Cell Phone Radiofrequency Radiation (RFR) Project: Investigative Studies

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NTP Board of Scientific Counselors Meeting
June 20, 2018
Goals for Investigative Studies

- Further clarify and fill knowledge gaps in the NTP studies on RFR
- Address issues/criticisms raised during the peer review
- Probe potential mechanisms for RFR-induced effects
- Confirm RFR-induced DNA damage in the brain of rats and mice
- Establish biomarkers of exposures to apply to studies of newer and emerging RFR-based communication technologies
**B6C3F1 Mice studies**

- **Equivocal evidence** of carcinogenic activity in male and female mice for both GSM and CMDA modulations
- Positive comet assay for frontal cortex in males (GSM and CDMA) and blood in females (CDMA only)

<table>
<thead>
<tr>
<th>Organ</th>
<th>GSM Males Lesion</th>
<th>CDMA Males Organ</th>
<th>CDMA Males Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Malignant Fibrous Histiocytoma</td>
<td>Liver</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>Lung</td>
<td>Alveolar/Bronchiolar Adenoma or Carcinoma (combined)</td>
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<tr>
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<tr>
<td>All organs</td>
<td>Malignant Lymphoma</td>
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Hsd: Sprague Dawley rat studies

- Some evidence of carcinogenic activity in male rats for both GSM and CMDA modulations based on increased incidences of malignant schwannomas of the heart

- Greater survival in all groups of exposed males compared to controls
  - Lower survival in control group attributed to high severity of chronic progressive nephropathy

- Perinatal effects (gestation and lactation)
  - SAR-dependent decrease in body weights of dams and pups
  - Decreased pup survival at higher exposures tested

- Comet assay results:
  - Positive in hippocampus; equivocal in frontal cortex of males (CDMA only)
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<th>CDMA Males</th>
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<tr>
<td><strong>Organ</strong></td>
<td><strong>Lesion</strong></td>
</tr>
<tr>
<td>Brain</td>
<td>Malignant Glioma</td>
</tr>
<tr>
<td>Brain</td>
<td>Meninges, Granular Cell Tumor (Benign and Malignant)</td>
</tr>
<tr>
<td>Pituitary Gland</td>
<td>Pars Distalis, Adenoma (Includes multiple)</td>
</tr>
<tr>
<td>Prostate</td>
<td>Adenoma or Carcinoma (combined)</td>
</tr>
<tr>
<td>Adrenal Medulla</td>
<td>Benign, Malignant or Complex Pheochromocytoma (combined)</td>
</tr>
<tr>
<td>Islets, Pancreas</td>
<td>Adenoma or Carcinoma (combined)</td>
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- Address issues/criticisms raised during the peer review
- Probe mechanisms for RFR-induced effects
  - Confirm RFR-induced DNA damage in the brain of rats and mice
  - Utilize knowledge from NTP GSM and CDMA studies to help characterize effects of newer and emerging RFR-based technologies that are more relevant to current and future human exposures
• Stress and Behavior
  – Issues:
    • Increases in pheochromocytomas and other neuroendocrine changes suggest a potential stress response
    • Potential impact of noise (mechanical or signal generated) should be further investigated
  – Some specific questions raised:
    • Does the animal’s behavior change at the initiation or cessation of exposure to RFR?
    • Are there behavioral changes during exposure that reflect increased stress?
    • Is food consumption affected by RFR exposure?
  – Proposed areas of research
    • Measure serum stress hormones
    • Record video animals during exposure periods (behavior, activity)
    • Perform functional observational battery
    • Measure food consumption
    • Measure gene expression in multiple tissues - evaluation of stress-responsive genes
    • Investigate potential effects on the hypothalamic-pituitary-adrenal axis and sympathetic nervous system
Organ-specific evaluations

Issues:

- As an unexpected target organ and the most robust finding in the NTP studies, the impact of RFR exposure on the heart requires further investigation
- Brain tumors considered equivocal, peer review panel recommended “some evidence”
- Adrenal gland considered equivocal, peer review panel recommended “some evidence”

Some specific questions raised:
- Why are glial cells affected in the heart and brain?

Proposed areas of research

- Evaluate cardiac parameters during exposure
- Evaluate RFR-induced changes in gene expression in the heart, brain, and adrenal gland
- Evaluate protein/enzyme expression as markers of damage or mechanisms of RFR-induced effects in target organs
Exposure factors

Issues:
- Frequency-dependent and/or modulation-dependent
- Intermittency of exposure

Some specific questions raised:
- What impact does the length of the exposure on/off cycling (10 minutes) have on the RFR response?
- Since both are RFR at the same frequency, can you combine GSM and CDMA exposure data?

Proposed areas of research
- Comparative studies evaluating cycles of various lengths (5/5, 15/15, 20/20, etc.)
- Co-exposure or alternating exposure to GSM and CDMA modulations
The role of heat in RFR-induced effects

Issues:

- Contribution of heat and disruption of thermoregulatory process to RFR-induced effects
- Some suggest that heating is the only mechanism by which RFR can induce a biological effect

Some specific questions raised:

- Are effects caused by constant challenge to thermoregulatory system?
- Are daytime body temperature measurements reflective of body temperature during animals’ nighttime period of high activity?

