NTP
National Toxicology Program

Toxicology and Carcinogenicity Studies of Cell Phone Radiofrequency Radiation

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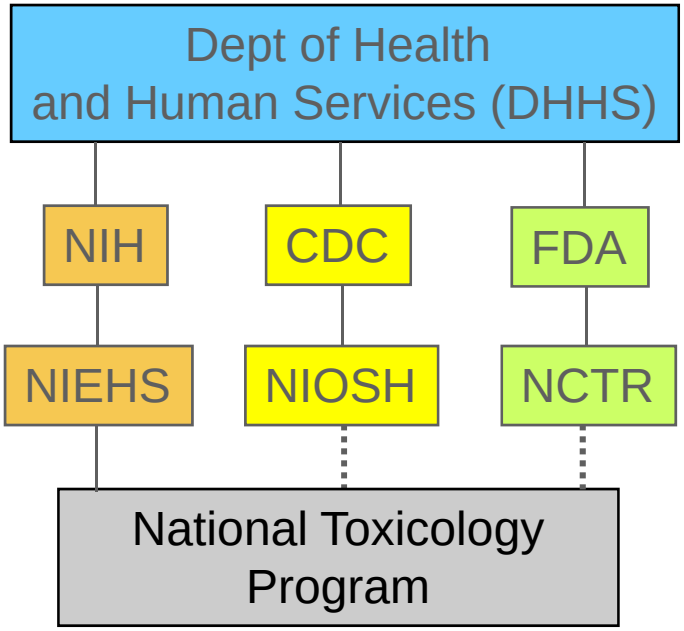
National Toxicology Program (NTP)
National Institute of Environmental Health Sciences (NIEHS)
National Institutes of Health (NIH)
U.S. Department of Health & Human Services (DHHS)

What is the National Toxicology Program?

- **Interagency program**
  - Established in 1978 to coordinate toxicology research in DHHS
  - Headquartered at NIEHS, part of NIH
- **Research on submitted "nominations"**
  - Thousands of agents evaluated in comprehensive toxicology studies
  - GLP compliant "testing" via government contracts



CDC – Center for Disease control
NIOSH – National Institute for Occupational Safety & Health
FDA – Food & Drug Administration
NCTR – National Center for Toxicological Research
NIH – National Institutes of Health
NIEHS – National Institute of Environmental Health Sciences

Where are we?

- NIEHS
  - NTP Headquarters
  - Research Triangle Park, NC
- NCTR
  - Little Rock, AK
- NIOSH
  - Morgantown, WV
  - Cincinnati, OH
- Contractors
  - Throughout the USA

Branches of the National Toxicology Program

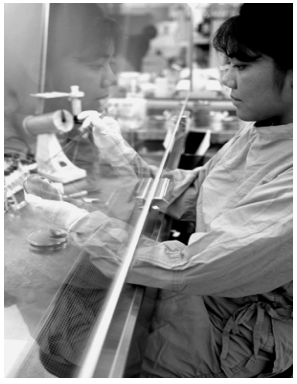
- Toxicology Branch
- Program Operations Branch
- Host Susceptibility
  - Study the genetic basis underlying biological response
- Biomolecular Screening
  - Identify mechanisms of action
  - Prioritize substances for further in-depth toxicological evaluation
  - Develop predictive models for in vivo biological response
- Cellular and Molecular Pathology

