The US National Toxicology Program study (2018)

On November 1st, 2018, the U.S. Government Research Program (NTP) [1], announced through the press the release of the "final reports of studies in rats and mice on radioactive radiation such as that used in 2G and 3G cellular telephone technologies" [2]. These had already been released in January 2018 [3] pending the opinion of a panel of reviewers appointed by the NTP. Following a vote by this panel, the NTP concluded that there was "clear evidence" of exposure-related cardiac tumors, as well as "limited evidence" of brain and adrenal gland tumors in male rats (not in females, nor in male or female mice).

However, the NTP does not say that the phones are dangerous and there are very mixed views on the relevance of these results. Why is this so?

1. What is the NTP study?

Here is a simplified presentation of the broad outlines of this large-scale study, which included more than 2400 animals in total. **The objective** was to identify potentially carcinogenic and toxic effects of radio frequency fields in two species of **laboratory animals** (rats and mice) exposed to two frequencies (900 MHz and 1900 MHz) with **2G** (European system, GSM and American system, CDMA) [4] and **3G** (American system, CDMA) telephony-type signal modulations. During the study, the animals were free to move in exposure chambers (reverberation chambers). They were exposed 7 days a week, with alternating 10 minutes of exposure followed by 10 minutes without exposure for 18 hours and 20 minutes, i.e. 9 h of effective exposure per day over a period of up to 2 years. The mice were about 10 days old at the beginning of the exposures. For rats, exposures began at the fetal stage*(in utero)* from 5 or 6 days of gestation (exposure of the mothers). Beforehand [5], subcutaneous temperature measurements were carried out on young and old rats and mice, as well as pregnant rats, exposed for 5 days to radiofrequencies with different specific absorption rates (SAR, up to 12 W/kg). The objective was to determine the **maximum level of exposure** that could be achieved without causing increased mortality or body heating greater than 1°C.

On this basis, rats were exposed to 900 MHz (GSM and CDMA) with SARs of 1.5 to 6 W/kg, while mice were exposed to 1900 MHz (GSM and CDMA) with SARs of 5 to 15 W/kg for 28-day experiments and 2.5 to 10 W/kg for 2-year experiments. Finally, a group of **control animals** was placed in similar cages, but without exposure to radio frequency fields. There were 90 animals in each group. The researchers monitored the development of tumours and a large number of biological parameters.

2. What were the results?

Overall, no deleterious effects of RF fields were reported on reproductive functions. The histopathological study shows some variations, but these data are of little significance due to a lack of consistency. Anomalies were found in the control rats and mice, including abnormally low levels of certain pathologies, compared to what is expected from the literature.

The most striking result announced in February was the increase in a rare heart tumour, malignant schwannoma [6], in male rats only, at the highest SAR (6 W/kg) [7]. Could this be related to a more sustained solicitation of the cardiac muscle to regulate body temperature due to the heating induced by exposure to waves in these conditions (less than 1°C but repeated over 2 years)? Could this be a non-thermal effect? However, it was surprising that only exposed male rats showed this pathology, which was not found in rats, nor in exposed male and female mice. In humans, cardiac schwannomas are generally benign tumours and constitute a very rare pathology, for which an increased rate of occurrence would necessarily be noticed. **In contrast, male rats exposed to RF fields live longer than unexposed (control) male rats.** According to the authors, the early excess mortality of the controls is due to a more pronounced chronic renal pathology in this group. This is a significant bias, as the older age of the animals in the exposed groups could lead to a higher apparent incidence of tumours (number of new cases per year). Indeed, the development of cancerous pathologies increases with age in all species. Moreover, in male rats, the number of cases of very rare adrenal gland tumours (pheochromocytomas) was significantly increased only with GSM modulation, with no logical evolution with the increase in exposure levels (not significant at 6 W/kg). In females, the only significant increase was observed with CDMA modulation at the lowest SAR.

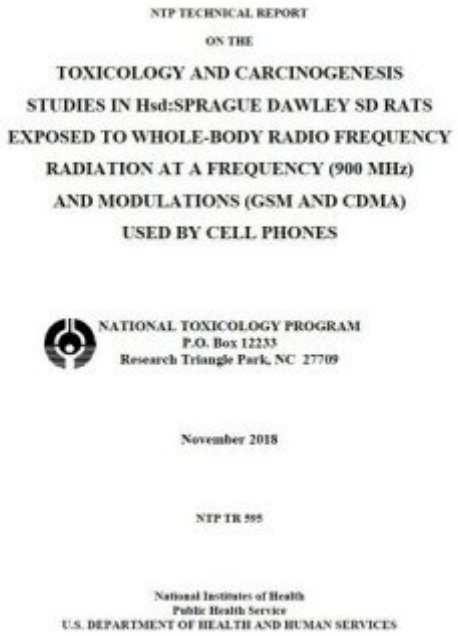
Finally, the data on **glioma** were particularly expected, as this is a brain tumour for which some epidemiological data have suggested a possible association with intensive mobile phone use. The only statistically significant difference observed was in male rats exposed to 6 W/kg with the CDMA signal compared to controls, but not in females or mice (male or female). In addition, the incidence of glioma observed in exposed male and female rats and mice (between 0 and 3 cases) did not exceed typical rates in these rodent lines (approximately 4%).

