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Listed below are my comments on Technical reports (TR 595 and TR 596) concerning the well-designed toxicology and carcinogenesis studies of GSM- and CDMA-modulated radio frequency radiation (RFR) in rats and mice, respectively.

Abstract (TR595)

DNA damage (page 14): the summary table indicates negative results for CDMA-modulated RFR in leukocytes of males and females. This conclusion is difficult to accept since, with the 150-cell method, the analysis showed a positive trend (P=0.012) and positive pairwise comparison (P= 0.026) between the control and 6 W/kg group. Similarly, for females the trend (P=0.013) and pairwise comparison (P=0.028) appear to be positive findings.

In the Report of Partial Findings from the NTP Carcinogenesis Studies of Cell Phone Radiofrequency Radiation in rats (Wyde et al., 2016), NTP concluded the hyperplastic lesions and glial cell neoplasms of the heart and brain observed in male rats are considered likely the result of whole-body exposures to GSM- or CDMA-modulated RFR. Six of eight expert peer reviewers of that report agreed with that conclusion. Based on the same data, the same authors of the 2016 report concluded in TR 595 that the incidences of malignant glioma in the brain may have been related (i.e., equivocal finding) to GSM- or to CDMA- modulated cell phone RFR at 900 MHz. What new evidence led to that change in the conclusion?

Abstract (TR596)

The conclusion in the summary table (page 13) for DNA damage in the liver of female mice exposed to CDMA-modulation (listed as negative) needs to be consistent with the text (evaluated as equivocal on pages 98).

Introduction (TR 595 and 596). Since the introductions are nearly identical, page numbers refer to TR595).

1) The issue of whole body dosimetry versus organ-specific dosimetry needs to be expanded in both the Introduction and the Discussion sections. Who suggested (page 29) that "quantifying SARs in small averaging regions is more relevant for evaluations of human health effects" (and health risks)? Explain why this is correct.

2) The review of previous toxicity and carcinogenicity studies (pages 30 – 37) on RFR, as well as mechanistic studies, are based almost exclusively on the IARC 2013 monograph on RFR. However, that monograph was prepared in 2011, and over the past 7 years there have been numerous published studies on health effects and cellular/molecular alterations induced by RFR. An update of the more recent findings is needed.

3) The statement (page 31) “changes of temperature up to 1° C are considered in the range of thermal noise” is not correct.

4) Important animal studies that need to be described include Chou et al., 1992 (Long-term, low level microwave irradiation of rats, Bioelectromagnetics 13: 469-496); Tillmann et al., 2010 (Indication of cocarcinogenic potential of chronic UMTS-modulated radiofrequency exposure in an ethylnitrosourea mouse model, Int. J. Radiat. Biol. 86, 529-541); Lerchl et al., 2015 (Tumor promotion by exposure to radiofrequency electromagnetic fields below exposure limits for humans, Biochem. Biophys. Res. Commun. 459, 585-590).

5) The conclusion by IARC (2013) on the cancer epidemiology of RFR is misstated; also, many important epidemiological findings are not mentioned in the NTP reports, including the numerous studies on brain cancer associated with exposure to RFR by Hardell et al., and the pooled and meta analyses on cell phone RFR. For glioma and acoustic neuroma (vestibular schwannoma), the IARC working group concluded that the results of **both** the INTERPHONE study and the Swedish case-control studies (by Hardell and colleagues), while susceptible to bias, “could not be dismissed as reflecting bias alone, and that a causal interpretation was possible.” In an important follow-up to the Interphone study, Momoli et al., 2017 (Probabilistic multiple-bias modeling applied to the Canadian Data from the Interphone study of mobile phone use and risk of glioma, meningioma, acoustic neuroma, and parotid gland tumors. Am. J. Epidemiol. 186, 885-893) showed that there was no effect on the risk of glioma after adjustments were made for selection and recall biases.

6) While the NTP reports emphasize potential limitations in the case control studies of cell phone users, they fail to point out the numerous and critical limitations in the cohort and time trend studies of cell phone usage when presenting the conclusions of study authors. Those limitations need to be included in these reports.

7) The genotoxicity section needs an update on studies of DNA damage induced by RFR, especially because that was an observed effect in the NTP studies.

8) Study rationale. The objectives of these studies need to be stated, i.e., to test the null hypothesis (particularly since many physicists and engineers claimed that adverse biological effects could not occur at exposure intensities near the FCC limit for maximum permissible exposure) and to provide dose-response data for assessing human health risks for any identified toxic or carcinogenic effects.

