

# Review of Published Literature between 2008 and 2018 of Relevance to Radiofrequency Radiation and Cancer

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## I. EXECUTIVE SUMMARY

As part of our core mission to protect and promote the public health, the FDA continually monitors new scientific evidence that might impact our understanding of the safety profile of medical devices and radiation-emitting electronic products that Americans are exposed to every day. The Agency has taken a comprehensive approach to evaluating the available scientific evidence regarding the impact of radiofrequency radiation (RFR) exposure on human health.

The FDA has completed an updated radiofrequency (RF) exposure risk analysis based on relevant peer-reviewed *in vivo* (animal) and epidemiological studies published from January 1, 2008 to August 1, 2018 for *in vivo* studies, and from January 1, 2008 to May 8, 2018 for epidemiological studies. This risk analysis was scoped to assess any possible causal relationship between RFR exposure and the formation of tumors.

In this technical report we provide a detailed summary of the substantial body of scientific evidence that has informed our determination regarding potential adverse health effects in humans caused by RFR exposures and the risk analysis we performed. As discussed in this report, this determination is supported by the considerable body of peer-reviewed scientific publications as well as public registries of, for example, cancer rates that show a slight decrease in brain tumors despite the enormous increase in cell phone use over the last two decades. This technical report summarizes the information on which the FDA has based its conclusion and was peer-reviewed by scientists specialized in areas such as epidemiology, health physics and public health, and the report incorporates comments by these external scientific reviewers. Subsequently, the report and our analysis were updated with more recent, relevant peer-reviewed publications through August 2019.

In the period covered by this risk analysis, there have been approximately 125 articles that are most relevant for the study<sup>1</sup> of any effects of RFR on animals. However, none have adequately demonstrated that localized exposure of RFR at levels that would be encountered by cell phone users can lead to adverse effects. Section IV of the report provides a detailed description of the *in vivo* studies.

*In vivo* studies assessing possible adverse or other effects of RFR are extremely challenging studies to design and undertake for several reasons, including the engineering considerations of applying an RFR field to animals that may specifically simulate, for example, the localized

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<sup>1</sup> Note that in this technical report, the terms study, experiment, investigation, and similar terms are used interchangeably.

exposure of tissue to a cell phone held to the ear. Many researchers therefore undertake whole-body exposure of the animals to RFR exposure to avoid the need to restrain the animals during each exposure. However, the effects of whole-body exposure do not reflect the real-world situation of localized exposure to the ear and head from a handset as used by humans.

It is difficult to measure and model with adequate accuracy and precision the specific dose of RFR that each animal absorbs in each study. Additionally, it is difficult to separate the effects of direct RFR exposure, if there are any that occurred, from the well-documented indirect effects of temperature rise (the only established biological effect of RFR on tissue) and the stress encountered by experimental animals, which confounds reported outcomes.

Given the difficulties of conducting *in vivo* studies on the effects of RFR exposure experienced by humans as described above and the widespread use of cell phones, strong epidemiological studies generally provide more relevant and accurate information. *In vivo* studies are of immense value in medical science, but they are less useful than studying effects on the human population, where that is feasible.

Based on the FDA's ongoing evaluation, the available epidemiological and cancer incidence data continues to support the Agency's determination that there are no quantifiable adverse health effects in humans caused by exposures at or under the current cell phone exposure limits.

In the last decade, there have been approximately 70 relevant epidemiological studies that have been published as peer-reviewed scientific evidence. As part of our ongoing monitoring activities, we have analyzed these publications for specific outcomes, including brain and other tumors as well as other potential adverse events. While some studies suggest a possible link between, for example, "heavy" users of cell phones and some tumors, there is no clear and consistent pattern that has emerged from these studies and these studies were subject to flaws and inaccuracies.

Epidemiological studies can also be subject to significant limitations; for instance, exposure assessment is understandably limited and potentially problematic. Specifically, cell phone usage is not necessarily an appropriate proxy for total RF exposure compared with, for example, the ability to capture total cumulative RF exposure from all relevant sources, including for example other communications devices. There are no direct measurements of RF exposure outside of a laboratory setting; rather, studies generally rely on the participants to track and self-report. Therefore, the actual RFR exposure remains an estimate at best. Based on the available data, there is no clear evidence as to whether frequency, duration, or intensity of exposure is the most important factor in assessing exposure and, as discussed above, there is no clear way to measure or estimate each of these factors. Additionally, there are generally various biases (e.g., recall

accuracy) and misclassification issues when individuals are asked to recollect behavior patterns. See Section V of the report for a summary of the epidemiological studies.

Based on the studies that are described in detail in this report, there is insufficient evidence to support a causal association between RFR exposure and tumorigenesis. There is a lack of clear dose response relationship, a lack of consistent findings or specificity, and a lack of biological mechanistic plausibility.

## II. ABBREVIATIONS

ASP	Annual Summarized Power
APC	Annual Percentage Change
APD	Annual Power Density
BS	Base Station
CDMA	Code-Division Multiple Access
CNS	Central Nervous System
DCS	Digital Cellular System
DMBA	12-Dimethylbenz(a)anthracene
EMF	Electromagnetic Field
FDA	US Food and Drug Administration
GFAP	Glial Fibrillary Acidic Protein
GSM	Global System for Mobile Communications
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
ICNIRP	International Commission on Non-Ionizing Radiation Protection
IEI- EMF	Idiopathic Environmental Intolerance attributed to Electromagnetic Fields
IRR	Incidence Rate Ratio
NAS	National Academy of Sciences
NeuN	Neuron-Specific Nuclear Protein
NTP	National Toxicology Program
OR	Odds Ratio
RF	Radiofrequency
RFR	Radiofrequency Radiation
ROS	Reactive Oxygen Species
RR	Relative Risk
SAR	Specific Absorption Rate
SCENHIR	Scientific Committee on Emerging and Newly Identified Health Risks
SEER	Surveillance Epidemiology, and End Results
SSM	Swedish Radiation Safety Authority
TCSE	Total Cumulative Specific Energy
UMTS	Universal mobile telecommunications system
USC	United States Code
WB	Whole Body
WCDMA	Wideband Code Division Multiple Access

### III. INTRODUCTION

The FDA is responsible for, among other things, ensuring the safety of electronic products that emit radiation, such as televisions and cell phones. These types of products are part of Americans' daily life, and we take our duty to protect consumers with the utmost gravity.

The FDA is required under 21 USC § 360ii(b)(1) to collect and make available, through publications and other appropriate means, the results of, and other information concerning, research and studies relating to the nature and extent of the hazards and control of electronic product radiation; and make such recommendations relating to such hazards and control, as appropriate. The FDA continually monitors new information and, when appropriate, undertakes formal risk analysis.

The FDA's doctors, scientists, and engineers have reviewed many sources of scientific and medical evidence related to the possibility of adverse health effects from RFR exposure in both humans and animals. We have relied extensively on a myriad of scientific evidence developed over many years to help inform our regulatory thinking regarding RFR exposure. Standard practice in scientific evaluation is to use the broadest set of credible information available and then to assess the significance of that information to the question at hand. The most commonly used source of information is the set of peer-reviewed publications that are indexed through Medline and typically retrieved through PubMed. The FDA uses this source as well as more specific sources of information, where appropriate. For the ongoing monitoring of possible effects of RFR, for example, we also use the Electromagnetic Frequency (EMF) Portal<sup>2</sup> as a potential source for peer-reviewed papers to ensure as wide a coverage as possible.

The FDA also considers independent studies that are separately published, although the Agency often undertakes its own review of the papers analyzed in those reports in order to assess validity and applicability to the United States. Recent examples of independent studies that the FDA considered include the 2013 International Agency for Research on Cancer (IARC) study<sup>3</sup>, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks<sup>4</sup>, the

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<sup>2</sup> EMF Portal (<https://www.emf-portal.org/en/article/overview/mobile-communications-med-bio/g-85/t-85002?pageSize=50&pageIndex=0&view=list#level-4>).

<sup>3</sup> IARC (2013). "Non-Ionizing Radiation, Part 2: Radiofrequency Electromagnetic Fields" Monograph 102.

<sup>4</sup> Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). 2015. 'Potential health effects of exposure to electromagnetic fields (EMF) ', European Commission Report.

Swedish Radiation Safety Authority's (SSM) Scientific Council reports on EMF<sup>5</sup>, and the 2017 reports from the National Toxicology Program studies on the effects of whole body irradiation of rodents<sup>6</sup>, as well as other sources as discussed in this report.

In this peer-reviewed technical report, we are providing a detailed summary of our updated RF exposure risk analysis based on relevant and available peer reviewed scientific information published from January 1, 2008 to August 1, 2018 for *in vivo* studies, and from January 1, 2008 to May 8, 2018 for epidemiological studies. This technical report is peer-reviewed by scientists specialized in areas such as epidemiology, health physics and public health, and the report incorporates comments by these external scientific reviewers.

The conclusions presented in this report are the result of a comprehensive analysis of information published within the following scope:

- i. The main health outcome focused on relates to the onset of cancer formation, known as tumorigenesis.
- ii. We reviewed articles on RF exposure in general and did not limit the analysis to any specific power levels or modulations used by cell phones.
- iii. The frequency range considered was 100 KHz to 6 GHz<sup>7</sup>.
- iv. These articles were indexed on Medline and typically retrieved through PubMed. The EMF portal (<https://www.emf-portal.org/en>) was also used to ensure as wide a coverage of the search as possible.
- v. Only articles that had been peer-reviewed were included, other than the final NTP *in vivo* reports which were published in November 2018, and are available from <https://ntp.niehs.nih.gov/>
- vi. The literature review was conducted using articles published from January 1, 2008 to August 1, 2018 for *in vivo* studies, and from January 1, 2008 to May 8, 2018 for

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<sup>5</sup> See e.g., Swedish Radiation Safety Authority (SSM)'s 2018. "Recent Research on EMF and Health Risk Twelfth report from SSM's Scientific Council on Electromagnetic Fields, 2017." In.: Swedish Radiation Safety Authority (SSM); Swedish Radiation Safety Authority (SSM)'s SSM's Independent Expert Group on Electromagnetic Fields. 2010. "Recent Research on EMF and Health Risk Seventh annual report from SSM:s Independent Expert Group on Electromagnetic Fields, 2010."

<sup>6</sup> National Toxicology Program (2018) Technical Report 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; and National Toxicology Program (2018) Technical Report TR-596. 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.

<sup>7</sup> This is the frequency range in which limits are based on specific absorption rate (SAR). Above 6 GHz power density is the appropriate metric for determining safe exposure limits.

epidemiological studies. These time periods overlap with the timeframe from the prior review on RF research needs undertaken by the National Academy of Sciences (available from <https://www.nationalacademies.org/>) and published in 2008.

- vii. In vitro studies were excluded as the analysis was focused on assessing evidence for tumorigenesis *in vivo*.

There were two main foci for the review: i) epidemiological evidence for the existence of any tumor risk from cell phone usage, and ii) *in vivo* (animal) studies assessing any causality of tumorigenesis from of RFR exposure.

The following sections of this technical report provide a summary of the currently available scientific evidence related to RF exposure safety and any causal relationship between such exposure and the formation of tumors that might impact the previous FDA findings.

## IV. In vivo Studies

This section provides a summary of the *in vivo* studies reviewed. Section IV.A. describes the search strategy and search terms we used to find relevant *in vivo* studies. Section IV.B. provides a summary of the studies reviewed along with a description of the limitations. In Section IV.C, the FDA's conclusions based on the reviewed and assessed *in vivo* studies is provided.

### A. Search Strategy

The literature search to identify all relevant *in vivo* studies was conducted in 3 parts. The goal of the review was to consider all evidence from *in vivo* animal exposure to RF from peer-reviewed papers which had endpoints related to tumorigenesis and involved a broad set of search terms as described below. The date range used for *in vivo* studies was January 1, 2008 through August 1, 2018. A wide search was initially conducted, which identified only a few relevant articles. The criteria were then expanded to include *in vivo* genotoxicity studies where the protocols involved exposure of animals to RF. Finally, a search identifying null results was undertaken to identify studies involving tumorigenesis, but which failed to find evidence for any link. This review is focussed on human cancer risk and consequently does not directly investigate RF mechanistic studies (*in vitro*) or review articles that pertain to *in vitro* RF exposure. The pool of potential papers was identified using the following search on PubMed:

("radio waves"[MeSH Terms] OR ("radio"[ALL FIELDS] AND "waves"[ALL FIELDS]) OR "radio waves"[ALL FIELDS] OR "cell phone?"[ALL FIELDS] OR "mobile phone"[ALL FIELDS] OR "Radio Waves/adverse effects"[MeSH] OR "Electromagnetic Fields/adverse effects"[MAJR] OR "Electromagnetic Fields"[MeSH] OR "radiofrequency"[ALL FIELDS] AND (cancer[*sb*] OR "Neoplasms"[MeSH] OR "carcinogenicity"[ALL FIELDS]) AND ("Rodentia"[MeSH] OR "Lagomorpha"[MeSH] OR rat? OR mouse OR mice OR rabbit?) AND English[*lang*]) NOT ("Humans"[MeSH] OR "MRI"[ALL FIELDS] OR "ablation"[ALL FIELDS] OR "Ablation Techniques"[MeSH] OR "Imaging"[ALL FIELDS] OR "Therapy"[ALL FIELDS] OR "ELF"[ALL FIELDS] OR "Synthesis"[ALL FIELDS] OR "cognitive"[ALL FIELDS] OR "60 Hz"[ALL FIELDS] OR "50 Hz"[ALL FIELDS] OR "hyperthermia"[ALL FIELDS] OR "healing"[ALL FIELDS] OR "adaptive"[ALL FIELDS] OR "In vitro"[ALL FIELDS] OR "extraction"[ALL FIELDS] OR "microwave-assisted"[ALL FIELDS] OR "paramagnetic"[ALL FIELDS] OR "Expression of "[ALL FIELDS]) AND ("2008/01/01"[Date - Publication] : "2018/08/01"[Date - Publication])

This initial search found 93 papers for consideration. The parameters after the 'NOT' term removed many, but not all, results that were outside the scope of the criteria for inclusion. The 93 articles were evaluated according to the search criteria. Articles not included in this review included many that were not assessing evidence of an adverse health effect

from RF exposure, many others had endpoints that were unrelated to tumorigenesis, and smaller sets of papers that either did not include exposure of live animals or in which the exposures were to extremely low frequency electromagnetic radiation rather than to RF.

The search results were compared to the bibliography of the International Agency for Research on Cancer's (IARC) Monograph 102's, *Non-ionizing radiation, Part 2: Radiofrequency electromagnetic fields*, animal experiments chapter (IARC 2013: 281 - 83). There were 4 papers in that bibliography that were not found by the search, but they were all published before 2008. Similarly, the search results were compared with the articles in an EMF portal search<sup>8</sup> for experimental studies relevant to RF and cancer and found 3 papers published after 2008 that were missed by the search. The 3 EMF portal papers were added to the pool of papers for consideration.

Search terms for the two supplementary searches are below:

- Genotoxicity Search, which added 20 papers.

((("radio waves"[MeSH Terms] OR ("radio"[All Fields] AND "waves"[All Fields]) OR "radio waves"[All Fields] OR "cell phone?"[all fields] OR "mobile phone"[all fields] OR "Radio Waves/adverse effects"[Mesh] OR "Electromagnetic Fields/adverse effects"[MAJR] or "Electromagnetic Fields"[Mesh] or "radiofrequency"[all fields]) AND (micronucleus or comet or genotox\*) AND ("Rodentia"[Mesh] OR "Lagomorpha"[Mesh] or rat? or mouse or mice or rabbit?) AND English[lang]) NOT ("Humans"[Mesh] OR "MRI"[ALL Fields] OR "ablation"[ALL FIELDS] OR "Ablation Techniques"[Mesh] OR "Imaging"[ALL FIELDS] OR "Therapy"[ALL FIELDS] OR "Synthesis"[ALL FIELDS] OR "cognitive"[ALL FIELDS] OR "60 Hz"[All Fields] or "50 Hz"[All Fields] or "ELF"[All Fields] OR "hyperthermia"[all fields] OR "healing"[All Fields] or "adaptive"[all fields] or "In vitro"[all fields] or "extraction"[all fields] or "microwave-assisted"[all fields] or "paramagnetic"[all fields] or "Expression of "[all fields]) AND ("2008/01/01"[Date - Publication] : "2018/08/01"[Date - Publication])

- Studies null (negative) results, which added 6 papers.

((("radio waves"[MeSH Terms] OR ("radio"[All Fields] AND "waves"[All Fields]) OR "radio waves"[All Fields] OR "cell phone?"[all fields] OR "mobile phone"[all fields] OR "Radio Waves/adverse effects"[Mesh] OR "Electromagnetic Fields/adverse effects"[MAJR] or "Electromagnetic Fields"[Mesh] or "radiofrequency"[all fields]) AND ("no evidence"[ALL Fields] or "does not alter"[ALL Fields] or "not provide any evidence"[all fields] or (("not" OR "no") NEAR "effect") or (("not" OR "no") NEAR "evidence") or "not promote"[ALL FIELDS] or ("not" NEAR "cause")) AND ("Rodentia"[Mesh] OR "Lagomorpha"[Mesh] or rat? or mouse or mice or rabbit?) AND English[lang]) NOT ("Humans"[Mesh] OR "MRI"[ALL Fields] OR "ablation"[ALL FIELDS] OR "Ablation Techniques"[Mesh] OR "Imaging"[ALL

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<sup>8</sup> <https://www.emf-portal.org/en>

FIELDS] OR "Therapy"[ALL FIELDS] OR "Synthesis"[ALL FIELDS] OR "cognitive"[ALL FIELDS] OR "60 Hz"[All Fields] or "50 Hz"[All Fields] or "ELF"[All Fields] OR "hyperthermia"[all fields] OR "healing"[All Fields] or "adaptive"[all fields] or "In vitro"[all fields] or "extraction"[all fields] or "microwave-assisted"[all fields] or "paramagnetic"[all fields] or "Expression of "[all fields]) AND ("2008/01/01"[Date - Publication] : "2018/12/31"[Date - Publication])

The list was compared with bibliographies from recently published expert reports to ensure a thorough assessment. The expert reports used for bibliographic comparison included the European Scientific Committee on Emerging and Newly Identified Health Risks report, *Potential health effects of exposure to electromagnetic fields (EMF)*(SCENIHR 2015), the Swedish Radiation Safety Authority (SSM)'s Scientific Council on Electromagnetic Fields' 7<sup>th</sup> (2010) through 12<sup>th</sup> (2018) reports (SSM's SCEF 2014, 2010, 2013, 2015, 2016, 2018), and the series of reports from the Health Council of the Netherlands (Health Council of the Netherlands 2013, 2014, 2016). No other animal experiment papers that might fit the criteria from the January 1, 2008 through August 1, 2018 timeframe were identified.

The pool of papers identified via the above process was then narrowed down to papers that considered experiments on live mammals (rats, mice, or rabbits) with endpoints related to cancer, carcinogenesis, tumorigenesis, oncogenesis, or genotoxicity. This reduced the list to 26 papers that were reviewed. After an initial review, 3 papers were found to be outside the report scope and were eliminated from further analysis (one had been retracted, one was an exposure of excised bones, and the third involved exposure of animals to pulsed magnetic fields not RF).

A peer reviewer identified 31 papers more papers as possibly relevant. About half of these papers fell outside our inclusion criteria. There were a few papers regarding RFR exposure of non-mammal animals. A few papers used frequencies above 6 GHz. A couple of papers had endpoints outside of our scope. The other papers that were excluded used cell phones as the source of RFR which renders these studies results uninterpretable. Dosimetry and modeling to calculate the SAR of the exposed animals is difficult with a defined RFR source. A normal cell phone is not a reproducible source of RFR.

A review of the 39 papers that met the inclusion criteria is described below. Additionally, the final National Toxicology Program reports on exposure of rats and mice to radiofrequency radiation and an associated paper, *Effect of cell phone radiofrequency radiation on body temperature in rodents: Pilot studies of the National Toxicology Program's reverberation chamber exposure system* (Wyde et al. 2018) were also reviewed. A complete list of the papers found by the searches for this section appears in Section VI References.

## **B. Summary and Limitations of In vivo Studies.**

### **1. National Toxicology Program RF Reports 2018.**

The National Toxicology Program released reports on whole-body exposures of rats and mice to radiofrequency radiation that was modulated using the signal patterns commonly used by third generation wireless mobile telecommunications technology (3G). The NTP study is the most comprehensive study of the impact of RFR on tumorigenesis to date. While the FDA does not agree with all the conclusions of the NTP RFR study, we do acknowledge that the study has added to the collective database and provided possible pathways for further investigation. The effects of a whole-body RFR exposure are not predictive of the results for a local RFR exposure in the same animal. Thus, results of whole-body RFR exposure to rats and mice cannot be directly related to the results of the local RFR exposure a human receives while using a cell phone.

There were three components to the NTP study. The first component was a 5-day thermal pilot study at specific absorption rates (SARs) of 4 – 12 W/kg (Wyde et al. 2018) which was published separately from the remaining portions of the study covered in NTP's reports. The second component was a 28-day pre-chronic toxicology study in mice and rats. The last component was a 2-year toxicology and carcinogenicity study in mice and rats<sup>9</sup>. The exposure system used in all three components of this study was a specially engineered reverberation chamber designed with the goal of providing nearly uniform whole-animal exposure without the need for stress inducing animal restraint systems (*Capstick et al. 2017*). The exposed rats and mice were exposed to either global system mobile communication (GSM) or code division multiple access (CDMA) modulated signals for 18 hours and 20 minutes / day in 10 minutes on and off cycles. The rats were exposed starting *in utero* to GSM- or CDMA-modulated signals at 900 MHz. The mice were exposed to either GSM- or CDMA-modulated signals at 1900 MHz. The results discussed here are from Wyde et al. 2018 and the NTP technical reports released to the public in November 2018.

The 5-day pilot study examined the impact of animal size on the subcutaneous temperatures in mice and rats, aged mice and rats, as well as pregnant rats. The aged rats in the

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<sup>9</sup> NTP report on Rats -

[https://ntp.niehs.nih.gov/ntp/htdocs/lt\\_rpts/tr595\\_508.pdf?utm\\_source=direct&utm\\_medium=prod&utm\\_campaign=ntpgolinks&utm\\_term=tr595](https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr595_508.pdf?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tr595) &

NTP report on Mice -

[https://ntp.niehs.nih.gov/ntp/htdocs/lt\\_rpts/tr596\\_508.pdf?utm\\_source=direct&utm\\_medium=prod&utm\\_campaign=ntpgolinks&utm\\_term=tr596](https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr596_508.pdf?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tr596)

pilot study were at most 270 days old while rats in the 2-year study reached 763 days old. The effect of animal age increasing from 270 days to 763 days was not investigated and could have resulted in further age-related weakening of the rats' thermoregulatory capacity. The temperatures measured were subcutaneous and not a measure of the core temperature of the animal. No temperature measurements were taken in the animals housed in RF environments during the 2-year study. The pilot study confirms that aged animals or pregnant animals cannot thermoregulate as well as young, non-pregnant animals. The study revealed that there were some incidences of increased subcutaneous temperature ( $>1^{\circ}\text{C}$ ) in aged rats exposed to 6 W/kg GSM radiation or 900 MHz CDMA RF radiation but not in young rats. Likewise, there were sporadic temperature increases in young or old mice exposed up to 12 W/kg GSM and CDMA 1900 MHz RFR. Measurements were made when RFR was off, and as such, allowed for external surface cooling which likely reduced the measured subcutaneous temperatures.

Additionally, NTP's assessment of organ SAR showed that local SAR in skin and fat was less than the whole-body and internal organ SAR which was higher. An animal's core temperature cannot be accurately estimated from subcutaneous temperature measurements. Considering the information, the animals' core temperature was likely to have exceeded the measured subcutaneous temperature. It is probable that during the 2-year study, as the male rats aged their core temperatures eventually routinely exceeded a  $1^{\circ}\text{C}$  rise in the 6 W/kg SAR exposure group. We believe that this study indicates a need for a greater understanding of the impact of cyclic heating and declining thermoregulation capacities of aged mammals.

The NTP has established 5 levels of evidence of carcinogenic activity that are used in NTP reports. The highest level is Clear Evidence. This is a dose-related (i) increase of malignant neoplasms, (ii) an increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy. The next lower level of evidence is called Some Evidence. For this level the test agent-related increased the incidence of neoplasms in which the strength of the response is less than that required for clear evidence. Equivocal Evidence is the next lower level. This is a marginal increase of neoplasms that may or may not be test agent-related. The two lower levels are No Evidence and Inadequate Study.

The histopathological analysis of the RF-exposed mice was reported as Equivocal Evidence. For GSM-modulated exposed male mice, the combined incidence of fibrosarcoma, sarcoma, or malignant fibrous histiocytoma of the skin and the combined incidence of alveolar/bronchiolar adenoma or carcinoma in the lung were described as marginally increased. For GSM-modulated exposed female mice, there was a marginally increased incidence of malignant lymphoma. For CDMA-modulated exposed male mice there was increased incidence of hepatoblastoma of the liver. For CDMA-modulated exposed female mice malignant lymphoma incidence was marginally

increased. All other tissues examined showed no test agent-related increase in neoplasms. The results shown for some of these equivocal results are above the rate for the sham control, but many are within the historical control range. This suggests that the equivocal results are describing fluctuations in the natural background of these tumors and not an increase caused by exposure to RF radiation.

Genetic toxicology testing was performed using the micronucleus assay and the comet assay in the RF-exposed mice and rats as part of their 14-week intermediate analysis. There was an increase in apparent DNA damage in male rats exposed to CDMA RFR, but the increase was not statistically significant. Other noted increases in DNA damage were also considered to be equivocal, and no statistically significant increases in DNA damage was observed in female rats or in either mouse sex. All results from the micronucleus assay in rats and mice were negative.

