. One example is time to first tumor information, especially for the key target organs, such as the malignant schwannomas in the heart. She suggested adding more context about the inherent qualities of cell phone RFR and the conditions under which they occur, as they should not simply be assumed.

Dr. Lin commented on the issue of the term "whole body SAR" and pointed out that the exposure would be the same regardless of the organ involved. Dr. Felter responded the presentation was that the exposure of all target organs would not be the same, with several elements such as tissue absorption affecting SAR sensitivity. Dr. Lin said that Dr. Felter's point about time to tumor is relevant. Dr. Kuster noted that the dosimetry was based on numerical animal models, and that all tissues were exposed to approximately the same levels for the same amount of time. He said the translation to thermal dose had not been fully addressed in these studies, so it could not be excluded that some tissues might have experienced mild hyperthermia at the highest dose. Dr. Adler noted that the study did not evaluate tissue-specific SAR.

Dr. Whiteley asked about the physics of how surrounding organs, such as the lungs or ribcage (in the case of the heart) affect radiation exposure. Dr. Barnes replied that the surrounding organs do affect absorption and distribution. Dr. Eaton agreed with Dr. Lin's assertion that the situation is similar to pharmacokinetic or pharmacodynamic modeling. Dr. Adler noted that the heart is surrounded by an electrolyte fluid-filled pericardial sac and uniquely sits in an air cavity, essentially its own reverberation chamber.

Dr. Bucher noted that SAR distribution is an important topic, and including the information in the report as accurately as possible is important. He noted that the goal of the report is to describe what was done in the studies as clearly as possible and asked that the focus return to evaluating this study in and of itself with regard to the exposures and what they mean. He said

that adding hyperlinks in the report to the video recordings of the Day 1 presentations was a consideration.

Dr. Kuster said that the view of the heart as sitting in its own reverberation chamber was not accurate. He said a dosimetric evaluation of the heart had been done, and although it did not provide extensive detail, it is a very good proxy of the heart exposure.

Responding to Dr. Felter's review comments, Dr. Wyde acknowledged the difficulty faced by the risk assessment community when addressing localized exposures. The goal of NTP's studies is hazard identification, so the goal in this study was to expose each organ to as much RFR as possible. Efforts were made to expose all organs to the same level of RFR, but how much that can be controlled is limited. It fell within a two-fold range. Dr. Wyde reiterated a lay summary would be prepared, and he endorsed the ideas of a glossary to help the public understand some of the EMF terminology and access to the Day 1 presentations. He acknowledged the presentations had aided understanding and pledged good effort to include much of the added information into the revised reports.

Regarding Dr. Felter's comments on pup mortality and body weight, he said the body weight changes were transient and NTP was unsure whether this was a dam effect or a pup effect. Dr. Felter asked that the report be more explicit in its discussion of this point, and Dr. Wyde agreed. Regarding the decreased survival in the highest CDMA dose group, Dr. Wyde said additional description would be added to the report. He addressed Dr. Felter's comment regarding similarities between the modulations. All information was taken into account, for both the rats and mice, in looking for similarities. Combining the GSM and CDMA modulations was the topic of much discussion. Doing so is challenging from a statistical standpoint, and NTP is looking at ways to do so, as it addresses the issue of whether modulation or frequency was important. He said further evaluation of the differences or similarities would likely be addressed in follow-up manuscripts. Regarding the time-to-tumor issue, he urged caution, but noted that more information would be added to the report, where appropriate. He committed to adding some of the more recent references and, in the introduction, clarifying how this study fits in with others that have been conducted.

Dr. Cline, the second peer reviewer, called for greater clarity on the reverberation chambers, particularly regarding the control chambers and how they were confirmed to be zero or near-zero exposure, to be explicit that they were shielded, and that no antenna was present. He suggested some assessment of the sympathetic and hypothalamic-pituitary-adrenal axis with respect to stress assessments in the animals. He noted that the adrenal gland weights were not presented in the body of the report and suggested they be moved, with discussion that the pheochromocytomas could have resulted from a stress response. Multiple indicators of stress are included in the report, and seeing if they occurred within the same animals would be interesting. He called for more discussion of the mammary gland assessments and differentiation of pituitary gland tumors. He requested clarification on the nature of the noise within the testing apparatus and how audible it was to the rats, including whether it was in the rat vocalization range, where it could be a source of stress. He agreed that the female reproductive system should be histologically examined; specifically, the 14-week assessment should be reevaluated. He asked for more mechanistic discussion of why the CPN was lower in the RFR-treated groups and asked why NTP attributed CPN in the control animals to decreased food consumption when it was not measured. He recommended that the auditory vestibular tissues be examined histologically. He disagreed with using historical and concurrent controls at the same time.

