



Abstract for TR-595

Toxicology and Carcinogenesis Studies in Hsd:Sprague Dawley SD Rats Exposed to Whole-body Radio Frequency Radiation at a Frequency (900 MHz) and Modulations (GSM and CDMA) Used by Cell Phones

Substances:

- GSM (CASRN CELLPRADGSM)
- CDMA (CASRN CELLPRADCDMA)

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ABSTRACT

The predominant source of human exposure to radio frequency radiation (RFR) occurs through usage of cellular phone handsets. The Food and Drug Administration nominated cell phone RFR emission for toxicology and carcinogenicity testing in 1999. At that time, animal experiments were deemed crucial because meaningful human exposure health data from epidemiological studies were not available. Male and female Hsd:Sprague Dawley SD rats were exposed to time-averaged whole-body specific absorption rates of Global System for Mobile Communications (GSM)- or Code Division Multiple Access (CDMA)-modulated cell phone RFR at 900 MHz in utero, during lactation, and after weaning for 28 days or 2 years. Genetic toxicology studies were conducted in rat peripheral blood erythrocytes and leukocytes, brain cells, and liver cells.

GSM

Twenty-eight-day study

Beginning on gestation day (GD) 6, groups of 20 time-mated F0 female rats were housed in specially designed reverberation chambers and received whole-body exposures to GSM-modulated cell phone RFR at power levels of 0 (sham control), 3, 6 or 9 W/kg for 5 to 7 days per week, continuing throughout gestation and lactation. Exposure was up to 18 hours and 20 minutes per day, 5 or 7 days per week, with continuous cycling of 10 minutes on and 10 minutes off during the exposure periods. The sham

control animals were housed in reverberation chambers identical to those used for exposed groups, but were not exposed to cell phone RFR; a shared group of unexposed rats of each sex served as sham controls for both cell phone RFR modulations. At weaning, 10 males and 10 females per group were selected across ten litters for continuation. Weaning occurred on the day the last litter reached postnatal day (PND) 21, marking the beginning of the 28-day study. Male and female F1 offspring continued to receive whole-body exposures to GSM-modulated cell phone RFR at the same power levels and under the same exposure paradigm, 5 to 7 days per week for up to 28 days. Prior to exposures, 10 F0 females per group and four male and four female F1 litters per group had temperature microchips implanted subcutaneously to monitor individual animal temperatures.

In F0 females, there were no exposure-related effects on survival or littering rates. There were significantly decreased maternal body weight gains in the 9 W/kg group during gestation (GD 6 through 21). During lactation, there were significantly decreased mean body weights and mean body weight gains at most time points. Mean body temperatures in the 9 W/kg group were significantly greater than those of the sham controls throughout most gestation and lactation. There were also sporadic increased mean body temperatures in the 3 and 6 W/kg groups.

In F1 offspring, there were no exposure-related effects on total and live litter size during lactation although there was a significantly increased number of dead pups per litter and decreased survival ratio in the 9 W/kg group from PND 1 to 4. There were also significant decreases in body weights of males and females exposed to 9 W/kg during lactation (PND 1 through 21). All offspring survived to the end of the study and body weights of 9 W/kg males were lower than those of the sham controls throughout the study. Mean body temperatures were generally similar between the exposed groups and the sham controls. There were no exposure-related effects on organ weights in either sex. There were increased incidences of chronic progressive nephropathy in the kidney of exposed female groups, but the incidences were not significant and the severity was minimal in all cases.

Two-year study

Beginning on GD 5, groups of 56 time-mated F0 female rats were housed in specially designed reverberation chambers and received whole-body exposures to GSM-modulated cell phone RFR at power levels of 0 (sham control), 1.5, 3, or 6 W/kg for 7 days per week, continuing throughout gestation and lactation. Exposure was up to 18 hours and 20 minutes per day with continuous cycling of 10 minutes on and 10 minutes off during the exposure periods. There were seven exposure groups per sex, including a shared sham control and three exposure groups for each modulation. At weaning, three males and three females per litter from 35 litters were randomly selected per exposure group for continuation. Weaning occurred on the day the last litter reached PND 21, marking the beginning of the 2-year studies. Groups of 105 male and 105 female F1 offspring continued to receive whole-body exposures to GSM-modulated cell phone RFR at the same power levels and under the same exposure paradigm, 7 days per week for up to 104 weeks. After 14 weeks of exposure, 10 rats per group were

randomly selected for interim histopathologic evaluation and five were designated for genetic toxicity evaluation.