The two-year carcinogenesis and toxicology study showed an unexpected finding in male rats. The exposed groups of animals had greater survival rates than the animals in the sham control. This might be attributed to amelioration of chronic progressive nephropathy: animal core temperature elevation resulting in reduced food consumption and increased water consumption in the RFR exposed animals could have improved the survival of the exposed animals. NTP's stated that their statistical analysis took these differences in survival rate into account during study analysis. The public health impact of these observations is unclear.

NTP's study conclusions in their final report for the two-year exposures in rats were:

Clear evidence of carcinogenic activity

- Incidences of malignant schwannoma in the heart of male rats for both GSM and CDMA.

Some evidence of carcinogenic activity (considered to be related to cell phone RFR exposure)

- Incidences of malignant glioma in the brain of male rats for both GSM and CDMA
- Incidences of pheochromocytoma (benign, malignant, or complex combined) in the adrenal medulla of male rats for GSM

Equivocal evidence of carcinogenic activity (may have been related to cell phone RFR exposure).

- Incidences of adenoma or carcinoma (combined) in the prostate gland of male rats for GSM.
- Incidences of benign or malignant granular cell tumors in the brain of male rats for GSM.
- Incidences of adenoma in the pars distalis of the pituitary gland of male rats for GSM and CDMA
- Incidences of pancreatic islet cell adenoma or carcinoma (combined) of male rats for GSM.

- Incidences of adenoma or carcinoma (combined) in the liver of male rats for CDMA.
- Incidences of malignant schwannoma in the heart of female rats for GSM
- Incidences of malignant glioma in the brain of female rats for CDMA
- Incidences of malignant schwannoma in the heart of female rats for CDMA
- Incidences of pheochromocytoma (benign, malignant, or complex combined) in the adrenal medulla of female rats for CDMA.

NTP reported that two-year exposure to GSM- or CDMA-modulated RFR revealed an increase in malignant schwannoma in the heart of male rats. NTP also reported that the incidence of schwannomas in all locations was not statistically significant compared to the control group. Cardiomyopathy was also seen in rats exposed to higher SARs (3 or 6 W/kg). The historical controls reported in NTP's preliminary reports published in 2016 (tumor incidence over time in a larger population of similar control rats in NTPs experiments) had approximately 9 out of 699 control rats that had malignant heart schwannomas (1.3% and a range of 0-6%). Only male rats exposed to higher SAR (6 W/kg) have higher percentage of malignant schwannoma than the maximum range of historical controls. However, NTP chose to use only three studies for historical controls in the final report. This set of studies had control groups of 50 rats each. There was a 2% incidence of cardiac schwannoma in 2 of the studies and no occurrences in the third study. NTP also determined (Wyde et al. 2018) that old, large male rats did not thermoregulate as well as younger rats. This is a possible indication of thermal confounding at 6.0 W/kg. It is not clear if there is a relationship between malignant schwannoma and cardiomyopathy.

NTP reported weaker responses to both modulations were found in other tissues. Glioma was one of the weaker responses and was not statically significant. The sham controls for gliomas show 0% incidence while the tumor incidence over time in a larger population of similar control rats in NTP experiments has a percent incidence of approximately 2-4%. Only the lowest RF exposure, 1.5 W/kg CDMA-modulation exceeds this historical control. Other tumors with increased incidence included pituitary tumors, benign and malignant pheochromocytoma, adenoma and carcinoma of the prostate. However, the highest increases were not consistently in the highest SARs and in some cases (adrenal medulla) the tumor incidence over time in control animals from other NTP experiments was as high as 28%.

The specific criteria for the categorization of data into the specific outcomes (e.g., clear evidence, etc.) remains unclear and there are inconsistencies in some of the interpretation of the data and the conclusions that have been drawn. As an example, the incidence of adenoma or carcinoma of the prostate gland in male rats subjected to GSM modulated RF was characterized as showing equivocal evidence of carcinogenicity with an incidence of 2.2%, 2.2%, 7.8% and 3.3% for the four doses of RF, whereas fibromas of the skin which showed incidences that are higher than the above (2.2%, 5.6%, 7.8% and 5.6%) were not classified as equivocal or any level above that.

In addition to the inconsistencies in the data interpretation, the importance attributed to dose response was also unclear in the final conclusions of the NTP reports. The incidence of benign, complex, or malignant pheochromocytoma in the adrenal medulla in male rats subjected to GSM modulated RF (12.5%, 26.7%, 31.5%, 16.1%) were classified as some evidence of carcinogenicity despite there being no clear dose response and no statistical difference between the highest RF dose and the control animals (P=0.472).

The strongest evidence found in the study was for malignant schwannomas of the heart in male rats, which were characterized originally as some evidence and after peer review changed to clear evidence and showed statistical significance at some doses of RF. It is notable that there was no incidence of heart schwannoma in the control group. An NIH reviewer noted that if there had been even one case in the control group then the statistical significance of this finding would not exist. It has also been noted that the histology review of samples was only partially blind in that the pathologists knew which group of samples was from the control group. This result was not consistent between the male rats and female rats or either sex of mice. As has been noted before, these extremely large whole-body RFR exposures (6 W/kg is 75 times higher than the limit for the public which is 0.08 W/kg) in rodents cannot be directly compared to real world partial body exposures to people using mobile phones<sup>10</sup>.

We do not know if there is a causal effect or if these results are due to weakening of the immune response due to animal stress from cyclic heating and thermoregulation decline in aging animals leading to whole-body temperature increase, possible sleep disruption due to the cyclic heating, or due to an RF-specific effect that has not been identified and has an adverse effect before heating becomes the dominant safety issue. It is possible that any form (ambient, IR, ultrasound) of cyclic whole-body heating of this magnitude may cause similar findings, but no such studies have been conducted to date.

## 2. *Papers Meeting the In vivo Review Criteria.*

In this section we summarize other relevant *in vivo* studies that we carefully considered and reviewed. Below is a summary of the results and limitations of these studies.

The largest animal exposure study published to date was conducted at the Ramazzini Institute's Cesare Maltoni Cancer Research Center in Italy (Falcioni et al. 2018). The goal of the

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<sup>10</sup> Note that the terms "wireless phone," "cell phone," and "mobile phone" are used interchangeably in this and other studies.

study was to examine the carcinogenic effect of 1.8 GHz simulated GSM in the far field whole body exposure for 19 hours/day for life on 2,448 Sprague Dawley rats. The size of the stacked dipole array antenna was not given but based on FDA expert analysis of the picture provided, the exposure may have been in the near-field. Exposure was based on fixed field strengths (V/m) and SAR (dose rate) estimates were based on a fixed “coupling factor”. However, for a given electric field SAR changes with the change of mass, which will change over the animal’s lifetime. As such, the estimation of the dose using a fixed “coupling factor” was not accurate.

The exposure groups were reported to be 0 (0 W/kg), 5 (0.001 W/kg), 25 (0.03 W/kg) or 50 V/m (0.1 W/kg). The animals were irradiated in their home cages, initially 5 rats per cage, but pictures show cages containing only one rat. The number of rats per cage is an important factor for the evaluation of potential stress and the possibility of localized RF current flow when animals touch. Because cages were exposed horizontally, rats could shield each other during exposure. As rats die and fewer are left in a cage their potential exposure increases unless survivors are rearranged to maintain full cages. Moreover, it was unclear if five animals per cage resulted in conflict and fights between animals, hence inducing stress.

There was no indication that animal core or other temperature was measured or recorded. Tissues from the heart and the brain were examined for malignancies and pre-malignancies. There was no mention of any other tissue being assayed. The authors state that the expected spontaneous tumor incidence and its fluctuations were based upon data derived from more than 20,000 historical controls; however, no reference to these data is provided. There were no differences in food or water consumption, mean body weight or survival index among the four exposure groups. This finding is different from the NTP rat exposure results where the water consumption was not monitored, and RF-exposed rats lived longer than control rats. Histopathological evaluation of the hearts and brains detected a statistically significant increase in the tumor incidence of heart schwannoma in the highest exposure for male rats (1.4%). The authors refer to historical controls with an incidence of schwannoma in male rats of 0.6% (10 out of 3,160 rats). Again, these historical control data were not available for analysis, and demonstrate very high inconsistencies with other reported historical rates of rodent schwannomas.

No statistically significant increases in malignant brain tumors and pre-malignant brain tumors were observed. The authors found a non-statistically significant exposure dependent increase in the incidence of malignant glial tumors in exposed female rats. After comparing this non-significant trend to historical control data where the amount of malignant glial tumors in

female rats was lower: 15 glial cell tumors out of 3,165 rats, or 0.5%<sup>11</sup>, it was determined that the 50 V/m exposure group had a greater incidence of glial cell tumors than the historical (but not the experimental) control.

Bartsch et al. (2010) reported on two long term and two life-long experiments that examined the effects of chronic exposure of rats to 900 MHz, pulsed at 217 Hz to stimulate a GSM signal on unrestrained animals. The exposure system was far-field simulated GSM 900 MHz exposure via a circularly polarized antenna. Fixed field strength, rather than SAR, was maintained throughout the experiments and thus the effective SAR changes over time as animals age and grow larger. The mean whole-body SAR was estimated to be 80 mW/kg by means of computational modeling and simulations based on an approach that has been extensively used in RF dosimetry literature. Twelve female rats per cage were exposed vertically so resonance effects are more likely. The exposure was for 23 hours and 45 minutes/day. Radiation exposure started at 52-70 days of age. The experiment was designed with animals irradiated in four different experiments with different time lengths, I. 24 months, II. 17 months, III. 36 months and IV. 37 months. The experimental endpoints included: animal general health, necropsy and histopathology but there was no mention of temperature monitoring, which could lead to confounding results. Experiments I and II recorded adverse health effects. Experiments III and IV showed, unlike the NTP study, that survival was decreased with RF exposure. It is unclear how the sham controls were treated or what elements the sham setup duplicated of the real exposure. Animal temperature measurement was not mentioned. The investigators concluded that chronic exposure to RF may exert negative health effects and shorten survival if exposure is applied sufficiently long. The investigators also noted that the month of birth may affect life span and stated that an experiment should be run to determine if the 11-year sunspot cycle could affect a rat's lifespan.

A series of investigations from Korea examined the impact of radiofrequency exposure on laboratory animals (Jin et al. 2011; Kim et al. 2008; Lee et al. 2011). Kim et al. (2008) exposed the heads of mice to 849 or 1763 MHz RFR for up to 12 months in a carousel-type head exposure system with a specifically-designed exposure chamber with real CDMA signal. The chamber was made of aluminum, the external size of which is 745 mm × 1,060 mm × 1,980 mm. To reduce reflections from the walls, absorber foam with a thickness of 4.5 inches was used. The SAR measurement was simulated. The SAR estimate was validated against thermal probe temperature measurements. The actual temperature within the animal was not validated. There was no animal core or head temperature monitoring to evaluate thermal impact. There was also no mention of blinding. The heads of the restrained mice were irradiated 1 hour/day, 5 days a week for 6 or 12

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<sup>11</sup> No reference was provided for these data

months with SAR of 7.8 W/kg. The weights of the irradiated animals were not significantly different from the controls. Furthermore, brain tissue taken from the animals showed no difference in histology, cell proliferation rate, cell death by TUNEL assay, and in the expression and distribution of NeuN and GFAP (markers of specific neuronal cell types) in the hippocampus and cerebellum between exposed and control animals. No evidence of brain tumorigenesis associated with RFR was found under microscopic examination. The authors concluded that exposure to the RFR at two different wavelengths did not result in alterations in cell proliferation, cell death, or gliosis.

Jin et al. (2011) whole-body irradiated rats in a reverberation chamber with two combined RF modulations, but without any core body temperature monitoring. The first was code division multiple access (CDMA), at 849 MHz and the second represents wideband code division multiple access (WCDMA), at 1.95 GHz. The animals were irradiated for 45 minutes/day, 5 days a week for one year. The SAR for these experiments was 2 W/kg for CDMA and 2 W/kg for WCDMA for a total combined SAR equal to 4 W/kg. No core temperature measurements were made to assess thermal effects. To prevent treatment bias, all the exposure and data analysis were performed using blinded methods. No significant differences in body weight or tumor incidence between exposed and control rats were found. There were some notable alterations in physiological parameters (complete blood count and serum chemistry) among exposed animals. However, the authors concluded that a 1-year simultaneous exposure to 4 W/kg CDMA and WCDMA did not increase chronic illness.

Lee et al. (2011) exposed AKR/J mice to CDMA and WCDMA RFR for 45 min/day, 5 days/week for 42 weeks at a total SAR of 4 W/kg. Exposure was given by using a reverberation chamber. SAR was calculated in rat voxel models by means of computational modeling and simulations based on the Finite Difference Time Domain (FDTD). Only whole-body SAR values were reported and no information on local SAR was included. Rectal temperature measurements were made before and after exposure and there was no elevation of temperature. Notably, AKR/J mice showed a high incidence of spontaneous lymphoma that was followed in these experiments. After examining body weight, survival, lymphoma incidence and splenomegaly, no differences were found between sham irradiated and irradiated animals. There were observed differences in infiltration of the brain by lymphoma: RFR-exposed male mice had lower brain infiltration compared with the controls and female mice had higher levels of brain infiltration compared with the controls. However, the authors concluded that RFR exposure did not affect lymphoma development in AKR/J mice.

Several investigations examined the impact of RFR exposure on the brain. Kesari, Behari, and Kumar (2010) examined the mutagenic response of 2.45 GHz RFR exposure on the brains of 12 male Wistar rats. The animals were whole-body exposed to a horn-antenna for 2 hours per day

for 35 days and sacrificed immediately after the last exposure and the brains of exposed and control animals assayed for DNA strand breaks (comet assay), antioxidant enzyme activity (glutathione peroxidase, catalase and superoxide dismutase) and histone kinase activity. The whole-body SAR was reported to be 0.11 W/kg. They detected an increase in DNA strand breaks, a decrease in glutathione peroxidase, superoxide dismutase and histone kinase activity and an increase in catalase activity. They concluded that chronic exposure may cause significant damage to the brain. Animal temperature measurement was not mentioned.

Chaturvedi et al., (2011) examined the impact of 2.45 GHz RFR exposure on circadian organization, spatial memory, DNA damage in the brain and blood counts of Parks strain male mice. The mice were exposed to RFR 2 hours per day for 30 days. RFR exposure was from an analog signal generator and horn antenna. Five of the ten animals were exposed individually and the whole-body SAR was 0.035 W/kg. The remaining 5 animals were sham exposed. Locomotor activity via a running wheel was recorded prior to and during RFR exposure. The Morris water maze was used from the 17<sup>th</sup> to the 22<sup>nd</sup> day of RFR exposure. After completion of the exposure blood was collected for hematological parameters, brain tissue for DNA strand breaks (comet assay), epididymis for sperm count and motility and serum for serum gluSGOT and SGPT. The authors concluded that RFR caused an increase in leukocyte and erythrocyte counts as well as altered the rate of DNA damage in exposed mice. Furthermore, the authors believe that RFR exposure altered the circadian system.

Deshmukh et al. (2013) studied the impact of 900 MHz (SAR= 0.595 mW/kg), 1800 MHz (SAR= 0.58 mW/kg) and 2450 MHz (SAR=0. 6.7 mW/kg) on the brain of rats. There were 24 rats that were organized into 4 groups (6 rats each). Three groups were exposed, and one group was sham exposed. The restrained rats were exposed for 2 hours/day, 5 days/week for 30 days. There were no statements regarding measurement of the animals' temperatures. Using the results from their modified alkaline comet assay, the authors concluded that low SAR exposures with any of the three frequencies may induce DNA damage.

Two other studies in rats from the same group evaluated the impact of RFR on cognitive function, heat shock protein levels and DNA damage (comet assay) in the brains of Fischer rats (Deshmukh et al., 2015, Deshmukh et. al., 2016). This group used a Gigahertz Transverse Electromagnetic cell as their exposure system. There were 24 rats in each study that were organized into 4 groups (6 rats each). In each study three groups were exposed, and one group was sham exposed. Restrained animals were irradiated 2 hours / day 5 days / week for 90 days (Deshmukh et. al., 2016) or 180 days (Deshmukh et al., 2015). The SARs were 0.5953, 0.5835 and 0.6672 mW/kg for exposures of 900, 1800 or 2450 MHz respectively. Body temperature of rats was noted by rectal measurements immediately before and after the MWR exposure in all the groups. There was no change in body temperature. For both exposures, (90 or 180 days) the

authors found cognitive function decline, elevated HSP synthesis and DNA damage and they concluded that chronic low-intensity microwave exposure may cause hazardous effects on the brain. The authors state that HSP synthesis can be from non-thermal effects. However, thermal effects even at these low SARs cannot be ruled out.

Sahin et al. (2016) evaluated the impact of 2100 MHz RFR on the brain of rats. The exposure system was composed of a vector signal generator and horn antenna. There were 30 rats divided into 4 groups. Exposure groups had 9 animals and sham exposure groups had 6 animals each. The exposed animals were exposed for 6 hr/day 5 days a week for 10 or 40 days. The SAR was reported to be 0.4 W/kg. No core temperature measurements were made to assess thermal effects. The authors assessed oxidative DNA damage (8-hydroxy-2'-deoxyguanosine determination) and the level of lipid peroxidation (malondialdehyde determination) in the brain of RFR exposed rats. The authors found no difference in oxidative DNA damage when exposed animals were compared to their individual controls, however, increased oxidative DNA damage was found in animals exposed for ten days compared to the 40-day exposed animals. Decreased lipid peroxidation was observed after 40 days of exposure. The authors postulated that the longer exposure may have increased DNA repair mechanisms.

Ibitayo et al., (2017) investigated the effect of RFR on the brains of male rats. There were 16 rats in 4 groups of 4. The authors described the exposure set up as follows: "The animals were pair housed in groups of four in steel mesh cages and placed about 10 cm away from installed devices that emitted RF EMF. The control group ( $n = 4$ ) was kept in a steel mesh cages with a glass barrier separating the control from the experimental animals." It appears the animals were whole body exposed to 2.5 GHz RFR for 30, 45 or 60 days. No description of the RF source nor a SAR determination was provided. No core temperature measurements were made to assess thermal effects. Histopathology and DNA damage was determined. The authors concluded that vascular congestion and DNA damage indicative of oxidative stress are evident in RFR exposed animal brains. The authors found that the 45-day exposed samples did not show severe histopathological changes seen in the 30- or 60-day exposed samples. There was also no report of malignant change in the investigation.

Three investigations examined the impact of 1800 or 2100 MHz on bladder cells of rats (Gurbuz et al. 2010; Gurbuz et al. 2014; Gurbuz et al. 2015). In these experiments, the rats were exposed to RF radiation and the bladder cell micronuclei were assayed for micronuclei *in vitro*. Gurbuz, et. al. (2010) exposed 6 female Wistar rats to 1800 MHz GSM-like RF for 20 minutes/day, 5 days/week for a month and assigned 6 others to a control group. Near field exposure was used to simulate cell phone exposure. Field strengths were controlled with a Narda EMR 300 meter and probe. The E-field was 4 V/m. The authors claim that because E-field values are much lower than the 41 V/m of ICNIRP, exposure is assumed to be non-thermal. However, temperature was not

monitored, and those statements cannot be confirmed. RFR exposure did not increase the frequency of micronuclei in exposed rats compared with the controls.

Gurbuz et al (2014) examined exfoliated rat bladder cells for micronuclei after whole body exposure (30 min/day, 6 days/week for one and two months) to 1800 MHz and 2100 MHz RF radiation. The animals were free to move in their cages during the RF exposure. The control animals were housed in their home cages during the entire experimental period without being subjected to any experimental manipulation. A vector signal generator was used to create a GSM modulated RF radiation in the experimental setup. The E-field was 17 V/m. The calculated average SAR was estimated to be 0.23 W/kg. No significant increase in micronuclei found in the exfoliated rat bladder cells was detected in cells from RF exposed rats compared to control rats.

Finally in a third study, the same group (Gurbuz et al. 2015) examined the influence of RFR on micronucleus formation in bladder cells of diabetic rats. They postulated that diabetes may accelerate oxidative damage in DNA molecules through glucose auto-oxidation and non-enzymatic glycation. The diabetic rats were exposed to 2100MHz RF for 30 min/day, 5 days/week for 30 days at a low SAR (0.24 W/kg). As in previous experiments, they used a near field exposure and the dosimetry was unclear. Again, this group found no statistically significant difference between the exposed population and the diabetes control or the non-diabetes control. Overall, based on the results presented, the studies indicate that rat bladder cells are not sensitive to RF exposure at low SARs.

Two separate experiments examined the co-carcinogenic potential of RF exposure in combination with a known carcinogen (Lerchl et al. 2015; Tillmann et al. 2010). In both cases the known carcinogen was ethylnitrosourea. Tillmann et al. (2010) exposed mice over the whole-body to a universal mobile telecommunications system (UMTS) signal. RF exposure lasted up to two years starting at embryo-fetal stage. Whole body SARs were estimated to be up to 4 W/kg. The animals were exposed once per day (2 GHz, continuous wave signal, 2 h/d) with a stepwise increased power density in one radial waveguide of a three-decker exposure system. Rectal temperature measurements simultaneously obtained in 10 mice (2 mice per cage) directly after termination of the RF exposure revealed regular body temperatures ( $37.1^{\circ}\pm 0.38^{\circ}\text{C}$  to  $37.7^{\circ}\pm 0.68^{\circ}\text{C}$ ) regardless of the RF power density applied. The low field intensity group was also given 40 mg ethylnitrosourea. The high UMTS exposure ( $48\text{ W/m}^2$ ), the sham exposure and the cage control all showed comparable tumor incidence. Animals exposed to ethylnitrosourea and  $4.8\text{ W/m}^2$  RF showed an increased incidence of lung carcinoma. Notably, the authors identified a *Helicobacter hepaticus* infection in these animals and discounted the high RFR liver tumor results. A review of the neoplastic and pre-neoplastic lesions in the protocol organs shows that UMTS RF exposure ( $48\text{ W/m}^2$ ) for up to two years did not produce tumors or other lesions of the cerebrum. Also, other tissues examined such as the lungs, kidneys, spleen and hematopoietic /

lymphopoietic system did not show increased tumors or increased pre-neoplastic lesions when the UMTS exposed animals were compared to the cage control or sham control animals.

Lerchl et al. (2015) also examined the co-carcinogenic potential of RFR exposure in combination with a known carcinogen (ethylnitrosourea). This investigation used 5 groups of 96 mice. Four groups were treated with ethylnitrosourea and exposed at SAR equal to 0 W/kg (sham), 0.04, 0.4 or 2 W/kg SAR for 23.5 hours per day up to 72 weeks. The fifth group was an untreated unexposed cage control. Details of the RFR exposure and exposure system were previously published (Reinhardt et al. 2007), presenting the 900 MHz UMTS waveguide exposure system and simulations to estimate whole body SAR based on typical arrangement of mice in the exposure area. The E-field inside waveguides was monitored. There was no data, either simulated or measured that correlated E-field with the desired treatment levels of whole-body SAR. There was no temperature monitoring. Further, this large experiment did not include an RFR only control. The authors concluded that the combination of ethylnitrosourea and RFR produces a greater number of tumors in the lungs and livers of exposed animals compared to the sham irradiated controls. Also, the results found lymphoma in RFR-exposed animals. The results do not demonstrate a clear dose response. A review of the neoplastic and pre-neoplastic data shows no significant tumors or pre-neoplastic lesions of the cerebrum compared to the cage control or the sham irradiated control.

Hruby (Hruby et al. 2008) examined the impact of 902 MHz GSM-type wireless RF radiation on 7, 12-Dimethylbenz(a)anthracene (DMBA)-induced mammary tumors in rats. DMBA is widely used in animal research as an immunosuppressor and a powerful organ-specific carcinogen. All animals received DMBA, there were two control groups (cage control, sham irradiation control) and three RFR exposure groups (0.4, 1.3 and 4.0 W/kg). Each group had 100 animals and another 20 were kept as sentinel animals for disease surveillance. RF exposure was simulated GSM at 902 MHz for 4hr/day, 5 days/week for 6 months. The animals were exposed individually, held in restraining tubes fitted into a 17 spoked waveguide exposure system. The authors cited references on the exposure system which provide credible evidence that the system was accurate, monitored in real-time, and well supported by simulations to estimate whole body SAR. The authors found the following statistically significant results: All RFR exposed groups, at different times had significantly more palpable masses; There were fewer animals with benign lesions in the RFR exposed groups and more malignant tumors in the highest RFR exposure group; The cage control group had more palpable tissue masses and more benign and malignant tumors compared with the sham irradiated control. However, the RFR exposure groups did not show a dose response. The authors concluded that, "In the context of the results of the cage-control group, in the light of controversial results reported in the literature, and given the fact that the DMBA-mammary tumor model is known to be prone to high variations in the results, it is the authors' opinion that the differences between the groups are rather incidental ones."

Paulraj and Behari (2011) investigated the impact of 2 frequencies of RFR on carcinogenesis in mice. There were 18 mice in each of the 7 groups. The study was divided into two parts. The first, involved the topical administration of DMBA on the skin followed by exposure to 112 MHz or 2.45 GHz 2 hours/day, 3 days / week for 16 weeks. There was insufficient information to determine how SAR was estimated but reported SARs were 0.75W/kg for 112 MHz and 0.1 W/Kg for 2.45 GHz. No core temperature measurements were made to assess thermal effects. The study also employed a positive control, DMBA + croton oil (a well-known tumor promoter). The positive control produced tumors in animal skin. However, no tumors were detected in the controls or the exposed populations. The second part consisted of transplanting Ehrlich ascites cells (originally established to produce ascites tumors in mice) intraperitoneally followed by exposure to 112 MHz RF for 14 days. There were no significant changes in mortality or cell proliferation between the control and the exposed groups. It is unclear if this was a sham or cage-control.