Responding to Dr. Cline's comments, Dr. Wyde said more detail would be added to the description of the control chambers and exposures in the report. He said that stress lesions were not examined in relation to specific animals; however, Dr. Cline's remarks about stress assessment would be kept in mind in the design of future studies. Moving the discussion of adrenal weights forward would be considered. Regarding the mammary gland and pituitary tumor assessments, Dr. Wyde said that histopathology suggestions would be taken into consideration for future studies. Dr. Wyde acknowledged that the noise was in the range of rat vocalization, but the correlation between noise and stress is only speculation at this point. He said that the noise was accounted for by piping the same sound into the low-dose chambers so that everything was normalized across the study. He noted that food consumption had not been monitored, so it should not have been related to the CPN rate. He said that assessment of the auditory vestibular tissues could still be done. He noted that the treatment of the controls would be discussed in more detail to help clarify the approach taken.

Dr. Eaton asked Dr. Wyde to clarify his statement that the high-dose noise had been piped into the other chambers, and whether that included the controls, which Dr. Wyde confirmed. Dr. Lin asked how the piping had been done. Dr. Capstick explained the process, which involved placing speakers in the air vents.

Regarding the incidence of CPN, Dr. Adler asked about evaluation of the feed exposed to RFR, and whether thermal degradation or micronutrient effects were observed. Dr. Capstick said they measured the power absorbed by food when the bowls were full, and the level was quite small, so no increase in food temperature was expected. Dr. Adler asked if any follow-up micronutrient evaluation of the feed had been done, to which Dr. Wyde replied no. Dr. Adler said that it might have a bearing, and that NTP should consider following up on that issue. Dr. Bucher said the diets are autoclaved and so are nutrient-enriched to take this into consideration. He felt it was unlikely that any heating from RFR would be anywhere near the autoclave temperature. Dr. Wyde added that because the radiation was non-ionizing, energy to strip any of the electrons was insufficient. Dr. Adler recommended transparency in the report on the issue. NTP laboratory animal veterinarian Dr. Angela King-Herbert corrected Dr. Bucher and stated that the diets are actually gamma-irradiated and not autoclaved, and nutrients are checked before and after irradiation.

Dr. Cesta commented further on the vestibular system and the intracranial nerve. He said a thorough gross review of those tissues had been completed, with no lesions identified. As to the pituitary tumors, individual animals were not examined to determine if they also had mammary gland tumors, although that could still be done, along with immunohistochemistry of the pituitary tumors to determine their types. Dr. Eaton asked if hormone analysis could be done on serum from the 28-day study, perhaps addressing Dr. Cline's concerns about stress-induced changes between controls and exposed animals. Dr. Cline said he assumed that the serum was no longer available, which Dr. Wyde confirmed.

Dr. Rinke noted that the Zymbal's glands, which are close to the auditory cavity, were examined so the absence of lesions would support that none occurred in that region. Dr. Cline noted that the section of interest might have been examined, and if that were the case, it could be stated in the report. Dr. Malarkey described how the system had been sectioned, and noted that if there were any gross masses, they would be detected at that point. Dr. Whiteley asked how frequently the vestibular system and inner ear were hit, to be able to evaluate those structures. Dr. Malarkey said this is not seen very often. Dr. Sills said NTP would go back, look carefully at the issue, and add to the report or do additional studies as necessary. Dr. Harkema stated that the third head section having gone through the vestibular region was doubtful. Dr. Cesta noted that during the Audit of Pathology Specimens, the brains would be re-reviewed grossly.

Dr. Malys, the third peer reviewer, noted the elevated tumor occurrences in the mid-dose range and the apparent non-linear dose-response trend. He recommended aggregating tumor occurrence information across dose range. He said he would be interested in a table for the rats that addresses the question of whether evidence supports a nonlinear, dose-dependent response, simply by exploring the existing data. He said he was both impressed and shocked to see how different the grades were for different types of tumors. He felt additional discussion of severity grading should be included in the report. He reiterated his point about the importance of a well fleshed-out system of controls, along with an emphasis on reproducibility of results. He asked NTP to better describe the relationship of the 2G and 3G technology used in the studies to the current 5G technology to make the data and exposures more relevant to casual cell phone users.

Dr. Andrews-Jones felt looking at the data more comprehensively was an excellent idea, particularly whole biological systems. For example, many of the equivocal tumors were in the endocrine or neuroendocrine system.

Dr. Harkema asked Dr. Malys about the implications of having six times more exposed animals than controls. Dr. Adler noted that that would increase the opportunities for random events, unrelated to treatment, to occur in the treated groups. Dr. Malys agreed. He emphasized that future studies should have more robust control systems to support reproducibility. He said the positive results were difficult to interpret in this study due to decreased survival in controls. Dr. Barnes stated that the effects noted in this study should be considered a real outcome.

Dr. Shockley agreed that summarizing results that suggest nonlinear responses would be useful. Although a linear-based trend test is used, with lower power to detect nonlinear trends, the pairwise test is also used, which can help detect nonlinear responses. He noted that NTP uses a weight-of-evidence approach and not just statistics, and that the current NTP statistics methods are well supported. Dr. Malys clarified that, when he spoke of aggregating tumor information from different tumor types, he was not talking about combining to perform a statistical test, but solely about the concept of exploring the data to examine the possibility that a trend might exist. This analytical distinction is subtle, but important. Although combining results can be quite challenging statistically, simply exploring the data to gain wider insights can be useful.

