

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

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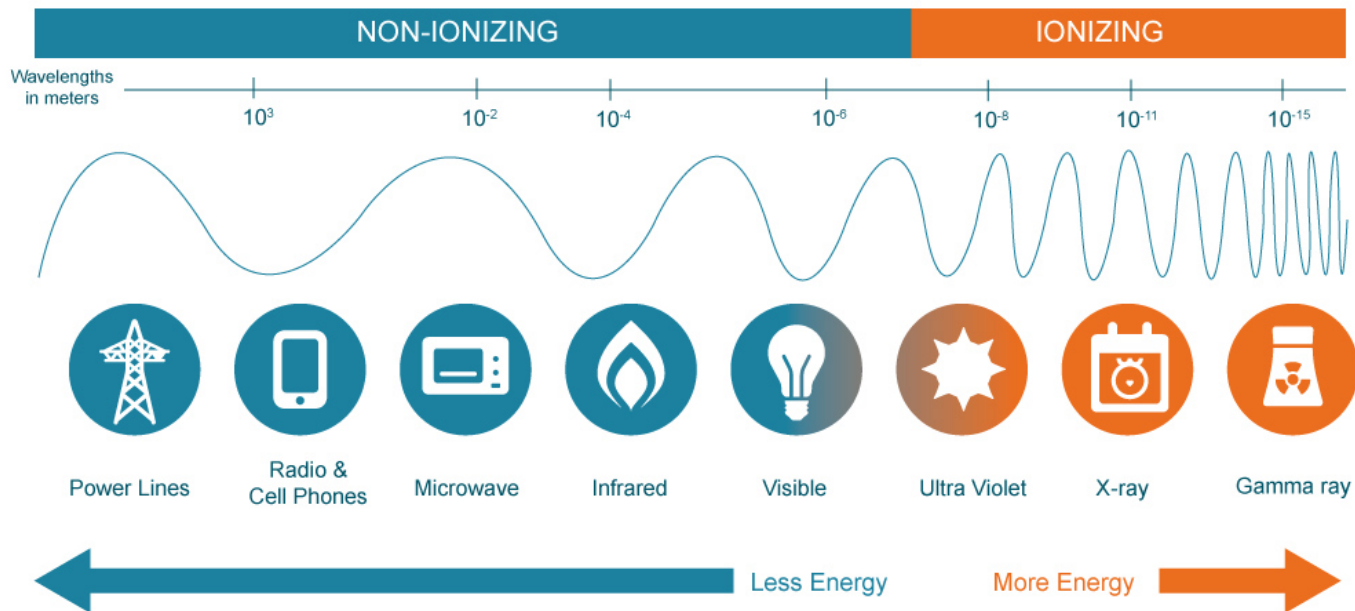


- Cell phones, radiofrequency radiation (RFR), and nomination
- Evaluation of state of RFR research
- Selection of exposure system
- Building the exposure facility
- Validation and toxicology studies



Cell phones and radiofrequency radiation

- Cell phone technology uses non-ionizing radiofrequency radiation (RFR) to communicate between a fixed base station and mobile users



<https://www.mirion.com/introduction-to-radiation-safety/what-is-radiation/>



Cell phones and radiofrequency radiation

- Cell phone technology uses non-ionizing radiofrequency radiation (RFR) to communicate between a fixed base station and mobile users
- Modulation and encoding schemes convert analog information to digital, compress it, and convert it back again
- Radiofrequency: 800-1900 MHz
- Two main technologies or modulations used by cell phone networks in US
 - Code Division Multiple Access (CDMA) – Sprint® and Verizon®
 - Global System for Mobile communications (GSM) – AT&T® and T-Mobile®



- The U.S. Food and Drug Administration (FDA) nominated cell phone radiofrequency radiation emissions for toxicology and carcinogenicity testing in 1999
 - There was widespread, expanding human exposure
 - Little was known about the potential for health effects of long-term exposure
 - Exposure guidelines were based on protection from acute injury from thermal effects
 - Sufficient data from human studies to definitively answer these questions would not be available for many more years