Two studies from the same group investigated the cytotoxic effects of 1800 or 900 MHz RFR exposure to rat bone marrow cells (Atli Sekeroglu, Z., Akar, and Sekeroglu 2013; Sekeroglu, V., Akar, and Sekeroglu 2012). The first study (Sekeroglu, V. , Akar, and Sekeroglu 2012) examined the effects of 1800 MHz RFR on immature and mature bone marrow cells (RIM and RMM). In each study a total of 48 animals were divided into 6 groups of 8 animals each. Rats with RIM and RMM were exposed to 1800 MHz RFR for two hours/day for 45 days. Some of the animals were tested immediately and others returned to their cage for 15 days before testing. Insufficient information was provided on dosimetry and there was no discussion about measuring the animals core temperature. The reported whole-body average SARs were 0.37 W/kg and 0.49 W/kg for RIM and RMM cells, respectively. The bone marrow cells were scored for common signs of bone marrow cell toxicity including differences in mitotic index, chromosomal aberrations, and micronucleus formation. Significant differences between control and exposed bone marrow cells were found in chromosomal aberrations, micronucleus formation, mitotic index, and the ratio of polychromatic erythrocytes. The authors found that the damage detected was greater in RIM cells than RMM and that an unirradiated recovery period after exposure did not improve the RIM cells. Additionally, it is not clear if the control animals were sham irradiated while in the irradiation restraining device.

The same group, (Atli Sekeroglu, Z., Akar, and Sekeroglu 2013) repeated the experiment with exposure to 900 MHz RF. The animals were exposed for 2 hours /day for 45 days. The estimated SARs were 0.38-0.78 W/kg for RIM and 0.31-0.52 W/kg for RMM. Significant differences between control and exposed bone marrow cells were found in chromosomal aberrations, micronucleus formation, mitotic index, and the ratio of polychromatic erythrocytes. The comet assay was not blinded, and the OECD approved %tail DNA was not used as the comet

assay damage metric. The authors found that the damage detected was greater in RIM cells than RMM and that an unirradiated recovery period after exposure did not improve for bone marrow cells. Conclusions from this study must be made with caution because no positive control with a known cytotoxic agent was included in this experiment and there was only one timepoint for the recovery experiment reported.

Ziemann (Ziemann et al. 2009) examined the genotoxic potential of 902 MHz GSM and 1747 MHz digital cellular system (DCS) communication signals in a two-year study in mice. Each group contained 65 animals, with the 15 animals used for interim examinations. There were additionally 30 male and 30 female mice assigned as sentinel animals. The animals were chronically exposed to RFR for 2 hours/day, 5 days/week for two years at whole-body averaged SARs of 0.4, 1.3 and 4 W/kg. There was no indication that animal core temperature was measured or recorded. Micronuclei frequency was determined in blood smears of cage control animals, sham irradiated animals, with animals exposed to SAR equal to 0.4, 1.3 and 4 W/kg as well as mitomycin C (MMC) as a positive control. MMC alkylates and cross-links DNA. No significant differences in micronuclei frequency were found between RFR exposed animals and cage controlled or sham irradiated animals. Only animals in the positive control group showed significant increase in micronucleus frequency.

Furtado-Filho (Furtado-Filho et al. 2015) examined the impact of 950 MHz RFR on ROS metabolism and DNA damage in the brains of young rats. RFR exposure was applied during pregnancy to 6 animals and to 6 pups for 6 days after birth, with estimated SAR ranging from 1.14-1.32 W/kg. Another 6 pregnant rats were sham exposed. 6 pups from both exposed parents and from sham exposed parents were dissected at 0 days old. Another 6 pups that continued exposure and those that had no exposure were dissected after 6 days. There was no temperature monitoring and no apparent blinding for the endpoint analysis. No positive control was included in this study. No genotoxicity and oxidative stress were identified in neonates and 6-day old mice.

Another small study investigated the impact of 915 MHz with GSM modulated RFR on DNA of brain, liver and kidney of rats (Trosic et al. 2011). 9 rats were in the exposed group and 9 rats in the sham exposed group. The animals were irradiated at 37°C for one hour/day, seven days a week for two weeks at a SAR of 0.6 W/Kg. Exposure was generated by a Gigahertz Transversal Electromagnetic Mode Cell and a signal generator. The elevated environmental temperature during exposure may have influenced thermal regulation of the exposed animals and thus increased the chance of thermal confounding. Before and after exposures a ThermoScan thermometer was used to measure body temperature. No significant changes were observed in the treated animals compared to the sham exposed animals. Genotoxicity was assessed via the comet assay used tail length and not the OECD approved endpoint %tail DNA to detect DNA

damage, which demonstrated no statistically significant correlation between dose and comet tail length.

Akdag et al. (2016) investigated the impact of long-term exposure to 2450 MHz RFR exposure on DNA damage in the brain, liver, kidney, skin, and testicular tissue of rats. There were two groups of 8 rats each. The control group was sham exposed. The animals were exposed 24 hours/day for 12 months using a signal generator. The animals' core temperature was not measured or not documented. There was no mention of blinding. Results from the comet assay appeared to show more DNA damage in the RFR-exposed rats compared to the sham irradiated rats. However, the results were not statistically significant for the DNA damage in brain, liver, kidney and skin. The only tissue in which RFR significantly increased DNA damage was in the testis.

Pandey et al. (2017) investigated histology and DNA damage in testicular cells in mice after 900 MHz RFR exposure. There were 5 groups of 15 mice each. The animals were exposed for either 4 hours or 8 hours/day for 35 or 70 days and the SAR was calculated to be from 5.4 to 5.16 mW/kg. The animals' temperatures were not measured. There was no blinding of quantitative endpoints. There is no description of a sham exposure for the control group. The authors concluded that oxidative stress caused DNA damage in germ cells of exposed mice without measuring oxidative stress, and the precise link between the apparent oxidative stress and DNA damage remains unclear.

Pandey and Giri (2018) investigated DNA damage with the comet assay and other oxidative stress endpoints in germ cells of male mice exposed to 900 MHz RF radiation. There were 60 animals in 4 groups of 12 animals each. The groups were: controls, mice dosed with melatonin, mice exposed to RFR, and mice dosed with melatonin and exposed to RFR. There was no mention of sham controls. The animals were irradiated for 3 hours/day, twice a day for thirty-five days. The SAR ranged between 0.052 and 0.0054 W/kg. The authors state that the samples and slides were carefully blind coded before analysis; however, blinding is mentioned specifically only in the histology section. The authors found that melatonin administration reduced DNA damage that they attributed to RFR exposure.

Megha et al. (2015) examined the impact of microwave exposure on oxidative stress and DNA damage in the hippocampus of Fisher Rats. There were 24 animals in 4 groups of 6 rats each. The rats were exposed in a GHz transverse electromagnetic cell to 900, 1800 and 2450 MHz at SARs of 0.59, 0.58 and 0.66 mW/kg respectively. The control group was sham exposed. Body temperature of rats was noted by rectal measurements before and after the microwave exposure in all the groups. The exposures were given to restrained animals for two hours/day, five days/week for 60 days. The slides prepared were randomized and coded to blind the comet

scorer, but no other blinding was done. The authors report that DNA damage was significant in all microwave-exposed animals and they believe that the increase in DNA damage is frequency dependent.

Guler et al., (2016) investigated the impact of 1800 MHz RFR on the brains of developing rabbits. The endpoints were oxidative DNA damage (8-hydroxy-2'-deoxyguanosine determination), lipid peroxidation (malondialdehyde determination) and apoptotic cell formation TUNEL assay). A signal generator with an integrated pulse modulation unit and horn antenna was used to expose the animals. The estimated SAR was 18 mW/kg. 36 female rabbits were exposed for 15 minutes /day for 7 days. 36 males were exposed for 15 minutes / day for 14 days. 36 of the infant rabbits were exposed for 15 minutes / day in the intrauterine gestational period. Animals were also exposed a month after birth. The animals were divided into 4 groups. Group I: no intrauterine + no extrauterine exposure; Group II: no intrauterine + extrauterine exposure; Group III: intrauterine exposure + no extrauterine exposure; Group IV: intrauterine and extrauterine exposure. Blinding was used to prevent bias during sample analysis. There was no measurement of the animals' temperatures reported. The authors found that intrauterine and extrauterine 1800 MHz RFR exposure may cause oxidative and DNA damage in the brain tissue of baby rabbits which are exposed while they are fetus and after they are 1-month old. However, there was no evidence of apoptosis in any of the groups.

Turedi et al. (2014) studied the effect of 900 MHz RFR prenatal exposure on the 21-day old male rat heart. The exposure system used was an ultra-high frequency oscillator attached to an uninterrupted power supply and a dipole antenna installed into a plexiglass box. The whole-body SAR was 0.025 W/kg. Three pregnant rats were exposed for 1 hour / day on days 13 to 21 of their pregnancy. Three other pregnant rats were assigned to the control group and there was no sham exposure. Six control and six exposed male pups were sacrificed on day 21 and hearts collected for microscopy, malondialdehyde, superoxide dismutase, catalase, and glutathione activity determination. There was blinding used to prevent analysis bias. Apoptotic changes and irregularities in the heart muscle of exposed animals were shown by microscopy. Crista loss, mitochondrial swelling, degeneration in myofibrils and structural impairments in z-bands were shown by electron microscopy. Malondialdehyde, superoxide dismutase and catalase values were found to be significantly higher. Glutathione activity was found to be lower. The authors concluded that RFR exposure in the prenatal period causes oxidative stress and histopathological changes in the heart, although the impact of any potential temperature increase during exposure was not determined and there was no measurement of the animals' core temperatures.

The genotoxic effects of 2.45 GHz RFR on the testis and ovary of rats was investigated by Usikalu et al., (2013). The exposure system was a microwave generator and all exposed animals were whole body irradiated for 10 minutes at various SARs. There were 30 male and 30 female

rats used in this study and one control and 9 experimental groups. There were 3 male and 3 female rats in each group. SARs were measured by insertion of a thermistor into the rectum. The animals were exposed to 0, 0.48, 0.95, 1.43, 1.91, 2.39, 2.9, 3.4, 3.8 and 4.3 W/kg. DNA damage was assessed by direct amplification of length polymorphism and the comet assay. Organ damage was assessed by histopathology. There was no blinding described in the paper nor was there a sham control described. The authors conclude that 2.54 GHz RFR exposure alters DNA bands patterns, induces single strand DNA breaks, and reduces the number of male germ cells in rats. Furthermore, the authors concluded that RFR exposure at 0.48 W/kg and above produces genotoxic effects on the testis or the ovary.

Ozturk Okatan et al., (2018) evaluated ovarian changes in adolescent rats exposed to 900 MHz RFR. The exposure system consisted of an oscillator, a continuous fixed power source and an EMF cage. Rats were exposed to 900 MHz for 1 hour a day between postnatal days 35 and 59. The calculated whole-body SAR was 0.0098 W/kg. Animals were divided into 3 groups: control, sham-exposed and 900 MHz exposed. Each group contained 8 rats. Animals' core temperatures were not measured. Ovaries and blood were collected at the end of the exposure for histopathological and biochemical analysis. Blinding was used to avoid analysis bias. Among the results of the histopathological examination was thinning in the zona granulosa and theca layers, shrinking in granulosa cells, reduced mitotic activity and leukocyte infiltration in the follicles and stroma of RFR exposed animals. Among the results of the biochemistry examination was an increase in superoxide dismutase, catalase and anti-Mullerian hormone levels in the RFR exposed and sham exposed animals. The authors conclude that RFR exposure may cause changes in the morphology and biochemistry of the ovary, although with changes also seen in the biochemistry of sham exposed animals, the conclusions appear unclear.

The Influence of 1800 MHz GSM RFR exposure on oxidative DNA and Lipid damage in liver of pregnant, non-pregnant, and new born rabbits was studied by Tomruk et al. (2010). Six groups of nine rabbits each were used. A signal generator, pulse modulator and horn antenna were used as the exposure system. Pregnant and non-pregnant rabbits were exposed whole-body to 1800 MHz GSM-like RFR signal for 15 minutes / day for a week. No estimation of SAR was provided. Core temperature measurements and blinding are mentioned. Oxidative DNA damage (8 OHdG/10<sup>6</sup>DG level) and lipid damage (malondialdehyde assay and ferrous oxidation in xylenol orange level) was determined in control and exposed pregnant and non-pregnant as well as in new born control and exposed rabbits. There was no difference in oxidative DNA damage between exposed and control livers. However, lipid damage was detected in the exposed groups. No increased oxidative DNA damage was detected in new born rabbits exposed to 1800 MHz RFR in utero. Increased lipid damage was detected in new born rabbits exposed to 1800 MHz RFR in utero.

Furtado-Filho et al., (2014) also investigated the impact of RFR on the liver of rats. These investigators used a generator and a half-wave dipole antenna to produce RFR at a power of 1 Watt and a frequency of 950 MHz. The SAR was 0.88 W/kg for neonate rats, 0.51 W/KG for 6-day old rats, 0.18 W/Kg for 15-day old rats and 0.06 W/kg for 30-day old rats. Six pregnant rats were exposed to SARs ranging from 0.01 to 0.03 W/kg. 6 other pregnant rats were assigned to the control group. The animals were exposed to RFR for thirty minutes / day for up to 51 days. The exposure was divided into 21 days of gestational exposure and up to 30 days outside the womb. Temperature was not measured and there is no mention of blinding. Damage to lipids, proteins and DNA (comet assay) was assessed. The authors found 950 MHz exposure does not cause oxidative stress and is not genotoxic to neonates or rats up to 15-days old. However, the authors also found that RFR exposure is genotoxic to 30-day old animals.

The excretion of 8-oxodG, an oxidative DNA marker in the urine of rats exposed to 1800 MHz RFR was conducted by Khalil et al. (2012). A GSM signal generator and antenna were used to expose the rats to 1800 MHz for 4 hours. There were 24 rats in two groups of 12. Sample analysis was blinded. The SAR was 1.0 W/kg. The results indicate that RFR exposure increased the urinary excretion of 8-oxodG compared to the control. The authors concluded the following: “the present results suggest that (a) exposure to RFR may augment oxidative stress; (b) urinary excretion of 8-oxodG may be a good and specific marker of oxidative stress. Further work is also required to understand the origin and validity of excreted urinary 8-oxodG as a marker of oxidative stress.”

Two investigations from the same group investigated the adaptive response in mice exposed to 900 MHz (Jiang et al., 2012; Jiang et al., 2013). Jiang et al., (2012) examined the impact of prior exposure of 900 MHz RFR for 4 hours / day for 1, 3, 5, 7 and 14 days to subsequent exposure to 3 Gy of ionizing radiation. There were 3 exposure groups containing 5 mice each. There was no blinding. The exposure system consisted of a GTEM chamber, power amplifier and an antenna. The calculated SAR was 0.548 W/kg. The exposed mice were restrained during exposure. DNA damage was assessed with the alkaline comet assay. One exposure for 4 hours to 900 MHz plus 3 Gy was not significantly different from 3 Gy alone. Mice pre-exposed for 3 or more days to 900 MHz show progressively less damage to 3 Gy suggesting adaptive response triggered by the conditions of the RFR exposure or the RFR.

Jiang et al. (2013), conducted a similar experiment that investigated the impact of prior exposure to 900 MHz RFR for 4 hours / day for 7 days on subsequent exposure to 3Gy of ionizing radiation. There were 6 groups of 10 mice each used in this study. The exposure system consisted of a GTEM chamber, power amplifier and an antenna. The calculated SAR was 0.548 W/kg. Genotoxicity was assessed via the micronucleus assay in immature erythrocytes in peripheral blood and bone marrow. Results of the micronucleus assay were similar for the non-exposed control mice and the 900 MHz RFR exposed mice. Exposure to 900 MHz RFR for 7 days before 3 Gy of ionizing

radiation resulted in a significant decrease in micronuclei compared to 3 Gy ionizing radiation only. This may indicate the conditions of RFR exposure or the RFR exposure activated an adaptive response.

Meena et al., (2013) studied the protective effects of Melatonin (antioxidant) on oxidative stress-mediated testicular impairment due to long-term exposure from RFR. The exposure system consisted of an anechoic chamber in a far field region from a horn antenna. The rats were exposed to 2.45 GHz RFR for 2 hours per day for 45 days. There were 24 rats in 4 groups of 6 rats each. The samples and analysis were blinded. There was no data regarding the animals' core temperature. The SAR was estimated to be 0.14 W/kg. Four groups were tested in this investigation: sham exposed, melatonin treated (2g/kg), 2.45 GHz RFR and 2.45 GHz plus melatonin. Oxidative stress related parameters were documented including lactate dehydrogenase activity, xanthine oxidase activity, reactive oxygen species, protein carbonyl content, DNA damage (comet assay) and malondialdehyde concentration. The authors found that melatonin reduced oxidative damage by increasing lactate dehydrogenase, decreasing malondialdehyde and reactive oxygen species. Melatonin also reversed the effects of 2.54 GHz RFR on xanthine oxidase, protein carbonyl content, sperm count, testosterone level and DNA strand breaks. The authors concluded that melatonin has a strong effect on the RFR mediated oxidative stress in testicular cells.

The effect of RFR adaption on bleomycin-induced DNA and oxidative damage and repair was studied by Zong et al. (2015). The exposure system was a GTEM chamber. 900 MHz RFR exposure was for 4 hours / day for 7 days. The mice were restrained. The SAR was estimated to be 50 mW/kg. There were 48 mice total. Six groups were tested. The animals' core temperatures were not measured. The samples were blinded. The groups included unexposed controls, RFR only, sham exposure only, Bleomycin only, RFR exposure plus bleomycin and sham exposure plus bleomycin. DNA damage was assessed via the comet assay. Oxidative damage was assessed via malondialdehyde levels and antioxidant status by superoxide levels. There was no indication for increased DNA and oxidative damage in mice exposed to RFR alone. Mice exposed to RFR plus bleomycin significantly reduced bleomycin damage and decreased malondialdehyde concentration in the plasma and lung and increased SOD levels in lung. The conclusion was that RFR exposure induced an adaptive response to bleomycin DNA and oxidative damage by activating certain cellular processes. There was no evidence for DNA strand breaks or oxidative damage caused by RFR exposure in this experiment. The authors suggested that RFR exposure activates an adaptive response through cellular processes that are not DNA or oxidation dependent.

### C. Conclusions from In vivo Review.

The *in vivo* studies conducted between January 1, 2008 and August 1, 2018 and summarized here have contributed to our collective understanding of the potential effects of RFR on mammals. Overall, based on certain limitations, these studies have not produced any clear evidence that RFR exposure has any tumorigenic effect. In some cases, the authors of these studies suggested the need for more research based on the reported results. Other authors stated that RFR exposure does not result in tumor-initiating or -promoting effects.

Most of the referenced literature did not include measurement of animal temperatures. The impact of potential temperature elevation from RFR exposure is a confounding factor in such studies and critical to assess. The NTP reports examined temperature increases in their 5-day pilot study. However, they did not adjust their highest exposure groups, exposures up to 6 W/kg in rats and 10 W/kg in mice, to address concerns with geriatric thermoregulation. The NTP pilot study confirms that pregnant animals and older animals have difficulty regulating body temperature when they are exposed to sources of heat such as RFR exposure. NTP reports indicate a need to further evaluate how mammals' thermoregulatory abilities decline as they age and how to address this issue to remove confounding heating as a factor in any future RFR exposure research. Similarly, some of the other literature we reviewed have results that are confounded by heating issues.

As with many areas of active investigation, the variety of experimental methods employed can result in significant differences in conditions experienced by the experimental animals, and in turn this can lead to a high degree of variability in study conclusions. For RFR studies, there are large differences in, for example, methods for dosing and restraining animals during the experimental procedure that will affect the specific stress levels of the test animals, confounding some conclusions. There are also important differences in the overall experimental designs, including the use (or lack) of both a control and sham exposed control group. Such differences may be one reason why there are many diverging and conflicting conclusions of the *in vivo* effects of RFR.

Another experimental issue that has an impact on the understanding of the interaction between RFR with animals and needs further research is how samples are handled and evaluated. The method of sacrifice (time since last exposure) and time from an animal's death to sample preparation have a large impact on the results of sensitive tests like the comet assay. In these experiments, there were differences in how biological samples were collected and processed that added confounding factors. One of the most prevalent problems we observed in these studies was the lack of adequate blinding of samples which generally leads to an unconscious bias in the evaluation of data. More clarity regarding potential confounders is needed in this area of research.

The FDA has followed RFR research developments for over 20 years. More than 100 peer reviewed articles about *in vivo* animal exposures were assessed for to determine if they met the scope of this review. 37 peer reviewed articles met our criteria and are included in this review. *In vivo* studies are of great value and contribute to our understanding of this topic. However, as described above, due to the critical limitations of *in vivo* studies in assessing the effects of RFR exposure to humans (e.g., whole-body RFR exposure), we cannot draw conclusions about the impact of such exposure to humans based on these *in vivo* animal studies. The results from such studies should not be applied to human cell phone usage as further research is needed.

## V. Epidemiological Studies

Section V.A. below discusses the search strategy and search terms we adopted to find relevant epidemiological literature. Section V.B. of the report provides a high-level narrative summary of the epidemiological studies reviewed and then followed by a description of the overall limitations of such studies in Section V.C. Specifically, Section V.B. summarizes general findings stratified by overall risk trends (e.g., increasing or decreasing), study types and/or sources (e.g., ecological trend analysis or case-control study), and outcomes of interest represented by different tumor types (e.g., glioma, meningioma, vestibular schwannoma, etc.). Section V.D. includes a more detailed description of the individual studies reviewed, including summary of the methodology and main results, along with the limitations for each referenced study. Section V.E describes the FDA's findings based on the review of the available epidemiological literature.

### A. Search Strategy.

As the primary source for Medline-indexed journals and peer-reviewed publications, PubMed was queried using the following search terms and limits:

- ("cell phone\*" OR "mobile phone\*" OR "non-ionizing radiation" OR "radiofrequency radiation") AND (cancer OR cancers OR carcinogen\* OR tumor OR tumors OR tumorigenesis)
- Filters: Full text, English and Humans

The initial PubMed query with no limits resulted in a total of 1,180 records. After applying PubMed filters for Full Text, English, and Humans, the number of records was reduced to 792 publications, which constituted the pool for 1<sup>st</sup> pass (*i.e.*, abstract-based) review. The 1<sup>st</sup> pass review excluded articles not directly related to the review's subject (*e.g.*, main outcomes other than cancer). Note: a relatively high number of excluded articles (343 of the 388) was due to the fact that in many studies, RF-related wireless technology was a part of the study design, but not the main research topic (*e.g.*, mobile phones were used for collecting data from cancer patients). The 1<sup>st</sup> pass review identified 449 records, which were focused on the RF-related cancer risk, but included animal (*in vivo*) studies as well as article formats such as meta-analyses, expert opinions, *etc.* The 2<sup>nd</sup> pass (full-text based) review was aimed to select the original clinical/epidemiologic studies assessing RF-related cancer risk. Per RF Working Group's request, the 2<sup>nd</sup> pass review also applied the publication date filter (January 2008 – May 2018) for deriving more recent evidence. After the 2<sup>nd</sup> pass review, a total of 69 records (with one cross-reference) were selected for the final review with qualitative evidence synthesis.

Note: this technical report includes some additional references, which have been used to support the overall data analysis and interpretation. In order to distinguish them from the

selected clinical/epidemiological publications (which are listed in the References section), the additional references cited are presented in the footnotes.

## B. Summary of Results.

This section only provides a high-level narrative summary of the epidemiological studies reviewed. For a description of the limitations of these studies see Section V.C below and for a more detailed description of each of the individual studies referenced here, see Section V.D.

### 1. *Studies reporting overall evidence that does not counter a global null hypothesis on tumor risk in relation to cell phones.*

Negative evidence on associations between use of cell phones and tumor incidence was shown in a number of **ecological trend analyses** reporting no population-level risk increases for the brain and central nervous system (CNS) tumors (*Inskip 2010; de Vocht 2011b; Ding and Wang 2011; Benson 2013; Hsu 2013; Kim 2015; Sato 2016*), which included glioma and meningioma (*Deltour 2009, 2012; Chapman 2016*), acoustic neuroma<sup>12</sup> (*Benson 2014*), and parotid gland neoplasms (*de Vocht 2011a*). In the study by *Barchana (2012)*, no increasing incidence in the period after introduction of mobile phones was reported for low-grade (but not high-grade) gliomas.

Similarly, no evidence for overall tumor risk increase in relation to cell phone use was shown in a number of **case-control and cohort studies** on acoustic neuroma (*Corona 2012; Han 2012; Schüz 2011*), glioma (*Gousias 2009*), pituitary adenoma (*Shoemaker and Swerdlow 2011*), uveal melanoma (*Stang 2009*), and salivary gland tumors (*Soderquist 2012*). Some studies (*Lankola 2008; Shrestha 2015*) reported overall reduced risk for meningioma (OR=0.76 [95% CI: 0.65; 0.89]) or pituitary tumors (OR=0.39 [95% CI: 0.21; 0.72]), which however indicated the presence of strong biases as discussed below.

However, some studies (*Aydin 2011, 2012; Cooke 2010; Coureau 2014; Frei 2011; Kaufman 2009; Poulsen 2013; Yoon 2015*) reported no overall risk increases in the entire study populations but found elevated risks in certain study subpopulations (for more details, see section IV.D. below). Risk increases among certain cell phone user categories were found even in the large-sample multi-country *INTERPHONE (2010, 2011)* studies that reported overall reduced risks for glioma and meningioma (OR=0.81 [95% CI: 0.70; 0.94] and OR=0.79 [95% CI: 0.68; 0.91], respectively) and acoustic neuroma (OR=0.85 [95% CI: 0.69; 1.04]).

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<sup>12</sup> Acoustic neuroma is also known as vestibular schwannoma; in this memo, both terms are being used interchangeably, as presented in original publications.

No overall risk increase corresponding to the increasing time of cell phone use was found in the Swedish population-based study on acoustic neuroma, where controls were assigned a reference date and a laterality for “fictive tumor” corresponding to their matched case (*Pettersson 2014*).

No significant risk changes in relation to cell phone use were found in the study on malignant brain tumors by *Spinelli (2010)*. Positive risk association, however, was reported for occupational computer exposure for  $\leq 4\text{h/day}$ . The lower risk reported for residing near cell phone towers was speculatively attributed by the authors to possible lack of EMF on the lower part of the base stations (BS), or to lower emissions from cell phones due to better connections in the surrounding areas.