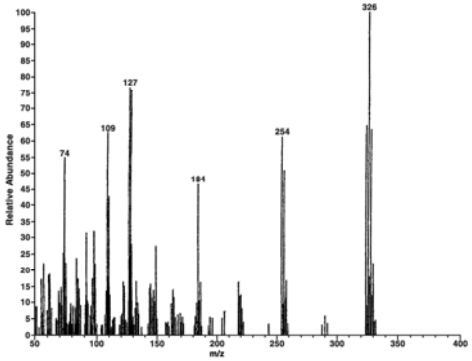
NTP Mission and Goals

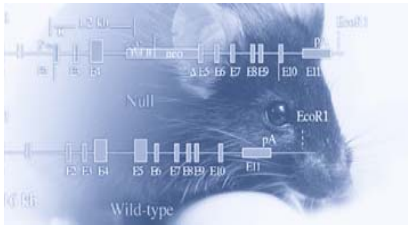
- Mission:
  - Evaluate agents of public health concern by developing and applying tools of modern toxicology and molecular biology
- Goals:
  - Coordinate toxicological testing programs within the Department of Health and Human Services.
  - Develop and validate improved testing methods and, where feasible, ensure that they reduce,refine, or replace the use of animals.
  - Develop approaches and generate data that strengthen scientific knowledge about potentially hazardous substances.
  - Communicate information about potentially hazardous substances to health regulatory and research agencies, scientific and medical communities,and the public.

NTP Toxicology Testing Program

- Utilizes NTP contracts, Interagency agreements and in house capabilities
  - GLP-compliant rodent in vivo studies
  - Mechanistic studies; ADME studies; toxicogenomics; genetically modified models
  - High quality physicochemical characterization and stability of materials
- Over 2500 distinct “test articles” studied
  - >600 cancer bioassays, >800 general toxicity studies, >2000 genetic toxicity studies
  - >200 reproductive/developmental toxicity studies, > 100 immunotoxicity studies
- Public peer-review and input on program activities and outputs







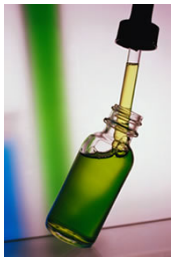
NTP Testing Program

- AIDS therapeutics
- Air/Food/Water contaminants
- Cardiovascular disease/toxicity
- Dietary supplements
- DNA-based therapeutics
- Endocrine disruptors
- Flame retardants
- Green chemistry
- Herbal medicines
- Mold
- Nanoscale materials
- Occupational exposures
- Phototoxicology
- **Radiofrequency radiation**
- Risk assessment issues/mixtures