Proposed areas of research

- Studies comparing changes observed during exposure to RFR and similar heating by another (non-RFR) source
- Comparative measurement of temperature during nighttime period of awake hours and daytime hours of animal inactivity
Goals for Investigative Studies

- Provide additional research to further clarify and fill knowledge gaps in the NTP studies on RFR
- Address issues/criticisms raised peer review of NTP studies
- Elucidate mechanisms for RFR-induced effects
- Confirm RFR-induced DNA damage in the brain of rats and mice
- Utilize knowledge from NTP GSM and CDMA studies to help characterize effects of newer and emerging RFR-based technologies that are more relevant to current and future human exposures
Confirm DNA Damage Results

- Replicate previously observed comet data to confirm DNA damage effects
  - No historical experience for comet assay in these sub-regions of the brain
  - Low sample size (n=5), high interindividual variability (responders vs non-responders) may have confounded interpretation

### Male Mouse Frontal Cortex

- Trend $P < 0.001$
- $P < 0.014$
- $P < 0.001$

### Male Rat Hippocampus

- Trend $P < 0.014$
- $P < 0.019$
Confirm DNA Damage Results

- Replicate previously observed comet data to confirm DNA damage effects
  - No historical experience for comet assay in these sub-regions of the brain
  - Low sample size (n=5), high interindividual variability (responders vs non-responders) may have confounded interpretation
- Conduct more robust and more targeted assays for DNA damage
- Evaluate activity and expression of DNA repair enzymes
Goals for Investigative Studies

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Applying Knowledge to Newer Technologies

**Mobile Wireless Networks - Evolution**

<table>
<thead>
<tr>
<th>Generation</th>
<th>Decade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1G</td>
<td>1980's</td>
<td>Basic analogue voice, No IP, 0 kbit/s, One network for voice, NMT, AMPS, TACS</td>
</tr>
<tr>
<td>2G</td>
<td>1990's</td>
<td>Digital voice, No IP, 14kbps, One network for voice, GSM, IS-95, 2.5G (GPRS, EDGE)</td>
</tr>
<tr>
<td>3G</td>
<td>2000's</td>
<td>Digital voice, WWW, multimedia, 2Mbps, One network for voice, Other network for IP, UMTS, CDMA2000, 3.5G (HSDPA, HSUPA, HSPA+, LTE)</td>
</tr>
<tr>
<td>4G</td>
<td>2010's</td>
<td>Voice over IP, HD Video, 300Mbps, One network for IP, LTE-Advanced, 4.5G (LTE-Advanced Pro)</td>
</tr>
<tr>
<td>5G</td>
<td>2020's</td>
<td>Voice over IP, VR, V2X, IoT, 1Gbps, One network for IP, LTE-Advanced Pro, NR</td>
</tr>
</tbody>
</table>


Image source: http://www.itilam.com/2016/04/what-is-difference-between-3g-4g-e-g-h-h.html
Applying Knowledge to Newer Technologies

- Newer technologies utilize different modulation schemes
- 5G will utilize higher frequencies (3.1 GHz to 40 GHz)

<table>
<thead>
<tr>
<th>Generation Features</th>
<th>1G</th>
<th>2G</th>
<th>3G</th>
<th>4G</th>
<th>5G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Rates</td>
<td>2kbps</td>
<td>14.4-54kbps</td>
<td>2Mbps</td>
<td>200 Mbps to 1 Gbps</td>
<td>1Gbps and higher</td>
</tr>
<tr>
<td>Service</td>
<td>Analog voice service No data service</td>
<td>Digital voice with higher clarity SMS, MMS Higher capacity packetized data</td>
<td>Enhanced audio video streaming video conferencing support Web browsing at higher speeds IPTV support</td>
<td>Enhanced audio, video streaming IP telephony HD mobile TV</td>
<td>Dynamic Information access, Wearable devices with AI Capabilities</td>
</tr>
<tr>
<td>Multiplexing</td>
<td>FDMA</td>
<td>TDMA, CDMA</td>
<td>CDMA</td>
<td>CDMA</td>
<td>CDMA</td>
</tr>
<tr>
<td>Switching</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core Network</td>
<td>PSTN</td>
<td>PSTN</td>
<td>Packet N/W</td>
<td>Internet</td>
<td>Internet</td>
</tr>
<tr>
<td>WEB Standard</td>
<td>www</td>
<td>www(IPv4)</td>
<td>www(IPv4)</td>
<td>www(IPv6)</td>
<td></td>
</tr>
<tr>
<td>Handoff</td>
<td>Horizontal only</td>
<td>Horizontal only</td>
<td>Horizontal &amp; Vertical</td>
<td>Horizontal &amp; Vertical</td>
<td></td>
</tr>
<tr>
<td>Shortfalls</td>
<td>Low capacity, Unreliable handoff, Poor voice links, Less secure</td>
<td>Digital signals were reliant on location &amp; proximity, required strong digital signals to help mobile phones</td>
<td>Need to accommodate higher network capacity</td>
<td>Being deployed</td>
<td>Yet to be implemented</td>
</tr>
</tbody>
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Newer technologies utilize different modulation schemes

5G will utilize higher frequencies (3.1 GHz to 40 GHz)
Applying Knowledge to Newer Technologies

- Newer technologies utilize different modulation schemes
- 5G will utilize higher frequencies (3.1 GHz to 40 GHz)
- RFR 2.0 can bridge the gap between older and newer technologies

**RFR 1.0 (chronic bioassay)**

**Older technology**
- Chronic bioassay
- Parallelogram approach to newer technologies

**Newer Technology**
- **RFR 2.0**
  - GSM and CDMA
  - 900 & 1900 MHz
- **RFR 2.0**
  - Newer modulations (3G, 4G)
  - 2600 MHz, 3100 MHz, 26-40 GHz
Questions?

Image sources: https://funalive.com/articles/the-evolution-of-cell-phones_W3M.html