In F0 females, there no exposure-related effects on pregnancy status, maternal survival, or the percentage of animals that littered. During gestation, mean body weight gains of 6 W/kg females were significantly lower than those of the sham controls from GD 15 through 18 and during the overall gestation period (GD 6 through 21). During lactation, the mean body weights of 3 and 6 W/kg females were significantly lower than those of the sham controls for the period of PND 4 through 21.

In F1 offspring, there was no effect on litter size, pup mortality or survival ratio. During lactation, mean pup weights were significantly lower at most timepoints in the 3 W/kg groups and at all timepoints in the 6 W/kg groups. At the end of 2 years, survival of all exposed male groups was significantly greater than that of the sham control group due to the effect of chronic progressive nephropathy in the kidney of sham control males. Survival of exposed female groups was similar to that of the sham controls. The mean body weights of all exposed males and females were similar to those of the sham control groups. There were no exposure-related clinical observations.

At the 14-week interim evaluation, there were no changes in clinical pathology parameters or organ weights that were considered to be related to exposure. There were no GSM exposure-related effects on reproductive organ weights or sperm parameters in males. The estrous cycle in females was not evaluated due to poor slide quality. In the heart, there were increased incidences of right ventricle cardiomyopathy and cardiomyopathy (all sites) in the 3 and 6 W/kg groups. Only the incidence of cardiomyopathy (all sites) in the 3 W/kg males was significantly greater than that of the sham controls.

In the heart at the end of the 2-year studies, malignant schwannoma was observed in all exposed male groups and the 3 W/kg female group, but none occurred in the sham controls. Endocardial Schwann cell hyperplasia also occurred in a single 1.5 W/kg male and two 6 W/kg males. There were also significantly increased incidences of right ventricle cardiomyopathy in 3 and 6 W/kg males and females.

In the brain of males, there were increased incidences of malignant glioma and glial cell hyperplasia in all exposed groups, but none in the sham controls. There was also increased incidences of benign or malignant granular cell tumors in all exposed groups.

There were significantly increased incidences of benign pheochromocytoma and benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla in males exposed to 1.5 or 3 W/kg. In the adrenal medulla of females exposed to 6 W/kg, there were significantly increased incidences of hyperplasia.

In the prostate gland of male rats, there were increased incidences of adenoma or adenoma or carcinoma (combined) in 3 W/kg males and epithelium hyperplasia in all exposed male groups. In the pituitary gland (pars distalis), there were increased incidences of adenoma in all exposed male groups. There were also increased incidences of adenoma or carcinoma (combined) of the pancreatic islets in all exposed groups of male rats, but only the incidence in the 1.5 W/kg group was significant.

In female rats, there were significantly increased incidences of C-cell hyperplasia of the thyroid gland in all exposed groups, and significantly increased incidences of hyperplasia of the adrenal cortex in the 3 and 6 W/kg groups.

CDMA

Twenty-eight-day study

Beginning on gestation day (GD) 6, groups of 20 time-mated F0 female rats were housed in specially designed reverberation chambers and received whole-body exposures to CDMA-modulated cell phone RFR at power levels of 0 (sham control), 3, 6 or 9 W/kg for 5 to 7 days per week, continuing throughout gestation and lactation. Exposure was up to 18 hours and 20 minutes per day, 5 or 7 days per week, with continuous cycling of 10 minutes on and 10 minutes off during the exposure periods. The sham control animals were housed in reverberation chambers identical to those used for exposed groups, but were not exposed to cell phone RFR; a shared group of unexposed rats of each sex served as sham controls for both cell phone RFR modulations. At weaning, 10 males and 10 females per group were selected across ten litters for continuation. Weaning occurred on the day the last litter reached postnatal day (PND) 21, marking the beginning of the 28-day study. Male and female F1 offspring continued to receive whole-body exposures to CDMA-modulated cell phone RFR at the same power levels and under the same exposure paradigm, 5 to 7 days per week for up to 28 days. Prior to exposures, 10 F0 females per group and four male and four female F1 litters per group had temperature microchips implanted subcutaneously to monitor individual animal temperatures.

In F0 females, there were no exposure-related effects on survival or littering rates. There were significantly decreased mean body weight gains in the 9 W/kg group from GD 15 through 18 and for the gestation period as a whole (GD 6 through 21). During lactation in the 9 W/kg group, there were significantly decreased mean body weights on PNDs 7 through 21 and a significant decrease in mean body weight gain over the whole period (PND 1 through 21). Mean body temperatures during gestation and lactation were significantly increased when compared to the sham controls at several time points in the 9 W/kg group and sporadically in the 6 W/kg group.