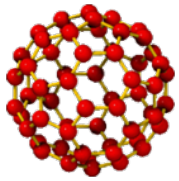






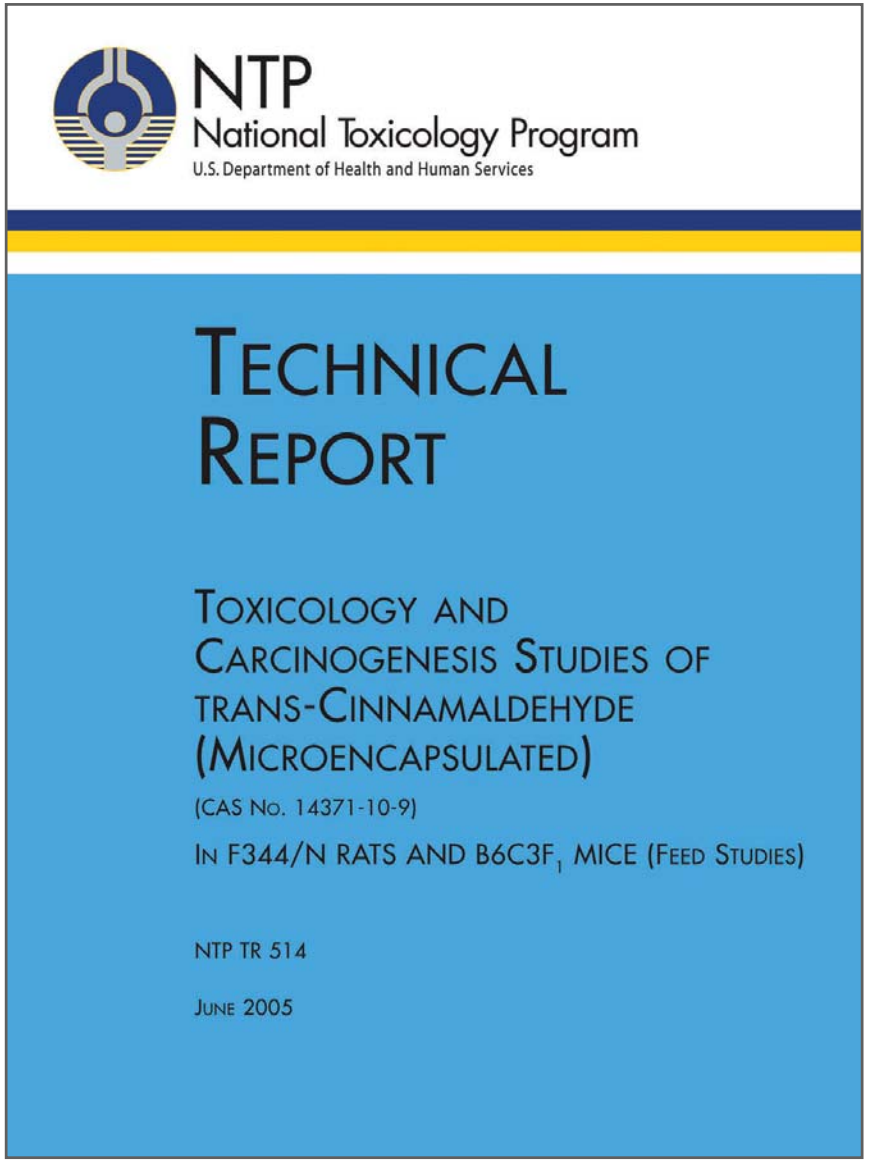




NTP Study Reports

- Subjected to public peer review
- Technical Reports
  - >500 two year cancer bioassays
- Toxicity Reports
  - Shorter-term toxicity studies
- Other reports
  - Immunotoxicity
  - Developmental toxicity
  - Reproductive Assessment by Continuous Breeding (RACB)
  - AIDS therapeutics toxicity reports
- All available for free download from the NTP website

http://ntp.niehs.nih.gov/



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NTP Radio Frequency Radiation Project

NTP Nomination for Radiofrequency Radiation

- The U.S. Food and Drug Administration (FDA) nominated cell phone radiofrequency radiation emissions for toxicology and carcinogenicity testing
- There is widespread human exposure
  - 85% of the U.S. population are cell phone subscribers (270 million people)
  - About 4 billion people world-wide
  - Greater than 50% teens use cell phones
- Current exposure guidelines are based on protection from acute injury from thermal effects
- Little is known about the potential for health effects of long-term exposure to radiofrequency radiation
- Sufficient data from human studies to definitively answer these questions may not be available for many years

Toxicology studies of radiofrequency radiation

- **Brain tumors –** but what about other effects?
- Animal studies suggests low level exposures may increase the risk of cancer
- Large number of biological effects have been reported in cell cultures and in animals
- Data is conflicting and studies have design flaws
  - Single exposure levels
  - Inadequate power levels
  - Limited exposure duration (hours per day or total number of weeks),
  - Focused only on single organ effects (usually the brain)
  - Most of this research was not conducted with actual cellular phone radiation

Regulation of radiofrequency radiation in the U.S.

- Cell phones are required to meet exposure guidelines of the Federal Communications Commission (FCC)
  - Current guideline for cellular devices is a maximum of 1.6 W/kg
  - 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

According to the U.S. FDA in 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."

Currently in 2009, there is still conflicting information regarding the safety of cellular communication devices…