Dr. Lin noted that because all tissues and organs were exposed to similar doses, he asked what would be the difficulty in comparing the occurrence of total tumors (e.g., adenoma, schwannoma, carcinoma, glioma) in all tissues and organs between the RF-exposed group and the concurrent control group? Dr. Shockley restated Dr. Lin's question as proposing that all tumors across all groups be combined as a total analysis of tumor burden. He noted that that is actually done in the report, although that information is not used to make the final decisions. Dr. Bucher noted the vast majority of total tumor burden comprises spontaneous tumors, which can lead to missing more subtle effects. Consideration of total tumor burden has been used historically in cancer studies but set aside as less useful.

Dr. Whiteley, the fourth peer reviewer, commended NTP for conducting the study, including its heroic efforts in engineering. He felt a written statement regarding tumor latency and whether it adds any value to the assessment of carcinogenicity for a given tumor should be included. He said distinguishing the different glial cell types would be important. He agreed adding a table of identified target effects, listing male and female and modulation, would be helpful. He said visualizing commonalities in the report is difficult, and that such a table would help. He addressed the report's discussion, noting several recently published and existing studies with a concordance of effects point in the same direction. He felt that that should be brought out in the

report, because it adds significance to the findings in the NTP study. He recommended a discussion about the possibility of nonlinearity and biphasic effects and how they might impact the interpretations of significance. He also recommended adding a clear statement in the report's abstract about the rationale for dose selection.

Dr. Wyde said that a discussion of time to tumor would be added. The issue of glial cell types would be evaluated further. He agreed that adding summary tables from the modalities to identify similarities and differences would be good. He said that more discussion and comparison of information from other published studies and reported tumor types, which had been present in the preliminary report, would be added to the 2-year study report. He said nonlinearity would be taken into consideration on a case-by-case basis, as many different factors are considered when making level-of-evidence calls. He agreed to add the dose-selection rationale to the report's abstract.

Dr. Adler, the fifth peer reviewer, commended NTP for its very high degree of integrity and transparency. He felt that the studies were well designed, well conducted, and robustly analyzed and reviewed. He felt that the report should make clear that the study is solely a hazard identification study, not a risk assessment study, and that FDA is the agency responsible for risk assessment decisions. He agreed that the dose-selection rationale and justification should be added, including an explanation of the dose spacing and why the doses changed between the 28-day and 2-year studies. He also recommended further discussion on the use of historical controls, including on the validity of control animal survival and CPN. A discussion of fluorescent versus incandescent lighting also should be included. He mentioned that in his company, the term "uncertain relationship to treatment" is used instead of "equivocal," and hoped that regulatory agencies would interpret that term in similar fashion, erring on the side of public health. He agreed with Dr. Corcoran's recommendation of a weighted decision rubric for making level-of-evidence calls, as there is a fine line between *equivocal* and *some* in many of these cases.

He requested better clarification between the non-SAR-dependent responses and nonlinearity of the dose response. He noted the maximum tolerated dose is based on thermal evaluations and clearly was not measured at night. He noted that thermal effects were measured during the day, although rodents are much more active at night, and asked that this be reconsidered in future studies. He said that information on specific biomarkers would be useful, particularly regarding time-to-tumor development. He agreed with Dr. Melnick that the studies should clearly name the target organs, such as the heart in rats. Regarding the right ventricular cardiomyopathy, he felt the occurrence in the study was unusual and should be brought out. He asked that the report discuss the perceived lack of associations between the right ventricular cardiomyopathy and the occurrence of schwannomas and Schwann cell hyperplasias. He also asked for more discussion on the rat hippocampus being positive in the comet assay in the CDMA-exposed group without an association with brain tumors, spatially. He noted that in the rat study, the heart is clearly sending a signal, and represents a ripe area for future exploration of the adverse outcome pathways to neoplasia. It was also noted that 2-year rodent bioassay and lifetime epidemiology studies for RFR exposure represented an undue time period to further identify a hazard to public health.

Dr. Lin noted that, for a true control, all aspects of the environment should be the same except for the agent involved. He questioned whether that was the case in the rat studies, particularly with respect to the noise exposure for the sham controls. The lighting also differed from those in the historical controls. Thus, the environmental conditions were not the same.

