Expert Report
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1. Charge

Mobile or cellular phones, cellular towers and wi-fi base stations are sources of radiofrequency electromagnetic field (RF-EMF or simply RF) exposure to humans. This exposure falls predominantly in the range of 850 to 2500 megahertz (MHz). Epidemiological studies have suggested that exposure to RF is associated with an increased risk of brain tumors (glioma, acoustic neuroma) in humans. After evaluating the body of existing scientific research and literature including very recent studies, I have now developed the conclusions set forth in this report on whether it is feasible that RF exposure can cause specific brain tumors in humans.

2. Qualifications

I received an undergraduate degree in mathematics in 1977 from Nicholls State University and a Master's degree and Ph.D. in biostatistics from the University of North Carolina School of Public Health in 1979 and 1981 respectively. My Ph.D. thesis addressed the optimal way to design a two-year rodent carcinogenicity study to assess the ability of a chemical to cause cancer[1, 2]; the optimal dosing pattern from my thesis is still used by most researchers. My first employment following my doctoral degree was a joint appointment at the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) to conduct research on the design and analysis of experiments generally employed in toxicology. After 5 years with NIEHS/NTP, I developed my own research group which eventually became the Laboratory of Quantitative and Computational Biology and then the Laboratory of Computational Biology and Risk Assessment (LCBRA). One highlight during this period was the development of the Poly-3 Test for survival adjustment of data from two-year carcinogenicity studies in rodents [3, 4]; this test is used as the main method of analysis of these studies by the NTP and many others. We also did a complete analysis of the historical controls animals from the NTP studies [5, 6]. The LCBRA focused on the application of computational tools to identify chemicals that are toxic to humans, to develop tools for understanding the mechanisms underlying those toxicities and to quantify the risks to humans associated with these toxicities. The main toxicological focus of the LCBRA was cancer and my laboratory developed many methods for applying multistage models to animal cancer data and implemented the use of these models in several experimental settings [7-19]. In my last few years at the NIEHS/NTP, my research focus expanded to the development of tools for evaluating the response of complex experimental and human systems to chemicals [20-24] and the name of the laboratory shifted to Environmental Systems Biology.

Over my 32 years with the NIEHS/NTP, I was involved in numerous national priority issues that went beyond my individual research activities. After Congress asked NIEHS to work with the Vietnamese government to address the hazards associated with Agent Orange use during the Vietnamese War, I was given the responsibility of working with my counterparts in Vietnam to build a research program in this area [25]. Congress also tasked NIEHS with

developing a research program (EMF-RAPID) to address concerns about the risks to humans from exposure to extremely low frequency electric and magnetic fields (ELF-EMF) from power lines and to report back to Congress on what we found. I was in charge of evaluating all research developed under this program and was responsible for the final recommendations to Congress on this issue [26-28].

While at the NIEHS/NTP, I also had administrative positions that relate to my qualifications. From 2000 to 2006 I was the Director of the Environmental Toxicology Program (ETP) at NIEHS. The ETP included all of the toxicology research laboratories within the NIEHS Intramural Research Program. It was my responsibility to ensure the research being done was pertinent to the mission of the NIEHS, addressing high priority concerns about toxic substances and human health and that the NIEHS had adequate resources to complete this research.

During this time I was also Associate Director of the NTP, a position in which I was the scientific and administrative director of the NTP (The Director of the NTP was also the NIEHS Director and gave me complete autonomy in the management and science of the NTP). These two positions were historically always combined at the NIEHS and the NTP so that one person was in charge of all toxicological research at the NIEHS/NTP. The NTP is the world's largest toxicology program, routinely having 15 to 25 active two-year carcinogenicity studies, numerous genetic toxicology studies and many other toxicological studies being conducted at any given time. The NTP two-year carcinogenicity studies and their technical reports are also considered the "gold standard" of cancer studies due to their extreme high quality, their tremendous utility in evaluating human health hazards and the rigor and transparency they bring to the evaluation of the data. All data from NTP two-year cancer studies are publicly available including data on individual animals and images from the pathology review of each animal. The NTP is also home to the Report on Carcinogens, the US Department of Health and Human Services official list of what is known or reasonably anticipated to be carcinogenic to humans. It was my responsibility to decide what items eventually went onto this list while I was Associate Director of the NTP. In 2006, I became an Associate Director of the NIEHS, a senior advisor to the director and the director of the Office of Risk Assessment Research (ORAR). ORAR focused on stimulating new research areas on the evaluation of health risks from the environment and addressed major risk assessment issues on behalf of the NIEHS/NTP. For example, in this capacity, I lead a multiagency effort to understand the health risks to humans from climate change and to develop a research program in this area [29].

I left the NIEHS/NTP in 2010 to become the Director of the National Center for Environmental Health (NCEH) at the Centers for Disease Control and Prevention and simultaneously Director of the Agency for Toxic Substances and Disease Registry (ATSDR). NCEH does research and supports activities aimed at reducing the impact of environmental hazards on public health. One well-respected research effort of the NCEH is the National Biomonitoring Program. This program tests for the presence of hundreds of chemicals in human blood and urine in a national sample of people in the United States. ATSDR advices the Environmental Protection Agency (EPA) and communities on the potential health impacts from toxic waste dump sites (superfund sites). ATSDR is required by law to produce ToxProfiles. These are comprehensive reviews of the scientific literature for specific chemicals generally found at superfund sites. They also provide an assessment of the safety of these chemicals. As part of my activities at ATSDR, I began a modernization of the

ToxProfiles to use systematic review methods in their assessments; this effort was linked to a similar effort that I had helped to implement at the NIEHS/NTP.

Aside from my official duties in my various federal jobs, I also served on numerous national and international science advisory panels. Most notable, for my qualifications for this statement, are my serving as Chair from 2005 to 2010 of the Subcommittee on Toxics and Risk of the President's National Science and Technology Council, member and chair of EPA'S Science Advisory Panel from 1998 to 2003 (focused specifically on advising their pesticides program) and chair of the International Agency for Research on Cancer (IARC) advisory group that updated and improved its rules for reviewing scientific data to ensure that conclusions on the carcinogenicity of human exposures are the best possible (Preamble) [30]. As part of my work on science advisory panels, I have served on EPA's Science Advisory Board, as an advisor to the Australian Health Council on risk assessment methods, as an advisor to the Korean Food and Drug Administration on toxicological methods and served on several World Health Organization (WHO) International Program on Chemical Safety scientific panels dealing with risk assessment. Besides the guidelines for evaluating cancer hazards used by the IARC, I have either chaired or served as a member of scientific panels developing guidance documents for other organizations including the EPA.

I have received numerous awards, most notably the Outstanding Practitioner Award from the International Society for Risk Analysis and the Paper of the Year Award (twice) from the Society of Toxicology Risk Assessment Specialty Section. I am a fellow of the American Statistical Association, the International Statistical Institute, the World Innovation Foundation and the Ramazinni Institute. I have published over 250 peer-reviewed scientific papers, book chapters and technical documents on topics in toxicology and risk assessment.

Finally, I have served on numerous national and international committees tasked with evaluating the risk and/or hazard of specific environmental chemicals, including RF exposure. For example, I have contributed to risk assessments for EPA, the Food and Drug Administration, the Centers for Disease Control and Prevention, the National Institutes of Health, the WHO and IARC.

3. Explanation of Bradford Hill Causality Evaluation

Most of the guidelines [31-33] used for cancer risk assessment trace their origins to a paper by Hill (1965) [34]. The IARC review of RF [35] followed guidelines derived from Hill (1965) and concluded RF exposure was "possibly carcinogenic to humans".

The evaluation of whether RF exposure can cause brain tumors in humans requires the review and synthesis of scientific evidence from studies of human populations (epidemiology), animal cancer studies, and studies investigating the mechanisms through which chemicals cause cancer. Many different approaches[36, 37] are used to synthesize these three areas of science to answer the question "Does this chemical/agent cause cancer in humans?" In any of these three science areas, the quality of the individual studies has to be assessed and summarized to make certain the studies included in the overall assessment are done appropriately. Once the quality of the individual studies has been assessed, a judgment needs to be made concerning the degree to which the studies support a finding of cancer in humans. To do this, the EPA, IARC, the European Chemical Agency (EChA), the US Report on Carcinogens, and many others use guidelines [30, 31, 33, 38] that rely upon aspects of the criteria for causality developed by **Hill (1965)** [34].

Hill listed nine (9) aspects of epidemiological studies and the related science that one should consider in assessing causality. The presence or absence of any of these aspects is neither sufficient nor necessary for drawing inferences of causality. Instead, the nine aspects serve as means to answer the question of whether other explanations are more credible than a causal inference. As noted by Hill:

> *"None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question — is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"*

The nine aspects cited by Hill include consistency of the observed association, strength of the observed association, biological plausibility, biological gradient, temporal relationship of the observed association, specificity of the observed association, coherence, evidence from human experimentation and analogy. These are briefly described below.

An inference of causality is strengthened when several of the studies show a **consistent positive association** between cancer and the exposure. This addresses the key issue of replication of studies which is critical in most scientific debates. If studies are discordant, differences in study quality, potential confounding, potential bias and statistical power are considered to better understand that discordance.

An inference of causality is strengthened when the **strength of the observed association** in several studies are large and precise. These large, precise associations lessen the possibility that the observed associations are due to chance or bias. A small increase in risk of getting cancer does not preclude a causal inference since issues such as potency and exposure level may reduce the ability of a study to identify larger risks. Meta-analyses provide an objective evaluation of the strength of the observed association across several studies with modest risks to help clarify strength of the observed associations.

An inference of causality is strengthened when there is data supporting **biological plausibility** demonstrated through experimental evidence. Animal carcinogenicity studies, in which tumor incidence is evaluated in experimental animals exposed to RF, play a major role in establishing biological plausibility. There are numerous types of mechanisms that can lead to cancer [39], most of which can be demonstrated through experimental studies in animals, human cells, animal cells, and/or other experimental systems. Occasionally, occupational, accidental or unintended exposures to humans allow researchers to evaluate mechanisms using direct human evidence.

An inference of causality is strengthened when there is a **biological gradient** showing a reasonable pattern of changing risk with changes in exposure (e.g. risk increases with increasing exposure or with longer exposure). In many epidemiological studies, this aspect cannot be examined due to limitations in the study design or due to a lack of clarity in the presentation of the results. When a study does address an exposure-response relationship, failure to find a relationship can be due to a small range of exposures, insufficient sample size or a changing exposure magnitude over time that has not been accounted for.

An inference of causality is strengthened when there is a **temporal relationship** in which the exposure comes before the cancer. This aspect is necessary to show causality; if it is not

present, a causal inference is not plausible. Because the latency period for cancers can be long (years), evaluation of studies should consider whether the exposure occurred sufficiently long ago to be associated with cancer development.

An inference of causality is strengthened when the exposure is **specific** for a given cancer. This would mean that the disease endpoint being studied is only due to the cause being assessed or that, even though many different cancers have been studied for an association with a given exposure, only one type of cancer shows a consistent association for the exposure of interest.

An inference of causality is strengthened when other lines of experimental evidence are **coherent** with a causal interpretation of the association seen in the epidemiological evidence. To evaluate coherence, information from animal carcinogenicity studies, and mechanistic investigations would be considered.

An inference of causality is strengthened when there is **experimental evidence in humans** supporting a causal interpretation. Seldom is this type of information available when addressing the toxicity of environmental exposures. However, experiments in which an individual reduces or limits exposures and the risk of cancer is reduced would carry considerable weight in the evaluation (e.g. studies evaluating the cancer risks of people who stop cigarette smoking compared with continuing smoking have demonstrated reduced lung cancer risks). No such data are available for RF exposures.

Finally, an inference of causality is strengthened when there are other agents with **analogous** characteristics showing similar effects in humans and/or animals and/or showing similar biological impacts in mechanistic studies.

The most logical approach to developing an inference of causality is to step through each of the aspects of causality developed **by Hill (1965**) [34] and apply them to the available data for RF exposures. This is done after a review of the relevant literature from human epidemiology studies, animal cancer studies, and mechanistic studies.

4. Human Epidemiology

The evidence on an association between cellular phone use and the risk of glioma and/or acoustic neuroma in adults is strong.

4.1 Glioma

4.1.1 Studies in Adults

4.1.1.1 Case-Control Studies

Muscat et al. (2000) [40] conducted a case-control study of cancers of the brain in five academic medical centers in the US from 1994-1998. Cases consisted of 469 patients with brain cancers (mainly glioma patients) and 422 controls matched from the same medical center as the cases. They basically saw no increased odds ratios for brain tumors overall or any subtype with the exception of neuroepitheliomatous tumors (14 exposed cases) where they saw an odds-ratio of 2.1 (0.9-4.7). Only 35 patients had these tumors and 14 of these used cellular phones. (Note, these are tumors arising in the neuroepithelial cells which serve as somewhat pluripotent stem cells in the brain). This study has a small number of cases, exposures were low and for short duration, they were predominantly analog

exposures and many study participants had never used a cellular phone. (Table 1) (other related papers include [41-43]).

Inskip et al. (2001) [44] performed a case-control study of intracranial tumors of the nervous system (brain tumors) and cellular phone use from 1994-1998 from three hospitals in the United States (Boston Brigham and Women's Hospital, Phoenix St. Joseph's Hospital and Pittsburgh Western Pennsylvania Hospital). They had 782 cases (489 with glioma, 197 with meningioma, and 96 with acoustic neuroma) and 799 matching hospital controls. Controls were predominantly hospital admissions without tumors however there were some neoplastic controls (leukemia/lymphoma patients excluded). Regular use was defined as 2 calls per week. Usage of handheld cellular phones increased dramatically during the study (e.g. controls doubled usage from 1994 to 1998 from ~20% to ~40%). The cases were older than the controls. They saw no increases in any ORs for any analysis done in the study (use/no use, frequency of use, years of use, cumulative use, year of first use) or any linkage between predominant side of use and the side on which tumors appeared. The study was basically negative in all aspects. Like the previous study, exposures were low and for short duration, they were predominantly analog exposures and many study participants had never used a cellular phone. (Table 1, Table 2, Table 3, Table 4, Table 5, Table 6)

Auvinen et al. (2002) [45] conducted a case-control study of brain tumors in males and females aged 20-69 in 1996 from the Finish Cancer Registry. There were 398 brain tumors (198 gliomas, 129 meningiomas, and 72 other unspecified types) and 5 age- and sex-matched controls for each case. For gliomas, there were 172 cases (86% response) and 921 controls (93% response). Each subject in the study was linked to a list of all subscribers to mobile phone networks in Finland to determine exposure. The OR for gliomas and any mobile phone subscription was 1.5 (1.0-2.4) with increasing ORs for increasing years of subscription (1.2 (0.5-3.0) for <1 year, 1.6 (0.8-2.9) for 1-2 years and 1.7 (0.9-3.5) for ≥2 years, 1.2 (1.0-1.4) increase in OR per year). The increases seen for analog phones was larger than that seen for digital phones. The major strengths of this study are their linkage to cancer records and mobile phone subscription records. It was limited by its size, inability to look at subscriptions of greater than 2 years and inability to look at the frequency of phone usage. (Table 1, Table 2)

Gousias et al. (2009) [46] conducted a hospital-based case-control study for cerebral gliomas and various exposures. The study included 41 cases (persons referred to the Neurosurgery and Neurology departments of University Hospital of Ioannina and surrounding hospitals) and 82 controls (2 neurosurgery patients per case matched for age, gender and district of residence with cervical myelopathy or disk herniation). They used one measure for cell phone use; minute-years of exposure (undefined). Logistic regression gave an OR of 1.00 (0.99-1.01, p=0.56). All evaluations were adjusted for alcohol consumption, smoking and history of severe cranial trauma. This is a small study with limited statistical power. (Table 1, Table 2)

Spinelli et al. (2010) [47] conducted a hospital-based case-control study in France on malignant primary brain tumors and various exposures. The study included 122 cases (new cases between Jan. 2005 and Dec. 2005 in the public reference hospitals in Marseilles and St. Anne's Hospital in Toulon) and 122 controls (neurosurgery patients matched for age and gender with no cancer diagnosis). They evaluated cell phone use in hour-years (number of hours of subscription per month x number of years of use in categories). They show ORs of 0.86 (0.30-2.44) for less than 4 hour-years of exposure, 1.45 (0.75-2.80) for 4 to 36 hour-

years and 1.07 (0.41-2.82) for ≥36 hour-years of exposure. All evaluations were adjusted for sex and age. This is a small study with limited statistical power. (Table 1, Table 3)

The **INTERPHONE Study** (IS) [48] is a interview-based multi-center case-control study on the use of cellular phones and histologically-confirmed cases of glioma, meningioma or acoustic neuroma. The study had 16 study centers in 13 countries with a common protocol (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, and the U.K.). Participants were mostly between 30 and 59 years of age (differing a bit by country), lived in a major metropolitan region, and were recruited from candidates over a 2-4 year timeframe from 2000 to 2004. Population controls were randomly selected from population registries (part of Canada, Denmark, Finland, Germany, Italy, Norway and Sweden), electoral lists (Australia, part of Canada, France, New Zealand), patient lists (U.K.) or random-digit dialing (part of Canada, France, Japan). Controls were either individually matched to cases or frequency matched to cases on year of birth, sex and study region. Glioma and meningioma patients had one matched control and acoustic neuroma patients had 2 controls. All patients or their proxies were interviewed in person using a questionnaire. Some centers also included a few other tumors which will not be discussed here.