Objective

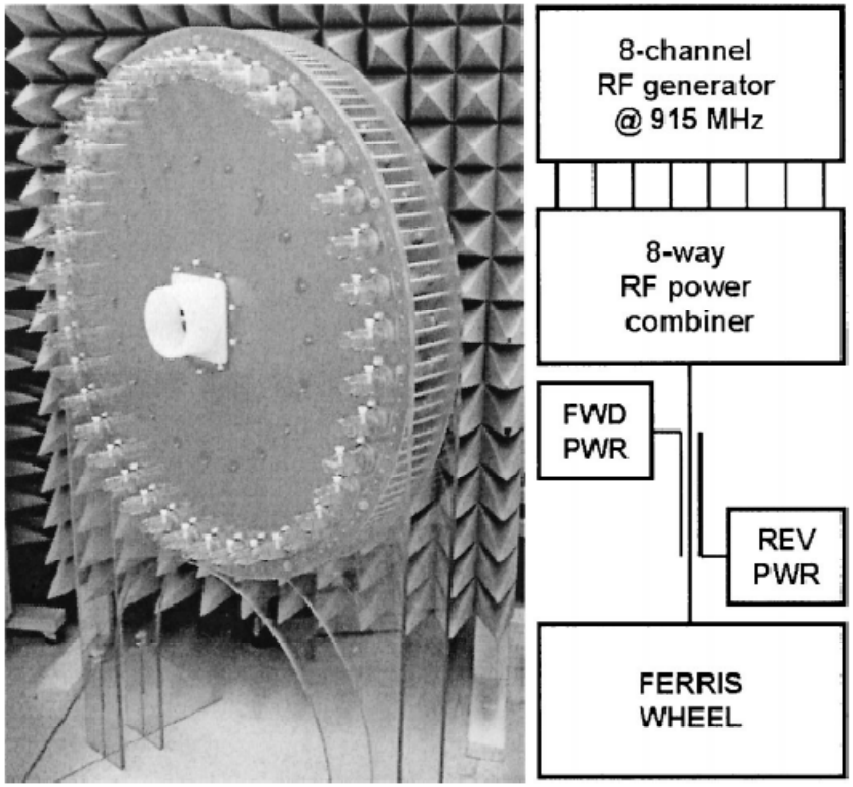
To identify potential toxic and carcinogenic effects associated with chronic exposure to modulated cell phone radiofrequency radiation (RFR) and to characterize dose-response relationships in animals

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 (non-thermal range)
- Frequencies and modulations that reflect those in use in the U.S.
  - 900 MHz and 1900MHz
  - CDMA and GSM modulations

Selecting an exposure system

- Other on-going animal studies using Ferris-wheel exposure system
  - Restrained animals
  - Short duration of daily exposures
- Reverberation chambers
  - Feasibility not tested
  - No field uniformity data
  - No SAR uniformity data
  - Excessive tail heating?



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

Selecting an exposure system

- Reverberation chambers suggested by National Institute of Standards and Technology (NIST)
- Test feasibility of reverberation chambers exposure system
  - Conducted via interagency agreement with NIST
- 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

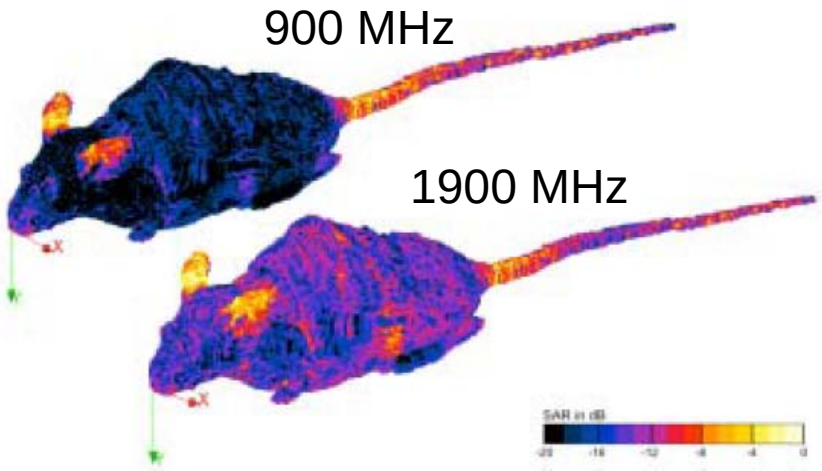
Selecting an exposure system

- Complementary computer-based dosimetric modeling study
  - Conducted by IT'IS (Zurich, Switzerland)
  - Model whole-body average specific absorption rates (SAR) and organ-specific SAR
  - Primary concern that overexposure of heat-sensitive organ might limit the maximal possible whole-body exposure
    - As a result, potentially sensitive organs (brain) might be underexposed due to the thermal limit of heat-sensitive organ
    - Example: will the tail act like an antenna and result in high exposures and increased temperatures in the tail?