## 2. *Studies Reporting Evidence on Possible Tumor Risk Modification in Relation to Tumor Types and/or Cell Phone Usage Practices.*

Tumor risk increases in relation to use of cell phones were extensively reported by *Hardell and Carlberg (2008-2017, Sweden)*. A recent ecological trend analysis by this group suggested an increase in thyroid cancer incidence concordant to mobile phone use (*Carlberg 2016*). Increasing rates of brain tumors of unknown type (with joinpoint 2007) were speculatively attributed to the glioma risk increase due to use of cell phones (*Hardell and Carlberg 2015*). As a further speculation, the increased brain tumor risk among users with the first use of a cell phone before the age of 20 was suggested as possible explanation for the increasing rates (2007–2015) of unknown type CNS tumors that were shown to be specifically elevated in the age group of 20–39y (*Hardell and Carlberg 2017*).

However, possible risk increases in relation to use of cell phones were also suggested in other ecological trend analyses based on non-Swedish populations. The UK-based study by *de Vocht (2016)* showed a faster than expected incidence increase for malignant neoplasms of the temporal lobe. The Israel-based study by *Barchana (2012)* found an increasing trend in the period after mobile phone introduction for high-grade gliomas (including glioblastoma multiforme), especially among females. Using worldwide GLOBOGAN 2008 data, *de Vocht (2013)* identified the rate of mobile/ cell communications subscriptions as a risk indicator for brain/nervous system cancer. Using data from cancer registries and GLOBOGAN 2012, *Neupane (2017)* identified positive associations between the mobile phone and personal computer densities and the elevated incidence of mortality in prostate cancer. According to the single available ecological trend analysis involving the US population (*Little 2012*), glioma incidence trends per US Surveillance, Epidemiology, and End Results (SEER) program did not confirm the risk increase

inferred from Swedish studies by *Hardell (2010)* but were consistent with the modest risk estimate derived from *INTERPHONE (2010)* study.

In addition to the aforementioned ecological trend analyses, evidence on possible tumor risk increases was found in numerous case-control and cohort studies, as presented below in the sections stratified by outcomes of interest.

### 3. Outcome of Interest – Brain Tumors (Glioma and Meningioma)

Combined analysis from case-control studies on brain tumors by *Hardell and Carlberg (Carlberg and Hardell 2009, 2014; Hardell 2010, 2011, 2013a,b)* showed increased hazards ratios (HR) for all gliomas with the latency >20 years (HR=1.7 [95% CI: 1.2; 2.3]) and astrocytoma grade IV (glioblastoma) with the latency >10 years (HR=1.3 [95% CI: 1.03; 1.7]). Highest HR of 2.3 [95% CI: 1.1; 4.7] was reported among individuals who started using mobile phones before the age of 20. Risk for malignant brain tumors was reported to vary, increasing with the latency<sup>13</sup> >1-5 years, decreasing in the next latency categories, and then increasing again with the latency >15- 20 years. Per analysis of deceased cases, risk for malignant brain tumors (mostly astrocytoma grade III-IV) was shown to increase with cumulative lifetime use ( $P_{\text{trend}}=0.02$ ). A borderline increased risk for meningioma (*Carlberg and Hardell 2015*) was found in the 4th quartile of cumulative phone use (>1,436 h).

Despite reporting the reduced overall risk as the main finding, *INTERPHONE (2010)* study found an increased risk for glioma and meningioma among ‘heavy’ mobile phone users with the latency of 1–4 (but not >4) years: OR=3.77 [95% CI: 1.25; 11.4] and OR=4.80 [95% CI: 1.49; 15.4], respectively. Note: some reported values in the ‘heavy’ use ( $\geq 1,640$ h) category, defined as the 10<sup>th</sup> decile of cumulative call time, were deemed “implausible” by the study authors.

The possibility for increased risks of glioma and meningioma (OR=2.89 [95% CI: 1.41; 5.93] and OR=2.57 [95% CI: 1.02; 6.44], respectively) among ‘heavy’ users ( $\geq 896$  h) was also supported in the CERENAT-based study by *Coureau (2014)*.

In the CEFALO-based study on children and adolescents (*Aydin 2011*) which did not find the overall risk increase for brain tumors, elevated risk was found among young individuals with >2.8 years of use (per operator-recorded data): OR = 2.15 [95% CI; 1.07; 4.29].

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<sup>13</sup> Latency is defined here and in other studies as a time period from first use of mobile phone to diagnosis of tumor.

In the large cohort study by *Frei (2011)* which found no indication of dose-response relations either by subscription years or by tumor location, a borderline increased risk for glioma was found among men with mobile phone use of 1-4 years: OR=1.20 [95% CI: 0.96; 1.22].

#### 4. Outcome of Interest – Acoustic Neuroma, or Vestibular Schwannoma.

The Swedish studies by *Hardell and Carlberg* showed a risk increase for acoustic neuroma among mobile and cordless phone users, especially with the latency >20 years (*Hardell and Carlberg 2009; Hardell 2013c*).

*INTERPHONE (2011)* study found an increased risk for acoustic neuroma in ‘heavy’ users ( $\geq 1640$  h) with the latency of 5 years: OR=2.79 [95% CI: 1.51; 5.16]. Note: some values reported in the ‘heavy’ use category were deemed implausible by the study authors.

Overall increasing risk trends for acoustic neuroma among mobile phone users with >5 min per call were found in the study by *Sato (2011)*. Substantial risk increases were reported among users with >20 min/day on average: OR=2.74 [95% CI: 1.18; 7.85] and OR=3.08 [95% CI: 1.47; 7.41] with the latencies for 1 year and 5 years, respectively.

The study on acoustic neuroma by *Pettersson (2014)* showed a risk increase among cordless phone users with higher cumulative use: OR=1.67 [95% CI: 1.13; 2.49]. Among histologically-confirmed cases, a risk increase was shown among users of analog phones for 5-9 (but not >10) years: OR=4.03 [95% CI: 1.07; 15.2].

The case-control study by *Moon (2014)* did not find evidence for increased incidence of acoustic neuroma in relation to mobile phone use; however, the case-case analysis from the same study found correlations between tumor volume and phone usage estimates (see below).

#### 5. Outcome of Interest – Parotid Gland Tumors.

In the study by *Sadetzki (2008)*, elevated risk for parotid gland tumors was associated with regular use of cell phones and high-exposure conditions. The risk elevation was confined mostly to rural areas, reaching a 2-fold increase among users with  $\geq 1,035$ h of cumulative call time: OR=1.96 [95% CI: 1.11; 3.44].

Increased likelihood of parotid gland tumors in relation to ‘heavy’ use of cell phones was reported by *Duan (2011)*. Risk for epithelial parotid gland malignancy was independently associated with 13 phone usage variables, with the greatest OR for the user category with >42,000 calls since first use: OR=15.36 [95% CI: 13.34; 17.38]. Possible risk increase was particularly

suggested for mucoepidermoid carcinoma with an average daily use of >2.5h: OR=31.25 [95% CI: 10.79; 90.45].

#### 6. *Outcome of Interest – Skin Cancers.*

In the large cohort study on skin cancers (*Poulsen 2013*), a borderline increase of adjusted incidence rate ratio: IRR=1.18 [95% CI: 0.98, 1.42] was reported for basal cell carcinoma among women with 5-9 years (but not 10-12y or >13y) of mobile phone subscription.

#### 7. *Outcome of Interest – Leukemia.*

Although the case-control study by *Cooke (2010)* did not find overall risk increase for leukemia, a borderline increased risk for acute myeloid leukemia was associated with  $\geq 15$  years of use of mobile phones: OR=2.08 [95% CI: 0.98; 4.39].

Possible risk modification due to certain usage practices was also suggested in the case-control study by *Kaufman (2009)* which found no clear overall association with use of cell phones. Increased risk for leukemia was found among subjects using Global System for Mobile communications (GSM): OR=2.1 [95% CI: 1.1; 4.1]. Risk increase in relation to cell phones was shown for myeloid leukemia (acute and chronic combined): OR=1.7 [95% CI: 1.0; 2.9]. Further, increased risks for combined myeloid leukemia and especially for acute myeloblastic leukemia (OR=4.3 [95%: 1.3; 15] and OR=5.5 [95% CI: 1.4; 21], respectively) were found among subjects whose work was affiliated with powerlines. Substantially elevated odds of having myeloid leukemia were found in cases when  $\geq 2$  putative etiological factors (*e.g.*, benzene, pesticides) were involved.

#### 8. *Putative Effect Modifier – Laterality of Tumor in Relation to Laterality of Phone Use.*

The Swedish studies by *Hardell and Carlberg (Carlberg and Hardell 2009, 2014; Hardell 2010, 2011, 2013a,b)* associated the highest risk for astrocytoma (a type of glioma) with the latency >10 years of ipsilateral use of mobile and cordless phones. The same authors (*Hardell and Carlberg 2009; Hardell 2013c*) also suggested the highest risk for acoustic neuroma among ipsilateral mobile phone users with >10 years of use.

A greater likelihood for ipsilateral vs. contralateral gliomas among regular users (OR=1.27 [95% CI: 1.19; 1.37]) was also reported in the *INTERPHONE (2010)* study.

In the case-case and case-specular analyses (*Larjavaara 2011*) where distances from actual and specular locations were compared using a hypothetical reference location assigned for each

tumor, a significant excess of gliomas was found on the self-reported side of use (this finding, however, was attributed by the authors to recall bias).

In the study by *Yoon (2015)* which did not find an overall risk increase, increased relative risks (RR) were reported for among regular users with the same laterality for glioma and phone use: RR=1.26 (P=0.05) and RR=1.43 (P=0.01) for all respondents and self-respondents, respectively.

In addition to intracranial tumors such as glioma and meningioma, laterality analysis was also performed for acoustic neuroma and parotid gland malignancies. *INTERPHONE (2011)* study found risk increases for ipsilateral tumors in 'heavy' users ( $\geq 1640$  h) with the latencies for 1 year and 5 years: OR=2.33 [95% CI: 1.23; 4.40] and OR=3.53 [95% CI: 1.59; 7.82], respectively.

In the study by *Sato (2011)*, a more frequent use of the affected ear was reported in all but one case (15/16) among 'persistent heavy' users (>20 min/day) with acoustic neuroma: OR=5.0 [95% CI: 1.3; 24.8].

In the study by *Sadetzki (2008)*, elevated risk of parotid gland tumors was found among regular – ipsilateral or bilateral – users with the latency of 5 (but not 10) years. The risk elevation was especially noticeable among ipsilateral users in the highest categories of cumulative number of calls and call time: OR=1.58 [95% CI: 1.11, 2.24] and OR=1.49 [95% CI: 1.05, 2.13], respectively.

#### 9. Putative Effect Modifiers – Location and Size of Tumors in Relation to Mobile Phone Use.

The Swedish studies by *Hardell and Carlberg (Carlberg and Hardell 2009, 2014; Hardell 2010, 2011, 2013a,b)* suggested increasing risk trends for brain tumors located in the temporal lobe or overlapping tumors in the temporal and adjacent lobes.

*INTERPHONE (2010)* study also reported higher likelihood of gliomas located in the temporal lobe, with the higher risk estimate among 'heavy' ( $\geq 1,640$ ) users: OR=1.87 [95% CI: 1.09; 3.22].

On the other hand, significantly increased risks for gliomas with locations *other than temporal/ frontal lobe* were shown in studies by *Coureau (2014)* and *Aydin (2011)*: OR=3.61 [95% CI: 1.00; 12.96] and OR=1.92 [95% CI; 1.07; 3.44], respectively. The cohort-based study on brain tumors by *Frei (2011)* reported increased risks for other/unspecified type tumors: OR=1.35 [95% CI: 1.05; 1.75], tumors in the cerebral ventricle: OR=2.58 [95% CI: 1.08; 6.15] as well as tumors in the occipital lobe among users for 1-4 years: OR=2.50 [95% CI: 1.18; 5.31].

The aforementioned analysis on the actual and specular tumor locations (*Larjavaara 2011*) did not show predominance of gliomas in the brain parts expected to have the highest RF fields.

In the study by *Moon (2014)* which did not find increased incidence for acoustic neuroma in relation to mobile phone use, the MRI-based case-case analysis showed a trend for larger tumors among regular users ( $p=0.001$ ), indicating correlation between tumor volume and cumulative hours of use ( $r^2=0.144$ ,  $p=0.002$ ).

#### 10. Evidence on Tumor Risk in Relation to Cell Phones from Studies Using RF Exposure Estimates Other Than Phone Usage Practices<sup>14</sup>.

In addition to the aforementioned studies using phone usage practices as the proxies for RF exposure, some studies assessed tumor-related outcomes based on the RF exposure estimates such as total cumulative specific energy (TCSE) and SAR.

No increased risk for brain tumors (glioma and meningioma) was found in the case-control study by *Takebayashi (2008)*, which included assessment of SAR-based spatial relationships between tumor location and intracranial RF distribution.

The TCSE-based analysis using INTERPHONE study components (*Cardis 2011*) showed an increased glioma risk ( $P_{\text{trend}}=0.01$ ), reaching OR=1.91 [95% CI: 1.05; 3.47] for the highest TCSE quintile category with mobile phone use for >7 years. The risk estimate was further increased for gliomas in the most exposed areas with >10 years of use: OR=2.80 [95% CI: 1.13; 6.94].

The INTERPHONE-based analysis using both SAR and TCSE (*Grell 2010*) showed an increased risk of observing a glioma within the shortest distance from preferred ear to gravity center of tumor (0-55 mm) with cumulative use  $\geq 200$  h: OR=4.06 [95% CI: 2.03; 11.6]. Overall, shorter distances were associated with larger tumors: OR=4.09 [95% CI: 1.90; 12.0].

In the SAR-based case-case analysis by *Hartikka (2009)*, a significant risk increase was shown for gliomas among *contralateral* (but not ipsilateral) mobile phone users: OR=4.93 [95% CI: 1.13; 21.5]. However, a risk change (OR=0.51 [95% CI: 0.27; 0.96]) based on the distance between handset and tumor midpoint among regular vs. non-regular users indicated that a distance increase by 1cm decreased the odds of glioblastoma by 49%.

In the study by *Dode (2011)*, which was conducted in the Brazilian region of Minas Gerais with a major concentration of cell phone transmitter antennas, SAR-based analysis of spatial

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<sup>14</sup> Evaluation of the evidence presented in this section is limited to epidemiological aspects only and it does not include the methodological validity of dosimetry assessments in the cited publications

correlation between BS clusters and corresponding mortality estimates (1996-2006) showed an increased risk of death by neoplasia (more details including the subsequent critical comments and authors' response can be found in the individual review of this publication in the section below).

In the population-based case-control study on RF exposure in relation to childhood neoplasms (*Li 2012*), annual summarized power (ASP, watt-year) was calculated for mobile phone BSs and annual power density (APD, watt-year/km<sup>2</sup>) of each township was computed as a ratio of the total ASP of all BSs in a township. As a result, typically encountered BS-emitted RF levels were found not to pose substantial childhood cancer risk. However, higher than median APD (168 watt-year/km<sup>2</sup>) was associated with borderline risk increases for all neoplasms and leukemia in particular: OR=1.13 [95% CI: 1.01; 1.28] and OR=1.23 [95% CI: 0.99; 1.52], respectively.

### C. Overall Limitations of Epidemiology Data.

As described in this section, despite the sizeable amount of retrieved and reviewed data, cross-cutting limitations that involved almost all manuscripts impacted the overall data interpretation and limited comprehensive conclusions on all possible aspects of RF-related tumor risk for humans.

#### 1. *Data Quality Affected by Limitations of RF Exposure Measurements.*

Epidemiologic evidence was mostly derived from observational studies that used phone usage practices as the proxy estimates for RF exposure. None of the available epidemiologic/clinical studies, including the ones that used SAR and TCSE based RF exposure measurements, attempted to estimate the entire accumulated RF dose from all possible EMFs in the individual environments of study subjects. The accuracy of indirect RF assessment per phone usage practices was further limited by use of self (or kin)-reported questionnaires that had varying definitions for measurables and that were mostly collected in the non-blind setting. In addition to possible inaccuracies in the RF exposure measurements based on phone usage patterns (which are not necessarily directly correlated), exposure misclassification was virtually unavoidable in ecological trend analyses (*de Vocht 2013; Neupane 2017*) or cohort studies (*Poulsen 2013*) that used mobile phone subscription data, without the means for further classification by actual phone usage practices at individual levels.

#### 2. *Strong Biases Affecting Data Analysis and Interpretation.*

Due to inevitable errors in the measurements of RF exposure, all studies were affected, to varying degrees, by the exposure classification bias. In addition to possible nondifferential bias with a systematic measurement error (similar between cases and controls), exposure misclassification, to an even greater extent, was likely caused by differential errors due to recall bias (*e.g.*, better memory of phone use among study cases vs. healthy controls) or ascertainment bias (*e.g.*, phone use information was influenced by tumor diagnosis). Recall bias is avoided in cohort studies as exposure is assessed prior to disease occurrence. Furthermore, the two available cohort studies, the million women study of Benson et al (2013) and the Danish cohort study of Schuz et al (2011) both failed to find an association between cell phone use and glioma or meningioma. Information on estimated RF exposure might have been also affected by mental status of interviewees with brain tumors or by hearing impairment in cases with acoustic neuroma (with the latter causing non-random variations in laterality analyses in particular). Many case-case studies were prone to selection and classification biases due to heterogeneity or limited availability of cases and/or controls, resulting in the study populations that were not fully

representative of cell phone use practices or tumor incidences. Some studies were also prone to possible assumption and interpretation biases due to their study designs based on uncertain postulations (e.g., hypothetical tumor location assigned for controls, or baseline risk estimates in ecological trend analyses). Exposure assessment is further limited by the fact that there is an absence of experimental evidence that can determine if frequency, duration, or intensity of exposure is the most important factor in potential cancer risk. The component of exposure that epidemiologists should target is unknown.

Even the most cited international studies such as *INTERPHONE (2010, 2011)* which collected individual phone usage data were affected by heavy multi-composite biases that resulted in the overall reduced tumor risk, undermining the validity of derived evidence. Although the *INTERPHONE* study authors rendered a genuine protective effect as implausible and referred to strong bias as the main explanation, their reports of reduced tumor likelihood (along with a number of elevated ORs) spurred widespread discussions, involving social and popular science media and resulting in some ungrounded statements such as “for most people cell phone use appeared to protect against brain tumors”<sup>15</sup>. On the contrary, increased risk trends that stemmed from multiple publications by the same group (*Hardell and Carlberg, 2009-2017, Sweden*) were likely affected by limitations of a single data source limited to one population.

### 3. *Lack of Evidence Based on the U.S. Population.*

The vast majority of reviewed studies, including multi-country studies (*INTERPHONE 2010, 2011; de Vocht 2013*), were conducted outside the US (mostly, in Europe), while very few studies assessed the risk of tumor in relation to mobile phone use based on the US population (*Inskip 2010; Han 2012; Little 2012*). There is compelling evidence from the Surveillance, Epidemiology and End Results (SEER) program, a highly regarded cancer registry, that the incidence of brain cancer has not increased over the last 20 years despite cell phones becoming nearly ubiquitous<sup>16</sup>.

It might also be noted here that the failure to detect a real increase in brain cancer rates is exceedingly unlikely because of the high specificity and sensitivity of the non-invasive diagnostic modalities of computerized tomography and magnetic resonance imaging.

Finally, it is worthy of note that there are currently no primary or secondary prevention efforts to reduce brain cancer incidence. There are no countervailing forces that would offset a potential increase in the rate of brain cancer from cell phone use. With the findings from these

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<sup>15</sup> <https://www.sciencenews.org/blog/science-public/interphone-study-finds-hints-brain-cancer-risk-heavy-cell-phone-users>

<sup>16</sup> <https://www.arpana.gov.au/news/new-arpana-study-finds-no-link-between-mobile-phone-use-and-brain-cancers>

three cited US studies mentioned in the Summary, “the very linear relationship between cell phone usage and brain tumor incidence” reported in an additional US study (Lehrer et al 2011) cannot be accepted as valid due the study’s flawed statistical assessment (for more details see Section V.D below).

#### 4. No Overall Risk Increase, with Some Evidence Pointing at Possible Subgroup Effects.

As discussed by the *INTERPHONE (2010, 2011)* authors, while systematic bias in these studies could result in spurious associations inflating certain risk estimates, the elevated ORs could also indicate small effects detectable only in subsets of the study population. The possibility of true risk elevations due to the small subgroup effects (rather than due to the falsely inflated risk estimates) appears even more plausible, when considering the presence of a strong bias that resulted in the overall reduced risk estimates in both *INTERPHONE* studies.

The possibility of subgroup effects was also indicated in studies other than *INTERPHONE 2010, 2011*. In most studies reporting no overall risk increase, the main conclusion was based on the absence of upward trends across all cumulative call time categories. However, the absence of a linear dose-dependent correlation does not exclude the possibility of an intricate risk modification, especially since the existing epidemiologic studies did not offer sufficient statistical power to detect relatively small – subgroup-based – effects. As hypothesized by *Deltour (2009)* and *de Vocht (2011)*, putative risk modification may be too small to be observed in the overall study population, as it may concern only certain individuals or tumor subtypes.

As examples indicating possible subgroup effects, some studies (*INTERPHONE 2010, 2011; Pettersson 2014; Sadetzki 2008; Benson 2013<sup>17</sup>*) reported risk increases among phone users with shorter vs. longer latencies. Some of these risk fluctuations might have been due to an earlier tumor detection in ‘heavy’ users, as was particularly suggested for acoustic neuroma (*Pettersson 2014*). However, risk increases in the intermediate latencies may also indicate earlier tumor development in the cases where a relatively short but intense RF exposure might have been sufficient for triggering tumorigenesis in more vulnerable subjects who were inherently predisposed to tumorigenesis due to various genetic and environmental reasons.

As referenced by *Sadetzki (2007)*, RF-EMF emissions from cell phones do not have enough energy to break chemical bonds or damage DNA and, therefore, are unlikely to initiate tumorigenesis. However, the lack of recognized direct genotoxicity or mutagenicity (as referenced

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<sup>17</sup> This reference refers to the increased risk for pituitary tumors and not for acoustic neuroma, as the latter finding was retracted in the subsequent publication (Benson 2014).

by *Takebayashi 2008* for RF-EMF exposure in the range of 800–1900 MHz and an SAR <2Wkg<sup>-1</sup>) does not preclude the possibilities for indirect tumor-modifying effects due to RF exposure. As suggested by *de Vocht (2011)*, rather than acting as a tumor-initiating factor, the RF exposure may act as a tumor promoter, whose effects may include inhibition of anti-tumor immune responses. Indicating possible tumor-promoting effects, the MRI-based analysis by *Moon (2014)* revealed positive correlation between ‘heavy’ RF exposure and the tumor size of acoustic neuromas. Although laterality analyses from different studies did not always confirm the tumor location coinciding with the preferred side of phone use, some studies (*Cardis 2011; Grell 2010; Hartikka 2009; INTERPHONE 2010, 2011; Sato 2011; Yoon 2015*) found the associations between tumor location and presumed RF exposure that indicated possible tumor-promoting effects. Further, the higher risk for myeloid vs. lymphoid leukemia found in some studies (*Cooke 2010; Kaufman 2009*) indicated possible RF-related risk modification which, similar to ionizing radiation, may involve the innate – myeloid cell related – immunity.

As suggested by *Sato (2011)*, possible subgroup effects raise the need for a biologically plausible explanation for reasons why exposure to RF-EMF may exert adverse effects only on a small fraction of ‘heavy’ users. Possible explanation, however, is compounded by a variety of genetic and/or other confounding factors that can underlie the RF-related risk modification. While comprehensive analysis of possible RF-related biological effects is beyond the scope of this analysis, the NIH/NCI-based study by *Rajaraman (2010)*<sup>18</sup> can be mentioned as a cursory reference on the existence of genetic risk factors for tumors such as glioma, meningioma and acoustic neuroma that are conventionally considered in the context of RFR-related risk. In addition to genetic factors, RFR-related confounding may involve behavioral and social patterns (*e.g.*, cognitive, sleep, eating, physical and emotional stress, exercise, *etc.*) that accompany use of mobile phones and other consumer sources of RFR exposure as well as environmental exposure to various unrelated to RFR carcinogens (*e.g.*, pesticides).

As summarized by *Corle (2012)*<sup>19</sup>, generation of decisive evidence on an association between cell phones and tumorigenesis has been very challenging due to the evolving nature of wireless technologies, the relative rarity and long induction periods in purported tumor types, and, the last but not the least, the varying likelihood of genetic tumor susceptibility among individual subjects. Due to these challenges, the risk assessment in some studies might have been affected by opposite risk trends: a higher tumor risk among the genetically (or otherwise) predisposed

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<sup>18</sup>Rajaraman P, Hutchinson A, Wichner S, Black PM, Fine HA, Loeffler JS, Selker RG, Shapiro WR, Rothman N, Linet MS, Inskip PD. DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma. *Neuro Oncol.* 2010 Jan;12(1):37-48. doi: 10.1093/neuonc/nop012

<sup>19</sup>Corle C, Makale M, Kesari S. Cell phones and glioma risk: a review of the evidence. *J Neurooncol.* 2012 Jan;106(1):1-13. doi: 10.1007/s11060-011-0663-9

individuals might have been counterbalanced by a comparatively reduced risk among other members of the same study population. As a general limitation that possibly skewed the overall RF-related risk assessment, the existing studies were likely to have a selection bias due to under-representation of susceptible individuals who are expected to be rare in the entire population and who, most likely, remain unidentified. In fact, some studies (*INTERPHONE 2010*; *Benson 2013-2014*) intentionally excluded subjects diagnosed with neurofibromatosis as potentially prone to acoustic neuroma.

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**D. Summary and Limitations of Individual Epidemiology Studies Reviewed.**

This section provides a summary of each of the studies reviewed and assessed followed by a description of limitations of the studies. The studies are listed in alphabetical order based on the author's name.