Rationale for interest in cell phones

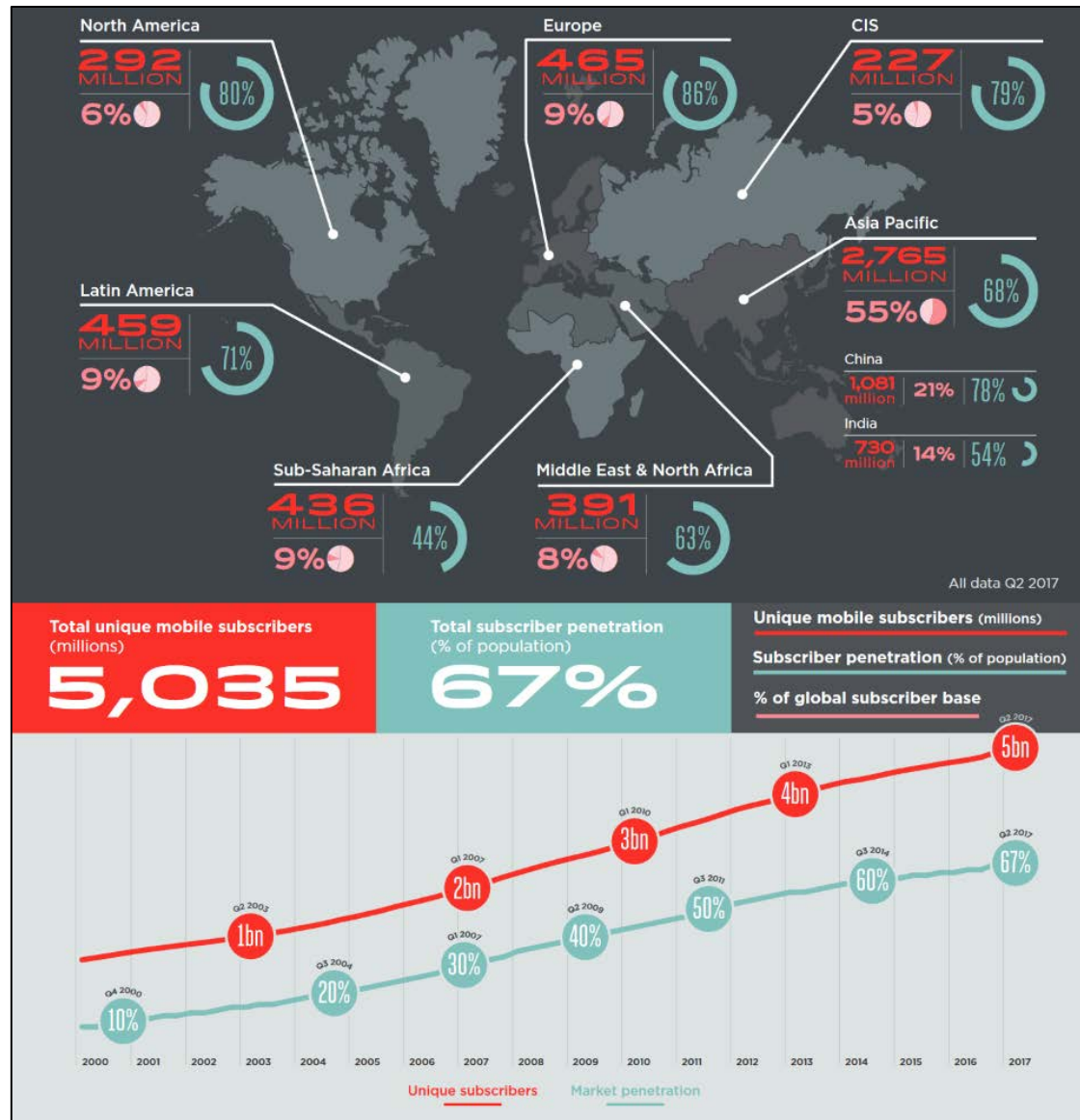
- Insufficient human data to conclusively evaluate health effects
 - Epidemiology studies may not have reflected the latency for development of brain tumors
- FDA statement, February 2000:
 - “There is currently insufficient scientific basis for concluding either that wireless communication technologies are safe or that they pose a risk to millions of users.”
- Cell phone usage has steadily increased
 - ~95% of adults in the U.S. own a cell phone (¹Pew Research, 2017)
 - In 2016, there were 395 million active wireless subscriber connections, which exceeds the population of the United States (²CTIA, 2017)

¹<http://www.pewinternet.org/fact-sheet/mobile/>

²<https://www.ctia.org/industry-data/ctia-annual-wireless-industry-survey>



Increasing worldwide cell phone usage



GSMA Infographic: <https://venturebeat.com/2017/06/13/5-billion-people-now-have-a-mobile-phone-connection-according-to-gsma-data/>



- FDA and the Federal Communications Commission (FCC) share regulatory responsibility for RFR
- Cell phone devices are required to meet exposure guidelines of FCC
 - Based on acute injury from thermal effects, and may not be protective against any non-thermal effects of chronic exposures
- FDA has jurisdiction for health-related issues under the 1968 Radiation Control for Health and Safety Act
 - FDA cannot mandate the cell phone industry to provide data on health effects



The early years (1999-2005)

Wrapping Our Heads Around the Issue

- Evaluate existing literature
- Determine what work was already underway
 - Interphone study (humans)
 - PERFORM-A (animals)
- Established collaborative research partnerships with RFR experts
 - National Institute of Standards and Technology (NIST) in Boulder, CO
 - IT'IS Foundation in Zurich, Switzerland
- Study laboratory
 - IIT Research Institute (IITRI) in Chicago, IL