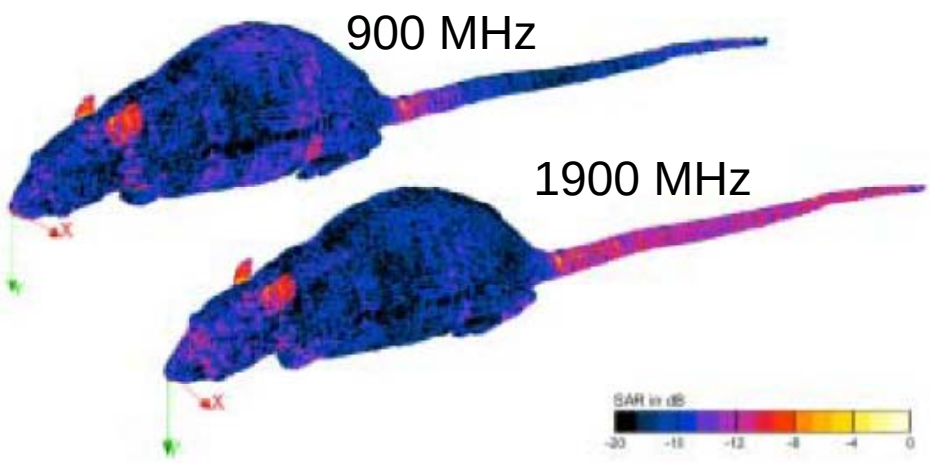
Dosimetric modeling study results

- Surface distributions clearly indicated overexposure of the tail in mice at 900MHz and rats at 1900 MHz

