

Follow-up Studies on Radiofrequency Radiation

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The NTP received the nomination to study cell phone radiofrequency radiation (RFR) from the FDA in 1999. In order to address this issue, NTP collaborated with technical experts at the National Institute for Standards and Technology (NIST) and the IT'IS Foundation to identify, test, and construct a novel exposure system based on the reverberation chamber concept. A series of feasibility and dosimetry modeling studies were conducted; the system was designed, constructed, and installed at the study lab. Before any studies were conducted, an independent validation of the RFR exposures was conducted by NIST. Once the exposure facility was established, toxicology and carcinogenicity studies were conducted in three phases with Code Division Multiple Access (CDMA) and Global System for Mobile (GSM) Communications modulated RFR in Hsd:Sprague Dawley SD rats and B6C3F1 mice at frequencies of 900 or 1900 MHz, respectively. Rats and mice were exposed to RFR for up to 9 hours and 10 minutes per day for up to 2 years. Exposures in rats were initiated *in utero*.

The primary finding observed in mice in these studies was increased DNA damage in cells of the frontal cortex of RFR-exposed male mice (both GSM and CDMA). This finding was not associated with any change in brain tumors in the 2-year studies; however, elevated incidences of neoplastic lesions were observed in male (skin and lung) and female mice (malignant lymphomas). These incidences may have been related to RFR exposure and were considered equivocal evidence of carcinogenicity for RFR at 1900 MHz for both GSM or CDMA modulations.

In the rat studies, exposures were initiated *in utero* and consistently resulted in exposure concentration-related decreases in pup body weight and body weight gains during the perinatal period. In general, decreased pup survival was observed at the higher levels of RFR tested. Increased DNA damage in cells of the hippocampus and frontal cortex was observed in RFR-exposed male mice from the CDMA study. Lower survival in control group was observed and attributed to high severity of chronic progressive nephropathy. At the end of the 2-year studies, increased incidences were observed in malignant schwannomas and right ventricular cardiomyopathy in the heart, malignant gliomas in the brain, and pheochromocytoma in the adrenal medulla (GSM only) of male rats. A number of neoplastic lesions were also observed that were considered equivocal findings that may have been related to RFR exposure in male (brain (granular cell tumors), pituitary gland, prostate, liver, adrenal gland, and pancreas) and female rats (heart, brain, and adrenal gland).

The NTP RFR studies have provided a great deal of knowledge regarding the toxicity and carcinogenicity of RFR exposure and have led to novel findings; however, they have also left knowledge gaps. Further mechanistic investigative studies will address these knowledge gaps and provide critical insight into the relationship between RFR exposure and the toxicity and carcinogenicity in rodents observed in the NTP studies. Follow-up studies will seek to investigate the perinatal effects, and further characterize organ-specific effects (heart, brain, adrenal medulla) in rats via immuno- and enzyme-histochemistry and molecular pathology

methods. The impact of RFR exposure on behavior and stress will be further investigated, including the assessment of activity, response to system-generated noise and RFR signals, evaluation of stress indicators, measurement of stress hormones, and heart rate. The primary areas of mechanistic research will include investigation into the role of heat as a contributing factor to RFR-induced effects, oxidative stress mechanisms, changes in gene expression in multiple tissues, and the effect on DNA damage and repair. Given the positive effects on DNA damage in both rats and mice and the high level of interindividual variability that was observed in the small number of animals evaluated per sex per dose group ($n=5$) in the comet assay, it is important to replicate the comet assays to confirm DNA damage effects, as well as conduct additional, more-specific and robust assays to evaluate DNA damage and DNA repair enzymes.

Additionally, follow-up studies will address issues and criticisms raised during peer review of the NTP RFR studies in March 2018, including temperature measurement during periods of animal inactivity, evaluation of stress markers, evaluation of behavior changes during exposures, and measurement of food consumption. Additional studies will have the potential to expand to newer, current technologies and those evolving technologies that will become the new standard in the telecommunications industry.