- Main health concern has primarily been brain tumors
 - Gliomas and acoustic neuromas (vestibular schwannomas)
- Large number of biological effects have been reported in cell cultures and in animals
 - Genetic toxicity; immunotoxicity; changes in gene and protein expression, oxidative stress, differentiation, cell proliferation, apoptosis, permeability of the blood brain barrier
- Animal studies have not consistently demonstrated increased incidences of tumors at any site associated with exposure to cell phone RFR in rodents

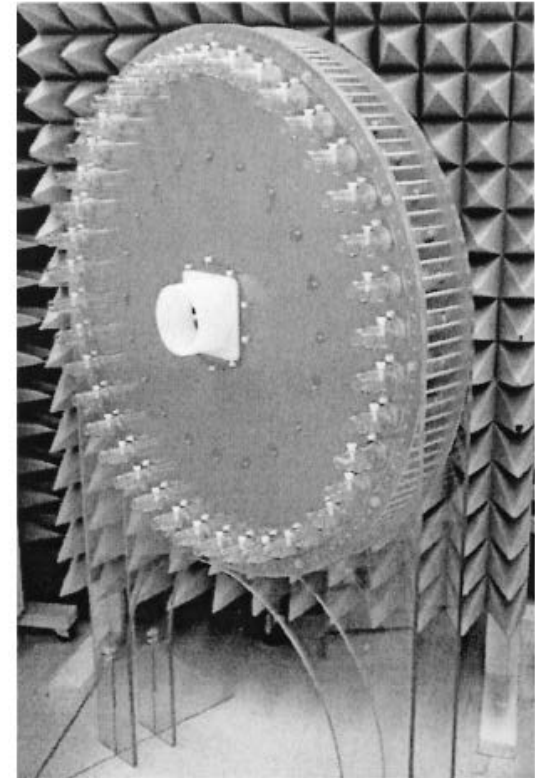


- Data are conflicting and many studies have design flaws
 - Single and/or inadequate power levels (poor quality studies)
 - Limited exposure duration (hours per day or total number of weeks),
 - Focused only on single organ effects (usually the brain)
 - Not conducted with the same frequencies or types of modulated signals used by cell phones (exposures may not be applicable to cell phone RFR)
- Primary limitations of previous studies were related to the exposure system



Selecting an exposure system

- Many previous animal studies used Ferris-wheel exposure system
 - Restrained animals
 - Short duration of daily exposures
- NTP set out to design an appropriate exposure system that addressed the limitations of existing animal exposure systems



Faraone *et al.* (2006) *Radiation Research* 165, 105–112



Study design considerations and criteria

- Exposures to begin *in utero*
- Unrestrained and individually-housed animals
- Exposure to a uniform field
- For a minimum of 6 hr/day
- Maximum power levels at which animals capable of thermoregulation
- Intermittent exposure
- Frequencies and modulations that reflect those in use
 - 900 MHz and 1900MHz
 - CDMA (IS-95) and GSM modulations
- Evaluate effects of RFR in all tissues
 - Dose-response up to maximally tolerated exposures



Reverberation chamber exposure system

- Reverberation chambers were suggested by National Institute of Standards and Technology (NIST)
- Test feasibility of reverberation chambers exposure system
 - Conducted via interagency agreement with NIST
- Determined important parameters for the development of reverberation chambers
- Demonstrated field uniformity
- Demonstrated specific absorption rate (SAR) uniformity





What are reverberation chambers?

- Large shielded room with excitation antennae and paddle to create a homogeneous electromagnetic environment
- Field exposure is from all directions, all polarizations
- Field variations occur over time and space; average field is uniform over a large volume
- Field distributions can be well characterized and monitored



Selecting an exposure system

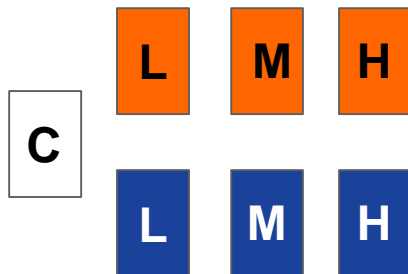
- NIST research complementary to computer-based dosimetric modelling conducted by IT'IS Foundation (Zurich, Switzerland)
- Model whole-body average specific absorption rates (SAR) and organ-specific SAR
 - Evaluation of selected frequencies (900 and 1900 MHz)
- Considerable difference in the whole-body averaged absorption efficiency of the mouse at 900 and rat at 1900 MHz
 - Greatest uniformity of RFR absorption for rats at 900 and mice at 1900 MHz
- IT'IS Foundation built and tested a prototype chamber based on the technical parameters obtained and optimized in the NIST studies