Dr. Wyde responded to Dr. Adler's comments. He appreciated the distinction Dr. Adler made that this was a hazard identification study and confirmed that FDA would be responsible for any risk assessment. He committed to describing the dose spacing more accurately in the report and would consider expanding the discussion of the historical controls. He felt that a decision-making rubric would not be fully appropriate in this case, as the studies are conducted on a case-by-case basis without a one-size-fits-all approach. Further discussion of some of the decisions made, however, would be appropriate. He acknowledged Dr. Adler's point about temperature taken during the day and not at night, and noted that in future studies, a different technology would be used for data collection of temperature, allowing for nighttime measurements. He agreed about the need for biomarkers. In terms of target organs, in the rat, the only one was the heart. He acknowledged that reorganizing and presenting the equivocal data in a more digestible, user-friendly form would help clarify several issues, including target organs. Dr. Wyde expressed confidence that NTP and other researchers would pursue the mechanism behind the effects observed in the heart. Dr. Cesta said that more information would be added to the report about the spatial associations with the right ventricular cardiomyopathy and the proliferative Schwann cell lesions, along with information about other spatial associations or lack thereof that the panel had mentioned.

Dr. Felter asked that the report make clear that the temperatures were taken subcutaneously.

Dr. Adler added that a discussion of the change of doses from the 28-day to the 2-year studies should be included in the report.

Dr. Andrews-Jones felt that Dr. Adler's point about hazard identification was important and should be included in the report's abstract.

Dr. Gamboa da Costa from FDA recommended caution when using the word "dose" for these studies, as W/kg is not dose—it is intensity of radiation. A better way to express the dose would be to integrate time of exposure and express it as Joules/kg.

Dr. Kaufmann, the sixth peer reviewer, agreed with the other reviewers' statements concerning the study's design and conduct. He asked that the rationale for the use of different frequencies for the rats and mice be added to the report. He said he would like to see more immunohistochemistry on the brain tumors and hyperplasias to aid in making decisions about the relevance of the brain effects. He agreed with the proposal to add a tumor totality table to the reports. He noted that distinguishing between a conclusion of *some* or *equivocal evidence* is very difficult, especially given the low survival in the controls.

Dr. Bucher noted that NTP does perform survival adjustments during the statistical evaluations, so survival differences are taken into account. Dr. Wyde said that the schwannomas occurred early, so the low survival in the controls is not believed to have influenced statistical interpretation. The gliomas occurred later. Dr. Eaton added that that is where it would be useful to discuss time to tumor.

Ms. Pant, the seventh peer reviewer, addressed the genetic toxicological aspects of the rat study. She noted the hippocampus was positive, whereas the frontal cortex showed a trend, which was not positive due to variability. She asked if the data could have been transformed for analysis or analyzed using nonparametric statistical methods. Because of so much variability in the percentage of damaged cells in the liver of control animals, and the percent tail DNA was very high, she asked if historical data were available. She asked if the slides were coded during the blinding process and speculated that shipping of the samples might have been a factor in the variability among controls.

Ms. Witt agreed with Ms. Pant's comment on the frontal cortex in the CDMA-exposed male rats, which was close to statistical significance. She noted the variation among animals made capturing the response statistically more difficult. She said that both parametric and nonparametric approaches were used. With regard to the liver, she agreed with Ms. Pant on the high values of percent tail DNA. The scorers were very conservative in using the scoring software, and visually eliminated cells that appeared to be hedgehogs. She described more details of the scoring process; the scoring was redone with the same slides and the software was confirmed as accurately determining tail DNA. She noted Ms. Pant's point about the potential impact of shipping, with a high level of DNA damage related to freezing of the cells, and added that in the past, the liver was not determined to be a cell type significantly affected by freezing.

Regarding the comet assay, Dr. Cline said there were different OECD methods of disaggregating the cells and having a description in the report of which was used in this study would be helpful. He said that, of 10 cell types in the brain, there is a range of survival during the disaggregation process and variability in cell degradation rates. He asked Ms. Witt if she had an opinion on which brain cell types would be most likely to survive and make it to the slide. She replied that an explanation of the method of disaggregation is provided in Appendix E of the report. She said that due to the method of preparation, she could not answer Dr. Cline's inquiry about the surviving brain cell types. She was not aware of a method to distinguish between degradation based on cell type.

Ms. Pant said that once single-cell suspensions are made, the suspension is a mixture of cells, and there is no way to determine cell types. Ms. Pant said that problems in evaluation develop with too many cells on a slide.

VIII.E. Panel Discussion and Recommendations

Dr. Eaton introduced the session, noting that at the end of the discussion, Panel 2 members would vote on the conclusions for the draft rat NTP Technical Report TR 595. Each preliminary conclusion was considered individually, with commentary from NTP staff.

VIII.E.1. GSM-Exposed Males

The deliberations began with male Hsd:Sprague Dawley SD rats exposed to GSM-modulated cell phone RFR at 900 MHz. The first finding was "*some evidence of carcinogenic activity* based on incidences of malignant schwannoma in the heart." Dr. Wyde explained the rationale behind the conclusion: an increase in incidence and a positive trend across the exposure groups with an incidence of zero in the controls. Dr. Harkema asked why the conclusion was not raised to *clear evidence*. Dr. Wyde said, although the level of the response exceeded the historical control range, it was not statistically significant and, therefore, was not raised to a higher level.