Mouse

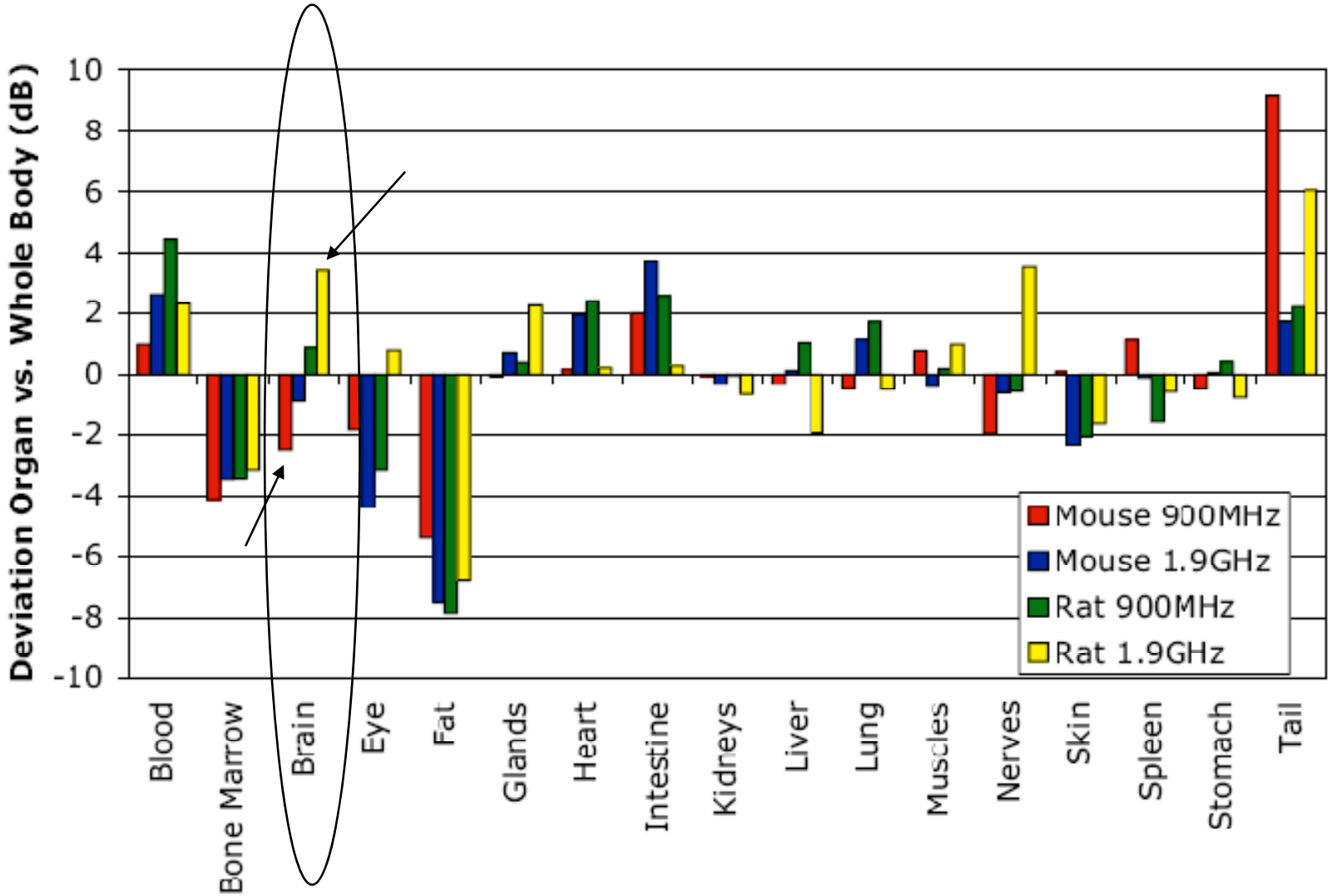


Rat



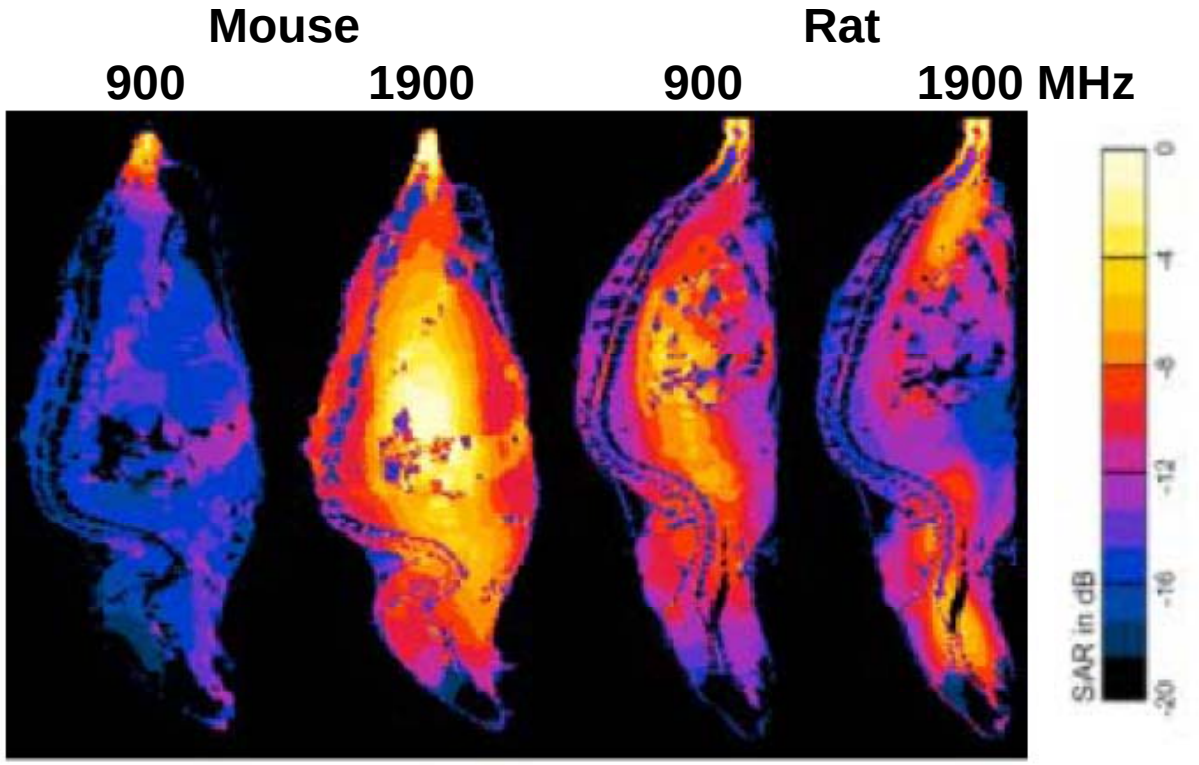
- Considerable difference in the whole-body averaged absorption efficiency of the mouse at 900 and 1900 MHz
  - Poor uniformity of absorption at 900 MHz in mice