Furthermore, the results concerning DNA breaks are **discordant**: an increase in DNA breaks was observed in the frontal cortex

in males (GSM and CDMA), in the hippocampus in male rats (CDMA) and in the leucocytes (white blood cells) in females (CDMA). These analyses are based on 15 animals collected after 14 days in the 2-year exposure groups and 5 from the control group. These could be interpreted as precursors of carcinogenicity, but no logical correlation is observed with the development of tumours in the groups concerned. It should be noted that the chances of obtaining **false positives** (by chance) classically increase when a large number of comparisons are made. In all cases, the number of tumours observed per group was low. Finally, there is no plausible explanation as to why the CDMA signal would have a different effect than GSM. It can therefore be seen that the results of the NTP study are not as clear-cut as they may appear at first sight.

3. What interpretation?

The NTP uses **four categories** to evaluate the **level of evidence** that a studied agent is the cause of an observed effect; in decreasing order: *clear evidence*, *some evidence*, equivocal *evidence*, no *evidence* [8].



NTP TECHNICAL REPORT

ON THE

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

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National Institutes of Health
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Figure 1. First page of the final NTP report released in late 2018 ("rats" section). [Source: NTP report]

In the reports released in early 2018, given the inconsistencies found the study authors had deemed the evidence "limited" for cardiac shwannomas, and at most "equivocal" for the other findings then indicating effects, including brain tumors (gliomas) and adrenal tumors (benign, malignant or combined pheochromocytomas). The final conclusions of the reports released on 1st November 2018 cover the same data, but the assessment of the levels of evidence was **revised upwards** following a vote by the reviewers (Figure 1). This led to the assignment of "clear evidence" for schwannomas and "limited" for gliomas and adrenal gland tumors, again in male rats only [9]. This decision remains **controversial** in the scientific community, as the inconsistencies have not disappeared.

4. Can the results be extrapolated to mobile phone use?

The answer is "No". As the NTP also mentions, the frequencies and modulation signals used correspond to those of 2G and 3G telephone networks, but **the exposure levels and durations tested are not comparable to the exposure of people using a mobile phone in the real world**. In all cases, the whole body of the animals was exposed to levels above the Icnirp recommended whole body exposure limit (SAR of 0.08 W/kg), and for the highest levels above the known threshold for thermal effects (see focus **Radiofrequencies, risk and regulation**).

5. Can we conclude that there are non-thermal effects?

Given the exposure levels tested, a **thermal effect** at the highest SARs cannot be excluded. This is all the more true since the temperature of the animals was **not monitored** during the NTP study, and various parameters are likely to interfere with the

metabolic responses to temperature variations (species, age, sex, body mass, etc.). German researchers have made a **thorough analysis** of temperature measurements preliminary to the NTP study published in 2020 [10]. At 6 W/kg, the increase in body temperature of rats immediately after exposure is all the greater as the body mass and age of the rats are higher. Conversely, measurements taken 3 hours after the exposure sessions were stopped showed a clear drop in temperature compared to normal, the more important the older and heavier the rats. Under the same conditions, the temperature of the mice did not vary significantly.

According to the scientific literature on energy metabolism and given that the ambient temperature in the NTP study chambers was relatively low (22°C) for rodents, adaptations of the body to maintain its energy balance during the exposure cycles were necessary. The authors conclude that the results obtained could "*be analogous, in part (as long as only very small increases in body temperature occur), to the effect of housing animals at different temperatures, which can lead to alterations in metabolism, cardiovascular function, respiration, immunological function, and even cancer in rodents*". Although not proven due to the lack of temperature measurements during the NTP study, this additional study provides strong support for the hypothesis of **heat stress**, the consequences of which could largely explain the effects observed in the NTP study, including the increased mortality in controls.

6. What do the relevant authorities say?

In its communication, the NTP stated that the exposures are not representative of mobile phone use. Nevertheless, it implied that it was studying the risk associated with mobile telephony at the request of the *Food and drug administration* (FDA, public health authority in the USA) [11]. However, as early as November 1st, 2018, the FDA made it known by press release [12], that it "*disagreed with the conclusions of the final report regarding the 'clear evidence' of carcinogenic activity in rodents*", pointing out the weaknesses of the study, also specifying "*we must remember that the study was not designed to test the safety of cell phone use in humans. Therefore, we cannot draw any conclusions about the risks associated with its use. We also need to thoroughly evaluate and consider the totality of the data in the context of the totality of the evidence, rather than drawing conclusions from the results of a single study*".

Several other agencies have scrutinized this work. **ANSES** has issued an opinion summarizing the results and pointing out the uncertainties associated with the biases and weaknesses of the study [13].