Numerous publications have resulted from this study for single countries [49-62], subsets of pooled countries [58, 63-66], and pooled analyses of the entire study [48, 67]. There were also numerous papers addressing methodological issues [68-75]. I will focus on the overall pooled results.

In the **IS (2010)** [48] study, the evaluation of the data is complicated, looking at four different ways to characterize exposure, three different types of referent populations, multiple sensitivity analyses and three different evaluations of tumor location relative to phone use. During the study period, the IS identified 3115 meningioma cases, 4301 glioma cases and 14354 controls. The IS eventually included 2708 glioma cases with 2972 matched controls and 2409 meningioma cases with 2662 matched controls resulting in participation rates of 64% (range 36-92%) among cases of glioma, 78% (56-92%) among meningioma cases and 53% (42-74%) among controls. Meningioma cases were predominantly female, glioma cases were predominantly male, mean age at diagnosis was 51 years for meningioma cases and 49 years for glioma cases and gliomas were diagnosed at a younger age than meningiomas.

The OR for meningiomas for regular users versus others was 0.79 (0.68-0.91) with four countries having individual ORs greater than 1. Breaking time since start of use into 4 categories yielded ORs below 1 for all categories (0.90, 0.77, 0.76, 0.83) and for cumulative number of calls with no hands-free device, divided into 10 categories, the ORs were also all below 1 with no obvious pattern (0.95, 0.62, 0.90, 0.80, 0.60, 0.81, 0.79, 0.92, 0.81, 0.80). Only for cumulative call time with no hands-free device was there a single OR>1 and only in the highest percentile of cumulative use with OR=1.15 (0.81-1.62) (0.90, 0.82, 0.69, 0.69, 0.75, 0.69, 0.71, 0.90, 0.76, 1.15). Digital phone users in the highest exposure category had a significant OR 1.84 (1.17-2.88) as did those who used both digital and analog phones OR=4.43 (1.42-13.9); analog-only phone users had an OR of 0.50 (0.25-0.99). When the data were divided into use 1-4 years before reference date (date of diagnosis), 5-9 years and ≥10 years, ORs in the highest quintile of cumulative use for the most recent groupings were greater that 1.0 (4.80 [1.49-15.4] for 1-4 years, 1.03 [0.65-1.65] for 5-9 years, 0.95 [0.56-1.63] for ≥10 years). The ORs for anatomical location were generally <1 for most analyses.

When analyzing for ipsilateral use or contralateral use independently, all ORs were <1.0. The ratio of ORs for ipsilateral use to contralateral use were always above 1 using any of the exposure metrics suggesting there was some degree of discernment in the results. A case-case analysis based on methods from **Inskip et al. (2001)** [44] showed an OR of 1.07 (1.00-1.16).

The OR for gliomas for regular users versus others was 0.81 (0.70-0.94) with three countries having individual ORs greater than 1. For time since start of use, ORs were below 1 for all categories (0.62, 0.84, 0.81, 0.98) and for cumulative number of calls with no hands-free device, the ORs were also all below 1 with a slightly increasing pattern (0.74, 0.71, 0.76, 0.90, 0.78, 0.83, 0.71, 0.93, 0.96, 0.96). For cumulative call time with no hands-free device two categories had ORs>1 and only in the highest tertile was it significant with OR=1.40 (1.03-1.89) (0.70, 0.71, 1.05, 0.74, 0.81, 0.73, 0.76, 0.82, 0.71, 1.40). Digital phone users in the highest exposure cumulative call time category had an increased OR 1.46 (0.98-2.17) as did those who used analog phones OR=1.95 (1.08-3.54). When the data were divided into use 1-4 years before reference date (date of diagnosis), 5-9 years and ≥10 years, ORs in the highest quintile of cumulative use for the most recent groupings were greater that 1.0 (3.77 [1.25-11.4] for 1-4 years, 1.28 [0.84-1.95] for 5-9 years, 1.34 [0.90-2.01] for ≥10 years). The ORs for anatomical location were generally <1 for most analyses except in the temporal lobe where the highest exposures in all three exposure measures were >1 (1.36 [0.88-2.11] for time since start of use, 1.87 [1.09-3.22] for cumulative call time, and 1.10 [0.65-1.85] for cumulative number of calls). When analyzing for ipsilateral use or contralateral use independently, all ORs were <1.0 except the highest exposures in all three exposure measures (1.21 [0.82-1.80] for time since start of use, 1.96 [1.22-3.16] for cumulative call time, and 1.51 [0.91-2.51] for cumulative number of calls). The ratio of ORs for ipsilateral use to contralateral use were all above 1 using any of the exposure metrics except for one category of time since first use suggesting there was some degree of discernment in the results. These ratios increased in an exposure-dependent fashion for cumulative number of calls. A case-case analysis based on methods from **Inskip et al. (2001)** [44] showed an OR of 1.27 (1.19-1.37) and was 1.55 (1.24-1.99) for the highest decile of cumulative call time.

An extensive sensitivity analysis on 13 separate factors did not substantively change the results for gliomas or meningiomas.

The reason for the low ORs seen in the various analyses could not be established. The authors examined sampling bias as a reason, arguing cases may have been missed and that controls may not have represented the study base, but concluded this was unlikely. Selection bias and participation bias may have contributed to the lower ORs, but they were unlikely to explain it all [48, 74]. When never regular users were excluded from the analysis and the lowest exposure category was used as the reference category (in an attempt to reduce participation bias), most of the ORs for gliomas increased above unity. Most notably, all three ORs for time since start of use became significant (1.7 [1.2-2.4] for 2-4 years, 1.5 [1.1-2.2] for 5-10 years, and 2.2 [1.4-3.3] for >10 years).

Some subjects reported very high cell phone use (>5h/day) and this was more common in glioma cases than controls. Truncating these at 5h/day had no effect on the resulting ORs. Thus, although there was some evidence of overestimation by heavy users [71], it is unlikely to have a large impact on the ORs.

The main strengths of the IS are the large sample size, the use of population-based controls and the extensive analyses performed on the data. One major limitation, as with most case-controls studies, is the use of a questionnaire for obtaining exposure information and the possibility of recall bias. Using a small sample of participants from three countries, the authors compared self-reported mobile-phone use with operator-recorded data and saw very little differential exposure misclassification. A second limitation was the low participation rate. There was some evidence that controls who regularly used mobile phones were more likely to participate than those who never used mobile phones; this could lead to a reduction in the ORs in the various exposure categories. The analyses using the lowest exposure category as the referent partially addressed this issue. (Table 1, Table 2, Table 3, Table 5, Table 6, Table 7)

In an effort to better refine the exposure in the IS, **Cardis et al. (2011)** [63] developed an estimate of the radio frequency (RF) dose as the amount of mobile phone RF energy absorbed at the location of a brain tumor in a selection of cases from the IS. This measure is a function of the frequency band and the types of phones the subjects had used and is multiplied by the duration of use to determine the total specific energy absorbed at the location of the tumor (TCSE, J/kg). After applying these exposure measures to the 5 countries in the IS where they could get the necessary usage information and tumor location data [63], they saw slight increases in both the glioma and meningioma ORs compared to the cumulative duration of mobile-phone use seen in the larger analysis [48]. The most significant finding was in the highest exposure group with a 7-year lag yielding an OR of 1.91 (1.05-3.47).

Grell et al. (2016) [76] used a model for spatial distribution of glioma occurrence developed by **Grell et al (2015)** [77] to reanalyze the tumor location data and laterality using the data from **Cardis et al. (2011)** [63]. The cases consisted of the 792 regular mobile phone users who provided data on preferred side of phone use and the center location of their tumor mass. The statistical test has the null hypothesis that the chances of getting the tumor are independent of side of use (in their parlance, the alphas for the four distances from the phone are all equal to 1 against the ordered alternative) with three different analyses based on slightly different assumptions. The p-value for the hypothesis of no association with mobile phone use was <0.01 for all three models. Dichotomizing (one variable at a time) by sex, age, tumor grade, tumor size, and years of mobile phone use yielded $p<0.01$ in all cases. The only weakness of this study would be if recall bias is driving the choice of which side of the brain the phone is typically used.

Cardis et al. (2011) [63] also conducted a case-case analysis in which mobile phone use was compared between cases whose probable tumor location was in the most exposed part of the brain region versus cases where the location of the tumor was elsewhere. The most exposed area was defined as falling within the 3 dB exposure volume of the brain regardless of laterality of use [78]. The OR for gliomas in regular users versus not regular users was 1.35 (0.64-2.87). For time since start of use, the ORs were 1.37 (0.59-3.19) for 1-4 years, 0.72 (0.27-1.90) for 5-9 years and 2.80 (1.13-6.94) for ≥10 years. A similar pattern was seen for cumulative call time. Because this uses only cases, case-case analysis is likely to have very limited recall bias but could still have exposure misclassification which is likely to be non-differential and reduce the ORs toward 1.0.

Larajavara et al. (2011) [79] also conducted a case-case analysis using seven European countries from the IS (Denmark, Finland, Germany, Italy, Norway, Sweden, and Southeast

England). In this analysis, distance between the midpoint of the glioma and the mobile phone axis was used to compare cases. Using the direct distance measurement, there was little difference between mean distance for various exposures categories with all p-values exceeding 0.39. Classifying tumors as ≤5 cm from midpoint of the glioma to the mobile phone axis or not yielded ORs that were below 1 for all but one situation and none were statistically significant. They also did a case-specular analysis of these same data. In a case-specular analysis, a mirror image of the location of the glioma is projected across the midpoint of the axial and coronal planes to use as the control. An association of cell phone usage with gliomas would exist if the ORs increased with increasing exposure; this was not seen. Using distance instead of exposure dose could lead to greater exposure misclassification since most exposures occur in the area of the brain closest to the ear and is not evenly distributed along the phone axis [63].

Hardell and colleagues conducted five separate case-control studies in Sweden on the risks of malignant brain tumors and exposure to cellular telephones [80-85]. All of the studies used self-administered questionnaires to ascertain mobile phone use followed by supplementary phone interviews to verify information provided in the questionnaire. All studies obtained matching controls for living cases from the Swedish Population Registry matching on gender and 5-year age group, and matching controls for deceased cases were obtained from the Death Registry of Sweden matched for year of death, gender, 5-year age group and medical region. The first study, **Hardell et al. (1999)** [85], was a small study with 233 patients identified from records in two regions of Sweden from 1994 to 1996. This study was effectively negative, probably due to the short latency periods for cellular phone use (Table 1, Table 6).

The next two studies were conducted back-to-back and used the same basic methodology. **Hardell et al. (2002)** [83] was conducted on males and females, aged 20-80 years, who developed a malignant brain tumor between 1997-2000 in Uppsala-Orebro, Stockholm, Linkoping and Goteborg; this study included 588 cases and 581 controls. Only cases that were alive at the time of the study were included in the evaluation. Ever use of an analog mobile phone showed an elevated OR for ipsilateral use of 1.85 (1.16-2.96) for malignant brain tumors. Digital phones showed a smaller OR for ipsilateral use of 1.59 (1.05-2.41). Multivariate analysis showed an elevated risk for all types of phones with confidence bounds that included 1. **Hardell et al. (2006a)** [81] was conducted in the same manner from 2000 to 2003 in Uppsala-Orebro and Linkoping and included 317 cases and 692 controls. No participants in this study overlapped with the previous study [83] and, as before, only cases alive at the time of the study were included. The use of analog cell phones yielded an OR for malignant brain tumors of 2.6 (1.5-4.3) and increased to 3.5 (2.0-6.4) for >10-year latency and 6.2 (2.5-15) for >15-year latency. The use of digital cell phones yielded an OR of 1.9 (1.3-2.7) and increased to 2.9 (1.6-5.2) for >10-year latency. Other exposure metrics were provided, some of which were also significant. A third case-control study [80] was conducted using those who had died prior the start of the previous two studies. Deceased cases were matched with two controls, one who had died of cancer and one who had died of another cause. The study included 346 cases (75% response rate, 314 cases of glioma) and 619 controls (67% response rate, 74% response rate from cancer controls). The OR for all malignant brain tumors and use of a mobile phone was 1.3 (0.9-1.9) increasing to 2.4 (1.4-4.1) with a latency of >10 years. They saw increasing ORs with increasing cumulative lifetime use (1.2 [0.8-1.8] for 1-1,000h, 2.6 [0.9-8.0] for 1,001-2,000h, and 3.4 [1.5-8.1] for

≥2,000h). The ORs were the same in the low exposure and high exposure groups regardless of whether cancer controls or other controls were used but differed in the middle exposure group with analyses using cancer controls showing no increased OR and using non-cancer controls showing an OR very similar to the analysis using all controls.

These three case-control studies [80, 81, 83] were combined in a pooled analysis in **Hardell et al. (2006)** [86]. The final study included 1,251 cases and 2,438 controls. This constitutes a response rate of 85% for cases and 84% for controls. For mobile phone usage and 1-year latency, they reported an OR for gliomas of 1.3 (1.1-1.6) that stayed at 1.3 (0.99-1.6) for 5-10-year latency and rose to 2.5 (1.8-3.3) for >10-year latency; the numbers were slightly higher if only a mobile phone was used (no cordless phone). They also saw a clear exposure-response relationship for lifetime use in hours where the OR was 1.2 (1.03-1.5) for 1-1000 hours of use, 1.8 (1.2-2.8) for 1001-2000 hours of use and 3.2 (2.0-5.1) for >2000 hours of use. The OR increase per 100 hours of use was 1.023 (1.013-1.034). In a follow-up to this study, **Hardell and Carlberg (2013)** [87] evaluated the survival of glioma patients until death or May 30, 2012 using Cox's proportional hazards model adjusted for age, gender, year of diagnosis, socioeconomic status and study. Exposed patients were those using a phone at least 1 year prior to tumor development, unexposed were all other patients. The hazard ratio (HR) for users of mobile phones was 1.1 (0.9-1.2) and increased with latency (0.9 [0.8-1.1] for 1-5 years; 1.1 [0.9-1.4] for 5-10 years; 1.3 [1.0005-1.6] for >10 years), and tertiles of cumulative use (0.9 [0.7-1.1] for T1; 1.0 [0.8-1.3] for T2; 1.3 [1.05-1.6] for T3). For lower grade astrocytomas (I and II), all HRs were below 1, for grade III astrocytomas, most HRs were below 1 and for grade IV, all HRs were greater than 1, but none were significant.