Methods (TR595 and 596)

1) A more complete description is needed on the determination of the whole body and organ specific SARs during the perinatal and 2-year exposure periods (page 40). Variations in organ specific SARs that are expressed in decibels (dB) and the meaning of field uniformity (page 42) need to be explained for most readers of these reports. The role of NTP in the development and selection of the exposure system should be mentioned.

2) An explanation is needed on why rats were exposed to 900 MHz and mice to 1900 MHz RFR.

3) The special choke for the drinking water system was developed to prevent potential RF burns that animals might experience when drinking during exposures to RFR.

4) For lactational exposures in rats (TR 595, page 57), was the whole-body dosimetry based on SARs in the dams or the pups? If based on the dams, what was the SAR in the pups? If based on the pups, what was the SAR in the dams?

5) Were early death animals not necropsied until the end of each study? Page 59 indicates "a complete necropsy was conducted on every animal at study termination."

6) It would be useful to specify the target organs identified by the pathology data review and by the QA pathologist. Were all sites in rats and mice with nonneoplastic effects or with "equivocal" tumor findings (rats: heart, prostate, brain, adrenal, thyroid gland, liver, and pituitary gland; mice: skin, lungs, liver) reviewed by the QA pathologists?

Results: (TR 596)
While I agree with the selection of the highest SAR (10 W/kg) for the 2- year studies, I disagree that the power capacity of the exposure system was a limitation for the selection of exposure levels (pages 70 and 86).

Discussion and Conclusions: Rat study (TR 595)
Page 151. In discussing the IARC evaluation of RFR, it is necessary to define the IARC term 'limited evidence' of carcinogenicity based on human studies. Limited evidence means "a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence". Also, there should be some comment on brain cancer risks identified in the INTERPHONE and Swedish studies in relation to latency, number of hours of exposure, and side-of-head use.

Page 152. This would be a good place to discuss the relevance of organ specific dosimetry versus whole body dosimetry for assessing human health risks from exposure to RFR from cell phones or other RF emission sources.

Page 153. The data (Tables 11 and 40) don't support the claim that in the 2-year studies, body weights and body weight gains of RFR-exposed dams were lower than that of sham controls during gestation.

Page 155. Why was the severity of chronic progressive nephropathy so unusually high in the control male rats? A mean severity score of 3.7 (where 3=moderate and 4=marked) is not expected in rats given NTP-2000 diet. In other NTP studies with male Harlan Sprague-Dawley rats, mean severity of CPN was 2.9, with a range of 2.5-3.2.

Page 156. In discussing the impact of survival on the detection of cardiac schwannomas in control male rats, it is important to note that survival was not statistically different between the sham control group and male rats exposed to CDMA-modulated RFR at 6 W/kg (the group with the highest incidence of cardiac schwannomas and Schwann cell hyperplasias). In fact, survival in the control group and this exposure group was identical at week-93 of the 2-year study. In addition, cardiac schwannoma was detected as early as week-70 in RFR exposed rats during the 2-year study. These observations indicate that survival was sufficient to detect schwannomas in the heart of control rats.

Page 157. Cardiomyopathy is claimed to have no clinical manifestation in rats. However, in the individual animal pathology data records, cardiomyopathy is indicated as the primary cause or contributory cause of death for 15 male rats exposed to 6W/kg CDMA-modulated RFR (I didn't review the GSM data) and 2 male rats exposed to 3 W/kg. This would suggest that cardiomyopathy in the right ventricle induced by RFR is an adverse effect of major concern.

Page 158. An evaluation on the impact of survival on the detection of gliomas in male rats should also be made for gliomas and glial cell hyperplasias (similar to that noted above for cardiac schwannomas); neither one of these lesions was observed in control male rats, yet, glial cell hyperplasia, a preneoplastic lesion, was detected as early as weak-58 in RFR-exposed rats. The fact that most gliomas and glial cell hyperplasias were observed after 101 weeks or at terminal sacrifice does not explain the lack of these proliferative lesions in sham control rats. Certainly, development of these lesions began before week 101 or terminal sacrifice, and the reason they were observed in RFR-exposed rats at those later time-points is because that is when most animals were sacrificed and necropsied.

In discussing the use of historical control data and the fact that the housing conditions used in the RFR studies were different from all other NTP studies, it would be worth noting that the uniquely designed reverberation chambers were fully shielded from external electromagnetic fields. Consequently, the concurrent control group is by far the most relevant group for understanding and characterizing effects of RFR exposures in experimental animals.