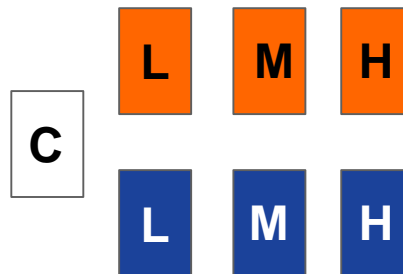
The NTP exposure facility at IITRI

- Constructed 21 reverberation chambers in Switzerland
- Separate chamber for each power level (SAR) for each modulation (GSM and CDMA)
 - To accommodate **GSM: low, med, high**; **CDMA: low, med, high**; **control chamber*** (without any RFR signals), 7 chambers were required
 - Due to marked weight differences between adult male and female rats, separate chambers were required for male rats and female rats
- Installed chambers at **IIT Research Institute** (IITRI) in Chicago, IL

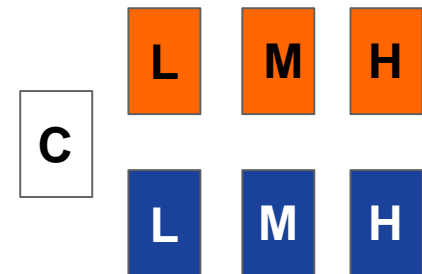
Mouse Chambers (1900 MHz)



Male Rat Chambers (900 MHz)



Female Rat Chambers (900 MHz)



*Each sex/species had a common control chamber for both GSM and CDMA modulations



Final RFR exposure facility at IITRI





Inside of the reverberation chambers





Validation and monitoring of RFR exposures

- NIST conducted third-party validation of the exposures in the chambers
 - Measured actual exposure levels in chambers
 - Homogeneity throughout chamber volume
- NIST confirmed the measurements for chamber RFR reported by the exposure system
 - NIST verified these measurements again prior to the initiation of the 2-year studies and after the termination of the 2-year studies
- All environmental and exposure parameters were recorded and monitored by both IITRI (Chicago, IL) and IT'IS (Zurich, Switzerland) throughout all studies



Cell phone RFR research program

- Three-phase toxicology and carcinogenicity studies in Harlan Sprague Dawley rats and B6C3F₁ mice
 - **5-day thermal pilot** studies at SARs of 4-12 W/kg in young and aged rats and mice and pregnant rats (10 studies)
 - **28-day prechronic** toxicology studies
 - **2-year** toxicology and carcinogenicity studies
- In all studies, daily exposure to RFR in reverberation chambers for 9 hrs 10 min (18 hrs 20 min per day in 10 min on/10 min off cycles)
 - Rats exposed to GSM- or CDMA-modulated signals at 900 MHz
 - Mice exposed to GSM- and CDMA-modulated signals at 1900 MHz



- Three Manuscripts
 - Capstick et al. (2017) – Exposure system
 - Gong et al. (2017) – Dosimetry
 - Wyde et al. (2018) – Thermal pilot studies
- Partial findings report (2016): 2-year neoplastic findings in brain and heart

A Radio Frequency Radiation Exposure System for Rodents Based on Reverberation Chambers

Myles H. Capstick, Sven Kuehn, Veronica Berdinas-Torres, Yijian Gong, Perry F. Wilson, *Fellow, IEEE*, John M. Ladbury, Galen Koepke, David L. McCormick, James Gauger, Ronald L. Melnick, and Niels Kuster
IEEE Transactions on Electromagnetic Compatibility, Vol. 59, No. 4, Aug 2017

Life-Time Dosimetric Assessment for Mice and Rats Exposed in Reverberation Chambers for the Two-Year NTP Cancer Bioassay Study on Cell Phone Radiation

Yijian Gong, Myles H. Capstick, Sven Kuehn, Perry F. Wilson, John M. Ladbury, Galen Koepke, David L. McCormick, Ronald L. Melnick, and Niels Kuster
IEEE Transactions on Electromagnetic Compatibility, Vol. 59, No. 6, Dec 2017




Cold
Spring
Harbor
Laboratory

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THE PREPRINT SERVER FOR BIOLOGY

Report of Partial findings from the National Toxicology Program Carcinogenesis Studies of Cell Phone Radiofrequency Radiation in Hsd: Sprague Dawley® SD rats (Whole Body Exposure)

Michael Wyde, Mark Cesta, Chad Blystone, Susan Elmore, Paul Foster, Michelle Hooth, Grace Kissling, David Malarkey, Robert Sills, Matthew Stout,  Nigel Walker, Kristine Witt, Mary Wolfe, John Bucher

doi: <https://doi.org/10.1101/055699>



Questions?



National Institute of
Environmental Health Sciences
Research Triangle Park, NC



Chicago, IL



Boulder, CO



Zurich, Switzerland