The fourth case-control study, **Hardell et al. (2013)** [82], covered all of the administrative regions of Sweden and included males and females aged 18-75 years who were diagnosed with a brain tumor between 2007 and 2009 (there were some differences by region). Deceased cases were excluded from the study. The study eventually included 593 cases (87% response rate) and 1368 controls (85% response rate). There were more female controls responding than males although there were more male cases than female cases. The OR for use of a mobile phone for more than 1 year and malignant brain tumors was 1.6 (0.99-2.7) with very little change by latency until a latency of 20-25 years where the OR was 1.9 (1.1-3.5) and >25 years where the OR was 2.9 (1.4-5.8). They conducted a novel analysis where they used meningioma patients as the controls and saw similar patterns but slightly higher ORs. The OR for ipsilateral use was slightly increased from the overall OR with a value of 1.7 (1.01-2.9). Analyses were also conducted separately for use of analog mobile phones with an OR of 1.8 (1.04-3.3), second-generation (2G) digital mobile phones 1.6 (0.996-2.7) and third-generation (3G) phones 1.2 (0.6-2.4). All of these had the highest ORs in the longest latency group. They also broke exposure to wireless phones (combined exposure to mobile phones and cordless phones) in the controls into quartiles and, using these categories, calculated ORs for malignant tumors and use of mobile phones. Regardless of phone type, the highest ORs were seen in the highest quartile of exposure and analog, 2G and the combined analysis of all mobile phones displayed significant trends with increasing ORs across quartiles. They also did a separate analysis for malignant tumors located in temporal and overlapping lobes and saw a similar pattern with latency, but higher ORs. Finally, they did a separate analysis for exclusive use of each type of phone, but numbers were small in most cases and this does not relate well to phone use (e.g. there

were no users of only analog phones since every phone user had moved on to digital phones by the time of this study).

Hardell and Carlberg (2015) [88] pooled the data on glioma patients from all of their case-control studies into one large study; they excluded deceased cases from all of the studies in this analysis. Cases and controls are described above. The pooled cases of malignant tumors number 1498 (89% response rate total) with 817 males and 563 females with gliomas. There are 3530 controls (87% total response rate) with 1492 males and 2038 females. The median latency time for use of mobile phones in glioma patients was 9 years (range 2-28 years). All analyses were adjusted for age at diagnosis, gender, socio-economic index, and year of diagnosis. Ever use (>1 year) of analog phones gave an OR of 1.6 (1.2-2.0), ever use of 2G phones gave an OR of 1.3 (1.1-1.6), ever use of 3G phones gave an OR of 2.0 (0.95-4.4), ever use of any 2G or 3G digital phone gave an OR of 1.3 (1.1-1.6) and ever use of any mobile phone gave an OR of 1.3 (1.1-1.6). For any use of mobile phones, all latency groups showed significantly increased ORs except for the >1-5 years group (OR=1.2, 0.98-1.5) and all phone groupings had their highest ORs for the longest latencies. Ipsilateral use of mobile phones gave an OR of 1.8 (1.4-2.2) whereas contralateral use gave an OR of 1.1 (0.8-1.4). Using the method of **Inskip et al. (2001)** [44] gave a relative risk (RR) of 1.5 with $p<0.001$. Dividing hours of exposure into quartiles (as done in [82]) yielded significant trends for use of any mobile phone as well as analog and 2G phones. Age at first use of a mobile phone was significant in all categories with <20 years showing the highest OR=1.8 (1.2-2.8) and the highest ipsilateral OR of 2.3 (1.3-4.2). Using meningiomas as the referent group led to similar results. Multivariate analysis yielded increases per 100 hours of cumulative use for analog mobile phones (1.025, 1.010-1.041) and 2G phones (1.009, 1.005-1.014) but not 3G phones (0.980, 0.944-1.017). Multivariate analysis also yielded increases per year of latency for analog mobile phones (1.056, 1.036-1.076) and 2G phones (1.030, 1.009-1.052) but not 3G phones (1.127, 0.955-1.329).

The greatest strengths of these studies are their use of population-based controls and the high participation rates of cases and controls. One major limitation, as with most case-controls studies, is the use of a questionnaire for obtaining exposure information and the possibility of recall bias. Overall, the studies show little indication of recall bias, especially since the meningioma cases used as the referent population showed little change in the ORs. (Table 1, Table 2, Table 3, Table 5, Table 6)

Baldi et al. (2011) [89] conducted a case-control study (CEREPHY) of brain tumors in the area of Gironde, France. Eligible cases were patients aged 16 and older diagnosed with a brain cancer from May 1, 1999 to April 30, 2001. The study had 221 (70% participation rate) cases and 442 (69% participation) controls matched on age, sex and residence. Gliomas were seen in 105 cases (26 ever used a cellular phone) and the OR for ever versus never use of a cellular telephone was 0.82 (0.53-1.26). The use of a cellular telephone exceeded 10 years for 1 user and 5 years for 12 users. (Table 1)

The CERENAT study by **Coureau et al. (2014)** [90] is a multicenter case-control study conducted in four areas of France. Cases were defined as all subjects aged 16 and over diagnosed between June 2004 and May 2006 and living in one of four French areas (Gironde, Calvados, Manche, Herault) with a benign or malignant brain tumor (with specific ICDO-3 codes). These tumors were verified either through neuropathological, clinical or radiological assessment. For each case, two controls with no history of CNS tumors were randomly selected from electoral rolls and matched on age (±2 years), sex and department

of residence. Exposures were determined through non-blinded, face-to-face application of questionnaires; proxies were given a simplified questionnaire. Regular users were defined as people who were phoning at least once per week for 6 months or more and at least one-year prior to diagnosis. An adjustment was made for subjects using hands-free calling or sharing their phones with others. The analyses for gliomas included 253 cases and 504 controls with a participation rate of 66% for gliomas and 45% for controls. The OR for regular users versus others was 1.24 (0.86-1.77) adjusted for level of education and exposure to ionizing radiation. Exposure-response analyses were conducted for time since first use (p=0.17, ≥10 years 1.61, 0.85-3.09), average calling time per month (p<0.001, ≥15 hours 4.21, 2.00-8.87), average number of calls per day (p=0.04, 5-9 calls 2.74, 1.33-5.65, ≥10 calls 1.78, 0.88-3.59), cumulative duration of calls (p=0.02, ≥896 hours 2.89, 1.41-5.93) and cumulative number of calls (p=0.41, ≥18,360 calls 2.10 (1.03-4.31). Analyses excluding proxies saw almost the same results. Among the heaviest users (≥896 hours cumulative duration of calls), the OR for 5-year latency was 5.30 (2.12-13.23), for occupational users the OR was 3.27 (1.45-7.35) and for exclusive use in an urban setting the OR was 8.20 (1.37-49.07). Ipsilateral use (0.70, 0.46-1.07) was higher than contralateral use (0.30, 0.17-0.52), however, these findings were questioned by **Hardell and Carlberg (2015)** [91] because the approach used was different than that used in their analyses and in the Interphone Study. The authors responded [92] and, using the same method as **Hardell and Carlberg (2015)** [88], obtained an OR for ipsilateral use of 4.21 (0.70-25.52) and for contralateral use of 1.61 (0.36-7.14). They also applied the same method used in **Inskip et al. (2001)** [44] and obtained an OR of 2.40 (1.002-5.73). The major weaknesses of this study are the response rates and the use of questionnaire data for exposure. The authors addressed concern for recall bias by carefully assessing exposure in the highest exposed individuals. They found that there may be some small concern for exposure misclassification, but it is likely to be non-differential and is unlikely to have affected the final results. (Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7)

Yoon et al. (2015) [93] conducted a case-control study in five areas of Korea (Seoul, Gyeonggi-do, Gyeongsang-do, Jeolla-do, Chungcheong-do, Gangwon-do, and Jeju-do). Cases (285 participated, 142 refused, 465 had excessive pain and 5 had no matched control) were identified as glioma patients between the ages of 15 and 69 years of age and controls (285 participated, 354 refused, 7 had excess pain and 405 had no matched case). Cases and controls came from the recruiting hospitals and were given a questionnaire during the initial interview. Cases were also excluded if they died during the course of the study. There were some significant differences between cases and controls (residential region, education, patient or proxy, use of dye, alcohol use, computer use and use of electric blankets). Users were defined as having more than 1 year of cellular phone use. The OR for users was 1.17 (0.63-2.14) for all respondents and 0.94 (1.46-1.89) for self-respondents. The largest group of users had used both analog and digital phones and they had an OR of 1.89 (0.96-3.81). Lifetime years of use, cumulative hours of use, average number of calls received daily, average number of calls sent daily and average duration of calls had ORs that were generally greater than 1.0, included 1.0 in the 95% confidence interval, and did not appear to show dose-response although no test was done. Using the method of **Inskip et al. (2001)** [44] gave a relative risk (RR) of 1.26 (p=0.05) for all respondents and 1.43 (p=0.01) for self-respondents. ORs for ipsilateral versus contralateral use were very mixed and seldom included the OR from the original evaluation as falling between the ORs for the two sides (it appears they used the same method as the **CERENAT study (2014)** [90] but this cannot be

verified). Besides the usual possibility of recall bias in these types of studies, this study's weaknesses include poor reporting of the methods, an unusual exclusion of patients due to pain and very high refusal rates for both cases and controls. (Table 1, Table 2, Table 3, Table 6)

4.1.1.2 Cohort Studies

Schuz et al. (2006) [94] extended the evaluation of a retrospective cohort study in Denmark [95]. They identified 723,421 cellular telephone subscribers in Denmark from 1982 to 1995, 420,095 of whom could be identified as individuals and became part of the cohort. The other 303,326 were excluded because the user was listed as a corporation (200,507) or excluded for other reasons (102,819). Approximately 85% of the cohort members were males. Only first cancer diagnoses were used in this analysis and the ending date of follow-up is December 31, 2002. The observed cancers in the cohort were compared to the expected numbers in the Danish population using the Danish Cancer Registry after subtracting the number of cancer case patients and person-years observed in the cohort from those in the registry.

There was a significant decrease in all cancers for males (RR 0.93, 0.92-0.95) and a marginally significant increase in females (1.03, 0.99-1.07). All of the RRs for cancers in males, including brain and CNS tumors (0.96, 0.87-1.05), lacked statistical significance with 14 of the 20 grouped organ sites having RRs below 1. In females, all smoking-related sites, cervix/uteri and kidney tumors showed significantly increased RRs with brain and CNS tumors non-significant (1.03, 0.82-1.26). For males and females combined, gliomas (1.01, 0.89-1.14), meningiomas (0.86, 0.67-1.09) and cranial nerve sheath tumors (0.73, 0.50-1.03) were all non-significant. There was no increase with years on use in both males and females for brain and CNS tumors (p=0.51) or leukemias (p=0.69).

Frei et al. (2011) [96] conducted an update of the Danish cohort study using the same information on cellular phone subscriptions (1982-1995); hence the update is only with regard to tumor rates and contains no information on cellular phone subscriptions post 1995. Only first cancer diagnoses were used in this analysis and the ending date of follow-up is December 31, 2007. To obtain information on socioeconomic factors, they used the CANULI cohort study data [97] which includes all Danes aged 30 or older born after 1925 in Denmark. Because of eligibility requirements for CANULI, the number of subscribers was reduced by 54,350; thus, the follow-up contained 358,403 subscription holders.

There was a significant decrease in all cancers for males with subscriptions (RR 0.96, 0.95-0.98) and a marginally significant increase in females (1.02, 0.98-1.06). There were slight increases in central nervous system tumors for both males (1.02; 0.94-1.10) and females (1.02; 0.86-1.22) with no apparent increase in risk as years of subscription increased. There was a stronger increase for gliomas alone in males (1.08; 0.96-1.22) but not in females (0.88; 0.69-1.40) with the highest RRs in males for only 1-4 years of subscription (1.20; 0.96-1.50) and the lowest for ≥13 years of subscription (0.98; 0.70-1.36); there was no exposure response in females. There is a chance some of the gliomas could have fallen in the "other and unspecified" category and those saw RRs above 1 for both males (1.12; 0.95-1.33) and females (1.19; 0.85-1.67). For men, RRs for mobile phone use and tumors in the frontal lobe (1.13; 0.89-1.45), temporal lobe (1.13; 0.86-1.48), occipital lobe (1.47; 0.87-2.48) and other or unspecified brain regions (1.35; 1.05-1.75) were above 1. (Table 1, Table 2, Table 7)

Schuz et al. (2009) [98] also looked at central nervous system diseases in this same cohort. They looked for hospital contacts for migraine (RR 1.2, 1.1-1.3), vertigo (1.1, 1.1-1.2), alzheimer's (0.7 , 0.6-0.9), vascular dementia (ns), other dementia (0.7, 0.6-0.8), Parkinson (0.8, 0.7-0.9), ALS (ns), MS (ns), epilepsy in men (0.7, 0.7-0.7) and women (ns).

The biggest concern with all these studies [94, 96, 98, 99] are the various sources of misclassification that could be differential and/or non-differential. By their own count, 303,326 phone contracts could not be assigned to specific users and were classified into the non-user category. In addition, a member of the cohort may have been the owner of the account but not the primary user of the cellular phone (e.g. parents or spouses paying for the account). Using information from a separate case-control study [49], it was estimated that 16% of the non-users could have been frequent users; this was used to suggest the potential impact of this bias on the overall RRs will be low; no sensitivity analysis was provided. No phone data past 1995 was used for any of these analyses. According to the World Bank (2020) [100], there were 15.714 subscriptions to mobile phones per 100 people in Denmark in 1995 against a population of 5,233,373 [101]. To compare, 723,421 subscriptions in Denmark from 1982 to 1995 would be 13.82 per 100 people (very close to the World Bank numbers). By 2002, when the Schuz et al. (2006) [94] follow-up ended, there were 83.341 subscriptions per 100 people (5.3x increase) and by 2007 when Frei et al. (2011) [96] follow-up ended, there were 115.322 per 100 people (7.3x increase); in 2018, there are 125.119 subscriptions per 100 people in Denmark. Thus, of the 1853 male and 1455 female non-subscribers who had gliomas, most of them will have had subscriptions of some sort by 2007. Hence, the exposure misclassification is extreme with many cellular phone users in the non-subscription category who are undoubtedly using mobile phones. Finally, in the **Frei et al (2011)** [96] update, the use of the CANULI database required dropping all cell phone users below the age of 30 before 1995 which appears to be the 54,350 subscribers they lost; hence the youngest phone users before 1995 were excluded from the study.