*The INTERPHONE Study Group (2010)* assessed brain tumor risk in relation to mobile phone use by conducting an interview-based study (2000-2004, 13 countries) incorporating cases with glioma and meningioma (2,708 and 2,409, respectively) and matched controls. In the case-control analysis, regular mobile phone users had reduced likelihood for both glioma and meningioma: OR=0.81 [95% CI: 0.70; 0.94] and OR=0.79 [95% CI: 0.68; 0.91], respectively. Similarly, ORs <1.0 were shown for all deciles of lifetime number of phone calls and nine deciles of cumulative call time. In the 10th decile of recalled cumulative call time (51,640 h), possible risk increase was shown for glioma: OR=1.40 [95% CI: 1.03; 1.89]; a similar trend for meningioma did not reach statistical significance. Notably, the excess risk for both glioma and meningioma (OR=3.77 [95% CI: 1.25; 11.4] and OR=4.80 [95% CI: 1.49; 15.4], respectively) was indicated in the highest call time category for those who started phone use 1–4 years (but not earlier) before the reference date. In the case-case analysis of the concordance between tumor side and preferred side of phone use, the likelihood of glioma was slightly elevated among regular users with the ipsilateral tumor location: OR=1.27 [95% CI: 1.19; 1.37]. In addition, the likelihood of gliomas located in the temporal lobe was shown to be greater among users with  $\geq 1,640$  h of cumulative call time: OR=1.87 [95% CI: 1.09; 3.22].

Limitations: Although this study represents one of the main available sources for evaluating brain tumor risk in relation to mobile phone use, overall validity of the results (including the main conclusion on no overall risk increase) is affected by a disproportionately high number of ORs <1, indicating a strong possibility of systematic bias (likely, due to different levels of participation as well as differential errors in reporting among users vs. non-users). With the possibility for genuine protective effect regarded as implausible, the authors referred to strong biases as the main explanation for the overall reduced tumor likelihood. With the study cases recruited mainly through clinics within the study area, selection bias could result of under-ascertainment due to

possible cases from non-participating clinics, or a failure to identify tumors that had been diagnosed but not treated (*e.g.*, due to their small size). Reporting and assessment of mobile phone use might have been affected by prodromal symptoms in subjects with brain tumor and/or by timing of interviews. The study results might have been also affected by methodology used for the imputation of missing data, or the assignment of the tumor location for controls. A finding of the increased glioma risk among users with highest cumulative call time was attributed by the authors to a recall bias, based on some ‘implausible’ values of reported use in this group. When compared with controls, glioma cases had a higher number of imputations for missing values as well as higher proportions of proxy respondents and subjects described as non-responsive or having poor memory. However, sensitivity analyses suggested that these differences alone cannot explain the results seen in the highest decile of cumulative call time. Thus, the main finding on reduced tumor risk along with a number of elevated ORs failed to produce conclusive evidence, prompting the need for plausible explanation of the observed effects and spurring further studies on the RF-related risk assessment.

*The INTERPHONE Study Group (2011)* assessed risk of acoustic neuroma (or vestibular schwannoma) in relation to mobile phone use by conducting an interview-based case-control study involving 13 countries and including 1,105 study cases and 2,145 matched controls. There was no indication of an overall risk rising with the increasing exposure measured by cumulative call time or number of calls. However, in the 10th decile ( $\geq 1640$  h) of cumulative call time, the risk was borderline increased with censoring at up to one year before the reference date and was further increased with censoring at 5 years: OR=1.32 [95% CI: 0.88; 1.97] and OR=2.79 [95% CI: 1.51; 5.16], respectively. In the tumor location analysis among regular users in the 10th decile of cumulative hours of use ( $\geq 1640$  h), the risk increase was indicated for ipsilateral (but not contralateral) use when censored at 1 year and 5 years: OR=2.33 [95% CI: 1.23; 4.40] and OR=3.53 [95% CI: 1.59; 7.82], respectively.

Limitations: Similar to the previously discussed INTERPHONE (2010) study on glioma and meningioma, causal interpretation in this study was similarly impaired by several aforementioned issues of major importance such as participation, selection, and reporting biases. Similar to INTERPHONE 2010, elevated ORs at the highest level of cumulative call time were regarded by the authors as a chance finding resulting from the reporting bias indicated by some ‘implausible’ values reported in this category. Since acoustic neuroma is a slowly growing tumor, the exposure interval since introduction of mobile phones might have been too short to observe an effect, if there is one. As a rare hereditary disorder associated with a high risk of acoustic neuroma, neurofibromatosis type II could represent an additional confounding concern specific for this and other studies on acoustic neuromas; however, a subanalysis excluding the diagnosed subjects (x10) did not alter the main results in this study.

*Aydin et al 2011* examined possible association between mobile phone use and brain tumors in children and adolescents aged 7-19 years, using an international (Denmark, Sweden, Norway, and Switzerland) case-control study (CEFALO, 2004-2008). Personal interviews on mobile phone use were conducted with both study cases (a total of 352 patients with astrocytoma – 46%, ependymoma – 6% or another glioma – 8.5%, primitive neuroectodermal tumors – 17.6%, other specified intracranial neoplasms – 15.1%, and unspecified intracranial neoplasms – 6.8%) and controls (646) randomly selected from registries and matched by age, sex, and geographic region. Per conditional logistic regression analysis, children using mobile phones for  $\leq 5$  years were not at increased risk compared to non-users: OR=1.26 [95% CI; 0.70; 2.28]. A slight trend for higher frequency of brain tumors among regular users of mobile phone vs. nonusers did not reach statistical significance: OR=1.36 [95% CI: 0.92; 2.02]. However, in the subset with available operator-recorded data on mobile phone use, users with the longest period since first subscription ( $>2.8$  years) showed a risk increase compared to controls: OR = 2.15 [95% CI; 1.07; 4.29],  $P < .001$ . The overall likelihood of brain tumors showed similar borderline increases among both ipsilateral and contralateral regular users. In the further tumor location analysis, no increased risk was shown for regular users with tumor locations in the expected higher exposure areas; however, a significant risk increase was shown for regular users with tumors located in the areas other than temporal/frontal lobes and cerebellum: OR=1.92 [95% CI; 1.07; 3.44]. In the analysis focused on tumor morphology, a borderline risk increase (OR=1.65 [95% CI: 0.93; 2.93]) was shown for regular users with tumors other than astrocytomas and other gliomas.

Limitations: Most mobile phone usage data were subject to recall bias, since they were reported by children and adolescents (or their parents) and were not based on the operator-recorded data. As a common limitation for population-based studies, this study was not statistically powered to detect small risk increases. Due to the study population limited to children and adolescents, amounts and durations of mobile phone use were relatively small. Interpretation of the results was complicated by the study cases including various brain tumors with different etiologies which, in case of a true effect, may have been differentially affected by mobile phone exposure.

In the authors' response to a commentary (*Söderqvist et al 2011*) that questioned the lack of causal association between mobile phone use and brain tumors (as reported in *Aydin et al 2011*, see above), *Aydin et al 2012* re-examined the results of CEFALO study per age-standardized incidence rates for brain/CNS tumors (NORDCAN). The relatively stable incidence rates in the age group of 5–19 years living in the Nordic Countries did not confer an elevated risk from use of cell phones that would correspond to the recent steep increase of their use by children and adolescents. However, the authors recommended further monitoring of childhood brain tumor incidence trends, referring to the possibility of risk increase associated with heavy mobile phone use, very early life exposure, and rare subtypes of brain tumors.

Limitations: This study was subject to the previously discussed limitations of CEFALO study (Aydin *et al* 2011). The main conclusion was also subject to limitations common for population based-studies which do not allow for identifying small-scale effects in certain subgroups.

*Balekouzou et al 2017* examined lifestyle and behavioral factors as possible risk factors for breast cancer among Central African women, using a case-control study on 174 histologically-confirmed breast cancer cases and 348 age-matched controls. A questionnaire regarding mobile phone use was limited to the habit to keep cell phones in their bras; per unconditional logistic regression analysis, the lack of this habit was associated with a reduced likelihood of breast cancer: OR=0.56 [95% CI: 0.35; 0.89].

Limitations: This relatively small study was not primarily aimed at the assessment of breast cancer risk in relation to mobile phone use; rather whether it was associated with the participant's habit of keeping their cell phones in their bras. A seemingly protective effect of non-habit to keep cell phones in bras might have been due to chance and/or confounding associated with some ethnic/ cultural factors.

*Barchana et al 2012* examined the incidence and tumor laterality of gliomas in Israeli population which was described as a population using mobile phone technologies very extensively. All glioma cases from the national cancer registry (1980-2009) were classified as low- or high-grade per their proliferative potentials. Analysis of tumor laterality in relation to mobile phone use was performed based on a questionnaire that was sent to randomly-selected adults ( $\geq 18$  years). When measured for 5-year intervals, incidences of low-grade gliomas (mostly, presented by astrocytomas) decreased from the period of 1980-1994 to the period of 1995-2009. From 1995 onward, a shift towards left-sided location was found for all gliomas (in both grade categories), especially among subjects aged 20-49 years ( $p=0.03$ ). This trend appeared contradictory to the survey results showing that 45% controls from the general population used a mobile phone only on the right side, compared to only 17% who used the phone (exclusively or mostly) on the left side. A significant decrease in *low-grade* gliomas in the 30-years period that coincided with a sharp increase of mobile phone use did not support the assumption of causal etiological association. However, in the period after mobile phone introduction (1994-2009) there was an increasing trend for *high-grade* gliomas including malignant glioblastoma multiforme, especially among females ( $p=0.01$ ).

Limitations: The study lacked individual information on mobile phone use among the study cases with glioma, as the self-reported questionnaires were available only for randomly-selected subjects who represented the comparator group. Since the study population was limited to a single ethnic group, the study results on the increase of high-grade gliomas coinciding with mobile phone introduction might have reflected possible genetic and ethnic/cultural confounding effects.

*Benson et al 2013* used a UK prospective cohort from the Million Women Study to examine possible relation between mobile phone use and incidence of intracranial CNS tumors and some other cancers among middle-aged women. Mobile phone use information was collected for the periods of 1999-2005 and 2009. In the corresponding 7-year period, 51,680 incident invasive cancers and 1,261 incident intracranial CNS tumors occurred. Based on adjusted RRs from Cox regression models, overall cancer risk among ever vs. never users of mobile phones was not increased when assessed for all intracranial CNS tumors, specified CNS tumor types, or non-CNS cancers at other (18) sites. No appreciable associations were found among long-term users (>10 years) compared to never users with regards to glioma or meningioma. Risk for acoustic neuroma was initially reported as elevated among the long-term users (RR=2.46 [95% CI: 1.07; 5.64]), but this finding was retracted in a subsequent publication by the same authors (see *Benson 2014* below). While the rapidly increasing prevalence of mobile phone use in the study cohort was consistent with the steep increase in mobile phone subscriptions in the UK from the early 1990s to 2003, little evidence was found to suggest a proportional increase in the incidence of acoustic neuroma. However, the RR for pituitary tumors was increased in short-term (<5 years) mobile phone users: RR=2.31 [95% CI: 1.31; 4.06], without a further risk increase with the increasing duration of use.

Limitations: Since individual information on mobile phone use was collected in a prospective cohort (*i.e.*, the Million Women Study), this study is considered to be less prone to the shortcomings of retrospective reporting on exposure (*e.g.*, recall bias). However, the survey on mobile phone use might have been still affected by participation and reporting biases. In a survey conducted between 1999 and 2005, only 65% of women recruited in 1996–2001 replied, and mobile phone use reported at baseline may have changed subsequently. Considering that brain tumor risk in general is associated with high socioeconomic status, the risk increase for acoustic neuroma might have particularly affected by confounding due to a higher proportion of Socioeconomic group (% in upper third) among ever vs. never users of mobile phone users (35.7% and 29.6%, respectively). Note: the study excluded 6 women who reported having neurofibromatosis which is known as possible cause of acoustic neuroma.

In the authors' response to a commentary (*de Vocht et al 2011*) that questioned possible risk elevation for acoustic neuroma among mobile phone users (as reported in *Benson et al 2013*, see above), *Benson et al 2014* re-examined their previously reported finding based on the updated follow-up data from 2011. As shown by the re-assessed RRs among users >10 years vs. never users, an association between long-term mobile phone use and acoustic neuroma was no longer significant: RR=1.17 (95% CI: 0.60; 2.27), with no trend for risk increase with duration of use (P=0.3). Note: this publication did not refer to a re-analysis of the previously reported findings on pituitary tumors.

Limitations: This commentary is subject to the limitations of the initial study (*Benson et al 2013*) discussed above.

*Cardis et al 2011* examined risk of brain tumors in relation to RF exposure estimates that were derived from the data on mobile phone usage from Australian, Canadian, French, Israeli, and New Zealand components of the INTERPHONE study. The study included subjects aged 30-59 years with glioma or meningioma (533 and 676, respectively; diagnosed between 2000 and 2004 and located by neuroradiologists) and corresponding controls (1762 and 1911, respectively) matched by age, sex, geographic region, and the assigned 'tumor location'. An algorithm was developed to estimate individual RF dose as cumulative specific energy absorbed at a given location in the brain for a given frequency band and communication system. Analysis of putative modifying factors included laterality of use, hands-free devices, network characteristics and, where appropriate, frequency of use in urban and rural settings. RF dose was based on multiple RF exposure determinants and was estimated as TCSE (J/kg) absorbed at the tumor's estimated center. Overall likelihood among cases ever having been a regular mobile phone user was not significantly changed either for glioma or meningioma. However, the likelihood for glioma was borderline increased among cases with the highest TCSE quintile: OR=1.35 [95% CI: 0.96; 1.90]. The likelihood further increased with the increasing TCSE in cases with >7 years of use before diagnosis ( $P_{\text{trend}}=0.01$ ), reaching OR=1.91 [95% CI: 1.05; 3.47] in the highest quintile. When compared with their counterparts located elsewhere in the brain, the likelihood of gliomas located in the most exposed areas of the brain was increased in cases with >10 years of mobile phone use: OR=2.80 [95% CI: 1.13; 6.94]. No increased likelihood was found for meningioma, despite some similar to glioma patterns.

Limitations: The study was potentially subject to the initial limitations of INTERPHONE study as discussed above as well as to additional selection bias since the study sample included only tumors assessed by neuroradiologists. Accuracy of the RF energy deposition might have been affected by reporting bias, especially in cases when a subject had no preference for laterality of use, or when it remained unknown. Although the study claimed improved ascertainment of RF exposure and no difference in accuracy between computer-based and neurologist-based assessments of the tumor's center, the developed algorithm and the study results were subject to considerable uncertainty and require replication before they can be considered as indication of a cause-effect relationship.

*Carlberg and Hardell 2014* examined survival of patients with glioblastoma multiforme in relation to use of mobile and cordless phones, using 1,678 glioma patients from their previous registry-based case-control studies (Sweden, 1997–2003 and 2007–2009). Cell phone use was assessed using mailed questionnaires. Based on the Cox proportional hazards model, use of cell

phones with the latency >20 years since first use was associated with increased HR for glioma: HR=1.7 [95% CI: 1.2; 2.3]. With the same latency, this association appeared to be stronger among cases with astrocytoma grade IV, or glioblastoma multiforme (n=926), with HRs reaching 2.0 [95% CI: 1.4; 2.9] and 3.4 [95% CI: 1.04; 11] for use of mobile phones and cordless phones, respectively. HR was highest for cases with first use of both mobile and cordless phones before the age of 20 years, with the HR for wireless phones reaching 2.3 [95% CI: 1.1; 4.7].

Limitations: In addition to recall bias which is common for retrospective studies and which may have affected the accuracy of phone usage details, the study was subject to other biases involving participation, reporting, selection (*e.g.*, exposed cases were younger than unexposed cases,  $p < 0.0001$ ) as well as interpretation (*e.g.*, an unlikely “protective” effect of cell phone use on survival in low-grade glioma). Putative differential survival effects in glioblastoma vs. low-grade glioma might have reflected a selection bias resulting in overrepresentation of high-grade gliomas in the study sample. The main finding of decreased survival among cases with high-grade gliomas may be due to unaccounted confounding factors rather than the alleged use of cell phones.

*Carlberg and Hardell 2015* examined risk of meningioma in relation to use of cell phones, by using their previous case-control studies (Sweden, 1997-2003 and 2007-2009) to perform a pooled analysis of 1,625 meningioma cases and 3,530 controls randomly selected from the Swedish Population Registry. No overall associations with use of mobile or cordless phones were found, per unconditional logistic regression analysis adjusted for sex, age, year of diagnosis, and socioeconomic index. However, in the fourth quartile of use (>1,436 h), a borderline increased likelihood was found for both mobile and cordless phones: OR=1.2 [95% CI: 0.9; 1.6] and OR=1.7 [95% CI: 1.3; 2.2], respectively. Similar trends indicating possible risk elevation were also shown for the highest decile (>3,358 h). No significant risk associations were found with regards to the longest latency time, ipsilateral use, or anatomical tumor location.

Limitations: In addition to conventional recall bias inherent for retrospective studies, this study might have been affected by selection bias due to exclusion of clinically-diagnosed cases with no histopathological confirmation. In addition, the study might have been affected by recall and classification biases which are typical for this type of studies and which might have resulted in misclassified exposure to mobile phones.

*Carlberg et al 2016* examined incidence of thyroid cancer (NORDCAN; Swedish Cancer Register, 1970–2013) in relation to some environmental factors including mobile phone use. An increasing incidence of thyroid cancer in Sweden and the Nordic countries was shown, with joinpoint regression analysis detecting different joinpoints for men and women and a common joinpoint in 2006. The incidence of thyroid cancer (mostly, papillary) increased during 2006–2013 in both women and men, with average annual percentage changes (APC) of +6.16 % [95 % CI: +3.94; +8.42 %] and +6.84 % [95 % CI: +3.69; +10.08 %], respectively. Comparison of the

incidences of thyroid cancer in Nordic countries in relation to the available information on mobile phone use (*i.e.*, total minutes of out-going mobile phone calls) for the same time period showed concordant increases, with a lag time for the thyroid cancer incidence.

Limitations: The study design did not permit assessment regarding causality and the study lacked individual information on tumor characteristics and mobile phone use. Use of data derived from the Swedish Cancer Register might have resulted in underreporting and selection bias due to the lack of histopathologically confirmed cancer diagnoses in all registry cases.

*Chapman et al 2016* examined putative association between brain cancer incidence and mobile phone use, using national cancer registration data (Australia). Age/sex-specific incidence rates were calculated among 19,858 males and 14,222 females diagnosed between 1982 and 2012; the derived rates were analyzed in conjunction with mobile phone usage from 1987 to 2012. Brain cancer incidence rates (20–84 years; per 100,000) were stable over 30 years in females, but slightly increased in males ( $p < 0.05$ ). Assuming a causal RR of 1.5 and a 10-year lag period, the expected incidence rates in 2012 were estimated as 11.7 [95% CI: 11; 12.4] and 7.7 [95% CI: 7.2; 8.3] for males and females, respectively. However, this assumption resulted in a much higher estimate for expected brain cancer cases in 2012 compared the observed cases (1,867 and 1,434 cases, respectively). Per the age-stratified analysis using modelled rates, significant increases in brain cancer incidence were observed only in the  $\geq 70$  years group (both sexes), with the increase starting in 1982, *i.e.*, before the introduction of mobile phones. Thus, the overall brain cancer incidence rates were considered unlikely to be related to mobile phone use; the observed partial increases were attributed to improved diagnostics due to introduction of new imaging technologies in the early 1980s.

Limitations: As conventional limitations for this type of studies, no data on individual mobile phone use and cancer-related outcomes were available. The results were subject to potential assumption bias due to the assumed RRs and lag period (*i.e.*, 1.5 in ever-users and 2.5 in 'heavy' users of mobile phone, with a 10-year lag period).

*Cooke et al 2010* examined risk of leukemia in relation to mobile phone use, using a case-control study (South-East England) involving 806 incident leukemia cases diagnosed between 2003 and 2009 at ages 18–59 years (acute myeloid leukemia – 449, acute lymphoblastic leukemia – 125, chronic myeloid leukemia – 154, hairy cell leukemia – 55, acute monocytic leukemia – 7, and other/mixed – 16) and 585 controls. Information on mobile phone use and other potential etiological variables was collected via interviews. Based on logistic regression analyses considering age, sex, ethnicity, area of residence, smoking, socioeconomic status as well as interview lag time, no significant association was found between overall mobile phone use and risk of leukemia: OR=1.06 [95% CI: 0.76, 1.46]. However, a borderline risk increase was found among subjects who

started using a phone  $\geq 15$  years ago: OR=1.87 [95% CI: 0.96; 3.63]. In the analysis stratified by leukemia type, there was a borderline risk increase for acute myeloid leukemia among subjects with the same latency: OR=2.08 [95% CI: 0.98; 4.39].

Limitations: The study results were likely affected by participation bias (only 50% of eligible cases participated in the study) and selection bias (controls were comprised of 585 non- blood relatives provided by 392 cases). Controls were not individually matched to cases, and the reference dates for controls were constructed by stratifying cases by half-year or whole-year interview lag times and then randomly allocating controls in each half-year interview period to lag time strata in the same proportions as the cases. As an indication of possible heterogeneity in the study sample, controls had less non-white and 55-59-year aged subjects, compared to cases. A possible recall bias with overestimated phone use in more distant time periods could contribute to the slightly increased trend in the highest category of cumulative hours of phone use.

*Corona et al 2012* examined risk factors associated with vestibular schwannoma, by conducting a case-control study (Brazil, 2006-2010) involving 44 cases and 104 controls. The study used a questionnaire which, among various potential risk factors, included exposure to non-ionizing radiation such as cell phone use and residing near a cell phone tower. While a history of chickenpox and exposure to  $>1$  cranial X-ray procedure were identified as potential risk factors, no significant risk changes were found regarding cell phone use (including laterality) or living near a cell phone tower.

Limitations: The study results, especially from stratified analyses, were undermined by the relatively small sample size. Since vestibular schwannoma is not a tumor type that must be reported in Brazil, the sample size was restricted by difficulties with locating potential study cases which was likely to cause selection bias. In addition, the study might have been affected by recall and classification biases which are typical for this type of studies and which might have been particularly caused by possible memory problems among study cases. The study results might have been also affected by the long latency period of vestibular schwannoma.

*Coureau et al 2014* analyzed possible association between mobile phone exposure and primary CNS tumors, using the multicenter population-based case-control CERENAT study (France, 2004–2006) on various potential etiologic factors for CNS tumors in adults. A study sample consisted of a total of 1,339 subjects (253 cases and 504 controls for gliomas; 194 cases and 388 controls for meningiomas), with controls matched on age, sex, and place of residence. Information on mobile phone use was collected via face-to-face interviews. Per conditional logistic regression analysis, no significant risk associations were observed when comparing regular mobile phone users with non-users: OR=1.24 [95% CI: 0.86; 1.77] and OR=0.90 [95% CI: 0.61; 1.34] for gliomas and meningiomas, respectively. However, ‘heaviest’ users defined by life-long

duration ( $\geq 896$  h) were shown to have increased risks for both gliomas and meningiomas: OR=2.89 [95% CI: 1.41; 5.93] and OR=2.57 [95% CI: 1.02; 6.44], respectively. 'Heavy' use defined by cumulative number of calls ( $\geq 18\ 360$ ) was associated with increased risk for gliomas only: OR=2.10 [95% CI: 1.03; 4.31]. Elevated risk for gliomas (but not meningiomas) was further suggested for users in the last decile compared to non-regular users. With the latency of 5 years, the OR for gliomas reached 5.30 [95% CI: 2.12; 13.23]. The highest risk increase was shown for gliomas with locations other than temporal and frontal lobes: OR=3.61 [95% CI: 1.00; 12.96]. The risk of glioma was shown to triple with occupational use of mobile phones (OR=3.27 [95% CI: 1.45; 7.35]) and was increased even greater with exclusively urban setting (OR=8.20 [95% CI: 1.37; 49.07]). A positive risk trend for ipsilateral glioma tumors did not reach statistical significance: OR=2.11 [95% CI: 0.73; 6.08].

**Limitations:** The CERENAT study was not exclusively focused on mobile phone use. The study results might have been affected by participation bias (*e.g.*, the rate for controls was only 45%, reaching 66% and 75% for glioma and meningioma cases, respectively). As an indication of participation and selection biases, non-included cases were older than included, and the level of education was higher in controls than in cases ( $p < 0.001$ ). The delay between index date and interview was longer for controls. Due to health status of some cases, a number of interviews had to be conducted using a proxy and a simplified questionnaire. The quality of data was further affected by the identified recall bias regarding exposure. The study did not include histopathological and radiological assessment.

*Czerninski et al 2011* examined risk of parotid malignant tumors by analyzing data from the Israel National Cancer Registry (1970–2006). The annual incidence of salivary gland cancer was estimated as 0.8 cases per 100,000, with the most common subtype being salivary gland carcinoma (60%). The total number of parotid gland cancers increased 4-fold (with the steepest increase after 2001), whereas other major salivary gland cancers remained stable. After excluding population growth as an explanation of the increased incidence of parotid gland cancers, the authors speculated about possible role of cell phones, referring to a 6-fold increase in their usage in the Israeli population from 1997 to 2006.

**Limitations:** The study was methodologically weak: as the incidence analysis for parotid tumors had no corresponding data on estimated or actual mobile phone exposure.

*de Vocht et al 2011(a)* examined possible association between use of cell phones and parotid cancer by using publicly available data from the UK Office of National Statistics (1986–2008). Rates of malignant neoplasms of the parotid gland increased from 0.5 to 0.8 cases per 100,000 in men ( $P_{\text{trend}} < 0.01$ ) and from 0.4 to 0.6 per 100,000 in women ( $P_{\text{trend}} < 0.01$ ). The number of new cases in the period between 1986 and 2007 increased for both sexes, more than doubling

in men. Rates of malignant neoplasms of other and unspecified salivary glands remained stable in men and increased only slightly in women. Meanwhile, cell phone use in England has increased dramatically as shown by the number of subscribers increasing from 50,000 in 1985 to over 52 million in 2003. However, no causal association was inferred, since the rates of malignant parotid gland neoplasms started increasing before widespread use of cell phones.