Dr. Felter noted a commonality of response across the other three test groups (females, both modulations), with malignant schwannomas in some of the treated animals and none in the controls. Dr. Adler asked about the line between *some evidence* and *clear evidence* and whether NTP would have called it *clear evidence* if the high-dose incidence had been statistically significant. Dr. Wyde said no, the level of response was not at the *clear evidence* level. Dr. Blystone clarified that NTP does try to look across reports to be consistent in level-of-evidence calls. NTP staff thought that the malignant schwannomas looked treatment-related but believed survival of the controls played a role in the observed effect.

Dr. Eaton called for a motion on the conclusion. Dr. Felter moved to upgrade the conclusion from *some evidence* to *clear evidence*. Dr. Adler seconded the motion. The panel voted 8 yes, 3 no, so the motion carried. The "no" votes were Drs. Harkema, Malys, and Cline. Dr. Malys said the numbers presented were not striking enough to justify the upgrade, along with the issues with the control group. Dr. Harkema and Dr. Cline said their reasons for voting no were similar to Dr. Malys's.

The panel next considered incidences that were deemed "May have been related to cell phone RFR exposure (*equivocal evidence of carcinogenic activity)*." The first conclusion in the category was "Incidences of adenoma or carcinoma (combined) in the prostate gland." Dr. Wyde explained the rationale for the conclusion: although the incidences did exceed the historical control range, it was not by much. Also, the only increased incidence was at the mid-dose, 3 W/kg, and that increase was not statistically significant. Dr. Lin questioned the relevance of including the current controls in the historical controls. Dr. Bucher said a 5-year window is associated with historical controls. In this case, a small number of historical control studies fell in that window, so the current study heavily weighted the historical controls, but they still added validity to the report. The control animals from the current study were the most appropriate to consider. Dr. Lin felt that the issue deserved further consideration. Dr. Harkema moved to accept the conclusion as written; Dr. Andrews-Jones seconded. The panel voted 11 yes, 0 no, so the motion carried.

Next in the equivocal evidence category was "Incidences of malignant glioma and benign or malignant granular cell tumors in the brain." Dr. Wyde explained the rationale behind the conclusion: Incidences occurred in all exposure groups, were flat across SARs, and fell within the historical control range. Replying to a query from Dr. Harkema, Dr. Wyde noted no statistical significance either by trend or pairwise comparison in this case. Dr. Eaton clarified instances can occur where a linear response is saturated at high doses, and, therefore, responses at lower doses cannot be ignored.

Dr. Felter moved to upgrade the conclusion from *equivocal evidence* to *some evidence*. Dr. Andrews-Jones seconded, but said she thought the discussion was solely about the gliomas. Dr. Felter noted that if the panel opted to change the conclusion to refer only to the gliomas, she would still move to upgrade based on the commonality of response observed across the different modalities and sexes, the lack of tumors in the controls, and considering the incidence of hyperplasia. The panel did elect to separate the conclusions. Voting on the upgrade moved by Dr. Felter just on the malignant gliomas, the panel voted 7 yes, 4 no, with Drs. Malys, Corcoran, Harkema, and Adler voting no. Dr. Malys explained his no vote stemmed from lack of statistical significance, lack of exceeding historical controls, and the appropriateness of how to put the information in the context of other findings. Explaining his no vote, Dr. Corcoran added the significant degradation of the control group due to premature death limited the strength of the controls as a comparison. Dr. Harkema agreed with Dr. Malys and Dr. Corcoran. Dr. Adler also agreed and felt that it was changing the rubric involved. He felt that the discussion of the report should look at what occurred across the two modalities to see patterns, as well as look for patterns across other studies. He also thought that patterns across studies should be considered for risk assessment, not hazard identification.

After splitting the brain conclusions, the panel next considered "Incidences of benign or malignant granular cell tumors in the brain" as a separate conclusion. Dr. Andrews-Jones move to accept the conclusion as written (equivocal); Dr. Adler seconded. The panel voted 11 yes, 0 no, so the motion carried.

The next conclusion under the equivocal evidence category was “Incidences of adenoma of the pars distalis in the pituitary gland.” Dr. Wyde explained the rationale for the conclusion: although the incidences in exposed groups exceeded the historical control range, the incidences were similar across the exposed groups and not statistically significant by trend test or pairwise comparison. Dr. Felter moved to accept the conclusion as written; Dr. Rinke seconded. The vote was 10 yes, 1 no. Dr. Andrews-Jones said her “no” vote stemmed from her feeling that the issue needed to be examined more carefully, including effects in different cell types. She felt that there were many effects in the endocrine system in general, and that the call should be upgraded to *some evidence*.