Benson et al. (2013) [102] used data from the Million Women Study (MWS; for details, see [103, 104]) to evaluate the linkage between brain tumors and mobile phone use. Researchers recruited 1.3 million middle-aged women in the UK into the MWS during the period of 1996-2001. Women completed an initial survey on lifestyle factors, sociodemographic factors and medical history and are resurveyed every 3-4 years. Questions on mobile phone use were asked in 1999-2005 and again in 2009. Information about incident cases of brain tumors were obtained through linkage to Hospital Episode Statistics in England and Scottish Morbidity Records. Of the 866,525 women who answered the questionnaire between 1999 and 2005, numerous women were excluded from the analysis (14,387 got a questionnaire without cell phone usage, 11,981 did not answer the cell phone usage question, 48,531 had CNS tumors at baseline and 6 had a genetic predisposition to get neurological tumors); eventually leaving 791,710 women in the study. Average follow-up time was 7 years (follow-up was through December 31, 2009 except for 1 region where the date was December 31, 2008). Cell phone usage was assessed with two questions: 1) About how often do you use a mobile phone? Never/less than once a day/every day; 2) For how long have you used one? Responses to mobile phone usage questions in 2009 were used to assess the repeatability of earlier questions for the 31,110 women who answered both; however, the questions were different and consistency is not easy to assess. Approximately half of those who reported no use of a mobile phone in the

first survey reported use in 2009. There were a number of demographic differences between mobile phone users and non users, including age, affluence, exercise, alcohol and smoking. In addition, the phone users saw less incident cancers (6.05%) than did non-users (7.32%) during the follow-up period. In total, there were 571 gliomas in this cohort. Risk ratios (RRs) for phone use were ever/never 0.91 (0.76-1.08), daily use 0.80 (0.56-1.14), <5 years 0.93 (0.71-1.21), 5-9 years 0.92 (0.75-1.13) and 10+ years of use 0.78 (0.55-1.10) (all adjusted for socioeconomic status, region, age (in 3-year groupings), height, BMI, alcohol intake, exercise and hormone therapy). In a letter responding to a letter by **de Vocht (2014)** [105], **Benson et al. (2014)** [106] updated their follow-up to 2011 but did not update cellular phone usage (still relying on the 1999-2005 response) and saw the RR for glioma for ever/never users of 0.86 (0.75-0.99). Note that with 7 years average follow-up, they saw 571 gliomas or 82/year but adding 2010 and 2011 increased the gliomas by over 100 per year. The main limitations of this study are the rapidly changing exposures to mobile phones and the short follow-up period. Both of these factors likely pushed the results toward the null. In essence, this study creates considerable challenges in terms of misclassification of exposure. For example, a case answering the question in 2005 with 1 year of usage would have 6 years of exposure. In contrast, a woman answering in 1999 with no cell phone usage who then gets a phone in 2000 has 10 years of use but is considered a non-user. This problem is exacerbated by the rapid increase in cellular phone usage in the UK during this period. Cellular phone usage in the UK increased dramatically during the actual study period as well as the recruiting period with rates per 100 people of 9.901 (1995), 12.473 (1996), 78.281 (2001), 108.598 (2005) and 121.73 (2009) [107] so some of the cases with no exposure are likely to have been exposed. They attempted to address these issues by excluding women who reported phone use in 1999-2000 since many of these will have changed their status but this discards the longest exposed individuals and removed 73 glioma patients with cellular phone usage (21.8%). In addition, the fact that the use of a cellular phone is associated with a significant reduction in all invasive neoplasms (e.g. ever use 0.97 [0.95-0.99]) could indicate a difference between the groups that is not being addressed in the analysis. (Table 1, Table 2)

Table 1: Results from epidemiology studies for ever versus never or regular versus non-regular use of a cellular telephone and the risk of glioma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Sample Size for all endpoints (% resp.)	Exposed (%) Cases	OR (95% CI)	Comparison group
Hardell et al. (1999)	CC	1994-1996 ,Sweden	20-80, Both	All Malignant Astrocytoma, glioblastoma	272 (90%) Gliomas 439 (91%) Controls	53 (19.5) 36 (38.3)	0.98 (0.63-1.50) 1.09 (0.64-1.84)	>1 year, all malignant (mostly gliomas, 4 NUD) >1 year, astrocytoma & glioblastoma (L&R match)
Muscat et al. (2000)	CC	1994-1998, US	18-80, Both	Astrocytic tumor Oligodendroglioma	354 cases 55 cases	41 (11.6) 9 (16.4)	0.8 (0.5-1.2) 0.9 (0.4-2.1)	Has subscription
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Glioma	782 (92%) Cases 799 (86%) Controls	201 (41.4) 121 (24.7)	1.0 (0.7-1.4) 0.9 (0.7-1.4)	Any use >5 times use
Auvinen et al. (2002)	CC	1996, Finland	20-69, Both	Glioma	198 (100%) Gliomas 989 (100%) Controls	32 (16.3)	1.5 (1.0-2.4)	Has subscription
Gousias et al. (2009)	CC	2005-2007, Greece	22-82, Both	Glioma	36 (ND) Gliomas 82 (ND) Controls	ND (ND)	1.0 (0.99-1.01)	ND
Spinelli et al. (2009)	CC	2005, France	≥18, Both	Glioma	122 (17.2%) Gliomas 122 (90.2%) Controls	85 (69.7)	ND (ND)	Used a phone
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Glioma	2765 (64%) Gliomas 7658 (53%) Controls	1,666 (61.5)	0.81 (0.70-0.94)	Avg 1 call per week for 6 mo (lag 1 yr)
Baldi et al. (2011)	CC	1999-2001, France	≥16, Both	Glioma	221 (70%) Brain 442 (69%) Controls	26 (24.8)	0.82 (0.53-1.26)	Ever versus never use
Coureau et al. (2014)	CC	2004-2006, France	≥16, Both	Glioma	596 (73%) Cases 1192 (45%) Controls	142 (57.0) Excluding proxies 123 (21.6)	1.24 (0.86-1.77) 1.33 (0.89-1.98)	Avg 1 call per week for 6 mo
Hardell et al. (2015)	CC	1997-2003, 2007-2009, Sweden	20-80, Both	Glioma	1498 (89%) Gliomas 3530 (87%) Controls	945 (68.5) Per year of latency	1.3 (1.1-1.6) 1.032 (1.017-1.046	>1 year
Yoon et al. (2015)	CC	2002-2007, Korea	15-69	Glioma	285 (32%) Giomas 285 (27%) Controls Excluding proxies 219 Gliomas 273 Controls	235 (83.9) 191 (87%)	1.17 (0.63-2.14) 0.94 (0.46-1.89)	>1 year (maybe also non-regular user)
Frei et al. (2011)	Cohort	1990-2007, Denmark	≥30 at time of entry	Glioma	358,403	324 (17.5) Male 32 (2.2) Female	1.08 (0.96-1.22) 0.98 (0.69-1.40)	Subscription >1 year between 1982 and 1995 Phone use only for before 1995
Benson et al. (2013)	Cohort	1999-2009, UK	Middle-aged women	Glioma	791,710 (65%) Follow-up to 2011	334 (58.5) Ever use 36 (6.3) Daily use Exclude first 3 years 261 (63.3) Follow-up to 2011	0.91 (0.76-1.08) 0.80 (0.56-1.14) 0.83 (0.68-1.02)	Ever used (asked 1999-2005) Every day (asked 1999-2005) Ever used (asked 1999-2005)

Benson et al. (2014)		1999-2011, UK			875 glioma cases vs 571 in 2009	Not given	0.86 (0.72-1.02)	Ever used (asked 1999-2005)

Table 2: Results from epidemiology studies for duration (years) of use of a cellular telephone and the risk of glioma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Duration	Exposed Cases	OR (95% CI)	P Trend	Comments
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Glioma	<0.5 years 0.5-3 years ≥3 years ≥5 years	24 31 30 11	0.6 (0.3-1.1) 0.9 (0.5-1.6) 0.9 (0.5-1.5) 0.6 (0.3-1.4)	ND	Any use 2+ calls/w
Auvinen et al. (2002)	CC	1996, Finland	20-69, Both	Glioma	<1 year 1-2 years >2 years	ND	1.2 (0.5-3.0) 1.6 (0.8-2.9) 1.7 (0.9-3.5)	ND	Has subscription Increase in OR per year 1.2 (1.0-1.4)
Gousias et al. (2009)	CC	2005-2007, Greece	22-82, Both	Glioma	Minute-years	ND	1.0 (0.99-1.01)	0.56	undefined
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Glioma	1-1.9years 2-4 years 5-9 years ≥10 years 1-1.9 Years as referent 2-4 years 5-9 years ≥10 years	156 644 614 252 460 468 190	0.63 (0.46-0.81) 0.84 (0.70-1.00) 0.81 (0.60-0.97) 0.98 (0.76-1.26) 1.68 (1.16-2.41) 1.54 (1.06-2.22) 2.18 (1.43-3.31)	ND	Avg 1 call per week for 6 mo (lag 1 yr), no hands-free Excludes hands-free usage
Coureau et al. (2014)	CC	2004-2006, France	≥16, Both	Glioma	1-4 years 5-9 years ≥10 years Excluding proxies 1-4 years 5-9 years ≥10 years	49 66 22 47 58 14	0.88 (0.56-1.39) 1.34 (0.87-2.06) 1.61 (0.85-3.09) 1.04 (0.64-1.69) 1.45 (0.91-2.33) 1.45 (0.68-3.08)	0.17 0.36	Avg 1 call per week for 6 mo
Hardell et al. (2015)	CC	1997-2003, 2007-2009, Sweden	20-80, Both	Glioma	1-5 years 5-10 years 10-15 years 15-20 years 20-25 years >25 years	262 301 211 92 50 29	1.2 (0.98-1.5) 1.5 (1.2-1.8) 1.4 (1.1-1.9) 1.6 (1.1-2.2) 2.1 (1.3-3.2) 3.0 (1.7-5.2)	ND	>1 year
Yoon et al. (2015)	CC	2002-2007, Korea	15-69	Glioma	1-5 years 5-8 years >8 years Excluding proxies 1-5 years 5-8 years >8 years	97 70 70 37 76 76	1.28 (0.62-2.64) 1.27 (0.63-2.56) 1.04 (0.52-2.09) 0.94 (0.42-2.13) 1.01 (0.45-2.23) 0.90 (0.40-2.02)	ND	>1 year (maybe also non-regular user)

Frei et al. (2011)	Cohort	1990-2007, Denmark	≥30 at time of entry	Glioma	Male 1-4 years 5-9 years ≥10 years 10-12 years ≥13 years Females 1-4 years 5-9 years ≥10 years	Male 85 122 117 80 37 Females 8 14 10	Males 1.20 (0.96-1.50) 1.05 (0.87-1.26) 1.04 (0.85-1.26) 1.06 (0.85-1.34) 0.98 (0.70-1.36) Females 0.87 (0.43-1.75) 1.02 (0.60-1.72) 1.04 (0.56-1.95)	ND	Subscription >1 year between 1982 and 1995 Phone use only before 1995
Benson et al. (2013) Benson et al. (2014)	Cohort	1999-2009, UK 1999-2011, UK	Middle-aged women	Glioma	<5 years 5-9 years ≥10 years Excluding first 3 years <5 years 5-9 years ≥10 years Follow-up to 2011 <5 years 5-9 years ≥10 years	89 185 40 66 148 29 Not given	0.93 (0.71-1.21) 0.92 (0.75-1.13) 0.78 (0.55-1.10) 0.77 (0.57-1.06) 0.86 (0.68-1.09) 0.75 (0.49-1.13) 0.96 (0.75-1.23) 0.86 (0.72-1.02) 0.77 (0.62-0.96)	ND	Ever used (asked 1999-2005) Ever used (asked 1999-2005)

Table 3: Results from epidemiology studies for duration (cumulative hours) of use of a cellular telephone and the risk of glioma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Cumulative use	Exposed Cases	OR (95% CI)	P Trend	Comparison group
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Glioma	<13 hours	55	0.8 (0.4-1.4)	ND	Any use
					13-100 hours	58	0.7 (0.4-1.3)		2+ calls/w
					>100 hours	54	0.9 (0.5-1.6)		
					>500 hours	27	0.5 (0.2-1.3)		
Spinelli et al. (2009)	CC	2005, France	≥18, Both	Glioma	≤48 (converted from hour years)	8	0.86 (0.3-2.44)	ND	Used a phone, cumulative use based upon subscription limits of hours/month
					48-432	58	1.45 (0.75-2.80)		
					≥432	13	1.07 (0.41-2.82)		
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Glioma	<5 hours	141	0.70 (0.52-0.94)		Avg 1 call per week for 6 mo (lag 1 yr), no hands-free
					5-12.9 hours	145	0.71 (0.53-0.94)		
					13-30.9 hours	189	1.05 (0.79-1.38)		
					31-60.9 hours	144	0.74 (0.55-0.98)		
					61-114.9 hours	171	0.81 (0.61-1.08)		
					115-199.9 hours	160	0.73 (0.54-0.98)		
					200-359.9 hours	158	0.76 (0.57-1.01)		
					360-734.9 hours	189	0.82 (0.62-1.08)		
					735-1639.9 hours	159	0.71 (0.53-0.96)		
					≥1640 hours	210	1.40 (1.03-1.89)		
					Using<5 hours referent				
					5-12.9 hours	92	0.88 (0.56-1.39)		Restricted to ever regular users
					13-30.9 hours	127	1.37 (0.87-2.14)		
					31-60.9 hours	108	1.13 (0.72-1.77)		
					61-114.9 hours	121	1.06 (0.68-1.67)		
					115-199.9 hours	129	1.13 (0.71-1.78)		
					200-359.9 hours	116	1.00 (0.63-1.58)		
					360-734.9 hours	142	1.17 (0.74-1.84)		
					735-1639.9 hours	126	1.09 (0.69-1.72)		
					≥1640 hours	160	1.82 (1.15-2.89)		
Coureau et al. (2014)	CC	2004-2006, France	≥16, Both	Glioma	<43	24	0.83 (0.48-1.44)	0.02	Avg 1 call per week for 6 mo
					43-112	20	0.77 (0.42-1.41)		
					113-338	28	1.07 (0.60-1.90)		
					339-895	28	1.78 (0.98-3.24)		
					≥896	24	2.89 (1.41-5.93)		
					Exclude proxies (weighted)				
					<29	19	0.73 (0.39-1.35)	0.03	Weighted for shared use and hands-free use
					29-86	20	0.97 (0.52-1.78)		
					87-326	31	1.56 (0.86-2.83)		
					377-835	22	1.62 (0.84-3.14)		
					≥836	18	2.83 (1.30-6.27)		
Hardell et al. (2015)	CC	1997-2003, 2007-2009, Sweden	20-80, Both	Glioma	Per 100 cumulative hours of use	NA	1.013 (1.009-1.017		>1 year
					Cumulative use	340		<0.0001	
					1-122	198	1.3 (1.05-1.5)		
					123-511	179	1.3 (1.02-1.6)		
					512-1486	228	1.4 (1.04-1.8)		
					>1486		2.2 (1.7-2.9)		
Yoon et al. (2015)	CC	2002-2007, Korea	15-69	Glioma	<300	97	1.25 (0.64-2.45)	ND	>1 year (maybe also non-regular user)
					300-900	70	1.59 (0.72-3.21)		
					>900	70	0.64 (0.30-1.34)		
					Excluding proxies				
					<300	73	0.99 (0.46-2.12)		
					300-900	61	1.17 (0.53-2.57)		
					>900	55	0.62 (0.27-1.43)		

Table 4: Results from epidemiology studies for average daily or monthly use of a cellular telephone and the risk of glioma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Measure	Exposed Cases	OR (95% CI)	P Trend	Comparison group
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Glioma	Average daily				
					<3 minutes	53	0.9 (0.5-1.6)	ND	Any use
					3 to 15 minutes	64	1.0 (0.6-1.6)		2+ calls/w
					≥15 minutes	51	0.5 (0.3-1.0)		
					≥60 minutes	24	0.7 (0.3-1.7)		
Coureau et al. (2014)	CC	2004-2006, France	≥16, Both	Glioma	Average monthly				Avg 1 call per week for 6 mo
					<2 hours	40	0.91 (0.57-1.46)	<0.001	
					2-4 hours	19	0.57 (0.30-1.10)		
					5-14 hours	36	1.70 (0.97-2.99)		
					≥15 hours	29	4.21 (2.00-8.87)		
					Excluding proxies	36	1.01 (0.61-1.69)	<0.001	
					<2 hours	16	0.59 (0.29-1.21)		
					2-4 hours	33	1.78 (0.99-3.22)		
					5-14 hours	25	4.04 (1.84-8.86)		
					≥15 hours				