Limitations: Reflecting typical limitations for ecological trend analyses, the study lacked data on individual mobile phone exposure among subjects with parotid tumors and lacked evidence inferring causal association.

*De Vocht 2016* analyzed the incidence of some brain cancer subtypes (England, 1985-2014) in comparison to counterfactual 'synthetic control' timeseries. Annual incidence of malignant glioma, glioblastoma multiforme, and malignant neoplasms of the temporal and parietal lobes were modelled based on population-level covariates, using Bayesian modeling and assuming 5-, 10- and 15-year latency periods. Hypothetical impact of mobile phone use was inferred from differences between measured and modelled time series. No increasing trends were found with regards to malignant glioma, glioblastoma multiforme, or malignant neoplasms of the parietal lobe. However, malignant neoplasms of the temporal lobe showed a faster than expected increase of 35% [95% CI: 9; 59] during 2005–2014, which was interpreted as an indication of possible association with the penetration of mobile phone technologies.

Limitations: The incident brain cancer cases were not linked to individual mobile phone use, and the study results may have been affected by methodological artefacts due to unconventional study design. As an example of possible reasons for assumption and interpretation bias, the inference about an effect relies on the assumption that the relationship between covariates and the incidence time series prior to the cut-off remains stable.

*de Vocht et al 2011(b)* examined rates of newly diagnosed brain cancer cases (per the UK's Office of National Statistics, 1998-2007) in relation to mobile phone use. No time trends were found in overall incidences of brain cancers in either sex- or age-stratified groups. Unlike decreased rates for cancers of the parietal lobe, cerebrum, and cerebellum in men, rates for cancers of the temporal lobe were increased in both men and women (0.04 and 0.02 new cases/year, respectively). However, no evidence connecting the incidence of brain cancer (1998-2007) to prior increase in use of mobile phones (1985-2003) was found. If caused by mobile phone use, the increase of cancers in the temporal lobe was estimated as <1 additional case per 100,000 people.

Limitations: The study did not examine trends pertaining to brain cancer subtypes, and the trend analysis on cancer incidence was not linked to corresponding data on mobile phone use.

*de Vocht et al 2013* examined environmental risk factors for cancers of the brain and nervous system, using national age-adjusted cancer incidence rates from the worldwide GLOBOCAN 2008 in conjunction with data from the United Nations Development Report and the World Bank list of development indicators. Cancer rates, potential confounders, and environmental risk factors were available for 165 countries. Based on multivariate regression models, the only exogenous risk factor consistently associated with higher cancer incidence was the penetration rate of mobile/ cell communications subscriptions.

Limitations: As in any listed ecological trend analyses, cancer cases were not linked to individual mobile phone use. The study's conclusion does not allow for casual inference as mobile phone use may have been a proxy for another, yet unknown, risk factors related to urbanization and development.

*Deltour et al 2012* investigated glioma incidence rates in the Nordic countries using 35,250 glioma cases (diagnosed between 1979 and 2008) and comparing the observed and expected incidence rates under various risk scenarios. Based on the joinpoint regression analysis of annual age-standardized incidence rates, APCs were estimated as 0.4% [95% CI: 0.1; 0.6] and 0.3% [95% CI: 0.1; 0.5] among men and women, respectively. Incidence rates increased slightly in older men (60–79 years) only. In simulations, assumed RRs were incompatible with the observed incidence time trends. Thus, no risk was shown to be associated with mobile phone use per adult glioma incidence trends (however, the induction period, if any, remained unknown).

Limitations: The study design was prone to assumption bias as simulation datasets were generated under the hypothesis that there is a risk related to mobile phone use and assuming various risk scenarios (eg, a 2-fold risk increase 10 years after first use of mobile phones). The real patterns may have been more complex than the simulated scenarios. In addition, simulation study was focused on 40–59-year-old men and did not account for other age and sex subgroups.

*Deltour et al 2009* examined time trends in the incidence of brain tumors (glioma and meningioma), using data from national cancer registries (Denmark, Finland, Norway, and Sweden; 1974–2003). During this period, 59,984 subjects aged 20–79 years were diagnosed with brain tumors in a population of 16 million adults. According to joinpoint regression models used to analyze annual incidence rates, the incidence rate of glioma increased by 0.5% [95% CI: 0.2; 0.8%] among men and by 0.2% [95% CI = -0.1; 0.5] among women and that of meningioma increased by 0.8% [95% CI: 0.4; 1.3] among men, and after the early 1990s, by 3.8% [95% CI = 3.2% to 4.4%] among women. Since brain tumor incidence rates were stable, decreased, or continued a gradual increase that started before the introduction of mobile phones, their use was suggested to have no observable effect on brain tumor incidence.

Limitations: As conventional study design limitation for similar ecological trend analyses, cancer incidence was not linked to the corresponding data on mobile phone use. The study might have been affected by selection bias due to possible incompleteness of cancer registration as well as by interpretation bias due to an unaccounted impact from improved diagnostics within the investigated time period.

*Ding and Wang 2011* examined time trends for brain and nervous system tumors (urban Shanghai, China, 1983-2007) by using joinpoint regression analysis of the observed and predicted annual incidence rates. The observed age-adjusted annual incidence rate of brain and nervous system tumors increased gradually by 1.2% [95% CI: 0.4; 1.9] among men and by 2.8% [95% CI: 2.1; 3.4] among women. The age-adjusted incidence of brain and nervous system tumors were estimated for 2020 as 7.4 and 10.9 per 100,000 person-years in men and women, respectively. Based on the analysis of observed and predicted trends, no association was found between cell phone use and risk of brain tumors.

Limitations: Similar to other ecological trend analyses, cancer incidence was not linked to corresponding data on mobile phone use. In addition, the study might have been affected by selection bias due to possible incompleteness of cancer registration as well as to interpretation and assumption biases (*e.g.*, the study did not account for improved diagnostics of brain tumors within the investigated time period).

*Dode et al 2011* tested a spatial correlation between BS clusters and cancer-related mortality (Belo Horizonte municipality, Minas Gerais state, Brazil, 1996-2006) by using ecological and epidemiological approaches and employing three data banks: 1) death by neoplasia documented by the Health Municipal Department, 2) BSs documented in ANATEL ('Telecommunications National Agency'), and 3) city population data from IBGE ('Brazilian Institute of Geography and Statistics'). Out of 856 BS installed through December 2006, 39.6% BS were placed in the Central-Southern region of the municipality. Within the area with the radius distance of 500m from BS, the mortality rate was estimated as 34.76 per 10,000 inhabitants, while outside of this area, there was a decrease in the number of deaths by neoplasia. The greatest accumulated incidence was 5.83 per 1000 in the Central-Southern region (compared to the lowest incidence of 2.05 per 1000 in the Barreiro region). Measurements for the largest and smallest accumulated electric fields were reported as 12.4 V/m and 0.4 V/m, respectively. Measurements for the largest and smallest density powers were 40.78  $\mu\text{W}/\text{cm}^2$  and 0.04  $\mu\text{W}/\text{cm}^2$ , respectively. Based on the RRs showing a decreased dose–response gradient with increasing distance from the

BSs, the authors proposed a spatial correlation between the cases of death by neoplasia and the BSs. Note: this publication resulted in the subsequent critical comments and authors' response)<sup>20</sup>.

Limitations: Due to study design limitations, the results could not have been extrapolated to individual cancer cases. The study might have been affected by the misclassification of exposure and interpretation biases due to possible errors in the secondary data entry and the lack of information on other putative ecological, genetic, and lifestyle factors. Further indicating possible selection/classification bias, neoplasia-related codes were limited to ICD-10, despite the study period (1996-2006) when ICD9 codes have been still in use. In addition, there was no information on actual exposure levels to RFEMF for individuals from the base stations, consideration of other sources of RFEMF, correction for age/demographic factors associated with different sectors in this city. Increased cancer deaths occurred within the first year of BS installation, inconsistent with the etiology of cancer development.

*Duan et al 2011* examined putative correlation between cell phone use and epithelial parotid gland malignancies by conducting a case-control study (Beijing, China) involving 136 study cases and 2,051 controls admitted to the same oral/maxillofacial surgery department between 1993 and 2010. Information on cell phone use and other demographic and lifestyle factors was obtained via personal or phone interviews. Per univariate analysis, frequency of cell phone use was associated with risk of epithelial parotid gland malignancies: OR=1.56 [95% CI: 1.08; 2.25]. Per multivariate analysis, risk for epithelial parotid gland malignancy was independently associated with 13 cell phone usage variables, with the greatest ORs for >42,000 calls since first use (OR=15.36 [95% CI: 13.34; 17.38]), use for >9-10 years (OR=7.70 [95% CI: 6.20; 9.20]), and average daily use for >2.5 h (OR=6.01 [95% CI: 1.47; 24.52]). Multivariate analysis also identified 12 cell phone usage variables that were independently associated with mucoepidermoid carcinoma, with the greatest ORs for use for 7-8 years (OR=19.63 [95% CI: 17.48; 21.78]), average daily use of at least 2.5 h (OR=12.73 [95% CI: 2.31; 70.22]), and 24,000- 42,000 total calls since first use (OR=11.85 [95% CI: 9.77; 13.93]). Per univariate analysis, risk of epithelial parotid gland malignancy was 1.7-fold greater for those who used cell phones bilaterally. However, no significant associations were found between tumor laterality and preferred side of use.

Limitations: Due to the study design, there was a possibility of recall bias and/or selection bias. The study results might have been specifically affected by lower participation rates among cases with epithelial parotid gland malignancies and mucoepidermoid carcinomas (62% and 47%,

<sup>20</sup> Foster, K. R., & Trottier, L. (2013). Comments on "Mortality by neoplasia and cellular telephone base stations in the Belo Horizonte municipality, Minas Gerais state, Brazil" by A. C. Dode et al. *Science of the Total Environment* 409 (2011) 3649–3665. *Science of The Total Environment*, 450-451, 366-368. doi: <https://doi.org/10.1016/j.scitotenv.2012.06.007>

Dode, A. C., Leão, M. M. D., & Tejo, F. d. A. F. (2013). Comments on "Foster KR, Trottier L, Comments on "Mortality by neoplasia and cellular telephone base stations in the Belo Horizonte municipality, Minas Gerais state, ..." *Sci Total Environ* (2012). *Science of The Total Environment*, 442, 553-556. doi: <https://doi.org/10.1016/j.scitotenv.2012.09.080>

respectively). Compared to other studies reporting possible risk increases, the ORs in this study appear to be inflated, pointing at possible ascertainment bias among the study cases.

*Elliott et al 2010* investigated the risk of early childhood cancers associated with mother's exposure to RF from macrocell mobile phone BS during pregnancy. A case-control study involved 1,397 cases of cancer diagnosed in children aged 0-4 years (per national cancer registry, Great Britain, 1999-2001) and 5,588 birth controls from national birth register, individually matched by sex and date of birth. Mean distance between the registered address at birth and a macrocell BS (per national database of 76,890 BS antennas, 1996-2001) was similar for cases and controls, as was total power output of BSs within the radius of 700m and modelled power density. No changes in cancer incidence were reported based on the modelled power density using address at birth and the exposure category, as shown by risk estimates close to unity (for all cancers, brain/CNS cancers, leukemia, and non-Hodgkin's lymphoma). However, addition of a quadratic term to the continuous exposure models showed a borderline significance ( $P=0.05$ ) for brain/CNS cancer.

Limitations: Due to the study design, the results might have been affected by assumption bias (*e.g.*, RF exposures from mobile phone BSs estimated at registered birth address were assumed to be representative of individual exposures during pregnancy) and misclassification bias (*e.g.*, information on other sources of RF exposure and personal measurements of individual exposures of the mothers were not available). In addition, the study did not address possible health effects from exposures to mobile phone BS after birth.

*Feltbower et al 2014* performed a pilot case-control study (Leeds and Manchester, UK) on putative etiological factors for brain tumors among children and young adults. The study involved 49 patients (aged 0-24 years) newly diagnosed with intracranial (described as neuroepithelial) tumors and 78 age/sex-matched controls drawn from general practice. Based on information collected from questionnaires, half of cases and two-thirds of controls reported using a mobile phone with the majority starting between 10-14 years of age.

Limitations: Due to the methodological weakness and study design limitations (*e.g.*, small study population, low response rates, incomprehensive information, *etc.*), no reasonable conclusions could be drawn as use of mobile phones was assessed by a single question: *Spoken on a mobile phone more than 20 times?*

*Frei et al 2011* conducted a nationwide cohort study (Denmark) to investigate the risk of CNS tumors among mobile phone subscribers. The study population included subjects aged  $\geq 30$  and born in Denmark after 1925, who were subdivided into subscribers and non-subscribers (before 1995). Information on CNS tumors was obtained from the Danish Cancer Register (10,729 cases, 1990-2007). Based on the sex-specific IRRs per log linear Poisson regression models (adjusted for age, calendar period, education, and disposable income), there was no indication of increased risk

for CNS tumors in the entire case cohort, or when restricted to subjects with longer mobile phone use ( $\geq 10$ -13 years). However, a borderline increased risk for glioma was found among men with the relatively short use of 1-4 years: OR=1.20 [95% CI: 0.96; 1.22]. No overall indication of dose-response relation was found either by subscription years or anatomical location of the tumor. However, the highest likelihood estimate was found for the cerebral ventricle location: OR=2.58 [95% CI: 1.08; 6.15]. A subgroup of users for 1-4 years showed a higher risk for occipital lobe tumors: OR=2.50 [95% CI: 1.18; 5.31]. Overall risk for “other and unspecified” tumor types was elevated among all users: OR=1.35 [95% CI: 1.05; 1.75], especially when restricted to  $\geq 10$  years of exposure: OR=1.44 [95% CI: 1.00; 2.06]. Borderline risk increases were found for entities described as “overlapping lesion of brain” and “brain, unspecified”, with the latter category showing the highest risk increase among subscribers for  $\geq 10$  years: OR=1.62 [95% CI: 1.00; 2.60].

Limitations: While use of data from cancer registry and other population-based sources minimized the participation and recall biases, the study was subject to potential exposure misclassification due to limitations of subscription data. Since dose-response analyses were based on the years after first subscription and not the actual patterns of mobile phone use, the results might have been affected by classification and interpretation biases.

*Gousias et al 2009* studied putative predisposing factors (including use of mobile phone) for cerebral glioma, by conducting a prospective case-control study on all patients diagnosed with gliomas in an area of the Northwest Greece (2005–2007). Information on mobile phone use and other factors was collected using a brief questionnaire. A total of 56 incident cases of glioma and glioblastoma were identified. Based on logistic regression analysis, no association was found between glioma and mobile phone use (minute-years) as independent variable.

Limitations: Since the study was focused on the area of Northwest Greece where incidence of gliomas is known to be significantly higher than in other populations, the results might have been affected by the presence of unidentified predisposing factors specific to the area. As pointed out by the authors, there might have been recording bias with underestimated cases from rural areas. Information on mobile phone use was scarce and subject to recall and misclassification biases.

*Grell et al 2010* examined the intracranial distribution of gliomas in relation to mobile phone use, by applying the 3-dimensional point process model for re-analyzing the INTERPHONE Study results on histologically-confirmed 792 glioma cases in regular mobile phone users (2000- 2004). Both SAR inside the tumor and TCSE absorbed for each tumor have been estimated and used as RF exposure measures. Re-analysis was based on an algorithm including call time, laterality of use, use of hands-free devices, frequency band, communication system, phone class, and network characteristics. A significant association was identified between the estimated intracranial RF distribution and the self-reported laterality of phone use, suggesting that more gliomas occurred

closer to the ear on the side of the head where the mobile phone was reported to have been used the most. The association was, however, independent of the cumulative call time and cumulative number of calls. The greatest estimated elevation in risk of observing a tumor within the shortest distance from preferred ear to gravity center of tumor (0-55 mm) was shown for mobile phone users with cumulative phone use for  $\geq 200$  hours: OR=4.06 [95% CI: 2.03; 11.6]; the shortest distance was also associated with the higher risk of larger tumor size ( $>18 \text{ cm}^3$ ): OR=4.09 [95% CI: 1.90; 12.0].

Limitations: The 3-dimensional point process model was based on the self-reported information on laterality of mobile phone use and therefore the results might have been affected by recall bias. Although the authors described this method (*i.e.*, the tumor localization data for each subject with a self-reported preferred side of phone use was “condensed” into a single point that was assumed to represent the origin of the tumor) as an alternative to conventional epidemiologic study designs, this approach may be subject to assumption and interpretation biases.

*Hallberg et al 2014* used publicly available records from the UK and Sweden to evaluate possible correlations between health parameters including cancer incidence in relation to the population density and other factors including FM-radio coverage. Based on Swedish data, the average output power from GSM mobile phones was shown to negatively correlate with the population density, unlike the density of FM towers which showed a positive correlation. In the Greater London (UK) which was shown to be covered by only one main FM transmitter, the total cancer incidence in 2002 was estimated as 79% of the average incidence in the UK measured as the crude rate, and 95% measured as an age-standardized rate.

Limitations: Due to the study’s methodological weaknesses, the collected data and provided interpretation were scientifically insufficient for drawing any reasonable conclusions regarding possible association between cancer risk and FM-radio coverage.

*Han et al 2012* evaluated putative risk factors (including use of cell phones) for vestibular schwannoma, by conducting a case-control study on 343 patients who underwent Gamma Knife surgery (1997-2007) and 343 age/sex-matched controls (Pennsylvania, USA). Based on the results of conditional multivariate logistic regression analysis adjusted for race, education, smoking, alcohol consumption, occupational exposure to noise, use of cell phones, and family history of cancer, the only factor associated with a higher risk of vestibular schwannoma was exposure to dental x-rays. Neither regular cell phone use (defined as  $\geq 1$  call per week for 6 months) nor use for  $>10$  years were found more frequently among cases with vestibular schwannoma: OR=0.95 [95% CI: 0.58; 1.58] and OR=1.29 [95% CI: 0.69; 2.43], respectively. No risk association was found between vestibular schwannoma and cordless phone use.

Limitations: Due to the lack of detailed information on use of cell/cordless phones, the study was subject to selection, recall, and misclassification biases. As detailed by the authors, the outpatient controls who had degenerative spinal disorders were not sufficiently representative of the general population (*e.g.*, a significantly greater proportion of controls had previous CT procedures). Selection bias might have been also due to other factors such as higher educational status and higher proportion of out-of-state residency among the study cases.

*Hardell and Carlberg 2009* reported the results from pooled analysis of their two previous case-control studies (Sweden, 1997, 2003) on the risk of brain tumors in relation to mobile/cordless phones. The malignant brain tumors (905) were divided into astrocytoma grade I-IV (663), oligodendroglioma (93), other/mixed glioma (78) and other types including medulloblastoma and ependymoma. The benign tumors (1,254) were divided into acoustic neuroma (243), meningioma (916) and other types (96). Per unconditional logistic regression analysis (adjusted for sex, age, socio-economic index, and year of diagnosis), use of cell phones was associated with astrocytoma grade I-IV and acoustic neuroma. Higher risk was especially suggested for subjects who started using cell phones before the age of 20 years. Highest astrocytoma risk for was reported for ipsilateral mobile phone use with the >10 years latency (OR=3.3 [95% CI: 2.0; 5.4]) as well as for cordless phone use (OR=5.0 [95% CI: 2.3; 11]). For acoustic neuroma, the highest likelihood was reported for ipsilateral mobile phone use with the >10 years latency (OR=3.0 [95% CI: 1.4; 6.2]).

Limitations: Due to the study design based on pooled analysis of the previous studies, the current results might have been affected by selection and classification biases. Use of cell phones was assessed by a self-administered questionnaire which might have been supplemented by phone calls; however, no further description of phone use details, or stratification of subjects per cumulative time were provided in the current publication. Controls were described as “the unexposed category [which] consisted of subjects that reported no use of mobile or cordless phones”. However, the accuracy of this description raises some questions about the numbers (which were not reported) of control subjects who never used cell phones while living in a European country with widespread use of wireless technologies by the time of the study. Recall and classification biases were further indicated by the 50% cut-off for laterality of use (*i.e.*, ipsilateral use was described per  $\geq 50\%$  and contralateral use per  $< 50\%$  of the calling time).

*Hardell and Carlberg 2013* used their previous case-control studies conducted in Sweden to analyze survival of patients with glioma in relation to use of cell phones. All cases (1,251) diagnosed with a malignant brain tumor (1997-2003) were included and followed from the date of diagnosis to the date of death or until May 30, 2012. The Cox proportional hazards model was used with adjustments for age, sex, year of diagnosis, socioeconomic code, and interview types;

the proportional hazards assumption was tested using Schoenfeld residuals. For glioma in general, use of wireless (mobile and cordless) phones was associated a slight increase reaching HR=1.2 [95% CI: 1.002; 1.5] with the >10-year latency ( $p_{\text{trend}}=0.02$ ). Opposite survival trends with regards to cell phone use were reported for low-grade and high-grade gliomas: astrocytoma grade I-II was associated with a decreased HR=0.5 [95% CI: 0.3; 0.9], while astrocytoma grade IV (glioblastoma) showed an increased HR=1.3 [95% CI: 1.03; 1.7] with the >10-year latency.

Limitations: Besides the inherent limitations of retrospective studies which may result in biases pertaining to sampling and classification, there might have been an additional bias due to possible differences from interviews with “living cases” vs. “next-of-kin”. The authors’ explanation of survival benefit for astrocytoma grade I-II due to the “RF-EMF exposure leading to tumor promotion and earlier detection and surgery with better prognosis” was not corroborated by the actual study results or supporting published evidence.

*Hardell and Carlberg 2015* analyzed the relevance of Swedish registry data as a source of information on possible associations between brain tumors and use of cell phones. Joinpoint regression analysis was used to analyze the incidence of brain tumors by comparing data from the Swedish National Inpatient Register and the Causes of Death Register to the Cancer Register data (1998–2013). Per the results of incidence-based analysis, the authors suggested possible underreporting to the Cancer Register (especially for brain/CNS tumors of unknown type). The joinpoint regression analysis results on unknown brain/CNS tumors (as numbers of patients or age-standardized death rates per 100,000 inhabitants) were plotted together with the mobile phone use estimates (as out-going mobile phone minutes in millions) for the same period (1999–2013). The increasing rates of brain tumors of unknown type (with joinpoint 2007) were suggested to be in accordance with the authors’ previously reported findings on possible increase of glioma risk due to use of cell phones.

Limitations: The referred results on glioma risk were subject to limitations pertaining to the authors’ previous retrospective studies (for more details, see other reviews on publications by Hardell and co-authors discussed in this report). In addition, the current study was mainly focused on the goals other than glioma risk due to use of mobile phones. The assumption that the authors’ previous findings on possible risk increase from mobile phone use support the increasing trends for unknown brain tumors is highly-speculative.

*Hardell and Carlberg 2017* followed their previously reported findings (*Hardell and Carlberg 2015*) by further analysis of the rates of brain tumors of unknown type (D43, 1998–2015) in relation to mobile phone use. An increased average APC of +2.06% [95% CI: +1.27; +2.86] was reported for both sexes combined. Joinpoint was found in 2007 with the afterwards APC (2007–2015) of +4.24% [95% CI: +2.87; +5.63]. Per APC-based analysis using data from both Swedish

Cancer Register and National Inpatient Register, the authors repeatedly concluded that brain tumor cases are underreported in the Swedish Cancer Register (the details are omitted as irrelevant to mobile phone use). The incidence analysis results were then juxtaposed to the results from the authors' previous case-control studies. The current analysis was limited to living subjects only: men and women aged 20–80 years (1997–2003) and 18–75 years (2007–2009) at the time of diagnosis. Population-based matched controls were ascertained from the Swedish Population Register. All cases had histopathologically confirmed gliomas (1,380), including astrocytoma grade I-II (221), astrocytoma grade III-IV (857), oligodendroglioma (162), and other/mixed glioma (140). Increased glioma risk was reported for ipsilateral users of mobile phones: OR=1.8 [95% CI: 1.4; 2.2], with the highest increase in the 18–39 years age group: OR=2.2 [95% CI: 1.2; 3.8]. Increased glioma risk was also reported for ipsilateral users of cordless phones: OR=1.7 [95% CI: 1.3; 2.1], with the highest risk in the same age group: OR=2.4 [95% CI: 1.3; 4.5]. As possible explanation for the increasing rates (2007–2015) of unknown CNS tumors (which were particularly elevated in the age group of 20–39 years at diagnosis), the authors referred to their current and previous findings on the higher risk for brain tumor in subjects with first use of a cell phone before the age of 20 years.

Limitations: The referred results on glioma risk are subject to limitations pertaining to the authors' previous retrospective studies (for more details, see other reviews of publications by Hardell and coauthors). In addition, the current study's conclusions on possible causal relationship are highly-speculative and are subject to the assumption and interpretation biases (*e.g.*, the authors presumed, with no supporting evidence, that if all MRI/CT-confirmed brain tumors had been reported, the frequency of diagnoses based on cytology/histology would have decreased in the register).

*Hardell et al 2010* investigated possible association between use of mobile/cordless phones and risk for malignant brain tumors, using deceased cases from their previously used cohort (Sweden). The study population was comprised of 346 cases (mostly astrocytoma grade III-IV) and 619 controls. Brain tumor cases (aged 20–80 years) were diagnosed during 1997–2003. The Death Registry was used to establish two control groups: controls who died from cancers other than brain tumor and controls who died from other diseases. Phone exposure was assessed by a questionnaire sent to the next-of-kin for both cases and controls. Unconditional logistic regression analysis was used with adjustments for sex, age, socioeconomic index, and year of diagnosis. Use of mobile phones was associated with an increased risk reaching the highest level in with the latency >10 years: OR=2.4 [95% CI: 1.4; 4.1]. The risk increase was associated with cumulative number of lifetime hours of mobile phone use ( $P_{\text{trend}}=0.02$ ), reaching the highest level in the >2,000 h group: OR=3.4 [95% CI: 1.6; 7.1]. Use for >2,000 h was associated with similar risk increases for users of analogue and digital phones: OR=5.1 [95% CI: 1.8; 14] and OR=3.4 [95% CI:

1.5; 8.1], respectively. Risk increases for mobile phone use in the high exposure group (>2,000 h) were shown in comparisons using both types of controls.