Next, the panel considered “Incidences of pheochromocytoma (benign, malignant, or complex combined) in the adrenal medulla.” Dr. Wyde explained the rationale for the equivocal call: a statistically significant increase in the low- and mid-dose groups, no statistical significance in the high-dose group, and the incidences in the low- and mid-dose groups were at or only slightly above the historical control range. Dr. Adler asked what it would take to upgrade the call to *some evidence*. Dr. Bucher explained that this particular tumor is quite variable in the NTP experience, so more evidence of a dose response with higher incidences would be needed to upgrade. Dr. Corcoran asked about the propensity for a benign lesion to progress. Dr. Malarkey said little progression to malignancy was seen in the study. Dr. Corcoran asked about progression in broader experience with this type of tumor. Dr. Malarkey said the tumor would be low to medium potential to progress. Dr. Rinke asked about the nature of the malignancy. Dr. Cesta said it was based on invasion into the surrounding tissues. Dr. Harkema asked whether much weight had been given to the fact that there was no dose response. Dr. Bucher said the decision was based mainly on the fact that they are variable tumors with predominance toward the benign forms. Dr. Cline moved to upgrade the call to *some evidence*. Dr. Adler seconded. Dr. Cline explained his motion in that he viewed all pheochromocytomas as potentially malignant, whether they progressed or not, and that he did not think dose response was a big factor here. The panel voted 6 yes, 4 no, 1 abstain, so the motion carried. Drs. Malys, Harkema, Rinke, and Kaufmann were the “no” votes and Dr. Corcoran abstained. Dr. Malys explained that he had voted no due to the lack of establishment of a reason behind the nonlinear dose-response curve, the previously cited control issues, and being very close to the upper end of the historical control range. Dr. Corcoran said he had abstained because he felt it was too close to call. Dr. Rinke explained his no vote because the tumor was quite common, no metastasizing malignancies were seen, and decreased survival occurred in the control group, so he did not believe the effect was a true effect. Dr. Harkema agreed with Dr. Rinke. Dr. Kaufmann agreed with Drs. Rinke and Harkema in that the tumor was a common tumor, the survival rate in controls was low, and that he did not believe this was a true effect.

The next conclusion was “Incidences of pancreatic islet cell adenoma or carcinoma (combined).” Dr. Wyde explained the conclusion, which was that the incidences were close to the historical control range and there was limited statistical significance. Dr. Andrews-Jones moved to accept the conclusion as written; Dr. Kaufmann seconded. The vote was 11 yes, 0 no, so the motion carried.

Dr. Cline moved to include adrenal cortical adenomas as *equivocal evidence*. He explained that there was a theme of potentially stress-related mechanisms and that the incidences of adenoma were striking compared to concurrent controls. Dr. Eaton clarified that the normal procedure would be to combine adenomas and carcinomas when in the same tissue. Following discussion by the panel, there was no second, so the motion did not carry.

VIII.E.2. GSM-Exposed Females

The panel moved on to female Sprague Dawley rats exposed to GSM modulation. The conclusion was *no evidence of carcinogenic activity*. Looking at the data related to the heart, Dr. Felter felt the data should be considered in relation to all heart findings across the studies. Dr. Eaton asked if she cared to make a motion. Dr. Felter moved to upgrade the incidences of malignant schwannoma in the heart to *equivocal evidence*; Dr. Andrews-Jones seconded. Dr. Harkema asked why this was not considered a significant effect. Dr. Wyde said that there was no statistical significance and no associated Schwann cell hyperplasia. Dr. Shockley said the incidences were not high enough to detect effects. Dr. Corcoran said that he was uncomfortable with this call, as low incidences similar to these occur in numerous findings across the report. He was concerned that too much thought was being put into specific findings relative to following hard evidence. The panel discussed the issue, and then voted 9 yes, 2 no; the motion carried. Dr. Corcoran and Dr. Harkema were the "no" votes. Dr. Corcoran voted no because he did not believe there was enough of a signal to elevate the call to equivocal. Dr. Harkema said he was equivocal about the upgrade itself.

VIII.E.3. GSM-Nonneoplastic Lesions

The panel next addressed the conclusions regarding nonneoplastic lesions in the GSM-treated males and females. The vote was divided by sex. For the males, Dr. Felter moved to accept the conclusion as written; Dr. Andrews-Jones seconded, and the panel voted 11 yes, 0 no. The motion carried. For the females, Dr. Andrews-Jones moved to accept the conclusion as written; Dr. Adler seconded, and the panel voted 11 yes, 0 no, and the motion carried.

VIII.E.4. CDMA-Exposed Males

The panel moved on to consider the conclusions for the male rats exposed to CDMA modulation cell phone RFR at 900 MHz.

The first draft conclusion was *some evidence of carcinogenic activity* due to incidences of malignant schwannoma in the heart. Dr. Wyde explained the rationale as being very similar to what had been seen in the GSM modulation: a statistically significant increase in the high-dose group and a statistically significant positive trend. Dr. Adler asked what influenced the decision to call for *some evidence* instead of *clear evidence.* Dr. Blystone responded that the rationale was the same as with the GSM modulation. Dr. Whiteley said a dose-related increase in latency was apparent and asked if that was considered. Dr. Wyde said yes. Dr. Andrews-Jones moved to upgrade the conclusion to *clear evidence of carcinogenic activity*. Dr. Felter seconded. The panel voted 8 yes, 3 no. The "no" votes were Drs. Malys, Cline, and Harkema. Dr. Malys said that the reasons for his no vote were the same as he had expressed for the GSM modulation. He noted that making some of these judgements would have been easier if the work had been done to integrate the information from the rats and mice and different modulations. Dr. Cline said he had voted no due to his concern about the low incidences. He said that he was comfortable with *some evidence* but not *clear evidence*. Dr. Harkema explained his no vote as stemming from the control issues.