Table 5: Results from epidemiology studies for other use measures of a cellular telephone and the risk of glioma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Measure	Exposed Cases	OR (95% CI)	P Trend	Comments
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Glioma	Year use began			ND	Any use
					1995-1998	61	0.8 (0.4-1.5)		2+ calls/w
					1993-1994	60	1.0 (0.6-1.6)		
					≤1992	50	0.6 (0.3-1.1)		
					<1990	23	0.3 (0.1-1.0)		
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Glioma	Cumulative use by recency of starting use			ND	Avg 1 call per week for 6 mo (lag 1 yr), no hands-free
					1-4 years before reference date				
					<5 hours	127	0.68 (0.50-0.93)		
					5-114.9 hours	449	0.82 (0.67-0.99)		
					115-359.9 hours	121	0.74 (0.52-1.03)		
					360-1639.9 hours	80	0.75 (0.50-1.13)		
					≥1640 hours	23	3.77 (1.25-11.4)		
					5-9 years before reference date				
					<5 hours	10	0.86 (0.32-2.28)		
					5-114.9 hours	180	0.86 (0.66-1.12)		
					115-359.9 hours	156	0.71 (0.53-0.95)		
					360-1639.9 hours	174	0.72 (0.54-0.95)		
					≥1640 hours	94	1.28 (0.84-1.95)		
					≥10 years before reference date				
					<5 hours	4	1.13 (0.16-7.79)		
					5-114.9 hours	20	0.63 (0.32-1.25)		
					115-359.9 hours	41	0.89 (0.53-1.50)		
					360-1639.9 hours	94	0.91 (0.63-1.31)		
					≥1640 hours	93	1.34 (0.90-2.01)		
Coureau et al. (2014)	CC	2004-2006, France	≥16, Both	Glioma	Cumulative # of calls				
					<660	23	1.06 (0.59-1.91)	0.41	Avg 1 call per week for 6 mo
					(660-2219)	27	1.06 (0.59-1.91)		
					(2220-7349)	28	1.48 (0.79-2.76)		
					(7350-18359)	12	1.30 (0.60-2.83)		
					≥18359	21	2.10 (1.03-4.31)		
					Excluding proxies (weighted)				
					<476	19	0.80 (0.43-1.47)	0.14	
					(476-1649)	26	1.26 (0.70-2.28)		
					(1650-6269)	35	1.71 (0.95-3.09)		
					(6270-14699)	11	1.14 (0.52-2.53)		
					≥14,700	20	2.11 (1.03-4.33)		
					Occupational use	45	3.27 (1.45-7.35)		
					Urban use only	16	8.20 (1.37-49.07)		
Hardell et al. (2015)	CC	1997-2003, 2007-2009, Sweden	20-80, Both	Glioma	Age				>1 year
					<20 years old	69	1.8 (1.2-2.8)		
					20-49 years old	605	1.3 (1.1-1.6)		
					≥50 years old	271	1.3 (1.1-1.6)		

Table 6: Results from epidemiology studies for laterality of cellular telephone use and the risk of glioma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Location or laterality	Ipsalateral OR (95%CI)	Contralateral OR (95% CI)	Inskip P.value	Comparison group
Hardell et al. (1999)	CC	1994-1996 ,Sweden	20-80, Both	All Malignant	Right side + right ear	1.43 (0.70-2.90)			>1 year
					Left side + left ear	0.58 (0.17-1.92)			
				Astrocytoma, glioblastoma	Right side + right ear	1.30 (0.54-3.13)			
					Left side + left ear	0.35 (0.07-1.81)			
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Glioma	Inskip method			0.77	2 or more calls/week + 6 months latency
					Left	0.9 (0.6-1.5)			
					Right	0.8 (0.5-1.3)			
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Glioma	Regular use	0.84 (0.69-1.04)	0.67 (0.52-0.87)		Avg 1 call per week for 6 mo (lag 1 yr)
					≥10 years since start	1.21 (0.82-1.80)	0.70 (0.42-1.15)		
					≥1640 hours cumulative	1.96 (1.22-3.16)	1.25 (0.64-2.42)		
					≥270 calls (hundreds)	1.51 (0.91-2.51)	0.61 (0.32-1.18)		
Coureau et al. (2014)	CC	2004-2006, France	≥16, Both	Glioma	Regular use	2.11 (0.73-6.08)	0.66 (0.23-1.89)		Avg 1 call per week for 6 mo
					Cumulative duration of calls (Interphone method)				
					<43	0.29 (0.11-0.80)	0.25 (0.07-0.95)		
					43-112	0.44 (0.16-1.23)	0.33 (0.10-1.08)		
					113-338	0.78 (0.27-2.24)	0.25 (0.06-1.02)		
					339-895	1.69 (0.52-5.49)	0.23 (0.05-1.11)		
					≥896	4.21 (0.70-25.52)	1.61 (0.23-1.89)		
					Inskip method	2.40 (1.002-5.73)			
Hardell et al. (2015)	CC	1997-2003, 2007-2009, Sweden	20-80, Both	Glioma	Regular use	1.8 (1.4-2.2)	1.1 (0.8-1.4)		>1 year
					Meningioma cases as referent	1.4 (1.1-1.8)	1.0 (0.7-1.4)		
					Latency groups				
					1-5 years	1.6 (1.3-2.1)	0.9 (0.7-1.2)		
					5-10 years	1.9 (1.4-2.5)	1.3 (0.9-1.8)		
					10-15 years	1.7 (1.2-2.3)	1.3 (0.9-2.0)		
					15-20 years	2.2 (1.5-3.4)	1.0 (0.6-1.7)		
					20-25 years	2.3 (1.3-4.1)	2.2 (1.1-4.6)		
					>25 years	4.6 (2.1-10)	3.2 (1.2-8.6)		
					Age groups				
					<20 years old	2.3 (1.3-4.2)	1.9 (0.9-3.7)		
					20-49 years old	1.8 (1.4-2.3)	1.1 (0.8-1.5)		
					≥50 years old	1.7 (1.3-2.2)	1.1 (0.8-1.5)		
					Inskip method	1.5 (ND)		<0.001	
Yoon et al. (2015)	CC	2002-2007, Korea	15-69	Glioma	Total respondents	0.95 (0.50-1.83)	0.90 (0.43-1.89)		>1 year (maybe also non-regular user)
					Inskip method	1.26		0.05	
					Self respondents (Inskip)	1.43		0.01	
					Cumulative hours of use	0.96 (0.37-2.47)	1.20 (0.43-3.29)		
					<300	1.04 (0.45-2.40)	1.09 (0.36-3.28)		
					300-900	1.77 (0.32-1.84)	0.63 (0.24-1.65)		
					>900				

Table 7: Results from epidemiology studies for cellular telephone use and the location of glioma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Location or laterality	Exposed Controls	OR (95%CI)	Comparison group
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Glioma	Temporal lobe	509	0.86 (0.66-1.13)	Avg 1 call per week for 6 mo (lag 1 yr)
					≥10 years since start	94	1.36 (0.88-2.11)	
					≥1640 hours cumulative	78	1.87 (1.09-3.22)	
					≥270 calls (hundreds)	61	1.10 (0.65-1.85)	
					Parietal lobe	871	0.77 (0.62-0.95)	
					≥10 years since start	129	0.92 (0.65-1.30)	
					≥1640 hours cumulative	105	1.25 (0.81-1.91)	
					≥270 calls (hundreds)	86	1.02 (0.67-1.57)	
					Other locations	248	0.79 (0.51-1.23)	
					≥10 years since start	32	0.41 (0.16-1.08)	
					≥1640 hours cumulative	18	0.91 (0.33-2.51)	
					≥270 calls (hundreds)	19	0.42 (0.13-1.33)	
Coureau et al. (2013)	CC	2004-2006, France	≥16, Both	Glioma	Temporal lobe	68	3.94 (0.81-19.08)	Avg 1 call per week for 6 mo
					Frontal lobe	76	1.87 (0.62-5.64)	
					Other locations	87	3.61 (1.00-12.96)	
Hardell et al. (2015)	CC	1997-2003, 2007-2009, Sweden	20-80, Both	Glioma	Temporal Lobe	367	4.3 (2.0-9.3)	
Frei et al. (2011)	Cohort	1990-2007, Denmark	≥30 at time of entry	Glioma	Cerebrum	52	0.90 (0.67-1.22)	Subscription >1 year between 1982 and 1995
					Frontal lobe	79	1.13 (0.89-1.45)	Phone use only before 1995
					Temporal lobe	65	1.13 (0.86-1.48)	
					Parietal lobe	33	0.73 (0.50-1.05)	
					Occipital lobe	18	1.47 (0.87-2.48)	
					Other and unspecified	77	1.35 (1.05-1.75)	

4.1.2 Studies in Children

Elliott et al. (2010) [108] conducted a case-control study of cancers in children aged 0-4 in Great Britain looking at a linkage to mobile phone base stations. Cases were all registered children with cancer in 1999-2001 (1926 cases) and four controls for each case were chosen from the national birth registry matched by sex and date of birth. Birth addresses (or approximate addresses) were needed for each case and each control leaving a total of 1397 cases and 5588 controls. Three exposure metrics were used, distance from the nearest mobile phone base station, total output from all base stations within 700 meters, and a modeled power density (dBm) from all base stations within 1400 meters of the birth address (modeling was based upon surveys and then validated against later additional survey data). Of the 1397 cases, there were 251 brain cancers (1004 controls). None of the mean exposures for any of the three metrics were different between cases and controls. ORs were very close to 1 for all exposure metrics when exposure was broken into tertiles and the referent group was the first tertile. Similar results were seen in an analysis using the continuous exposure measure directly. The same patterns were true for all cancers and leukemias. (Table 8)

The CEFALO study (**Aydin et al. (2012)** [109]) is an international case-control study conducted in Denmark, Norway, Sweden and Switzerland of children and adolescents aged 7-19 years at time of diagnosis of a brain cancer. Cases had brain tumors with a specific ICD-10 classification and were identified by a combination of factors. Controls were matched on year and month of birth or just year of birth (Norway) with two cases per control. The study included 352 cases (83.2% response) and 646 controls (71.1% response); 213 of the cases had gliomas. Exposure was obtained by personal interviews with mobile phone use 6 months prior to diagnosis excluded from the analyses. Cases were asked for permission to access usage data from mobile phone operators. In Denmark and Sweden, data covered the entire period of usage whereas in Switzerland, data was only kept for 6 months so data were only available for after diagnosis; data from providers in Norway was not obtained. The OR for regular use (one call per week for at least 6 months) versus not was 1.36 (0.92-2.02). All ORs for time since first use were above 1 (1.35 (0.89-2.04) for <3.3 years, 1.47 (0.87-2.49) for 3.3-5.0 years, 1.26 (0.70-2.28) for > 5 years). Similar patterns were seen for cumulative duration of subscriptions (≤2.7 years, 1.34 [0.89-2.01]; 2.8-4 years, 1.45 [0.83-2.54]; >4 years, 1.58 [0.86-2.91]) , cumulative duration of calls (≤35 hours, 1.33 [0.89-2.01]; 36-144 hours, 1.44 [0.85-2.44]; >144 hours, 1.55 [0.86-2.82]) and cumulative number of calls (≤936 calls, 1.34 [0.89-2.02]; 937-2638 calls, 1.47 [0.86-2.51]; >2638 calls, 1.42 [0.79-2.53]). Stratifying the analysis for only gliomas yielded an OR of 1.14 (0.66-1.97) but only included 192 cases (it appears they excluded the 21 ependymomas even though these are gliomas). When they analyzed brain tumors using the operator-recorded data (35% of cases, 34% of controls), they saw a significant trend for time since first subscription (p=0.001) with the highest exposure group (>2.8 years) having a statistically significant OR of 2.15 (1.07-4.29). The same analysis using self-reported use had a trend test with p=0.22 and an OR in the highest exposure class of 1.47 (0.81-2.67). Other exposure metrics saw generally higher ORs using the operator-recorded use data than self-reported use; this is likely due to some degree of differential exposure misclassification since a study showed cases overestimated their numbers of calls (9%) and duration of calls (52%) much less than controls (34% and 163% respectively) [110]. The OR for ipsilateral use (1.74, 0.91-3.33) was not larger than that for contralateral use (2.07, 0.95-4.52), although the definition used for ipsilateral and contralateral was unique to this study [111]. For ipsilateral and contralateral use, exposure-response relationships were seen for all exposure measures and the highest exposure groups had the biggest ORs, many statistically significant. The major strengths of this study include the participation rates and the

exposure information. The major weaknesses include a failure to analyze all gliomas and to do the ipsilateral analysis and operator-generated usage on the gliomas alone. There were other criticisms of this paper [112]. (Table 8)

Li et al. (2012) [113] conducted a population-based case-control study of incident cases of all cancers in Taiwan in children and adolescents <15 years of age between 2003 and 2007. Thirty controls were randomly selected for each case and matched on year of birth. The annual power density (APD; wattwatt-year/km^2) for each township was calculated from the 71,185 mobile phone base stations in Taiwan. Exposure was calculated as the average APD five years prior to diagnosis for cases and prior to July 1 for the controls in the year their matched case was admitted. For brain tumors there were 394 cases and 11,820 controls. OR for above median versus below median exposure was 1.09 (0.88-1.36) for the crude estimate and 1.14 (0.83-1.55) for the adjusted estimate (calendar year, age, gender, high-voltage transmission line, and urbanization of township). When the exposures were divided into tertiles, there was an indication of a trend (crude: 1.01 [0.84-1.42] T2, 1.09 [0.77-1.32] T3; adjusted: 1.03 [0.73-1.45] T2, 1.14 [0.70-1.85] T3), but no test for trend was used. The major limitation of this study is that the exposure metric does not pertain to the individual's exposure, but exposure to anyone in the township. Nearness to a tower, use of a cellular telephone, and other sources of RF that might have been related to disease incidence were not assessed. Thus, this study is closer to using an ecological exposure measurement than an individual personal exposure measurement. (Table 8)

Feltbower et al. (2014) [114] conducted a pilot case-control study of children and young adults ages 0-24 in two UK cancer treatment centers. Eligible cases were 0-24 years of age presenting with a diagnosis of intracranial tumor during an unspecified period. At one center, cases were matched by age and sex with a target of 2 controls per case and randomly selected from the general practice. At the second center, 3 friend controls were envisioned but the researchers were unable to attain any controls. Eventually, they were able to interview 49 cases (52% response) and 78 controls (32% response). The study was designed to be compatible with the CEFALO study [109]. The OR for brain cancer and having spoken on a mobile phone more than 20 times was 0.9 (0.2-3.3). The main weaknesses of this study are its size, response rate, and failure to get controls from the second center. (Table 8)

Table 8: Results from epidemiology studies RF and brain tumors in children and adolescents

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Sample Size for all endpoints (% resp.)	Exposed (%) Cases	Group	OR (95% CI)	P trend	Comparison group
Elliott et al. (2010)	CC	1999-2001, Great Britain	0-4, Both	Brain and CNS tumors	251 (ND) Brain and CNS		Base station distance			Referent is lowest exposure group
						85	Medium	0.95 (0.67-1.34)		
						81	High	0.95 (0.65-1.38)		Most adjusted analyses
						251	15-18 centile change	1.12 (0.91-1.39)		
							Total power			
						56	Medium	1.02 (0.72-1.46)		
						45	High	0.83 (0.54-1.25)		
						251	15-18 centile change	0.89 (0.73-1.09)		
							Modelled Power			
						80	Medium	0.97 (0.69-1.37)		
						78	High	0.76 (0.51-1.12)		
						251	15-18 centile change	0.82 (0.55-1.22)		
Aydin et al. (2012)	CC	1999-2001, Denmark, Norway, Sweden, Switzerland	7-19, Both	Brain and CNS tumors	352 (83.2%) cases 646 (71.1%) controls	194	Regular use	1.36 (0.92-2.02)		>1 call per week, 6 months lag
							Years since first use			
						95	≤3.3	1.35 (0.89-2.04)	0.37	
						53	3.3-5.0	1.47 (0.87-2.49)		
						46	>5.0	1.26 (0.70-2.28)		
							Operator-recorded first use			
						19	≤1.8 years	0.78 (0.43-1.40)	0.001	
						19	1.8-2.8 years	1.71 (0.85-3.44)		
						24	>2.8 years	2.15 (1.07-4.29)		
							Cumulative years use			
						94	≤2.7	1.34 (0.89-2.01)	0.14	
						45	2.8-4.0	1.45 (0.83-2.54)		
						52	>4.0	1.58 (0.86-2.91)		
							Operator-recorded cumulative use			
						13	≤1.8 years	1.14 (0.55-2.37)	0.15	
						10	1.9-3.3 years	1.73 (0.71-4.20)		
						11	>3.3 years	1.84 (0.74-4.58)		
							Cumulative hours			
						94	≤35	1.33 (0.89-2.01)	0.42	
						48	36-144	1.44 (0.85-2.44)		
						49	>144	1.55 (0.86-2.82)		
							Operator-recorded cumulative use			
						14	≤11 hours	1.24 (0.61-2.55)	0.36	
						11	12-27 hours	1.95 (0.81-4.73)		
						9	>27 hours	1.38 (0.53-3.61)		
							Tumor Location			
						83	Temporal, frontal, cer.	1.00 (0.58-1.72)		
						75	Other	1.92 (1.07-3.44)		
							Morphology			
						84	Glioma	1.14 (0.66-1.97)		
						74	Other	1.65 (0.93-2.93)		
Li et al. (2012)	CC	2003-2007, Taiwan	<15 years	Brain tumors	394 (ND) Cases 11820 (ND) Controls		RF exposure density			
						174	≥median	1.14 (0.83-1.55)	0.426	Referent <median
						106	1st-2nd tertile	1.03 (0.73-1.45)	0.875	Referent 1st tertile
						121	≥2nd tertile	1.14 (0.70-1.85)	0.599	
							Per 1 SD exposure			Most adjusted analyses
						394	density	1.09 (0.95-1.25)	0.230	
Feltblower et al. (2014)	CC	2007-2010, UK	0-24, Both	Brain tumors	49(52%) Brain tumors 78 (32%) Controls		Cumulative speaking on phone			Referent spoken on phone ≤20 times
						26	>20 ties	0.9 (0.2-3.3)		

4.1.3 Discussion

The strongest evidence for an effect of RF on the risks of glioma come from the case-control studies. Case-control studies are designed to compare the exposure characteristics of cases (people who have or have had a glioma) against a collection of controls (people without a history of gliomas). In evaluating the results from case-control studies, researchers must consider two possible sources of bias; selection bias and recall bias. Selection or participation bias occurs when the people who are selected to be a part of the study (both cases and controls) are not willing to participate and that participation is related to both the status of the person (case versus control) and to the exposure (cellular phones) being investigated. For example, if participants that do not use a cellular phone are less willing to participate than participants who do use a cellular phone and that controls are less likely to participate than cases, this can reduce the odds ratio[1] (OR) and hide a potential risk.