The **International Commission on Non-Ionizing Radiation Protection** (Icnirp) examined in parallel a publication by the Ramazzini Institute published in April 2018 [14], whose authors claim to have confirmed the results of the NTP [15] despite differences in the experimental conditions [16]. In conclusion "*ICNIRP considers that the NTP and Falcioni et al. studies, do not provide a consistent, reliable and generalizable body of evidence that can be used as a basis for revising current human exposure guidelines.*"

The Australian Radiation and Nuclear Safety Agency [17] (ARPANSA) notes that **"***the study has a number of strengths, including the use of a large number of animals exposed throughout their lives. A thorough analysis of the NTP study shows a number of limitations, which call into question the relevance of the results to human health***".**

In Germany, the Federal Office for Radiation Protection (BFS) [18], "*sees indications but neither clear nor certain evidence of a carcinogenic effect at high whole-body exposures, which were well above the limit values. Methodological weaknesses and inconsistencies in the study results clearly limit the significance of the study.*" He also points out that "*The whole-body exposures used in the animal experiments are about 20 times (and more) above the limit value for whole-body exposures in the general population. They therefore cannot be transferred to mobile phone exposures that occur in people's daily lives.*" The BFS also highlights the "*extraordinary transparency of the NTP*" in making a large amount of data and tissue sections available on its server, allowing other teams to do further analysis.

7. What are we to make of all this?

In the end, while the questions raised call for further research, the NTP study, which reportedly cost $30 million, did not revolutionize the state of knowledge. Indeed, its results support the fact that when effects of mobile phone radio frequency fields are observed, exposure levels are well above the maximum permissible exposure values. This study has received a lot of media attention and has given rise to a cacophony, due in part to **ambiguous communication** by the NTP [19]. It is sometimes presented as proof that mobile phones or radio frequencies are carcinogenic, notably in support of claims or petitions to fight against 5G, to demand a revision of the IARC classification or a revision of the regulations. Now, Japan and Korea have in turn launched similar studies to verify these findings [20], while the NTP plans short studies with other signals and new equipment.

Notes and references

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[1] https://ntp.niehs.nih.gov/

[2] Press release, "National Toxicology Program releases final reports on rat and mouse studies of radio frequency radiation like that used in 2G and 3G cell phone technologies" 1 Nov 2018.

https://www.niehs.nih.gov/news/newsroom/releases/2018/november1/index.cfm

[3] NTP report on Toxicologyand 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.

and NTP report on Toxicology and carcinogenesis studies in B6C3F1/N MICE exposed to whole-body radio frequency radiation at a frequency (1,900 MHz) and modulations (GSM and CDMA) used by Cell phones.

[4] GSM : Global System for Mobile Communications. CDMA : Code Division Multiple Access

[5] Wyde M. & al.,2018. Effect of cell phone radiofrequency radiation on body temperature in rodents: Pilot studies of the National Toxicology Program's reverberation chamber exposure system. Bioelectromagnetics 39:190-199.

[6 Peripheral nerve sheath tumor.

[7] see also Perrin A., Lagroye I., Yardin C., What does the National Toxicology Program study on radiofrequency fields tell us? European Scientist, March 2018.

[8] https://ntp.niehs.nih.gov/whatwestudy/testpgm/cartox/criteria/cancercriterialoe.jpg

[9] Cell Phone Radiofrequency Radiation. At https://ntp.niehs.nih.gov/go/cellphone

10] Kuhne J. & al, Thermoregulatory Stress as Potential Mediating Factor in the NTP Cell Phone Tumor Study. Bioelectromagnetics, 2020 Sep;41(6):471-479.0

[11] NTP, National Toxicology Program releases final reports on rat and mouse studies of radio frequency radiation like that used in 2G and 3G cell phone technologies. Nov. 1, 2018 press release

[12] FDA, Statement from Jeffrey Shuren, M.D., J.D., Director of the FDA's Center for Devices and Radiological Health on the National Toxicology Program's report on radiofrequency energy exposure For Immediate Release, November 1, 2018.

[13] ANSES opinion on an analysis of the draft reports of the U.S. National Toxicology Program's study on radiofrequency energy exposure in animals, 28 Sept. 2018.

[14] Falcioni L. & al, Report of final results regarding brain and heart tumors in Sprague-Dawley rats exposed from prenatal life until natural death to mobile phone radiofrequency field representative of a 1.8 GHz GSM base station environmental emission. Environ Res. 2018 Aug;165:496-503.

[15] ICNIRP, Note on Recent Animal Carcinogenesis Studies. Icnirp.org, 4 Sep 2018

[16] Cardiac shwannomas are observed in exposed male rats, in barely discernible proportion to controls, and at the highest exposure level in the study (about 0.1 W/kg), which is well below the lowest SAR levels in the NTP study.

[17] ARPANSA, ARPANSA opinion on the National Toxicology Program animal study, January 2019. At arpansa.gov.au

[18] BFS, Technical statement of the Federal Office for Radiation Protection on the results of the NTP study, 2019. At bfs.de

[19] For example: Health Magazine, Study finds clear link between phone waves and cancer, Nov. 5, 2018

[20] Microwave News, Japan and Korea Planning Their Own Cell Phone Animal Studies, 23 Oct. 2018.