The next conclusions were under "May have been related to cell phone RFR exposure (*equivocal evidence of carcinogenic activity*)." The first was for incidences of malignant glioma in the brain. Dr. Wyde explained the rationale for the call: the only incidences were in the high-dose group and the incidences were within the historical control range, but hyperplasia was observed. Dr. Lin asked if the historical control data for the brain were continually updated. Dr. Blystone said only three historical control studies could be used for the brain due to differences

in histopathology sectioning (seven sections). Dr. Andrews-Jones moved to upgrade the call to *some evidence of carcinogenic activity* based on looking at the response observed across all groups (both modalities, both sexes). Dr. Rinke seconded the motion. The panel voted 6 yes, 4 no, 1 abstain, so the motion carried. The "no" votes were Drs. Malys, Corcoran, Harkema, and Cline. Dr. Adler abstained. Dr. Malys explained his no vote as due to lack of exceeding historical controls and the reasons he had discussed previously. Dr. Corcoran explained his no vote by reiterating the four items that had been discussed on a recurring basis for the negative votes for upgraded classification. Dr. Harkema, the third no vote, agreed, as did Dr. Cline, the fourth no vote. Dr. Adler, who abstained, said he could not decide on a yes or no vote based on the current information.

Continuing with the CDMA males, the next conclusion under *equivocal evidence* was "incidences of adenoma of the pars distalis in the pituitary gland." Dr. Wyde explained the call, and that the rationale was that the only response occurred at the mid-dose. Dr. Felter moved to accept the conclusion as written; Dr. Adler seconded. The vote was 11 yes, 0 no, so the motion carried.

The final equivocal call for the CDMA males was "incidences of adenoma or carcinoma (combined) of the liver." Dr. Wyde explained the rationale for the call, which was that the incidence at 4 W/kg exceeded the historical control but was not statistically significant, and there was no dose response. Dr. Corcoran moved to accept the conclusion as written; Dr. Andrews-Jones seconded. The vote was 11 yes, 0 no, so the motion carried.

VIII.E.5. CDMA-Exposed Females

For female Sprague Dawley rats exposed to CDMA modulated cell phone RFR, the initial conclusions were for *equivocal evidence of carcinogenic activity*. Starting with "incidences of malignant glioma in the brain," Dr. Wyde explained the call. Dr. Wyde said that the rationale was that the only incidences were in the lowest exposure group, the incidences were not statistically significant nor was there a positive trend, and the incidences were very close to the historical control range. Dr. Andrews-Jones moved to upgrade the call to *some evidence* for the same reasons cited for the gliomas in the other groups. Dr. Felter seconded, citing the grade of 2.0 for the hyperplasia in the glial cells, which was high compared to what was seen elsewhere. The vote was 4 yes, 6 no, 1 abstain, so the motion did not carry. The "no" votes were Drs. Malys, Corcoran, Harkema, Whiteley, Cline, and Adler. Dr. Rinke abstained. Drs. Malys, Corcoran, Harkema, Whiteley, and Cline explained their no votes as stemming from lack of statistical significance. Dr. Adler explained his no vote was because he felt that the data needed to be looked at in totality, and the patterns needed to be considered. Dr. Rinke explained his abstention based on indecision about whether raising the call was appropriate. Dr. Corcoran moved to accept the original conclusion as written; Dr. Harkema seconded. The vote was 8 yes, 3 no. The "no" votes were Drs. Felter, Pant, and Andrews-Jones. Dr. Felter voted no due to biological plausibility combined with the overall weight of evidence from all of the data and the degree of severity of the hyperplasia. Dr. Pant, the second no vote, agreed, as did Dr. Andrews-Jones, the third no vote.

Dr. Andrews-Jones moved to add "incidences of malignant schwannoma in the heart" to the *some evidence* category. Dr. Felter seconded. The panel voted 4 yes, 6 no, 1 abstain, so the motion failed. Drs. Andrews-Jones, Felter, Whiteley, and Pant voted in favor of the motion; Dr. Rinke abstained. Dr. Rinke said he would agree with an equivocal call as there was no positive trend. Dr. Rinke moved to add the heart schwannoma to the *equivocal evidence* category. Dr. Corcoran seconded. Dr. Harkema asked why this did not rise to *equivocal evidence* in the first place. Dr. Wyde said it was because the incidences were low and there was no statistical

significance. The vote was 9 yes, 2 no. The "no" votes were Dr. Malys and Dr. Harkema. Dr. Malys explained his no vote as being due to the relatively low incidence and a lower severity score in the higher dosage group. Dr. Harkema explained his no vote as stemming from trouble with the controls.