Case-control studies rely on measures of exposure that are generally obtained through a questionnaire administered to both the cases and the controls about their past exposures. Because they are recalling past exposures, there is a possibility that this recall may be linked in some way to their status as a case or a control. This is recall bias. For example, if cases are more likely to say they have used a cellular phone than controls or they are more likely to overestimate their cellular phone usage, this could increase the ORs and lead to an overestimation of the risk from cellular phone use. The recall must be different for the cases than the controls for this to cause a bias; errors in recalling past exposures that are similar for both cases and controls would not be recall bias.

Cohort studies generally do not have these two problems since they are asked about their exposure prior to getting the disease of interest. Cohort studies are usually aimed at identifying causes for disease in a large population of people who are followed over time. As the diseases appear in the population, an analysis is done to evaluate the risk ratio[2] (RR) in order to find exposures that are associated with the disease. Exposure is generally determined using a questionnaire administered during the course of the study where participants are asked about their exposures. Disease status (e.g. presence or absence of a glioma) is usually determined through periodic evaluations of cancer registries and publication of the results; thus the study has a baseline date (the date a participant enters into the study) and a follow-up date (the last date of update of the cancer registry or the date the participant got the tumor or the date the participant left the study). In evaluating the results from cohort studies, researchers must consider a different source of bias; exposure

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[1] The odds ratio (OR) is calculated as the proportion of exposed cases with disease to exposed controls divided by the proportion of non-exposed cases to non-exposed controls. For rare diseases, this value approximates the population risk ratio (PRR) which is the probability of having the disease in exposed individuals divided by the probability of having the disease in non-exposed individuals. If the PRR is 1, then there is no difference in the probability of having the disease regardless of your exposure. Values of PRR greater than 1 imply the risk is higher in the exposed population. Because the OR is an estimate of the PRR for rare diseases, it is usually accompanied by a 95% confidence interval that describes the probable range of the estimate. If the OR is greater than 1, then the exposure is associated with the disease. If the lower 95% confidence bound for the OR is greater than 1, this is typically used to say the association is statistically significant.

[2] The rate ratio (RR) is estimated as the incidence in the exposed population divided by the incidence in the unexposed population. Incidence is calculated as the number of events in a fixed period of time divided by the person years at risk. Unlike the OR, the RR does not require the assumption of a rare disease to serve as a good estimate of the population risk ratio (PRR). Like the OR, RR>1 implies an association between the disease and the exposure.

misclassification. Exposure misclassification occurs when the exposure for participants is incorrectly applied. For example, if a participant is asked on Tuesday about their cellular phone use and they do not use a cellular phone, they would be classified as a non-user. If on Wednesday, they go to the store and purchase a phone, they are now a user, but if they do not get asked again about their use prior to the follow-up date, they would be misclassified in any evaluations. Non-differential exposure misclassification occurs when the probability of an error in determining whether an individual is exposed or not is the same for both those with the disease and for those without the disease. Non-differential exposure misclassification generally results in RRs that are closer to 1 than the true underlying risk would imply and can hide risks that are really there. Differential exposure misclassification occurs when there is a difference in the exposure misclassification between those with the disease and those without. Depending on the direction of the misclassification relative to disease status, this can either hide risks or inflate risks. For example, if those with the disease are more likely to be misclassified as non-exposed, the estimated RRs will be smaller than they should be and this would result in a reduced estimate of the risk.

Finally, one other problem to be carefully considered is confounding. Confounding occurs when exposure is correlated with another factor that is also associated with the disease of interest. For example, if age is associated with the incidence of gliomas and is also correlated with cellular phone usage, failure to recognize this potential confounding could lead to an association between cell phone usage and the incidence of gliomas that is spurious. To avoid this, researchers, when evaluating their data, will "adjust" the analysis for other potential confounders. Thus, in evaluating the findings from these studies, it is important to evaluate what adjustments were made for potential confounders in the analysis. This problem can affect both case-control studies and cohort studies.

In evaluating the epidemiological evidence, there are three areas that need to be carefully explored: consistency of the association, the existence of an exposure-response relationship (definitions to follow), and the strength of the association.

4.1.3.1 Consistency of the Association

I will focus on the main studies listed in Table 1. All of these studies did a reasonable job of addressing confounders in their analyses and so this problem will not be discussed further. First, we should consider timing of the study. According to the **World Bank** [115], 0.001% of people globally had subscriptions to mobile phones in 1980. By 1990, that was 0.2% and by 2000 it was 12%. In the US, by 1990, 2% of people had subscriptions and by 2000, 39% had cellular phones. Thus, for studies in the 1990s, we are looking at a rare exposure and trying to associate it with a rare disease (gliomas) and probably with very little time from the beginning of exposure to disease onset. Thus, it is unlikely that studies like **Hardell et al. (1999)** [85], **Muscat et al. (2000)** [40], **Inskip et al. (2001)** [44], and **Auvinen et al. (2002)** [45] would show much of an association. And that is basically the case, with these studies producing ORs of approximately 1.0 except for **Auvinen et al. (2002)** [45] with an OR of 1.5 (1.0-2.4). Thus, the later studies are more likely to show an effect if one exists than are the earlier studies and these should be given greater weight.

The size of a study will also matter since studies with greater numbers of cases and controls (especially exposed cases) will generally have smaller confidence bounds and have a greater chance of seeing an effect if one exists. Thus, the studies by **Gousias et al. (2009)** [46] and **Baldi et al. (2011)** [89] will carry less weight in an overall evaluation.

There are also studies where the referent group was "never used a mobile phone" versus studies where the referent group was "not a regular user of mobile phones" defined by different measures. Less weight should be given to studies with comparisons to "never used" simply because the "ever used" group could include people who used a phone only a few times.

Given these caveats, there are 4 case-control studies that should carry the greatest weight; **Interphone (2010)** [48], **Coureau et al. (2014)** [90], **Hardell et al. (2015)** [88] and **Yoon et al. (2015)** [93]. Three of these studies show ORs >1 for regular use of a cellular phone with only one showing a significantly increased OR (**Hardell et al. (2015)** [88], 1.3 (1.1-1.6)).

The largest study, **Interphone (2010)**, has an OR<1 and more cases and controls than the other three studies combined. The ORs also did not increase with increasing duration of the use of a mobile phone (Table 1). This study used cases that were both living and, by proxy information, those who had died before interview. However, in the Interphone study there was some degree of participation bias [48, 116] that could have resulted in a reduction of the ORs by as much as 10% according to some analyses [74, 116]. For example, just looking at the cases and controls from Canada in the Interphone study, the OR for regular use of a cellular phone went from 1.0 (0.7-1.5) to 1.1 (1.0-1.2) when this bias was theoretically corrected [116]. Applying this same bias correction to the Interphone study yields an OR of 0.9, still below 1. Another correction one could use to account for participation bias, and to some degree recall bias, is to use the lowest category of usage as the reference category rather than the non-regular user category. When this was done for the Interphone study, using the lowest duration of use as the reference group, all longer durations were significantly greater that 1.0 (Table 2). Analyses of recall bias in the Interphone study showed very little impact of recall bias on the evaluation of regular usage [74, 116].

The studies demonstrating the greatest ORs for regular use are the studies that went into the pooled analysis by **Hardell et al. (2015)** [88]. Their pooled study showed an overall OR of 1.3 (1.1-1.6) for regular use. In addition, all of the 5-year groupings of duration of use were greater than 1 and all usage longer than 5-years was significantly greater than 1 (Table 2). Only living cases were included. Their response rate was high enough that participation bias is unlikely to have lowered the OR values. It is possible that participation bias could have occurred from the use of only live cases, but in a separate analysis from a subset of the pooled studies, they saw no important differences between their analyses using live cases when compared to analyses using only deceased cases. On the other hand, recall bias could have increased the ORs. In one of the original case-control studies [117] used in their pooled analysis, they evaluated this issue and saw little indication of recall bias. In addition, in their pooled analysis, they used meningioma cases as the reference group since they were likely to have the same recall bias as the glioma cases if recall bias was a problem. The OR from the population-based reference group was 1.3 (1.1-1.6) and dropped slightly to 1.2 (0.97-1.5) with the meningioma reference group. It is unlikely recall bias explains these results.

Spinelli et al. (2010) [47] is also a very small study, but they provided no information on ever versus never use of mobile phones.

Coureau et al. (2014) [90] is about 12 times smaller than the Interphone study and about 7 times smaller than **Hardell et al. (2015)** [88]. Their evaluation showed an overall OR for regular users of 1.24 (0.86-1.77) which rose slightly to 1.33 (0.89-1.98) if proxies are removed. Duration of use was weakly associated with duration of cellular phone use but had the highest OR (1.61 [0.85-3.09]) in the longest duration group (≥10 years) (Table 2). This study used cases that were both living and, by proxy information, those who had died before interview. This study had a lower participation rate

than the other two studies and a large difference in participation between cases (66%) and controls (45%). They did not have a questionnaire for non-participants so there is no information on whether participation bias is a problem in this study. Exposure from mobile phones was done by interview using a standardized questionnaire which limits mistakes, but does nothing to control for potential recall bias. The fact that ORs for analyses with proxies versus those without proxies gave equivalent results helps to reduce the possibility of recall bias, but the number of proxy respondents was small.

Yoon et al. (2015) [93] has about twice as many exposed cases as **Coureau et al. (2014)** [90]. The OR for regular use was 1.17 (0.63-2.14) dropping to 0.94 (0.46-1.89) if proxy responders are removed. The OR for duration of use was >1 for all categories but showed no obvious pattern and dropped slightly when proxies were removed. The participation rates in this study were very low (32% cases, 27% controls) mostly due to cases refusing to participate or not participating due to excess pain. Participation bias and recall bias are certainly possible from this study.

One way in which to evaluate the consistency of these findings across the various studies is by means of a meta-analysis. A meta-analysis is a technique of synthesizing research results by using various statistical methods to retrieve, select, and combine results from previous separate but related studies. There have been numerous meta-analyses on the relationship between cell phone use and gliomas [118-125]. The three most recent studies are worth a quick review. **Roosli et al. (2019)** [118] explored the risks of glioma using the two cohort studies [96, 102] and 10 case-control studies [40, 44, 45, 47, 48, 85, 88-90, 93] based upon an inclusion criteria of 1) a clearly defined source population, 2a) provide a comparison of ever versus never use of a mobile phone (they also included regular use) and/or 2b) allow for an evaluation of long-term use (≥10 years of use before glioma diagnosis) and 3) where there are multiple publications on the same data or subsets of the same data, they included the most recent comprehensive analysis. Where there were multiple publications of subgroups of studies (e.g. Interphone), they did sensitivity analyses to examine the impact of using the subgroups rather than the pooled publications. Meta-estimates of glioma risks (mRRs) were calculated using a random-effects model using the DerSimonian and Laird method using Stata (version 11.2, Stata Corp, College Station, Texas). Unless noted otherwise, all of the meta-analyses used the same method of a random-effects model and the DerSimonian and Laird method).

The main analysis from **Roosli et al. (2019)** [118] is shown in their Figure 1 and give the mRRs for the analyses of studies showing ORs for ≥10 years exposure. For the case-control studies, they get an mRR of 1.30 (0.90-1.87). For the Cohort studies, they show an mRR of 0.92 (0.72, 1.16) and for all studies combined they get 1.11 (0.85-1.46). Entering their numbers into Stata (v 16.2 for MAC), I am able to reproduce their mRRs, however, they had to first calculate an mRR for ≥10 years in the study by Hardell et al. (2015) [88] by combining results from multiple 5-year categories. They list this combination as giving an mRR for ≥10 years for that study of 1.69 (1.40-2.03) whereas when I do the same analysis, I get 1.81 (1.35-2.43). The only way I was able to achieve the same results as **Roosli et al. (2019)** [118] for the mRR was to use a fixed-effects model rather than a random-effects model (this appears to be a mistake in the paper). They also did a meta-analysis of ever versus never use for all 10 case-control studies (1.03 [0.86-1.22]) and the cohort studies (0.97 [0.82-1.15]) with a combined mRR of 1.00 (0.89-1.13). They also conducted a cumulative meta-analysis of the studies with ≥10 years of use splitting the Hardell group studies into those from 1997-2003 and 2007-2009 yielding a slightly higher mRR (1.24 [0.93-1.66]) for all studies combined. They also did several other analyses of ever versus never use with no appreciable changes in the results. One problem with these meta-analyses is that they give very little weight to the largest studies. For

example, in their analysis of the 12 ever versus never studies, **The Interphone (2010)** [48] study with 1666 exposed cases got a relative weight of 13%, **Hardell et al. (2015)** [88] with 945 exposed cases got a relative weight of 11.6% and the remaining studies with a total of 1586 exposed cases got a relative weight of >75%. In addition, all of these analyses showed highly significant heterogeneity. Roosli et al. (2019) [118] did not consider laterality or tumor location in the brain.

Wang et al. (2018) [119] did a meta-analysis like that done by **Roosli et al. (2019)** [118] for ever versus never use, but did not include the **Spinelli et al. (2010)** [47] study (no reason given) and instead of using all malignant brain tumors from **Muscat et al. (2000)** [40], they included separate ORs for astrocytic tumors (0.80 [0.50-1.20]) and oligodendrogliomas and mixed gliomas (0.90 [0.40-2.10]). They also included wireless telephones from **Hardell et al. (2015)** [88] in their analyses. Their analysis resulted in an mRR of 1.03 (0.92-1.16). They also did meta-analyses on the data for 0-5 years (0.92 [0.77-1.09]), 5-10 years (1.07 [0.88-1.30]) and ≥10 years (1.33 [1.05-1.67]). Their ≥10 years category was done differently than **Roosli et al. (2019)** [118] in that they did not include **Yoon et al. (2015)** [93] and the 4 exposure categories for **Hardell et al. (2015)** [88] were entered directly into the analysis rather than being pooled first. All of these analyses showed significant heterogeneity which they said was reduced by removing either the Interphone study or the study by **Hardell et al. (2015)** [88]. For ipsilateral tumors and ever versus never use, they saw an mRR of 1.26 (0.87-1.84) in comparison to contralateral use that showed an mRR of 1.10 (0.85-1.42). Finally, evaluating gliomas located in the temporal lobe, again for ever versus never use, they saw an mRR of 1.61 (0.78-3.33) [Note that in the text of the manuscript rather than their table, they list this mRR as 0.93 (0.69-1.24); I was able to verify the mRR of 1.61 but could not find a reasoning behind the number in the text]. The relative weights for the individual studies also fail to match the sample sizes in these evaluations.