Greater deviation of brain SAR in mice at 900 MHz and rats at 1900 MHz



SAR distributions within rats and mice

- SAR distribution within mice at 1900 MHz and rats at 900MHz shows a maximum penetration to the middle of the animals
- Exposure is focused at the tail of the mouse at 900MHz in the head and body/tail transition of the rat at 1900 MHz



Conclusions and implications

- Optimal exposure frequencies of 900 MHz in rats and 1900 MHz in mice
  - SAR distribution within rats at 900MHz and mice at 1900 MHz provide a maximum and more uniform penetration to the middle of the animals
  - Overexposure of the tail in mice at 900MHz and rats at 1900 MHz
    - Use of these frequencies would lead to under-exposure in brain and other potential targets of radiofrequency radiation
  - Poor uniformity of absorption at 900 MHz in mice
- Provided data necessary in parallel with feasibility studies to assess required parameters for actually designing and manufacturing the reverberation chamber exposure system
- Decision was made to move forward with reverberation chambers

Next steps

- Request for proposals (RFP) to identify study laboratory and award contract (IIT Research Institute)
- Construct and evaluate prototype reverberation chamber (IT'IS Foundation, Zurich Switzerland)
- Architectural design and facility renovation
- Manufacture and ship 21 reverberation chambers to Chicago
- Install and validate
  - Installed in a basement-level section of the IITRI facility
  - Dropped in by crane through a removable slab on the street level

Installation of Reverberation Chambers at IITRI

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And finally…

Final RFR exposure facility at IITRI

Inside of the reverberation chambers

Study Design

- Exposure to RFR in reverberation chambers
  - Unrestrained and individually-housed animals
- Frequencies and modulations
  - 900 MHz, GSM & CDMA modulated signals – Rats
  - 1900 MHz, GSM & CDMA modulated signals – Mice
- Three-phase studies
  - Thermal pilot (5 days)
  - Subchronic (28 days)
  - Chronic (2 years)

“Thermal pilot” studies

- Determine power levels for exposure at which rodents can maintain thermoregulation
  - Rationale – known thermal effects, but human exposure in non-thermal range
  - Identify power levels that do not induce an increase in core body temperature
  - Acceptable increase defined as < 1ºC
- Determine impact of animal size and pregnancy status on body temperature
  - Evaluated effects in young (5 weeks) and old (20 weeks) rats and mice, and pregnant rats
- Exposures
  - Harlan Sprague-Dawley rats and B6C3F1 mice
  - 20 hours intermittent (10 min on/off) exposure/day
  - 5 days of exposure
  - GSM or CDMA modulation
  - Power levels 4-12 W/kg

Subchronic studies

- Perinatal study in Sprague-Dawley rats (900 MHz)
  - 10 pregnant rats per power level, per modulation beginning on gestation day (GD) 6
  - 20 hours intermittent (10 min on/off) exposure/day, 5 days/week
  - At weaning (PND-21), litter size will be reduced to 2 male and 2 female pups (n=20) and exposure continued for 28 more days (PND 49)
  - Animals individually housed on PND 35
- 28-day study in B6C3F1 mice (1900MHz)
  - 10 male and female mice per power level, per modulation
  - 5-week old at study initiation
  - Individually-housed