Limitations: According to the authors, the study design using deceased subjects was less subject to recall error; however, *post mortem* next-to-kin responses might have been still subject to recall and ascertainment biases due to behavioral differences in reporting about past cell phone exposures, especially for deceased cancer victims. Such biases might have particularly inflated the risk associated among the study cases with brain cancer. The results might have been also affected by participation bias: the responses were obtained for 75% cases, 74% cancer controls, and only 60% controls with other diseases. In addition, the study did not stratify risk based on malignant brain tumor types.

*Hardell et al 2011* examined possible association between use of mobile/cordless phones and malignant brain tumors, using pooled analysis of their two case-control studies (1997-2003). Unlike the previously reported results, this study combined data on both living and deceased cases which were stratified by tumor type (the remaining study design details can be found in reviews for *Hardell et al 2009 and 2010*). The current analysis was based on the interview replies obtained for 1,251 (85%) cases and 2,438 (84%) controls. Overall risk increase was reported in relation to latency periods and cumulative use for both mobile and cordless phones. Among tumor types, highest risk was found for astrocytoma (the most common type of glioma) with the >10 years latency: OR=2.7 [95% CI: 1.9; 3.7] and OR=1.8 [95% CI: 1.2; 2.9], for mobile and cordless phones respectively. The highest risk for astrocytoma was associated with first use of a cell phone before the age of 20: OR=4.9 [95% CI: 2.2; 11] and OR=3.9 [95% CI: 1.7; 8.7], for mobile and cordless phones, respectively.

Limitations: Due to the same study population, this study was subject to same limitations as previous studies by Hardell and Carlberg (as discussed in other reviews on the group's publications, 2009-2017). As a limitation specific for this study, inclusion of the deceased cases and controls (which was intended to increase the study sample) might have resulted in possible heterogeneity and biases affecting sampling and reporting. The results regarding the highest risk for subjects with first use at the <20 years of age were based on relatively low subject numbers (*i.e.*, <20-30 in each case/control subgroup stratified by cell phone type).

*Hardell et al 2013(a)* explored possible relationship between long-term (>10 years) use of cell phones and development of malignant brain tumors. The results were based on the group's previous case-control study (2007-2009, Sweden) which has been used in other publications; however, the current study was focused on malignant cases (593) and included all available controls (1,368), with meningioma cases (709) used as additional reference. Using information on use of cell phones from self-administered questionnaires, unconditional logistic regression

analysis was performed with adjustments for age, sex, year of diagnosis, and socioeconomic index. Use of analogue type phones was associated with a risk increase: OR=1.8 [95% CI: 1.04; 3.3], raising with the latency >25 years: OR=3.3 [95% CI: 1.6; 6.9]. Use of digital 2G mobile phones rendered a borderline likelihood: OR=1.6 [95% CI: 0.996; 2.7], increasing with the latency >15-20 years: OR=2.1 [95% CI: 1.2; 3.6]. Cordless phone use yielded an OR=1.7 [95% CI: 1.1; 2.9], which slightly increased with the latency of 15-20 years: OR=2.1 [95% CI: 1.2; 3.8]. Digital cell phones (2G and 3G mobile phones, cordless phones) showed increased risk trends with the latency >1-5 years, decreasing in the next latency groups and then increasing again with the latency >15-20 years. Overall, ipsilateral use of mobile and cordless phones showed higher ORs compared to contralateral use. Relatively higher ORs were also obtained for the temporal lobe tumors, or the overlapping brain tumors in temporal and adjacent lobes.

Limitations: Due to the study samples used, this study shared limitations with other studies by Hardell and Carlberg (as discussed in other reviews for the group's publications, 2009-2017). The study included specific limitations. For example, owing to unexplained administrative reasons, the 2008 data from one of the study's regions (Gothenburg) were unavailable and therefore were not included in the current analysis which was meant to summarize data from the 2007-2009 period. The study results might have been affected by the exclusion of deceased cases which constituted a substantial subgroup (n=520), mostly with astrocytoma grade IV, *i.e.*, glioblastoma multiforme. Histopathological reports were supplemented with records from pathology departments and then used "to classify all brain tumors based on WHO codes", indicating additional possibilities for selection and classification biases. Additional interpretation bias was indicated by the authors' statement that using meningioma cases as reference "gave somewhat higher ORs indicating that the results were unlikely to be explained by recall or observational bias". The study's conclusion that the "results are consistent with initiation carcinogenesis for analogue phones, and both initiation and promotion carcinogenesis for digital cell phones" reflected overinterpretation bias.

*Hardell et al 2013(b)* investigated possible associations between acoustic neuroma and use of mobile and cordless phones, by conducting pooled analysis of their two case-control studies on (1997-2003 and 2007-2009, Sweden). Population-based controls, matched on sex and age (within 5 years), were established using the Swedish Population Registry. Phone exposures were assessed by a self-administered questionnaire supplemented by a phone interview. The pooled results from both study periods were based on 316 histologically-confirmed cases of acoustic neuroma and 3,530 controls. Unconditional logistic regression analysis was performed with adjustments for age, sex, year of diagnosis, and socioeconomic index. Use of analogue phones was associated with an overall risk increase: OR=2.9 [95% CI: 2.0; 4.3], reaching OR=7.7 [95% CI: 2.8; 21] with the latency >20 years. An increased risk was also reported for users of cordless phone: OR=1.5 [95% CI: 1.1; 2.1], reaching OR=6.5 [95% CI: 1.7; 26] for the latency >20 years. Use of digital type cell phones

(2G and 3G mobile phones and cordless phones) resulted in the OR of 1.5 [95% CI: 1.1; 2.0], further increasing with the latency >20 years: OR=8.1 [95% CI: 2.0; 32]. For total cell phone use, the highest risk increase was shown for the longest latency >20 years: OR=4.4 [95% CI: 2.2; 9.0]. For all studied phone types except digital 3G, the ORs for ipsilateral vs. contralateral cell phone use were slightly higher. Tumor volume showed an increase per year of latency and per 100 h of cumulative use, which reached statistical significance for analogue phones only.

Limitations: There were only 73 cases described as “new”, and the results were based on a pooled analysis from two previously published studies (1997-2003 and 2007-2009). There might have been sampling bias due to some age and region related differences between the two study cohorts: subjects from the 1997-2003 study were 20-80 years old and were diagnosed “in parts of Sweden”; whereas subjects from the 2007-2009 study were 18-75 years old and were selected “throughout the country”. In addition to inherent recall bias in the questionnaire-based retrospective studies, this study might have been affected by the possibility of impaired hearing among the study cases with acoustic neuroma (who might have changed their phone use habits). Possible reporting bias was also indicated by the fact that in some cases, a self-administered questionnaire was supplemented by a phone interview (this bias, however, was ruled out by the authors since no differences were found “by comparing change of exposure in cases and controls after these interviews”). Some calculations in the long latency category were based on low numbers of exposed cases. The laterality of phone use was based on a cut-off of >50% of the time for one side, and therefore might not have reflected the true predominant side of phone use. The authors’ assumption that recall or observational biases can be ruled out since the results obtained with population-based controls were similar to those with meningioma cases as reference does not appear valid, as previously discussed.

*Hartikka et al 2009* assessed the glioma risk among users of mobile phones by conducting a case–case analysis (99 glioma cases, Finland) on distances between the tumor and the presumed location of the mobile phone (as the source of exposure). The tumor midpoint was defined from radiological imaging using GridMaster software designed for the INTERPHONE study. A higher proportion of gliomas among mobile phone users vs. non-users was observed within 4.6 cm from the presumed phone location (28% vs. 14%). Logistic regression analysis showed a significant risk increase among contralateral users: adjusted OR=4.93 [95% CI: 1.13; 21.5]. When a univariate logistic model was applied to the distance analysis on glioblastomas (38) versus other gliomas (61), a significant risk association for glioblastomas was shown for the distance between handset and tumor midpoint among regular users vs. non-regular users: OR=0.51 [95% CI: 0.27; 0.96], indicating that a distance increase by 1cm decreased the odds of glioblastoma by 49%.

Limitations: In addition to inherent possibilities for sampling and recall biases due to the questionnaire-based retrospective study design, possible selection bias was indicated by an

uneven distribution with regards to mobile phone use; most study cases were regular users, with only 22% of subjects described as never or non-regular users. Interpretation of the study results was limited by the small size and subsequent lack of stratification per histological tumor type.

*Hsu et al 2013* examined the incidence of and mortality from malignant brain tumors in relation to cell phone use. A population-based study (Taiwan) was carried out using nationwide data on cell phone users (National Communication Commission) and cancer cases (National Cancer Registry). A total of 4 incident cases and 4 deaths due to malignant brain neoplasms were reported for the 2000-2009 period which was characterized by 100% user rate of cell phone use. However no apparent correlation was found between the incidence and death rate due to malignant brain tumors and the annual numbers of cell phone users.

Limitations: Due to the weaknesses in study design and the small study sample, the results were subject to classification and interpretation biases. The latter was further indicated by the authors' statement urging "international agencies to publish only confirmatory reports with more applicable conclusions in public" [to] "help spare the general public from unnecessary confusion".

*Inskip et al 2010* examined temporal trends in the brain cancer incidence rates in relation to cell phone use in the US, using data from the SEER program. Among females aged 20–29 years, there was a significant increasing trend (1992-2006), mostly driven by the frontal lobe cancers. The respective increase of frontal lobe cancer rates among 20–29-year-old males began earlier (*i.e.*, before cell phone use was highly prevalent). The apparent temporal increase in overall brain cancer incidence was attributed to improved diagnosis, largely due to the introduction of CT scans in the 1970s and MRI scans in the 1980s. No rise in incidence was apparent for temporal lobe tumors, representing the part of the brain that was expected to be most heavily exposed to the radiation from cell phones. Overall SEER-based analysis did not support the association between brain cancer and use of cell phones.

Limitations: Trends in the incidence of benign intracranial tumors, such as meningioma and acoustic neuroma, have not been assessed, as SEER only recently began to systematically collect data for these tumors. Population-level analysis is not well suited for detecting minor effects. This 2010 study may not have captured the trends relating to long-term use and/or long induction, which may not have been detectable yet by incidence rates in the general population.

*Kaufman et al 2009* conducted a case-control study (Thailand, 1997-2003) to explore possible role of cell phone use and other factors in the etiology of adult-onset leukemia. The study population included a total of 180 cases, including acute myeloblastic leukemia (87), acute lymphoblastic leukemia (40), and chronic myelogenous leukemia (44) were compared with age/sex-matched hospital controls (756). In addition to demographics and medical history, information collected via interviews included EMF exposures (*e.g.*, residence near powerlines) and

cell phone use (e.g., frequency, duration, and length of calls). Unconditional logistic regression analysis did not find a clear association between leukemia and cell phone use. However, use of cell phones was more frequent among study cases compared to controls (19% and 14%, respectively), with multivariate OR reaching 1.5 [95% CI: 1.0; 2.4]. Use of cell phones was especially prevalent among cases with myeloid leukemia (acute and chronic) combined: OR=1.7 [95% CI: 1.0; 2.9]. Compared to controls, patients with leukemia used the following practices more frequently: initiated phone calls (7% vs. 3%), extended the antenna (6% vs. 4%) at least 75% of the time, and wore metal glasses (7% vs. 3%). When these three factors were combined into a single variable with “high risk” denoted by the presence of at least one of them, multivariate OR slightly increased, especially for myeloid leukemia. The risk was elevated for subjects using GSM service (OR=2.1 [95% CI: 1.1; 4.1]), especially for lymphoid leukemia. The odds were highest for GSM customers who used that service exclusively (OR=3.0 [95% CI: 1.4; 6.4]) or who were in the high-risk category (OR=3.0 [95% CI: 1.2; 7.0]); however, duration of GSM service or lifetime hours of use were similar among study cases and controls. Compared to controls, more subjects with combined myeloid leukemia and especially acute myeloblastic leukemia worked with or near powerlines: OR=4.3 [95%: 1.3; 15] and OR=5.5 [95% CI: 1.4;21], respectively.

Limitations: Cell phone use-related information from interviews was not validated by an objective source such as billing records. Durations of cell phone use were relatively short, limiting the risk assessment among long-term users. Despite a modestly higher prevalence of cell phone use among study cases (mostly confined to myeloid leukemia), there was no evidence that this trend was due to a more intense use of cell phones, as measured by duration of ownership, lifetime hours of use, or amount of use per year. Although the study indicated trends pertaining to usage practices that might have potentiated the RF emissions as well as showed the increased odds of developing leukemia among GSM users, these risk elevations were not related to amount of use, detracting from their credibility as an indication of increased risk.

*Kim et al 2015* used data from the New Zealand Cancer Registry to estimate incidence rates of primary brain cancer in relation to mobile phones. The study sample consisted of 4,212 cases diagnosed between 1995 and 2010. Of these, 3,684 tumors were gliomas (87%). Log-linear regression analysis did not reveal consistent increases in the incidence of brain tumors, including gliomas located in temporal/parietal lobe. However, a sex/age-stratified analysis revealed the increasing trend for all brain tumors among 30-49-year-old females, especially for the parietal/temporal gliomas (APC: 3.63 [95% CI: 1.21; 6.10]); males of the same age showed a non-significant decline. In the 70+ age group, an increasing trend in the incidence of glioma was seen mostly in males; in both sexes, the increase was not greater for temporal/parietal lobe glioma. Per the authors’ analysis, in case of the causal relationship, mobile phone exposure (which has been high in New Zealand since 2000) would have caused a detectable increase in risk for brain tumors with a latency of <10 years.

Limitations: The study lacked detailed information on mobile phone exposure and other risk factors as well as on possible effects due to improved diagnostics. Possibility of a small effect risk increase, especially with the latency of >10-15 years, could not be excluded.

*Lankola et al 2008* conducted an international (Denmark, Finland, Norway, Sweden, UK-Southeast England) case-control study of 1,209 meningioma cases and 3,299 population-based controls in relation to mobile phone use. Based on conditional logistic regression analysis, risk of meningioma among regular users was found to be lower compared to never or non-regular users: OR=0.76 [95% CI: 0.65; 0.89]. No other differences were found, except an apparent association with cumulative hours of use, which was attributed to a small number of extreme, likely erroneous, values.

Limitations: Mobile phone use and other exposures were based on self-reports and therefore prone to recall, reporting, and exposure misclassification biases. Participation rate especially among controls was low. The decreased risk among mobile phone users indicated a possibility of further bias due to their possibly greater willingness to participate, with the subsequently overestimated exposure and underestimated risk.

*Larjavaara et al 2011* analyzed location of gliomas in relation to mobile phone use using case- case and case-specular analyses. In the case-case analysis using unconditional logistic regression, tumor locations were compared in relation to presumed exposure levels. In the case-specular analysis using conditional logistic regression, distances from actual and specular locations to the handset were compared using a hypothetical reference location assigned for each glioma. The study included 888 glioma cases (collected from 7 European countries, 2000–2004), with tumor midpoints defined on a 3-dimensional grid based on radiologic images. In the case-case analysis, no excess risk for the highly exposed parts was found among regular users with the high intensity or duration of use. In the case-specular analysis, the mean distances between exposure source and location were similar for cases and speculars. Although glioma cases were found to be closer to the exposure line in long-term users, the differences remained nonsignificant. Analyses on digital vs. analog phones or histologic subgroups did not show substantially different results. Overall, gliomas in mobile phone users were not preferentially located in the parts of the brain expected to have the highest RF fields. A significant excess of gliomas on the self-reported side of use was attributed by the authors to recall bias.

Limitations: The main limitation was the relatively short time since first exposure: only 5% had used mobile phones for 10 or more years. As additional caveats, case-specular analysis ignored the side of use and classification of histologic subtypes of glioma was limited to 2 subgroups. Assessment of possible risk associations was impaired by the fact that both etiologic

factors and preferential locations may vary by the molecular subtypes of glioma which have not been investigated in this study. The applied novel approach utilizing tumor location in relation to the postulated distribution of RF field within the brain was considered by the authors advantageous compared to conventional assessment of RF exposure per phone usage patterns. However, the results based on the presented case-specular approach are subject to methodological uncertainty until replicated in another study.

*Lehrer et al 2011* examined brain tumor incidence based on the Statistical Report: Primary Brain Tumors from 19 US States (2000–2004) in relation to cell phone subscription data (2007). A significant correlation ( $r = 0.950$ ,  $P < 0.001$ ) was reported between numbers of cell phone subscriptions and brain tumors in the US states (19) with available registry data on brain tumors. Per multiple linear regression analysis using the number of brain tumors as a dependent variable and the estimates for cell phone subscriptions, population, mean family income, and mean age as independent variables, the effect of cell phone subscriptions was reported as significant ( $P = 0.017$ ) and independent of the effects associated with family income, population, and age. However, on the contrary to the authors' interpretation, the P-value reported for population ( $P = 0.003$ ) indicated a highly-significant effect of the population size, as demonstrated by a greatest difference between the less populated North and South Dakotas versus the largest states such as New York and Texas.

Limitations: Flawed statistical analysis and misinterpretation of the statistical significance for population growth undermine the study's conclusion on "the very linear relationship between cell phone usage and brain tumor incidence" which was erroneously described as "disturbing." In the comments by *Boniol et al (2011)*<sup>21</sup> the methodology in this study was described as "significantly flawed and the conclusions [as] impossible to accept based on this analysis".

*Leng and Zhang 2012* performed a population-based case-control study (China) aimed to identify potential risk factors of pituitary tumors. Interviews were used to collect medical history from 204 pituitary tumor cases and 246 controls aged 6-82 years. Among other factors, risk of pituitary tumors was associated with "mobile phone use" (OR=7.6 [95% CI: 2.6; 21.4]), including "duration of use" (OR=8.5 [95% CI: 2.8; 24.4]).

Limitations: Limitations reported by the authors were confined to the long latency time and the need for stratifying pituitary tumors which have not been addressed in this study. However, the study had major deficiencies in study design and methodology. The study's conclusion on possible association of mobile phone use with pituitary tumors was flawed by the lack of rigorous

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<sup>21</sup> Boniol M, Doré JF, Boyle P. Re. Lehrer S, Green S, Stock RG (2011) Association between number of cell phone contracts and brain tumor incidence in nineteen U.S. States. *J Neurooncol* 101:505-507. *J Neurooncol*. 2011 Nov;105(2):433-4; author reply: Lehrer, S. *J Neurooncol* (2011) 105: 435

statistical assessment and by poor definition of mobile phone-related usage patterns (no details were provided on actual usage and other characteristics such as “taking vitamins” and “spicy food.”

*Li et al 2012* conducted a population-based case–control study (Taiwan) on RF exposure in relation to childhood neoplasms. The study population was comprised of incident cases ( $n=2,606$ ) aged 15 years or less who were admitted (2003-2007) for different neoplasms, including 939 leukemias and 394 brain neoplasms. Non-neoplasm controls were randomly selected and matched on year of birth, with a case/control ratio of 1:30. ASP (watt-year) was calculated for each of 71,185 mobile phone BSs in service between 1998 and 2007. APD (watt-year/km<sup>2</sup>) of each township ( $n=367$ ) was computed as a ratio of the total ASP of all BS in a township. Exposure to RF was defined by the averaged APD within 5 years prior to the neoplasm diagnosis. After the adjustment made for calendar year, age, sex, high-voltage transmission line density, and urbanization of township, a higher than median averaged APD (168 watt-year/km<sup>2</sup>) was associated with an increased risk for all neoplasms: OR=1.13 [95% CI: 1.01; 1.28]; the adjusted OR for the highest tertile exposure, however, was not significantly elevated: OR=1.10 [95% CI: 0.90; 1.33]. A borderline risk increase was shown for leukemia, but not brain neoplasms: OR=1.23 [95% CI: 0.99; 1.52] and OR=1.14 [95% CI: 0.83; 1.55], respectively. Overall, typically encountered BS-emitted RF levels were considered not to pose substantial childhood cancer risk.

Limitations: Exclusive reliance on the claims data might have resulted in misclassification bias: while claims represented the study cases that were limited to already diagnosed in-patient population, the controls might contain subjects who have been mixed up with new onset or yet undiagnosed neoplasm. The study did not include use of personal dosimeters. Due to limited access to personal information, the study lacked details representing possible confounding factors (*e.g.*, socioeconomic status, pollutants, viral infection, *etc.*). However, the main source of bias was, most likely, misclassification of RF exposure due to co-existing (non-BS) sources (*e.g.*, radio and television broadcasting, wireless local area networks, *etc.*). The study did not distinguish between RF exposures from BSs vs. mobile phones which might have been used by older children. There might have been subject-to-exposure misclassification since exposure measures did not consider within-township variability. A proxy for individual RF exposure did not account for possible unusual distributions which may have provided possible explanation why the increased likelihood of all neoplasms was shown in dichotomous exposure categorization (*i.e.*,  $\geq 50\%$  vs.  $< 50\%$ ), but not in the tertile categorization (when the 1<sup>st</sup> tertile proportion was much greater than that of controls, leading to a reduced OR).

*Little et al 2012* compared observed and projected incidence rates of glioma in the US (1997-2008), using the 2010 INTERPHONE study and the 2011 Swedish study by Hardell and colleagues. US data from the SEER program yielded 24,813 non-Hispanic white subjects diagnosed with

glioma at age 18 years or older. Age-specific incidence rates of glioma remained constant ( $-0.02\%$  change per year, 95% CI:  $-0.28; 0.25$ ) within the 1992-2008 period which coincided with an increase in mobile phone use by the US population from close to 0% to almost 100%. Gliomas of the temporal lobe and other specified sites showed modest annual rate increases:  $0.73\%$  [95% CI:  $0.23; 1.23$ ] and  $0.79\%$  [95% CI:  $0.40; 1.19$ ], respectively. However, no significant acceleration in the rates of temporal or other gliomas ( $P=0.279$  and  $P=0.09$ , respectively) was detected when the rates before and after 1996 were compared. According to the authors, if mobile phone use was associated with glioma risk, the observed glioma incidence rates would have been higher. Per RRs by tumor latency and cumulative hours of phone use from the Swedish study, predicted rates should have been at least 40% higher than the US rates observed in 2008. The actual glioma incidence trends in the US population did not confirm the elevated glioma risk derived from one – Swedish – study which formed the basis of IARC's (International Agency for Research on Cancer) re-evaluation of mobile phone exposure. However, the US population data on glioma incidence were consistent with a modest excess risk suggested by the INTERPHONE study.

Limitations: The study results might have been affected by sampling bias. Data based on the SEER registries might not be representative of glioma rates and the ownership and use of mobile phones in the entire US population. Subscription data may have not been entirely accurate for estimating the proportion of mobile phone users and the age distribution of users might not have matched that of the SEER population. The study was subject to assumption bias, since a critical assumption in both statistical models was that the underlying cancer rates remained constant at the levels when mobile phone use was relatively modest (1992-1996). However, this assumption might not have been valid for endpoints such as low-grade tumors and those of poorly specified anatomical locations (their reduced rates in 1992-2008 might have indicated improvements in diagnosis). As in any population-based study, risks of glioma in small susceptible subgroups might not have been detectable by aggregate population-derived risk analyses. Delays in registration of glioma cases could have resulted in underestimation of the true rates. In addition, differences in estimated cumulative use from the Swedish and INTERPHONE studies could have affected the accuracy of predicted incidence changes.

*Moon et al 2014* examined possible association between mobile phone use and vestibular schwannomas using two – case-control and case-case – studies (South Korea). Study cases (119) with diagnosis confirmed after surgical tumor removal were matched with controls (238) who underwent comprehensive examination including brain MRI. Both cases and controls were interviewed using a questionnaire on mobile phone use. No significant differences between the two groups were found per duration, daily amount, and cumulative use hours. However, in the case–case study on MRI-based tumor characteristics, a significant correlation ( $r^2=0.144$ ,  $p=0.002$ ) was found between tumor volume and cumulative hours, with regular phone users having larger tumors, compared to non-regular users ( $8.10\pm 10.71\text{ cm}^3$  and  $2.71\pm 3.78\text{ cm}^3$ , respectively;

$p=0.001$ ). Tumor volume was similar among long-term and short-term users, but significantly larger in heavy vs. light users ( $11.32\pm 15.43\text{ cm}^3$  and  $4.88\pm 5.60\text{ cm}^3$ , respectively;  $P=0.026$ ), as defined per daily amount of mobile phone use. A similar correlation with cumulative hours ( $r^2=0.144$ ,  $P=0.002$ ) confirmed the larger volume trend in heavy vs. light users ( $13.31\pm 14.07\text{ cm}^3$  and  $4.88\pm 6.16\text{ cm}^3$ ;  $P=0.007$ ). An association between phone laterality and tumor side did not reach significance ( $P=0.148$ ). Local thermal effects which may promote growth of an already existing schwannoma were suggested as possible explanation for the presumed association between mobile phone use and tumor growth.

Limitations: Although the authors suggested that use of mobile phone could have been overestimated among controls, selection bias and/or recall bias might have affected the risk assessment in both study arms. Selection bias might distort the results if heavy users with ipsilateral mobile phone use were more likely to participate in the study. Bias might have also resulted from reclassification for the frequently used ear in cases where mobile phone use pattern was changed due to possible hearing loss on the lesion side. The study results might have been also affected by a higher frequency of systemic diseases among study cases vs. controls (18.4% and 8.8%, respectively;  $p=0.077$ ). As additional caveats, the study did not consider possible effects of age, cell phone type, residency, and other sources of RF exposure, and their possible impact on findings.