In F1 offspring, there were no exposure-related effects on total and live litter size during lactation although there was a slightly greater number of dead pups in exposed groups from PND 1 to 4 and in the 6 and 9 W/kg groups from PND 4 to 21. There were significantly decreased mean body weights in 6 and 9 W/kg males and 9 W/kg females during lactation. All offspring survived to the end of the study. Only the mean body weights of 9 W/kg males were significantly lower than those of the sham controls throughout the study. Mean body temperatures in exposed groups were similar to those of the sham controls throughout the study. There were no exposure-related effects on organ weights in either sex. There was a significantly increased incidence of chronic progressive nephropathy in the kidney of 6 W/kg females but the severity was minimal in all cases.

Two-year study

Beginning on GD 5, groups of 56 time-mated F0 female rats were housed in specially designed reverberation chambers and received whole-body exposures to CDMA-modulated cell phone RFR at power levels of 0 (sham control), 1.5, 3, or 6 W/kg for 7 days per week, continuing throughout gestation and lactation. Exposure was up to 18 hours and 20 minutes per day with continuous cycling of 10 minutes on and 10 minutes off during the exposure periods. There were seven exposure groups per sex, including a shared sham control and three exposure groups for each modulation. At weaning, three males and three females per litter from 35 litters were randomly selected per exposure group for continuation. Weaning occurred on the day the last litter reached PND 21, marking the beginning of the 2-year studies. Groups of 105 male and 105 female F1 offspring continued to receive whole-body exposures to CDMA-modulated cell phone RFR at the same power levels and under the same exposure paradigm, 7 days per week for up to 104 weeks. After 14 weeks of exposure, 10 rats per group were randomly selected for interim histopathologic evaluation and five were designated for genetic toxicity evaluation.

In F0 females, there no exposure-related effects on pregnancy status, maternal survival, or the percentage of animals that littered. During gestation, the mean body weights and mean body weight gains of exposed groups were similar to those of the sham controls. During lactation, mean body weights were significantly lower than those of the sham controls at most time points in the 6 W/kg group, at several time points in the 1.5 and 3 W/kg groups, and the mean body weight gains for the period as a whole (PND 1 through 21) were significantly lower in the 3 and 6 W/kg groups.

In F1 offspring, there were no effects on litter size on PND 1. On PND 7 through 21, there were significant decreases in live litter size in the 6 W/kg group when compared to the sham controls. Throughout lactation, the male and female pup mean body weights in the 6 W/kg groups were significantly lower than those of the sham controls. At the end of 2 years, survival in all exposed male group was greater than that of the sham control group due to the effects of chronic progressive nephropathy in the kidney of the sham control males. In females, there was a small, but statistically significant increase in survival in the 6 W/kg group. Although there were some differences in mean body weights in exposed male groups, at the end of the study, the mean body weights of exposed male and female groups were similar to those of the sham controls. There were no exposure-related clinical observations.

At the 14-week interim evaluation, there were changes in clinical pathology or organ weights that were considered to be related to exposure. There were no CDMA exposure-related effects on reproductive organ weights or sperm parameters in males. The estrous cycle in females was not evaluated due to poor slide quality. In the heart, there were increased incidences of right ventricle cardiomyopathy in all exposed male groups, but the severities were minimal in all cases. There were marginally increased incidences of cardiomyopathy (all sites) in the 3 and 6 W/kg females.

At the end of the 2-year study, malignant schwannoma of the heart occurred in all exposed male groups and the incidence in the 6 W/kg group was significantly increased; this neoplasm did not occur in the sham controls. There was also an increased incidence of endocardial Schwann cell hyperplasia in 6

W/kg males. In females, malignant schwannoma occurred in two animals each in the 1.5 and 6 W/kg groups.

In the brain, malignant glioma occurred in 6 W/kg males and 1.5 W/kg females; none occurred in the sham control groups. Glial cell hyperplasia also occurred in 1.5 and 6 W/kg males and 3 and 6 W/kg females.

In males, there was a significantly increased incidence of pituitary gland (pars distalis) adenoma in the 3 W/kg group, and increased incidences of hepatocellular adenoma or carcinoma (combined) in the liver of all exposed groups.

In the adrenal medulla of females, there were increased incidences of benign, malignant, or complex pheochromocytoma (combined) in all exposed groups, but only the incidence in the 1.5 W/kg group was significantly increased compared to the sham controls.

In the prostate gland of male rats, there were increased incidences of epithelial hyperplasia in all exposed groups, but only the incidence in the 6 W/kg group was significantly increased compared to the sham control group.