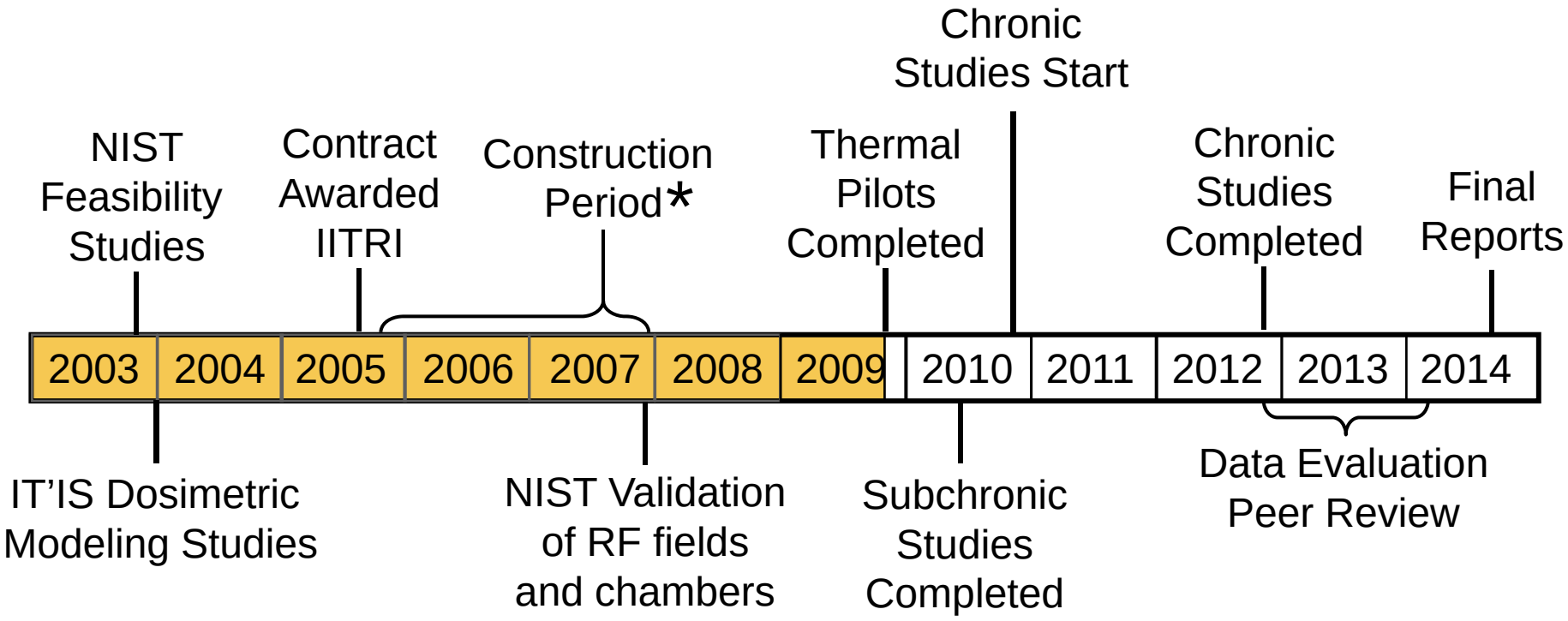
Chronic toxicology and carcinogenicity studies

- Male and female Sprague-Dawley rats and B6C3F$_1$ mice
  - Perinatal exposure in rats (GD-6) with litters reduced to 2 males and 2 females at weaning
  - Exposures in mice beginning at 5 weeks of age
- 20 hours intermittent (10 min on/off) exposure/day, 5 days/week
- Interim time point at 19 weeks (n = 15) and study termination at 110 weeks of age (n = 90)

Endpoints

- Body weights and clinical signs
- Core body temperature
- Organ weights
  - Brain, liver, thymus, kidney, testes, adrenal gland, heart, lung,
- Complete necropsy and histopathology
- Blood brain barrier permeability to 10 and 70 kD fluorescent dextrans
- Hematology
- Micronuclei: mouse peripheral blood, rat bone marrow cells
- Sperm morphology/vaginal cytology evaluation
- DNA strand breaks in rat and mouse brain cells

Timeline



* Architectural design of facility renovation
Prototype chamber construction/evaluation
Facility renovation
Purchase exposure/monitoring systems
Install and validate

Acknowledgements

NIEHS
National Institute of Environmental Health Sciences
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