Yang et al. (2017) [120] also performed a meta-analysis on some of the studies included in this review. Their analysis excluded both the **Hardell et al. (2015)** [88] pooled analysis and the **Interphone (2010)** [48] pooled analysis. Instead, they included the **Hardell et al. (2011)** [126] study that included the pooled analysis of the 1997-2003 studies with the inclusion of deceased cases and individual Interphone studies from separate countries [49, 52, 54, 55, 59, 61] or a pooled analysis from 5 countries [64]. For ever versus never use, they saw an mRR of 0.98 (0.88-1.10) and for ≥10 years duration of use, the mRR was 1.44 (1.08-1.91); both evaluations showed substantial heterogeneity. For ipsilateral use and ever/never exposures, the mRR was 0.97 (0.88-1.06) whereas for contralateral use it was 0.75 (0.65-0.87) with marginal heterogeneity. For ≥10 years use, the ipsilateral mRR was 1.46 (1.12-1.92) and contralateral use was 1.12 (0.81-1.55) with no heterogeneity. The studies on laterality did not include the study by **Hardell et al. (2011)** [126] for low-grade (1.11 [0.87-1.42] ever/never, 2.22 [1.69-2.92] ≥10 years) and high grade (0.82 [0.68-0.99] ever/never; 1.16 [0.85-1.59] ≥10 years) gliomas.

The remaining meta-analyses are older and use fewer and fewer of the individual studies. One meta-analysis worth mentioning is the one done by **Hardell et al. (2013)** [127] directly comparing the results of **Hardell et al. (2011)** [128] with the results from the pooled **Interphone (2010)** [48] study. For a latency of ≥10 years, the saw the following mRRs: all users 1.48 (0.65-3.35); ipsilateral 1.84 (0.80-4.25); contralateral 1.23 (0.40-3.73); temporal lobe 1.71 (1.04-2.81). For a cumulative use ≥1640 hours, they saw the following mRRs: all users 1.74 (1.07-2.83); ipsilateral 2.29 (1.56-3.37); contralateral 1.52 (0.90-2.57); temporal lobe 2.06 (1.34-3.17). An important point of this report is that the **Interphone (2010)** [48] study included adults 30-59 years of age and **Hardell et al. (2011)** [128] extracted the same group from their 1997-2003 pooled analysis [86] and adjusted the exposure groupings to match the Interphone groupings. They did not present these numbers in

their meta-analysis, but that can be done. The results of the same random-effects modeling as done by **Hardell et al. (2011)** [128] yields the following results: ≥10 years 1.30 (0.72-2.33); ≥1640 hours 1.48 (1.13-1.92); ≥1640 hours ipsilateral 2.03 (1.37-3.00); ≥1640 hours contralateral 1.32 (0.76-2.28).

It is clear from these numerous meta analyses, that the choice of which studies to use, how to enter the multiple studies by Hardell et al. and whether to use the pooled analysis from the Interphone study or some of the single analyses can have an impact on the final values. To provide a better view of the results, Figure 1 is a forest plot of all of the ORs from individual publications that evaluated regular use versus minimal or never use or ever use versus never use (if both were given in a study, regular use is shown). The column labeled "Study" provides the reference to the publication and the years in which cases and controls were collected for case control studies and the years when phone use information was collected for cohort studies and the year in which follow-up ended. Some studies are pooled evaluations of multiple other studies, so the other studies are indented. For example, the **Interphone (2010)** [48] study (Study F) is the pooled analysis of studies from 13 countries. **Lahkola et al. (2007)** [64] (Study F3) is a pooled analysis of the data from 5 of those countries and **Christenson et al (2005)** [49] (Study F3a) is the publication for data from one of those 5 countries. The column labeled "RR" is the risk ratio (OR, RR or mRR) from the study, "Lower" and "Upper" are the lower and upper bound on a 95% confidence interval around the RR. The graphic on the right simply plots the RR as a square or diamond with the "whiskers" (blue line running through the box) showing the width of the 95% confidence interval. The vertical line passing through 1 represents no effect. If the box and both whiskers are to the right of this line (greater than 1) and not touching it, this finding is statistically significant with a positive effect; if they fall completely to the left of the vertical line (below 1), then the risk is significantly reduced. The blue boxes that are filled in are major studies, the blue boxes that are white in the middle are the sub-studies and the red diamonds are all meta-analyses.

The graphic in Figure 1 is very useful for examining these types of data in a single view. Looking just at the filled in blue blocks (Studies A,B,C,D,E,F,G,H,I,J,K,L), it is clear some studies (D, I) fall clearly above the vertical line and demonstrate statistically significant increased risk. One study (F) shows a significant reduction in risk. The remaining studies show increases (H, J, K) or decreases (A, B, E, G, L) or no risk (C). The question to be addressed is what is the overall tendency of these data? The meta-analyses address this issue. The first meta-analysis (Meta Analysis A,B,C,D,E,F,G,H,I,J,K,L) combines the information from all of the major studies to produce an mRR of 1.01 (0.92-1.11) for ever versus never exposure suggesting that all of the positives and negatives balance out to give no overall effect. This meta-analysis also shows these studies are very different (Homogeneity Test: p=0.01) which suggests the combination is not accounting for all of the variability in the RRs. However, as mentioned earlier, the newer, larger studies represent longer exposures, so I have also done meta-analyses on four large, recent case-control studies (F,H,I,J) and the two cohort studies (K,L) which should carry the greatest weight in any decision. Combining the four case-control studies (Meta Analysis F,H,I,J) results in a mRR of 1.09 (0.8-1.49), a slight increase in risk from the use of a mobile phone, but still heterogenous across studies. The combined cohort studies yield a mRR of 0.97 (0.74-1.27) suggesting no risk, and no heterogeneity (p=0.84). Combining the 4 case-control studies and the 2 cohort studies (Meta Analysis F,H,I,J,K,L) yields an mRR of 1.03 (0.86-1.24) again suggesting no risk but with significant heterogeneity (p=0.00).

As mentioned earlier, the Interphone study did an alternate set of analyses where the referent group was different depending upon the exposure metric being used (Appendix 2 Table, **Interphone (2010)**). It is possible to use meta-analysis to combine these results to get a pseudo regular/not

mRR for each exposure metric[3]. The rows labelled F6, F7 and F8 are the mRR values for these meta-analyses: F6 is an estimate of ≥2years since start of regular use compared to 1-2 years of regular use [mRR 1.75 (1.40-2.18)], F7 is ≥5 hours of cumulative hands-free use compared to <5 hours [mRR 1.16 (1.00-1.35)], and F8 compares ≥1500 cumulative calls to <1500 cumulative calls [mRR 1.12 (0.96-1.30)]. To evaluate the sensitivity of the meta-analyses to the use of this alternative set of reference groups, I applied the least significant evaluation (F8) to the meta-analyses as a replacement for the Interphone study value (F). For the full analysis (Meta Analysis A,B,C,D,E,F8,G,H,I,J,K,L), the mRR becomes almost statistically significant; mRR 1.06 (0.98-1.15). Using just the larger and recent case-control studies (Meta Analysis F8,H,I,J), the mRR is significant [mRR 1.19 (1.07-1.33)] as is the combination of these case-control studies with the cohort studies [mRR 1.12 (1.01-1.24)]. None of these meta-analyses substituting F8 for F show significant heterogeneity. Thus, the meta-analysis is highly sensitive to the use of the reference group for the Interphone study.

Figure 2 is a forest plot of all of the ORs from individual publications that reported on duration of use ≥8 years or more. There are 6 studies; 5 of these studies show groupings of 1-4 years, 5-9 years and ≥10 years and one study with groupings of 1-5 years, 5-8 years and ≥8 years. For the study by **Hardell et al. (2015)** [88], groupings of 10-14, 15-19, 20-24 and ≥25 years were combined by meta-analysis to get a single mRR for ≥10 years. For **Frei et al. (2011)** [96], individual male and female RRs were combined by meta-analysis to get a single mRR for males and females combined. There are 4 groups of meta-analyses each with three separate meta-analyses for 1-4 years, 5-9 years and ≥10 years (combined with 1-<5 years, 5-8 years and ≥8 years respectively for **Yoon et al. (2015)** [93]). The four groups are case-control studies, case-control studies and cohort studies, then the same two groups substituting the original analysis in the Interphone study with their alternative analysis using 1-1.9 years as the referent group. A few things are noticeable in the Forest plot; with the exception of **Yoon et al. (2015)** (D), all of the case-control studies (A, B and C) show increasing ORs with increasing duration of use. The cohort studies (E and F) generally have decreasing RRs with increasing duration. In the meta-analyses, regardless of how the data are combined, there are increasing mRRs with increasing duration. The case-control studies generally show larger mRRs than the case-control and cohort studies combined and using the alternative referent group from the Interphone study yielded the largest mRRs with the highest 2 categories of duration being statistically significant for case-control studies using the alternate referent group.

The studies in adults are consistent.

Aydin et al. (2012) is the only study in children that looked at regular use of a mobile telephone and saw an OR of 1.36 (0.92-2.02). For years since first use, they saw ORs of 1.35 (0.89-2.04), 1.47 (0.87-2.49) and 1.26 (0.70-2.28) for lag times of ≤3.3 years, 3.3-5 years and >5 years respectively. When they used operator-recorded first use and lag times of ≤1.8 years, 1.8-2.8 years and >2.8 years, they saw a significant increasing risk (p=0.001) and ORs of 0.78 (0.43-1.40), 1.71 (0.85-3.44) and 2.15 (1.07-4.29) respectively. When they divided the tumors into gliomas or other tumors, they saw an OR for gliomas of 1.14 (0.66-1.97) and for other of 1.65 (0.93-2.93). They saw no

[3] To build this combination, a meta-analysis is done on all of the risk ratios for a specific exposure metric (e.g. 1-5 years, 5-10 years and ≥10 years latency). To check if this yields reasonable mRRs, meta-analyses were used to combined the various categories under the three exposure metrics in the cases where the referent group is non-regular users. There analysis yielded OR=0.81 (0.70-0.94) whereas doing a meta-analysis to get an equivalent estimate yielded mRR=0.84 (0.72-0.99) for latency years, mRR=0.82 (0.72-0.94) for cumulative hours and mRR=0.82 (0.75-0.90) for cumulative number of call.

relationship with the temporal lobe (1.00 (0.58-1.72). **Feltblower et al. (2014)** saw an OR of 0.9 (0.2-3.3) for young adults who used a mobile phone more than 20 times.

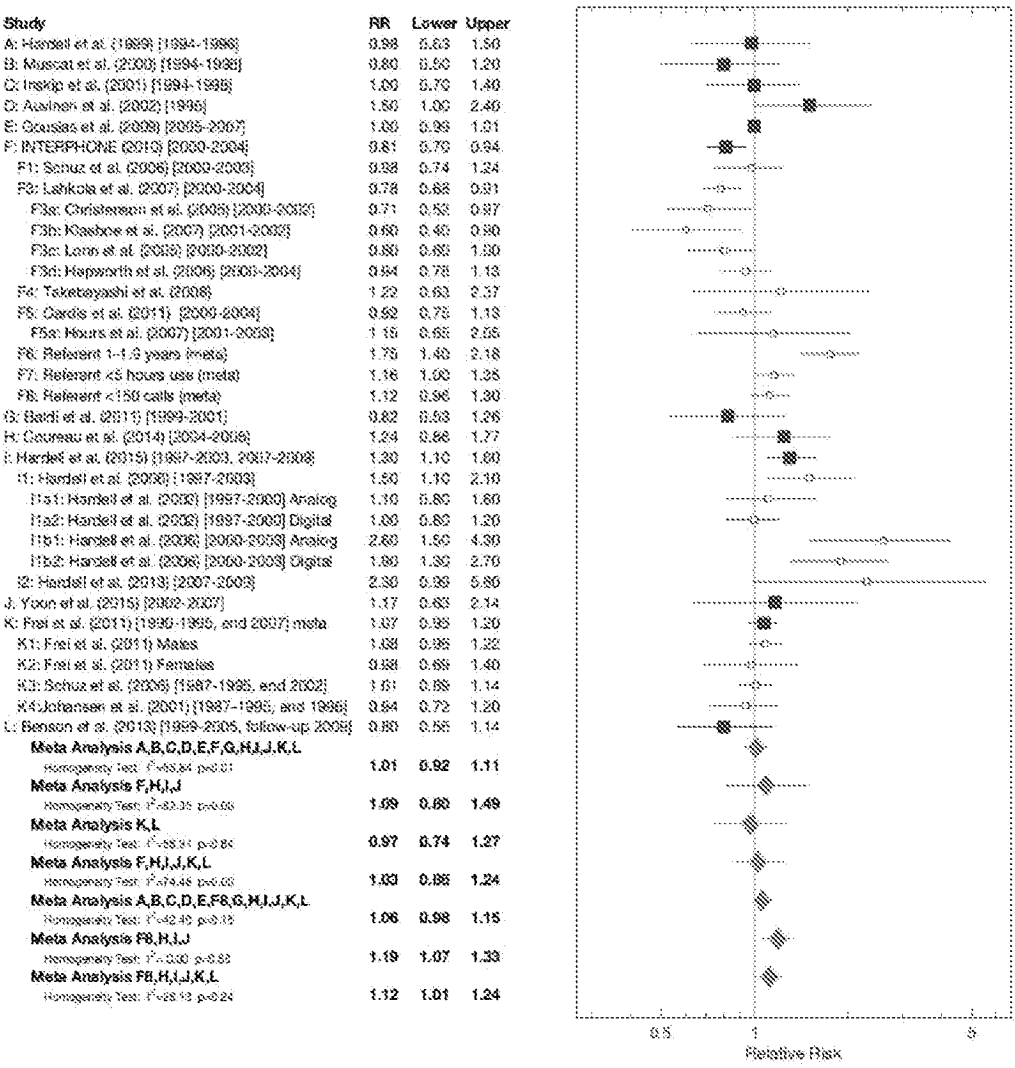


Figure 1: Forest plot and meta-analyses of regular use or ever use of cellular telephones and the risk of glioma [studies with a solid blue square either single studies that stand alone or pooled studies that encompass numerous single studies; open squares are individual studies or smaller pooled studies; red diamonds are meta-analyses][a]

[a] - The column labeled "Study" provides the reference to the publication and the years in which cases and controls were collected for case control studies and the years when phone use information were collected for cohort studies and the year in which follow-up ended. Some studies are pooled evaluations of multiple other studies, so the other studies are indented. For example, the Interphone study (Study F) is the pooled analysis of studies from 13 countries. Lahkola et al. (2007) (Study F3) is a pooled analysis of the data from 5 of those countries and Christenson et al (2005) (Study F3a) is the publication for data from one of those 5 countries. The column labeled "RR" is the risk ratio (OR, RR or mRR) from the study, "Lower" and "Upper" are the lower and upper bound on a 95% confidence interval around the RR. The graphic on the right simply plots the RR as a square or diamond with the "whiskers" (blue line running through the box) showing the width of the 95% confidence interval. The vertical line passing through 1 represents no effect. If the box and both whiskers are to the right of this line (greater than 1) and not touching it, this finding is statistically significant with a positive effect; if they fall completely to the left of the vertical line (below 1), then the risk is significantly reduced. The blue boxes that are filled in are major studies, the blue boxes that are white in the middle are the sub-studies and the red diamonds are all meta-analyses. "Homogeneity Test" provides the I^2 statistic and the p-value for the Q-test.