Genetic toxicology

Comet assay

As part of the 14-week interim evaluation, samples of frontal cortex, hippocampus, cerebellum, liver, and blood leukocytes were evaluated for DNA damage using the comet assay (two sexes, two cell phone RFR modulations, and five tissues per animal). Samples of peripheral blood from these same animals were also evaluated for chromosome damage in the micronucleus assay. Results in the comet assay are based on the 100-cell scoring approach that was standard at the time of the studies; data obtained using a second, 150-cell scoring approach recommended in a recently adopted international guideline for the in vivo comet assay, are noted for the few instances where results differed between the two methods. A significant increase in DNA damage (% tail DNA) was observed in hippocampus cells of male rats exposed to the CDMA modulation. Although the levels of DNA damage in hippocampus cells were also increased in an exposure-related fashion using the 150-cell scoring approach, the increases were not statistically significant. An exposure-related increase in DNA damage seen in the cells of the frontal cortex of male rats exposed to the CDMA modulation was judged to be equivocal based on a significant trend test. Although results from scoring 100 cells were negative for male rat blood leukocytes exposed to either CDMA or GSM modulations, the results (both CDMA and GSM) were judged to be equivocal when evaluated using the 150-cell scoring method. No statistically significant increases in DNA damage were observed in any of the female rat samples scored with the 100-cell approach; with the 150-cell approach, results in peripheral blood leukocytes of female rats (CDMA) were judged to be equivocal.

Micronucleus assay

No significant increases in micronucleated red blood cells or changes in the percentage of immature erythrocytes among total erythrocytes were observed in peripheral blood of rats of either sex exposed to either modulation of cell phone RFR.

Conclusions

GSM-modulated RFR

Under the conditions of this 2-year whole-body exposure study, there was clear evidence of carcinogenic activity (see a summary of the peer review panel comments and the public discussion on this Technical Report in Appendix L) of GSM-modulated cell phone RFR at 900 MHz in male Hsd:Sprague Dawley SD rats based on the incidences of malignant schwannoma of the heart. The incidences of malignant glioma of the brain and benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla were also related to RFR exposure. The incidences of benign or malignant granular cell tumors of the brain, adenoma or carcinoma (combined) of the prostate gland, adenoma of the pars distalis of the pituitary gland, and pancreatic islet cell adenoma or carcinoma (combined) may have been related to RFR exposure. There was equivocal evidence of carcinogenic activity of GSM-modulated cell phone RFR at 900 MHz in female Hsd:Sprague Dawley SD rats based on the incidences of schwannomas of the heart.

Increases in nonneoplastic lesions of the heart, brain, and prostate gland in male rats, and of the heart, thyroid gland, and adrenal gland in female rats occurred with exposures to GSM-modulated RFR at 900 MHz.

CDMA-modulated RFR

Under the conditions of this 2-year whole-body exposure study, there was clear evidence of carcinogenic activity (see a summary of the Peer Review Panel comments and the public discussion on this Technical Report in Appendix L) of CDMA-modulated cell phone RFR at 900 MHz in male Hsd:Sprague Dawley SD rats based on the incidences of malignant schwannoma of the heart. The incidences of malignant glioma of the brain were also related to RFR exposure. The incidences of adenoma of the pars distalis of the pituitary gland and adenoma or carcinoma (combined) of the liver may have been related to RFR exposure. There was equivocal evidence of carcinogenic activity of CDMA-modulated cell phone RFR at 900 MHz in female Hsd:Sprague Dawley SD rats based on the incidences of malignant schwannoma of the heart, malignant glioma of the brain, and benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla.

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

National Toxicology Program (NTP). 2018. Technical report on the toxicology and carcinogenesis studies in Sprague Dawley (Hsd:Sprague Dawley SD) rats exposed to whole-body radio frequency radiation at a

frequency (900 Mhz) and modulations (GSM and CDMA) used by cell phones. Research Triangle Park, NC: National Toxicology Program. NTP Technical Report 595. <https://doi.org/10.22427/NTP-TR-595>

STUDIES

Summary of the Two-year Carcinogenesis and Genetic Toxicology Studies of GSM- and CDMA-modulated Cell Phone RFR Exposure in Rats