*Neupane et al 2017* examined the role of macroeconomic factors including mobile phone and personal computer density (per 1000 people) in prostate cancer incidence and mortality, using data (2003–2007) from the Cancer Incidence in Five Continents Vol. X (C15) monograph compiled by the IARC and GLOBOCAN 2012. Per unadjusted (bivariate) Poisson regression model, prostate cancer incidence was associated with both mobile phone and personal computer densities:  $RR=2.99$  [95 % CI: 2.99; 3.00] and  $RR=3.79$  [95 % CI: 3.79; 3.80], respectively. Use of multivariable-adjusted model reduced both associations, especially for mobile phone density:  $RR=1.07$  [95 % CI: 1.05; 1.08]. In unadjusted (but not in multivariate) model, both mobile phone and personal computer densities were associated with mortality due to prostate cancer:  $RR=2.45$  [95 % CI: 2.27; 2.65] and  $RR=1.59$  [95 % CI: 1.50; 1.68], respectively. Healthcare expenditure as the single most important predictor of prostate cancer incidence clearly indicated the role of effects (*e.g.*, early detection programs) other than mobile phone or computer use.

Limitations: Significance of the findings might have been affected by differences in lifestyle-related and other risk factors (*e.g.*, diet, exercise, obesity, ethnicity, genetic background, access to medications, *etc.*) which were not addressed in the study. Different time points for macroeconomic indicators (2000), incidence data (2003–2007), and mortality data (2012) may have resulted in possible disconnect between the incidence and mortality results. The choice of data sources was motivated by the emphasis on data quality and comparability, but it may have

limited generalizability of the results: a third of the study's observations were from European countries and other populations such as African countries were not included.

*Pettersson et al 2014* examined acoustic neuroma risk in relation to long-term mobile phone use by conducting a population-based case-control study (Sweden). The study included 451 cases (aged 20 to 69 years) diagnosed between 2002-2007 and 710 controls randomly selected from the registry and matched on age, sex, and residential area. Controls were assigned a reference date and a "fictive tumor" laterality corresponding to their matched case. Overall risk for acoustic neuroma did not increase with the increasing time of mobile phone use, but it was increased among users with the higher cumulative hours of cordless phone use: OR=1.67 [95% CI: 1.13; 2.49]. Among histologically-confirmed cases, there was a trend for higher risk among users of analog (but not digital) phones with the latency of 5-9 (but not >10) years: OR=4.03 [95% CI: 1.07; 15.2]. A borderline elevated risk (OR=1.69 [95% CI: 0.94; 3.05]) was shown for contralateral tumors among users with minimal cumulative use (<38 hours). According to the authors, use of mobile phones does not increase overall risk for acoustic neuroma, but it may increase the likelihood of its detection.

Limitations: Due to conventional limitations of retrospective study design, information on cell phone use might have been subject to recall and classification biases. Postal questionnaires were completed by only 65% of controls (compared to 83% of cases), further suggesting participation and selection biases.

*Poulsen et al 2013* examined possible association between mobile phone use and skin cancer, using a nationwide cohort study (Denmark) involving 355,701 mobile phone subscribers since 1987 to 1995 who were followed up through 2007. All cases of skin cancers diagnosed in the study population were obtained from the Danish Cancer Registry. IRRs were calculated for melanoma, basal cell carcinoma, and squamous cell carcinoma, using Poisson regression models adjusted for age, calendar period, educational level, and income. No evidence was found on overall risk increase for basal cell carcinoma, squamous cell carcinoma, or melanoma of the head and neck. However, the IRR ratio for the head/neck basal cell carcinoma relative to the torso/legs basal cell carcinoma for subscribers vs. nonsubscribers was slightly elevated among subscribers with the longest time since first subscription. Possible sex-dependent risk modification was indicated by borderline trends such as a slight risk increase (fully-adjusted IRR=1.18 [95% CI: 0.98, 1.42]) for basal cell carcinoma among women with 5-9 (but not >10-12) years of subscribing.

Limitations: The lack of details on mobile phone use prevented evaluation of potential risks among 'heavy' users. Possible misclassification of exposure might have occurred due to the lack of information on use of hands-free kits and cordless phones, or inability to distinguish between single and non-single subscriptions. Possible bias (although likely nondifferential) might have been

caused by the lack of histological characterization of skin tumors. As concluded by the authors, the lack of detailed information on the precise location of the skin tumors might have concealed small excess risks of skin cancers close to the exposed ear.

*Sadetzki et al 2008* conducted an Israel-wide case-control study which followed INTERPHONE-based methodology for evaluating possible association between cell phone use and risk of parotid gland tumors. The study population included incident cases (402 benign and 58 malignant) diagnosed between 2001 and 2003 in subjects aged  $\geq 18$  years as well as 1,266 individually matched controls. Based on overall analysis including 460 cases (58 malignant, 264 pleomorphic adenomas, 117 Warthin's tumors, and 21 others), no increased risk was found for any measure of exposure investigated. However, when restricted to regular users or to conditions that may yield high exposure (*e.g.*, 'heavy' use in rural areas), analysis showed consistently elevated risks. For ipsilateral use, elevated risk was found in the highest category of cumulative number of calls and of call time without use of hands-free devices: OR=1.58 [95% CI: 1.11, 2.24] and OR=1.49 [95% CI: 1.05, 2.13], respectively. The elevated risk of parotid tumors was found among ipsilateral or bilateral users with regular use for 5 (but not 10) years. The increased risk was confined mostly to rural areas, reaching a 2-fold increase among users with  $\geq 1,035$  hours of cumulative call time (with no hands-free devices): OR=1.96 [95% CI: 1.11; 3.44].

Limitations: Indicating potential selection bias, study participants tended to be younger than non- participants ( $P=0.003$ ), and a larger proportion of the recent Israeli immigrants could not be traced ( $P=0.001$ ). The proportion of smokers was higher among study cases vs. controls ( $P<0.001$ ). The response rate was influenced by time since immigration, and it was higher in males vs. females ( $P=0.06$ ) and Israeli born vs. non-Israeli born ( $P=0.01$ ) subjects. Since compliance was higher among cases compared to controls (87% and 65%, respectively), it might have resulted in self-selection and ascertainment biases, especially since the study was presented as a "cellular phone study." Possible differential recall bias might have resulted in cases being more likely to overestimate their use of cell phones and overreport their predominant side of use as the side where the tumor occurred. However, based on some findings (*e.g.*, nonparticipants who responded to the short telephone questionnaire reported a significantly lower rate of regular use than control participants), the authors suggested that in the presence of a real association, a differential non-compliance bias would likely diminish (rather than increase) risk estimates.

*Sato et al 2011* examined possible risk of acoustic neuroma in relation to mobile phone use in the case-case study (Japan) using a self-administered postal questionnaire. Out of a total of 1,589 cases of acoustic neuroma diagnosed between 2000 and 2006, only 787 (51%) subjects participated. Analysis was focused on possible associations between tumor location and laterality of mobile phone use. There were borderline increased risk trends for regular mobile phone use for 1 and 5 years before diagnosis: OR=1.08 [95% CI: 0.93; 1.28] and 1.14 [95% CI: 0.96;1.40],

respectively. A significantly increased risk was identified for mobile phone use for >20 min/day with the same latencies for 1 year and 5 years: OR=2.74 [95% CI: 1.18; 7.85] and OR=3.08 [95% CI: 1.47; 7.41], respectively. Similarly, the increased risk trends were observed for users with >5 min per call: OR=1.51 [95% CI: 0.95; 2.75] and OR=1.68 [95% CI: 1.0; 3.28] for 1 year and 5 years, respectively. Among 16 cases defined as “persistent heavy” users (>20 min/day for both reference points), all but one cases reported more frequent use of the affected ear: OR=5.0 [95% CI: 1.3; 24.8]. Indicating possible earlier detection, tumor diameter tended to be smaller in cases with ipsilateral vs. contralateral use; however, the difference was significant ( $P=0.033$ ) only among “heavy” users at 1 year before diagnosis.

Limitations: Although the participating hospitals (22) were from various parts of Japan, the study population might not have been representative of the overall country population. The possibility of biased sampling and participation was also indicated by the low response rate (51%). Only patients who were alive at the time of invitation were included and the data collection was limited to a self-administered postal questionnaire, further indicating possible selection and recall biases. As an additional caveat for sampling, the proportion of cases with histological diagnosis was only 44.7%. As a detection bias possibility, cases with ipsilateral vs. contralateral use might have been likely to be diagnosed earlier, since “heavy” mobile phone use on the affected ear could enhance the chance of the patient noticing slight hearing changes.

*Sato et al 2016* conducted a study aimed to examine whether there is an increase in incidence of malignant CNS neoplasms (1993-2010, Japan) among young people, and whether it could be explained by the increased mobile phone use in that population. An epidemiological survey (based on the nationwide Internet survey) allowed to register participants (7,550) and conduct surveys on mobile phone use. After performing joinpoint regression analysis of the incidence data per cancer registries, the expected incidence rate was calculated per the assumed RR of 1.4 for users with cumulative mobile phone use >1640 h. APCs were estimated as 3.9% [95% CI: 1.6; 6.3] for men in their 20s; 12.3% [95% CI: 3.3; 22.1] for women in their 20s; 2.7% [95% CI: 1.3; 4.1] for men in their 30s; and 3.0% [95% CI: 1.4; 4.7] for women in their 30s. Changes in incidence rates from 1993 to 2010 were 0.92 per 100,000 people for men in their 20s; 0.83 for women in their 20s; 0.89 for men in their 30s; and 0.74 for women in their 30s. Changes in expected incidence rates from the same time period were 0.08 per 100,000 people for men in their 20s; 0.03 for women in their 20s; 0.15 for men in their 30s; and 0.05 for women in their 30s. Due to inconsistent incidence patterns, the overall increase of malignant CNS neoplasms in Japan was considered not associated with heavy mobile phone use among the young population.

Limitations: In addition to conventional limitations of similar retrospective studies and ecological trend analyses, the study had three major limitations, as identified by the authors. First, national estimates of incidence rate were based on regional cancer registries (due to the lack of a

nationwide population-based registration system in Japan). Second, data on mobile phone use was obtained from a cohort based on a survey sent to schools throughout the country, but its patterns in the created cohort may have been different from those in the general population. Third, cumulative call time presented a rough trend which may not have not reflected actual mobile phone use accurately.

*Sato et al 2017* examined the ownership and patterns of mobile phone use among young Japanese patients (aged 6-18 years) who were diagnosed with brain tumors between 2006 and 2010. The target population consisted of 82 patients, who were divided into two groups: 16 patients who were mobile phone owners 1 year before diagnosis, and 66 patients who did not own mobile phones (non-owners). Analysis of the tumor location showed that supratentorial tumors (93.8%) were most common among mobile phone owners, while among non-owners, 59.1% were supratentorial and 37.9% were infratentorial ( $P=0.003$ ). Although among mobile phone owners, tumors tended to be localized to one side (left or right), the difference between lateral vs. central tumors was not significant ( $P=0.0791$ ). The expected number of mobile phone owners was calculated using the ownership rates from three general-population surveys; all three age-adjusted standardized ownership ratios were  $<1$ , with no significant differences as shown by 95% CIs crossing 1: 0.83 [95% CI: 0.56; 1.22], 0.51 [95% CI: 0.24; 1.04], and 0.75 [95% CI: 0.42; 1.32]. Thus, the prevalence of mobile phone ownership among the young Japanese patients with brain tumors did not differ from calculated estimates for the general population of corresponding age.

Limitations: As the main limitation, mobile phone subscription and the relatively small sample was not sufficient for an accurate assessment of RF exposure. In the absence of controls, comparisons were made based on the general population, which might have reduced the reliability of the study results. Possible bias was also indicated by mobile phone ownership rates which were somewhat different among the referenced populational surveys.

*Schoemaker and Swerdlow 2011* examined risk of pituitary adenomas in relation to cell phone use, by conducting a case-control study (2001-2005, Southeast England) involving 291 cases (aged 18–59 years) from neurosurgical/oncology hospitals and registries in the study region. Randomly-selected controls (630) were matched by age and residence. Information on cell phone use was collected by personal interviews. Tumor risk was not associated with regular cell phone use which was defined as having used it for at least 6 months during the period of  $>1$  year prior to diagnosis: adjusted OR= 0.9 [95% CI: 0.7; 1.3]. The risk was not appreciably increased after  $\geq 10$  years since first use, or after  $\geq 10$  years of cumulative use. Risk estimates were close to unity for users in the highest quartiles per cumulative number of calls and hours of use: OR=1.2 [95% CI: 0.7; 1.9] and OR=1.1 [95% CI: 0.7; 1.7], respectively.

Limitations: Exposure assessment was based on self-reported information and therefore was subject to measurement errors and misclassification and recall biases. Selection bias was indicated by low participation rates: only 43% of mailed controls and 63% of cases took part in the study, with a resultant disparity between cases and controls. As cell phone use might have been associated with greater affluence, the analyses were adjusted for Townsend deprivation score; however, there was still a possibility of residual confounding by socioeconomic status. There might have been also latent disease bias (especially due to the slow growth of pituitary gland tumors) which might have affected the patient's behavior including use of cell phone. Only 24 cases and 48 controls started using a cell phone between 10 and 17 years prior to the study, indicating the lack of long-term exposure.

*Schüz et al 2011* examined risk of vestibular schwannomas in relation to long-term mobile phone use, using two Danish nationwide cohort studies: 1) a study on all adult Danes who subscribed for a mobile phone in 1995 or earlier, and 2) a study on sociodemographic factors and cancer risk. Subjects from both cohorts were followed for occurrence of vestibular schwannoma up to 2006 inclusively. After creating a nationwide cohort by linking these 2 cohorts, each of the 2.88 million identified subjects was classified as either a long-term mobile phone user (defined by having the first subscription 11 years ago or longer), or comparator. The 11 years cutoff for longer-term exposure was based on the assumed slow development of vestibular schwannoma. A total of 806 subjects (404 men and 402 women) from the combined cohort were diagnosed with vestibular schwannoma. However, no cases of vestibular schwannoma were observed among long-term female subscribers and the subsequent analysis was focused on male subjects only. Long-term ( $\geq 11$  years) mobile phone subscription was not related to an increased risk for vestibular schwannoma in men. Overall comparison between long-term mobile phone subscribers vs. short-term subscribers or nonsubscribers did not differ with regards to tumor incidence, size, or laterality.

Limitations: As the major limitation, data on mobile phone subscription could not have been sufficient for an accurate assessment of RF exposure. Although the study was focused on the risk due to long-time use of mobile phones, the observation period of 10–15 years after the widespread introduction of mobile phones and the 11 years cut-off used in this study might have been still insufficient given the slow growth of vestibular schwannoma. In addition, the study was unable to address the risk among women or other subgroups of mobile phone users. As a result, the study was prone to a number of biases including misclassification of exposure and inadequate sampling (in addition to other conventional biases associated with this type of cohort studies).

*Shrestha et al 2015* examined risk for pituitary tumors in relation to mobile phone use, using the population-based case-control study (Finland) on 80 eligible cases identified from five university hospitals. Controls (240) were identified from the national population register and were

matched by age, sex, residence, and date of interview. Information on mobile phone use was obtained using a structured interview. Per conditional logistic regression analysis, regular mobile phone users had reduced likelihood (OR=0.39 [95% CI: 0.21; 0.72]) compared to never/non-regular users. The pituitary tumor risk was not increased with regards to duration (including >10 years), cumulative hours of use, or cumulative number of calls, or phone type (analog and digital).

Limitations: As the major caveat, a main finding of the reduced likelihood among regular mobile phone users most likely reflected methodological limitations such as selection and participation bias, especially among controls: Only 42% of invited controls vs. 77% of cases took part in the study and only a small proportion of the participants reported use beyond 10 years. As an additional source of exposure misclassification, only self-reported information on use of mobile phones was available.

*Söderqvist et al 2012* examined the risk of salivary gland tumors in relation to use of cell phones by conducting a case–control study (Sweden) involving 63 cases and 262 randomly-recruited controls. Per unconditional logistic regression analysis (adjusted for age at diagnosis, sex, year of diagnosis and socioeconomic index), use of cell phones was not associated with an increased risk of salivary gland tumors: OR=0.8 [95% CI: 0.4; 1.5]. No increased risk was shown in analyses on different phone types, or when cumulative use was divided into three groups (1–1000 h, 1001–2000 h and >2000 h).

Limitations: In addition to conventional recall bias, the study results might have been affected by the relatively small sample and exposure estimates limited to self-reported information on use of mobile phones. Little evidence was offered on the risk of parotid tumors in relation to more frequent and/or prolonged use (>10 years) of mobile phones.

*Spinelli et al 2010* examined possible role of some environmental factors, including cell phone use, in development of malignant primary brain tumors (mostly glioblastomas). A case-control study included all new cases (n=122) diagnosed in 2005 in the cancer centers of Provence-Alpes- Côte d’Azur region (France). Age-, sex-, and hospital-matched controls (n=122) were selected from neurosurgery departments of the same hospitals. Information on putative risk factors was collected using a questionnaire in face-to-face interviews with all subjects. Cell phone use was categorized by duration of the monthly subscription, years of use, and cumulative use (as number of hours of subscription per month multiplied by number of years of use). Collected information included the amount of time (hours per day) spent using a computer during leisure time and at work over the past five years. Exposure to radiation was assessed per questions about high- tension cables, cell phone towers, airports, and highways. Unconditional logistic regression analysis was performed with age and sex as covariates and other adjustments for potential confounders. Occupational computer exposure  $\leq 4$ h (but not  $>4$ h) per day was associated with the

elevated risk for brain cancer: OR=1.93 [95% CI: 1.03; 3.65]. Use of cell phone was not associated with significant risk changes; however, residing near cell phone towers was associated with lower risk: OR = 0.49 [95% CI: 0.26; 0.92]. The latter finding was speculatively explained by the lack of EMF on the lower part of the BSs and, alternatively, by the lower emissions from cell phones due to better connections in the areas near towers.

Limitations: As a major caveat, the study was not focused on exposure to mobile phones. Risk assessment might have been affected by the relatively small study sample. Conventional recall and reporting biases in retrospective studies might have been further exaggerated by neurological damage and/or potential memory loss among cases, or by greater likelihood for cases to remember their exposure. Controls were not representative of the general population, and the lack of blinding might have resulted in additional differences due to different interviewing styles between cases and controls. The study did not distinguish between analog and digital phones.

*Stang et al 2009* re-examined their previous report on increased risk of uveal melanoma among mobile phone users by conducting a case-control study involving 455 cases from the University of Duisburg-Essen (Germany) who were matched by 827 controls. A questionnaire was used to assess mobile phone use. Based on conditional logistic regression analysis, risk of uveal melanoma was not associated with regular mobile phone use, as shown by CIs crossing 1 in comparisons with population-based controls (OR=0.7 [95% CI: 0.5; 1.0]), ophthalmologist-based controls (OR=1.1 [95% CI: 0.6; 2.3]), and sibling controls (OR=1.2 [95% CI: 0.5; 2.6]). In addition, no trend associated with cumulative measures of exposure was observed. As a result, the current study did not corroborate the authors' previous conclusion (*Stang et al, Epidemiology 2001*) on increased risk of uveal melanoma among regular mobile phone users.

Limitations: In an attempt to reconcile the contradicting results from current and previous studies, the authors pointed out that the earlier study had only 118 case patients and used only a crude exposure assessment which was particularly restricted to the intensive regular exposure (*e.g.*, workplace) at a time when mobile phone technology was not very common. As a result, study cases might have differed from controls in ways that were not controlled in the previous analysis, given that they had unusual high-intensity exposure to mobile phones and radio sets in an era when such exposures were rare. The current study results might have been affected by selection bias, since regular mobile phone use was more prevalent among participating controls (45% in men and 25% in women) vs. nonparticipating controls (37% in men and 16% in women). However, when this potential influence was quantified using probabilistic bias with an error model for the selection bias among population controls, the putative selection bias could not account entirely for the reported null results.

*Stewart et al 2012* investigated an alleged cancer cluster in response to the residents' concern regarding the number of incident cancers (n=19) after the installation of a nearby mobile phone BS (Sandwell, West Midlands county, England). In an attempt to explore, whether the BS's proximity could have been responsible for these cancer cases, medical records of the local residents were collected and analyzed in juxtaposition to the ward-level cancer incidence and mortality data for over 43-year period. Standardized mortality ratios and incidence ratios were calculated by comparing the actual number of incident cases or deaths in the ward (Observed) to the expected number that would have been expected to occur (Expected) in the same ward if the age-specific rates for the West Midlands had applied to the population of the ward. Compared to West Midlands estimates (2001–2003), standardized mortality ratios for all malignant neoplasms (excluding non-melanoma skin cancers) were significantly higher in all study subjects (1.27 [95% CI: 1.06; 1.51]), especially in females (1.38 [95% CI: 1.08; 1.74]). However, standardized incidence ratios for different cancers among study cases showed more diverse trends when compared to West Midlands estimates. No single type of cancer was dominant, ten (10) cancer cases were registered after installation of the BS. There was evidence that lifestyle and family history factors could have contributed to some individual cases. Although the age range among the cancer cases was found to be younger than expected, the collection of cancers did not fulfil the criteria for a cancer cluster.

Limitations: Although the review of these incident cancer cases was not associated with the mobile phone BS, it was unlikely that information regarding a single BS could either demonstrate or exclude a causal association.

*Takebayashi et al 2008* examined risk of brain tumors in relation to mobile phone use, by using the case–control study (Japan) based on a novel approach for estimating SAR inside the tumor and considering spatial relationships between tumor localization and intracranial RF distribution. The study involved 322 patients (aged 30-69 years) who were diagnosed with different brain tumors (glioma - 88, meningioma - 132, and pituitary adenoma - 102) as well as 683 individually matched controls (with 4:1 ratio). Interviews to collect information on age, sex, mobile phone use, and lifestyle factors were carried out using a Japanese version of the computer-assisted system developed for INTERPHONE study. For regular phone users, two indices were used, *i.e.*, cumulative length of use and cumulative call time. All maximal SAR values were estimated as far lower than the level at which thermal effects may occur ( $0.1 \text{ Wkg}^{-1}$ ). With the reference date being at one year before diagnosis, the adjusted ORs for different tumor risks among regular mobile phone users were as follows: 1.22 [95% CI: 0.63; 2.37] for glioma, 0.70 [95% CI: 0.42; 1.16] for meningioma, and 0.90 [95% CI: 0.50; 1.61] for pituitary adenoma. No further risk increase was found with the reference date at 5 years. No overall risk increases were found in relation to SAR-derived exposure indices including the maximal SAR value inside the tumor tissue.

No differences were identified when maxSAR-derived indices were compared between actual and hypothetical opposite tumor locations.

Limitations: According to the authors' interpretation, recall bias (which is typical for this type of studies) could particularly affect risk assessment among the heavily exposed patients. Only cases with surgically removed tumors have been verified histologically. The participation rate of controls in the full study was only 51.2% (with the additional 28.8% of controls answering a brief survey about mobile phone use), which suggested possible reporting and selection biases.

*Yoon et al 2015* investigated possible association between mobile phone use and development of gliomas, by using data on 285 histologically-confirmed cases (aged 15-69 years) with gliomas diagnosed between 2002 and 2007 (South Korea). Individually matched controls (285) were characterized as healthy individuals from the same hospitals. Based on unconditional logistic regression analysis with non-users or non-regular users as reference, no significant relationship was found in relation to use of mobile phones including phone types, lifetime use, monthly service fee, and other exposure indices. However, in the Inskip method-based analysis on tumor laterality with respect to laterality of phone use, increased RRs for glioma were reported among regular users: RR=1.26 (P=0.05) and RR=1.43 (P=0.01), for all respondents and self-respondents, respectively.

Limitations: The study sample was derived using 9 regional hospitals and was not representative of the entire Korean population (as was implied by the publication's title). Controls were described as healthy individuals who, however, were having their medical check-ups in hospital setting, indicating the possibility of miscategorization of their health status. Sampling bias was also indicated by significant differences between cases and controls with regards to variables such as the area of residence, education level, hair coloring, alcohol drinking, and use of computers and electric blankets. The study excluded subjects aged 70 or older (due to "difficulty of deriving accurate responses"). As detailed by the authors, the study subjects aged 60 or older rarely used mobile phones, compared to younger subjects. In addition to inherent recall bias and self-reported selection/participation bias (*e.g.*, persons interested in mobile phone radiation might have been more likely to participate), possible reporting bias was indicated by significant differences in the respondent types described as Self and Proxy: 76.8% and 23.2% among cases, compared to 95.8% and 4.2% among controls, respectively (P<0.01). As further possibility for selection and interpretation biases, only patients who survived during the research period were included, and therefore the current findings might be reflective only of cases with mild glioma.

***E. Conclusions from Reviewed Epidemiological Studies.***

In summary, the epidemiological data published between January 1, 2008 to May 8, 2018, continue to support the FDA's findings that there is no quantifiable causal link between RFR exposure and tumor formation. The data suggest the need for shifting the focus from the general population with undetectable overall risk to a very small subset of people who might be inherently predisposed to the risk for tumorigenesis and who therefore might be more susceptible to putative risk modification by the intense RF-EMF exposure. The currently available epidemiologic studies lack evidence stratified by the inherent tumorigenesis risk. In addition, as stated in the NCI-issued fact sheet on cell phones<sup>22</sup>, direct measurements of RF exposure are not yet possible outside of a laboratory setting, which further prevents collection of an adequate RF-related evidence in epidemiological studies.

Further, existing epidemiologic evidence is insufficient to suggest that use of cell phones can be considered as an independent etiological factor capable of influencing the incidence of intracranial and some other tumors in the general population. Existing epidemiological evidence indicates that if any risk does exist, it is extremely low compared to both the natural incidence of the disease and known controllable risk factors. As further research is conducted, we will continue to monitor the available information.

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<sup>22</sup> <https://www.cancer.gov/about-cancer/causes-prevention/risk/radiation/cell-phones-fact-sheet>

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#### F. *In vivo* Articles Meeting Search Criteria.

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**G. In vivo Articles Not Meeting Search Criteria.**

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- a. Retracted
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