Still within the equivocal category, the panel moved on to "incidences of pheochromocytoma (benign, malignant, or complex combined) in the adrenal medulla." Dr. Wyde explained the rationale behind the conclusion: The highest incidence was in the low-dose group and the incidence was within or right at the high end of the historical control range. Dr. Corcoran moved to accept the conclusion as written; Dr. Adler seconded. The vote was 10 yes, 0 no, 1 abstain. Dr. Felter, who abstained, said she was considering what had been seen in some of the adrenals from the other studies, and was not convinced it did not rise to the level of *some evidence*.

VIII.E.6. CDMA-Nonneoplastic Lesions

As with the GSM modulation, the panel elected to split the calls on nonneoplastic lesions between the males and females.

Dr. Andrews-Jones moved to accept as written the conclusion for males; Dr. Corcoran seconded. The vote was 11 yes, 0 no, so the motion carried.

Dr. Felter moved to accept as written the conclusion for females; Dr. Andrews-Jones seconded. The vote was 11 yes, 0 no, so the motion carried.

VIII.F. Final Conclusions

The final list of conclusions recommended by the panel for the RFR studies in rats follows:

Technical Report TR 595: Cell Phone Radiofrequency Radiation Studies in Rats

<u>GSM Modulation</u>

Male Hsd:Sprague Dawley SD rats, exposed to GSM-modulated cell phone RFR at 900 MHz

- ***Clear evidence of carcinogenic activity***
  - Incidences of malignant schwannoma in the heart
- ***Were considered to be related to cell phone RFR exposure*** **(some evidence)**
  - Incidences of malignant glioma in the brain
  - Incidences of pheochromocytoma (benign, malignant, or complex combined) in the adrenal medulla
- ***May have been related to cell phone RFR exposure*** **(equivocal evidence)**
  - Incidences of adenoma or carcinoma (combined) in the prostate gland
  - Incidences of benign or malignant granular cell tumors in the brain
  - Incidences of adenoma in the pars distalis of the pituitary gland
  - Incidences of pancreatic islet cell adenoma or carcinoma (combined)

Female Hsd:Sprague Dawley SD rats, exposed to GSM-modulated cell phone RFR at 900 MHz

- ***Equivocal evidence of carcinogenic activity***
  - Incidences of malignant schwannoma in the heart

Increases in nonneoplastic lesions in the heart, brain, and prostate gland of male rats occurred with exposures to GSM cell phone RFR at 900 MHz.

Increases in nonneoplastic lesions in the heart, thyroid gland, and adrenal gland of female rats occurred with exposures to GSM cell phone RFR at 900 MHz.

CDMA Modulation

Male Hsd:Sprague Dawley SD rats, exposed to CDMA-modulated cell phone RFR at 900 MHz

- ***Clear evidence of carcinogenic activity***
  - Incidences of malignant schwannoma in the heart
- ***Were considered to be related to cell phone RFR exposure*** **(some evidence)**
  - Incidences of malignant glioma in the brain
- ***May have been related to cell phone RFR exposure*** **(equivocal evidence)**
  - Incidences of adenoma in the pars distalis of the pituitary gland
  - Incidences of adenoma or carcinoma (combined) of the liver

Female Hsd:Sprague Dawley SD rats, exposed to CDMA-modulated cell phone RFR at 900 MHz

- ***Equivocal evidence of carcinogenic activity***
  - Incidences of malignant glioma in the brain
  - Incidences of malignant schwannoma in the heart
  - Incidences of pheochromocytoma (benign, malignant, or complex combined) in the adrenal medulla.

Increases in nonneoplastic lesions of the heart, brain, and prostate gland in male rats occurred with exposures to CDMA cell phone RFR at 900 MHz.

Increases in nonneoplastic lesions of the brain in female rats occurred with exposures to GSM cell phone RFR at 900 MHz.

Dr. Eaton opened the floor to any final comments from the panel members.

Dr. Andrews-Jones recommended that NTP follow up on Dr. Malys' remarks about nonlinearity and on the endocrine system as a whole. Dr. Malys added to his comments about data integration and recommended, as NTP moves forward with the results of these studies, that approach should be kept in mind, as the pressure for data integration will only increase.

Dr. Adler asked if the panel would receive a copy of the revised report. Dr. Bucher explained how the process would proceed, culminating in a final version accepted by the NTP director and made public at that point. Dr. Wolfe added that there would be a peer-review meeting report to be shared with the panelists to ensure that their comments were captured accurately.

IX. Adjournment

Dr. Eaton thanked the panel for its work on a very complicated, challenging, and important study. He adjourned the meeting at 3:38 pm, March 28, 2018.

X. Approval of the Peer-Review Report by the Chair of the Peer-Review Panel

This peer-review report has been read and approved by the chair of the March 26−28, 2018 NTP Technical Reports Peer-Review Panel.

David Eaton, PhD, DABT, ATS

Peer-Review Panel Chair

Date: 6/19/2018