While the discussion on effects of RFR focuses on the determination of carcinogenic activity, a deficiency of this approach is that it fails to identify the brain as a target organ for proliferative lesions (gliomas and preneoplastic glial cell hyperplasias) induced by RFR in male rats. It should be noted that glial cell hyperplasias, which are within the continuum of proliferative lesions leading to malignant glioma, was diagnosed as 'marked severity' in a male rat in the GSM (3 W/kg and 6 W/kg) and the CDMA (6 W/kg) exposure groups, respectively. Also, the combined incidences of glioma and glial cell hyperplasia need to be analyzed because there appears to be a significant increase with exposure to GSM- (1.5 and 3 W/kg) and to CDMA- (6W/kg) modulated RFR.

A similar analysis of the combined incidences of schwannoma and Schwann cell hyperplasia should also be added to the report, because the significant increases with GSM- (6 W/kg) and CDMA- (6W/kg) modulated RFR clearly demonstrate that Schwann cells of the heart are a

target for induction of proliferative (neoplastic and preneoplastic) lesions by cell phone RFR in male rats.

Pages 160-161. Data on the prostate gland (Tables 21 and C4) also provide compelling evidence that the prostate is a target organ for proliferative lesions (neoplasms and/or preneoplastic epithelial hyperplasias) induced by RFR in male rats that are not associated with cytotoxicity. In rats exposed to GSM-modulated RFR, the incidence of adenoma or carcinoma (7.8%) in the 3 W/kg group was greater than the sham control group (2.2%) and greatly exceeded the historical rate (0.8%, range 0-2%), as well as the historical control range for all strains of rats used by NTP. The incidence of prostate epithelial hyperplasia was increased in all exposure groups, and the mean severity of this lesion increased with increasing SAR (control = 1.2; 1.5 W/kg = 1.6; 3 W/kg = 1.9; 6 W/kg = 2.4). The combined incidence of prostate neoplasms and epithelial hyperplasia in GSM exposed rats is 7.7% (sham control), 16.6% at 1.5 W/kg, 20.0% ($p<0.05$) at 3.0 W/kg, and 14.4% at 6 W/kg. In rats exposed to CDMA-modulated RFR, there was an exposure-related increase in the incidence and severity of hyperplasia of the prostate epithelium (control = 1.2; 1.5 W/kg = 1.6; 3 W/kg = 1.7; 6 W/kg = 2.2). The combined incidence of prostate neoplasms and epithelial hyperplasia in CDMA exposed rats is 7.7% (sham control), 12.2% at 1.5 W/kg, 12.2 % at 3.0 W/kg, and 18.7% ($p<0.05$) at 6 W/kg. Based on these findings, the prostate gland should be specified as a target organ for induction of proliferative lesions by RFR.

Page 162. The list of primary effects of cell phone RFR should include DNA damage in the brain and the induction of proliferative (neoplastic and preneoplastic) lesions in the brain and prostate gland.

Page 163. Basing conclusions separately for neoplastic and nonneoplastic lesions overlooks critical findings from these studies, namely that the brain and prostate gland are target organs for proliferative effects induced by both GSM- and CDMA-modulated RFR in male rats.

<u>Discussion and Conclusions</u>: Mouse study (TR 596)

In my view, there is some evidence of carcinogenic activity of GSM-modulated cell phone RFR in the lung and skin of male mice:

> In the lung, there was a significant positive trend (P=0.04) with increasing SAR for alveolar/bronchiolar adenomas or carcinomas (adjusted rates: 28.1% for sham control, 29.2% for 2.5 W/kg group, 36.8% for 5 W/kg group, and 39.9% for 10 W/kg group). The incidence of lung tumors in the mid and high-exposure groups exceeded the range of historical control incidence in male mice (mean 24.0 ± 5.3%, range 16%-34%). Also, there were more A/B carcinomas in the higher exposure groups than in the sham control group.
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> Malignant fibrous histiocytoma of the skin is a rare neoplasm in B6C3F1 mice (mean historical control incidence 2/589 = 0.3% ± 0.7%, range 0%-2%). The incidence of this neoplasm in male mice exposed to GSM-modulated RFR greatly exceeded the historical control incidence in the 5 W/kg group (5/90, 5.6%) and in the 10 W/kg group (3/90, 3.3%). Based on these findings, *some evidence of carcinogenicity* is a more fitting conclusion than

equivocal evidence of carcinogenic activity for the increased incidences of lung and rare skin neoplasms observed in male mice exposed to GSM-modulated RFR.

Many comments listed above for TR 595 should also be addressed in TR 596, including:

An explanation for why mice were exposed to 1900 MHz while rats were exposed to 1900 MHz RFR.

A discussion on the relevance of organ specific dosimetry versus whole body dosimetry for assessing human health risks from exposure to RFR from cell phones or other RF emission sources.

When discussing epidemiology studies on RFR, it is necessary to point out limitations in the cohort studies, particularly in the exposure assessments.