	GSM-modulated Cell Phone RFR Male Rats	GSM-modulated Cell Phone RFR Female Rats	CDMA-modulated Cell Phone RFR Male Rats	CDMA-modulated Cell Phone RFR Female Rats
Whole-body GSM- or CDMA- modulated cell phone RFR exposure	0, 1.5, 3, or 6 W/kg	0, 1.5, 3, or 6 W/kg	0, 1.5, 3, or 6 W/kg	0, 1.5, 3, or 6 W/kg
Survival rates	25/90, 45/90, 50/90, 60/90	48/90, 53/90, 48/90, 57/90	25/90, 43/90, 56/90, 43/90	48/90, 46/90, 50/90, 61/90
Body weights	Exposed groups similar to the sham control group	Exposed groups similar to the sham control group	Exposed groups similar to the sham control group	Exposed groups similar to the sham control group
Non-neoplastic effects	<u>Heart</u> : ventricle right, cardiomyopathy (54/90, 62/90, 72/90, 74/90); Schwann cell hyperplasia (0/90, 1/90, 0/90, 2/90) <u>Brain</u> : glial cell, hyperplasia (0/90, 2/90, 3/90, 1/90) <u>Prostate gland</u> : epithelium, hyperplasia (5/90, 13/90, 11/90, 11/90)	<u>Heart</u> : ventricle right, cardiomyopathy (4/90, 9/90, 14/90, 15/90) <u>Thyroid gland</u> : C- cell, hyperplasia (28/90, 49/88, 45/90, 43/88) <u>Adrenal medulla</u> : hyperplasia (13/86, 19/90, 14/90, 25/86)	<u>Heart</u> : Schwann cell hyperplasia (0/90, 0/90, 0/90, 3/90) <u>Brain</u> : glial cell, hyperplasia (0/90, 2/90, 0/90, 2/90) <u>Prostate gland</u> : epithelium, hyperplasia (5/90, 11/90, 9/90, 15/85)	<u>Brain</u> : glial cell, hyperplasia (0/90, 0/90, 1/90, 1/90)

	GSM-modulated Cell Phone RFR Male Rats	GSM-modulated Cell Phone RFR Female Rats	CDMA-modulated Cell Phone RFR Male Rats	CDMA-modulated Cell Phone RFR Female Rats
Neoplastic effects	<u>Heart:</u> schwannoma malignant (0/90, 2/90, 1/90, 5/90) <u>Brain:</u> glioma malignant (0/90, 3/90, 3/90, 2/90) <u>Adrenal medulla:</u> benign, malignant, or complex pheochromocytoma (11/88, 24/90, 28/89, 14/87)	None	<u>Heart:</u> schwannoma malignant (0/90, 2/90, 3/90, 6/90) <u>Brain:</u> glioma malignant (0/90, 0/90, 0/90, 3/90)	None
Equivocal findings	<u>Brain:</u> meninges, granular cell tumor benign or malignant (1/90, 3/90, 4/90, 3/90) <u>Prostate gland:</u> adenoma or carcinoma (2/90, 2/90, 7/90, 3/90) <u>Pituitary gland:</u> pars distalis, adenoma (17/89, 28/90, 26/90, 26/90) <u>Islets, pancreatic:</u> adenoma or	<u>Heart:</u> schwannoma malignant (0/90, 0/90, 2/90, 0/90)	<u>Pituitary gland:</u> pars distalis, adenoma (17/89, 25/90, 34/90, 13/90) <u>Liver:</u> hepatocellular adenoma or carcinoma (combined) (0/90, 2/90, 4/89, 1/88)	<u>Heart:</u> schwannoma malignant (0/90, 2/90, 0/90, 2/90) <u>Brain:</u> glioma malignant (0/90, 3/90, 0/90, 0/90) <u>Adrenal medulla:</u> benign, malignant, or complex pheochromocytoma (1/86, 9/89, 5/87, 4/88)

	GSM-modulated Cell Phone RFR Male Rats	GSM-modulated Cell Phone RFR Female Rats	CDMA-modulated Cell Phone RFR Male Rats	CDMA-modulated Cell Phone RFR Female Rats
	carcinoma (13/90, 27/89, 19/86, 16/85)			
Level of evidence of carcinogenic activity	Clear evidence	Equivocal evidence	Clear evidence	Equivocal evidence

Genetic Toxicology

Assay	Results
DNA damage: GSM-modulated: CDMA-modulated:	Negative in frontal cortex, hippocampus, cerebellum, liver, and leukocytes (males and females) Positive in hippocampus (males); equivocal in frontal cortex (males); negative in hippocampus and frontal cortex (females), cerebellum, liver, and leukocytes (males and females)
Micronucleated erythrocytes in peripheral blood in vivo: GSM-modulated: CDMA-modulated:	Negative in males and females Negative in males and females

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NTP is headquartered administratively at the National Institute of Environmental
Health Sciences, part of the National Institutes of Health