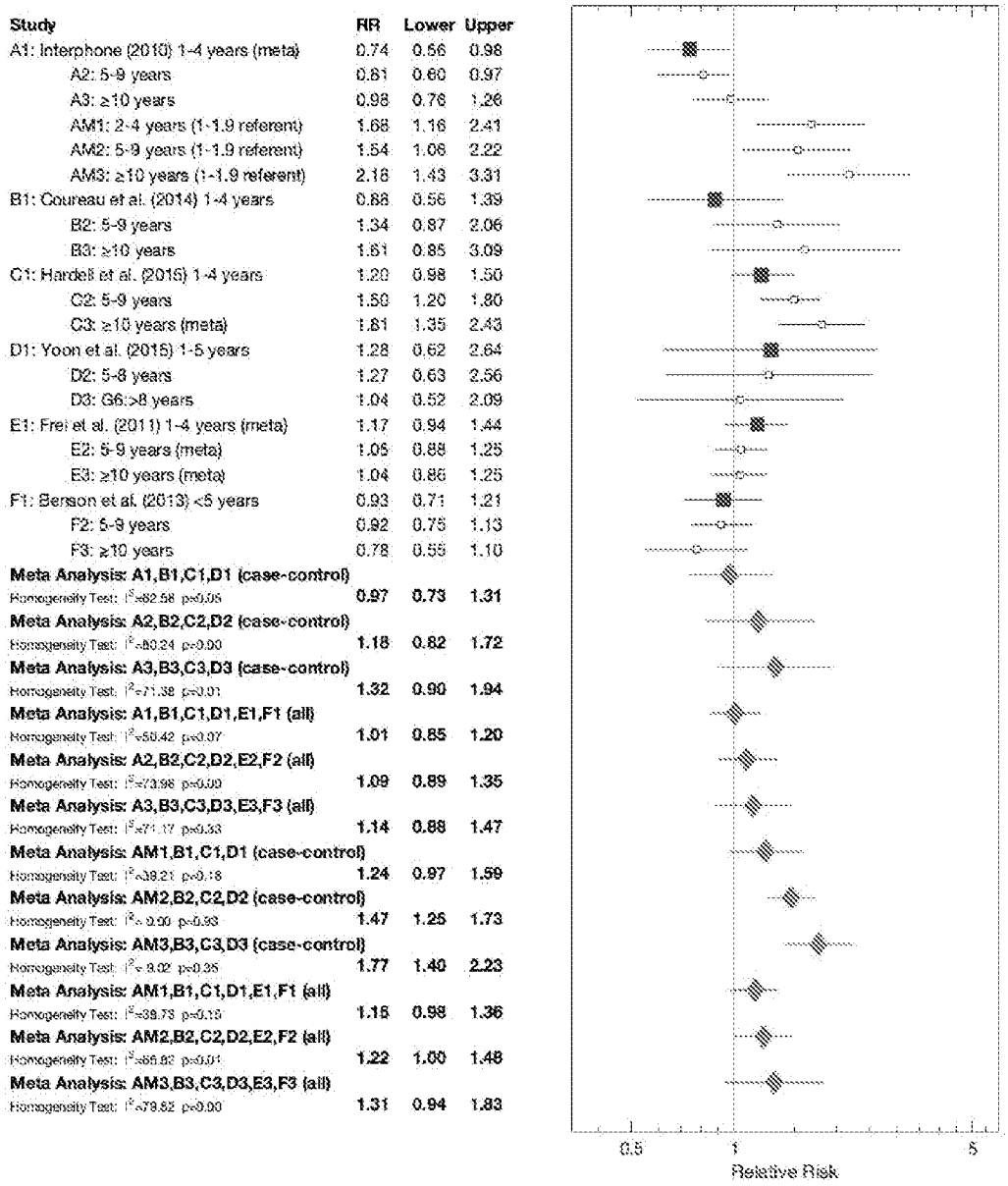


Figure 2: Forest plot and meta-analyses of duration of use of cellular telephones and the risk of glioma [studies with a solid blue square are either single studies that stand alone or pooled studies that encompass numerous single studies; open squares area second analysis from that same paper; red diamonds are meta-analyses, the columns and the figure are as in Figure 1].

4.1.3.2 Exposure-Response Relationship

The best measure for exposure-response relationships is the cumulative hours of use of a cellular telephone since it includes both the frequency of use and the duration of use. While duration of use is also a form of exposure-response, it is more likely that, similar to ionizing radiation, total

accumulated exposure is related to the risk of glioma if a relationship exists. Table 3 provides the results for all of the epidemiology studies with estimates of the cumulative use of cellular phones.

Inskip et al. (2001) shows no consistent exposure-response and has all of the ORs below 1. **Spinelli et al. (2005)** show an increase in the OR for use of 48-432 cumulative hours, but this drops for ≥432 hours. In addition, their measure of cumulative hours is different from the remaining studies in that they calculated frequency of use based upon the number of hours allowed in the subscription rather than the actual usage as recounted by the user. This could lead to misclassification of exposure and may have affected the ORs. The **Interphone study (2010)** basically shows flat exposure-response for the entire study until the largest exposure category, that is significantly elevated in risk with an OR of 1.40 (1.03-1.89). Using greater than 0 but less than 5 hours as the referent group, they see higher ORs with a slight increasing pattern and again the highest exposure group significantly elevated. **Coureau et al. (2014)** saw a clearly increasing exposure-response pattern with ORs below 1 in the low exposure categories and becoming marginally significant in the second highest exposure group [1.78 (0.98-3.24)] and significant in the highest exposure category [2.89 (1.41-5.93)]. Excluding proxies did not change this pattern. **Hardell et al. (2015)** saw a clear pattern of increasing risk with increasing exposure with all of their categories statistically significant. They also did a regression resulting in an OR of 1.013 (1.009-1.017) per hundred cumulative hours of use with a $p<0.0001$. Finally, **Yoon et al. (2015)** saw a similar up-down pattern as **Spinelli et al. (2009)**, but with lower ORs and none of them significant.

It is not possible from the published results to find categories of exposure that match across the various studies in order to do a simple meta-analysis by category. However, it is possible to do a meta-regression where the exposure categories are turned into a single exposure and the meta-regression tests to see if the slope of the data from the various studies is increasing with exposure. In order to do this analysis, I set the exposure for each category equal to the center of the interval defined for the category (e.g., if the category is 512-1486 hours, the midpoint exposure is (512+1486)/2=999 hours). For Inskip et al. (2001), the last category is ≥100 hours and had 54 cases and ≥500 hours had 27, so I chose 500 for the highest exposure. For the remaining studies, it is not clear how to choose the exposure of the highest category. To follow the same pattern seen with **Inskip et al. (2001)**, I chose 5x the lower limit of the last category as the regression point for that category. **Hardell et al. (2015)** did a regression through their data and saw an OR of 1.013 (1.009-1.017) per 100 hours; doing a meta-regression using only the **Hardell et al. (2015)** data with the highest category dose set at 5x1486=7430 hours yields an mRR of 1.011 (1.005-1.018), similar to the result seen by **Hardell et al. (2015)**. A second dosing approach for the last category was to take the difference between the middle of the second largest category and the lower bound of that category and add it to the upper end of the second highest category to get the exposure for the highest category (e.g. if 512-1486 hours is the second highest category and the last category is ≥1486 hours, I set the center of the highest category as (512+1486)/2-512+1486=1973 hours). The exposures for all of the categories of the studies entering into the main meta-regression are shown in Table 9. The study results from **Spinelli et al. (2009)** are excluded from the meta-regression because of the difference in their exposure metric.

Table 10 provides the results of the meta-regression for the 5 case-control studies with duration of exposure where all of the ORs are a comparison against non-regular users. There is a significant association between exposure and risk with an mRR of 1.007 (1.002-1.012, $p=0.004$). Dropping the **Interphone (2010)** study from the meta-regression results in a highly significant trend (1.011 [1.005-1.017]; $p<0.001$), almost doubling of the risk, and reduced heterogeneity between the studies. In contrast, dropping the study by **Hardell et al. (2015)** reduces the risk by almost half

(1.004 [0.998-1.010; p=0.184) but the heterogeneity remains. Dropping any of the other studies has little impact on the findings. The alternate dosing strategy for the highest dose yielded the same pattern but mRRs that are roughly 3 times higher than those presented in Table 10 (not shown). (Table 10)

To examine the sensitivity of the analysis to the use of a different referent population in the Interphone study, their analysis using greater than 0 and <5 hours of cumulative exposure as the referent group was plugged into the same analysis. Table 11 provides the results of the meta-regression for the 5 case-control studies with duration of exposure using the alternative referent group. There is an increase in the mRR to 1.010 (1.006-1.014) per 100 hours of use. This fit demonstrated less heterogeneity with I^2=33.95. None of these results change substantially if any one study is dropped from the meta-regression. The alternative high dose yielded the same pattern but higher ORs per 100 hours (not shown). (Table 11)

There were other measures of exposure used in the various studies that are worth mentioning. **Inskip et al. (2001)** used average daily exposure and saw no exposure-response relationship (Table 4). **Coureau et al. (2014)** used average monthly exposure and saw a fairly clear exposure-response relationship (Table 4). **Inskip et al. (2001)** also considered the year that cellular telephone use began and again saw no exposure-response (Table 5). The **Interphone Study (2010)** considered cumulative use by years of duration of use (1-4 years, 5-9 years and ≥10 years). In each duration category, they saw the same pattern of flat exposure-response except for the highest cumulative exposure group that was increased in all categories. The shortest duration had the highest OR in the highest cumulative use category, but also had only 25 exposed cases with that much usage (to get greater than 1640 hours of usage in 4 years would require >1 hour of usage every day) (Table 5). **Coureau et al. (2014)** considered cumulative number of calls and saw a non-significant increasing risk with increasing exposure (Table 5). **Hardell et al. (2015)** used age and saw no pattern (Table 5).

Elliott et al. (2010) compared distance to power station, total power and modeled power to evaluate the contributions of mobile phone towers on the rates of brain and central nervous system tumors in young adults and basically saw no relationship. **Li et al. (2012)** did something similar but calculated exposure for an entire township instead of individuals. They saw slightly increased ORs for different types of divisions of the data and an increase in the risk of brain tumors of 1.09 (0.95-1.25) per standard deviation of their exposure density measure.

Aydin et al. (2013) looked at total cumulative years of use of a mobile phone by self-reporting and operator recorded cumulative years of use and saw marginal increases in risk with increasing exposure (p=0.14 and p=0.15 respectively, (Table 8)). When they also looked at cumulative hours of use for the self-reported and operator-recorded data, they saw no relationship although all ORs were greater than 1.

Table 9: Meta-Regression Exposure Values for Tables 11 and 12

Author (year)	Exposures (times 100 hrs)
Inskip et al. (2001)	0.065, 0.57, 5.00
Interphone (2010)	0.025, 0.09, 0.22, 0.46, 0.88, 1.575, 2.80, 5.475, 11.875, 82
Coureau et al. (2014)	0.215, 0.775, 2.255, 6.27, 44.8
Hardell et al. (2015)	0.615, 3.17, 9.99, 74.3
Yoon et al. (2015)	1.50, 6.00, 45

Table 10: Meta-Regression Analysis with Sensitivity Analysis of ORs for Five Case-Control Studies using Cumulative Hours of Use as the Exposure Metric and the Original Referent Groups

Meta Regression Studies[a,b]	Coefficient	P>|Z|	95% Confidence Interval		I^2	pQ
All	1.007	0.004	1.002	1.012	68.18	<0.001
drop Inskip et al. (2001)	1.007	0.004	1.002	1.012	71.34	<0.001
drop Interphone (2010)	1.011	<0.001	1.005	1.017	54.36	0.006
drop Coureau et al. (2014)	1.006	0.02	1.001	1.011	71.65	<0.001
drop Hardell et al. (2015)	1.004	0.184	0.998	1.010	61.27	0.001
drop Yoon et al. (2015)	1.008	0.001	1.003	1.013	69.85	<0.001

a – studies included in the analysis are Inskip et al. (2001), Interphone (2010), Coureau et al. (2014), Hardell et al. (2015), Yoon et al. (2015); b - Interphone Study uses <1 year duration of use as the referent group

Table 11: Meta-Regression Analysis[a] with Sensitivity Analysis of ORs for Five Case-Control Studies using Cumulative Hours of Use as the Exposure Metric and the Alternative Referent Group for the Interphone Study

Meta Regression Studies[a,b]	Coefficient	P>|Z|	95% Confidence Interval		I^2	pQ
All	1.010	<0.001	1.006	1.014	33.95	0.054
drop Inskip et al. (2001)	1.010	<0.001	1.006	1.014	38.66	0.037
drop Interphone (2010)	1.011	<0.001	1.005	1.017	54.36	0.006
drop Coureau et al. (2014)	1.009	<0.001	1.005	1.013	35.34	0.065
drop Hardell et al. (2015)	1.008	0.003	1.003	1.013	0.49	0.451
drop Yoon et al. (2015)	1.011	<0.001	1.007	1.014	27.65	0.118

a – studies included in the analysis are Inskip et al. (2001), Interphone (2010), Coureau et al. (2014), Hardell et al. (2015), Yoon et al. (2015); b - Interphone Study uses greater than 0 and <5 hours cumulative use as the referent group

4.1.3.3 Strength of the Association

The strength of the association is tied to the magnitude of the response and the statistical significance of that response. For all of these studies, the actual magnitude of the RRs seen in the studies are small, in many cases falling below 1. It is clear from Figure 2, that the longer the duration, the larger the mRR and the more statistical significance to the risk. It is also clear from Figure 2 that the actual analysis used from the **Interphone study (2010)** can make a difference in the magnitude of the response. This is a strong set of findings.

In addition, laterality matters for addressing the strength of the association. Laterality seems to become more pronounced with a longer duration of exposure or greater cumulative hours of use. For ≥10 years of usage, the **Interphone study (2010)** has an ipsilateral RR of 1.21 (0.82-1.80) and a contralateral RR of 0.70 (0.42-1.15) whereas **Hardell et al. (2015)** saw an ipsilateral mRR of 2.24 (1.61-3.11) (pooling all categories above 10) and contralateral of 1.52 (0.99-2.34). Combining these by meta-analysis yields an mRR of 1.66 (0.91-3.04) for ipsilateral and 1.04 (0.49-2.23) for contralateral with significant heterogeneity (not shown). For cumulative duration of use in the highest category, the **Interphone study (2010)** has ipsilateral 1.96 (1.22-3.15) and contralateral 1.25 (0.64-2.43), **Coureau et al. (2014)** has ipsilateral 4.21 (0.70-25.42) and contralateral 1.61 (0.56-4.62), and **Yoon et al. (2015)** has ipsilateral 1.77 (0.32-1.84) and contralateral 0.63 (0.24-1.65). Combining these by meta-analysis yields an mRR of 1.99 (1.33-3.00) for ipsilateral and 1.11 (0.68-1.80) for contralateral with no heterogeneity (not shown). These results are surprisingly consistent and suggest a strong effect on laterality.

Finally, since the temporal lobe gets some of the highest fields when using a mobile phone, many researchers have looked at whether this location seems to associate with the use of mobile phones.

The Interphone study evaluated this for ≥10 years duration [1.36 (0.88-2.11)] and for ≥1640 hours cumulative use [1.87 (1.09-3.22)]. **Hardell et al. (2015)** did not address this issue for longer latency, but in one of their earlier studies, **Hardell et al. (2013)**, they found the following : 10-15 years latency 1.6 (0.7-4.1), 15-20 years 2.0 (0.8-5.2), 20-25 years 2.7 (1.02-7.3) and ≥25 years (4.8 (1.7-14). A meta-analysis of these numbers from **Hardell et al. (2013)** yields mRR 2.41 (1.49-3.89) (no heterogeneity) which, when combined with **Interphone (2010)** yields an mRR of 1.79 (1.02-3.14) (some heterogeneity, pQ=0.08). Regretfully, no other study looked at this issue for the highest exposure categories. However, 4 studies addressed this for the evaluation of ever versus never exposure and saw ORs of 0.86 (0.66-1.13) (Interphone), 3.94 (0.81-19.08) (Coureau), 4.30 (1.99-9.27) (Hardell) and 1.13 (0.86-1.48) (Frei.). The combined mRR for these 4 is 1.56 (0.88-2.77) with significant heterogeneity (not shown).

4.1.4 Ecological Epidemiology Studies of Malignant Brain Tumors and Gliomas

Ecological epidemiology studies attempt to look at trends of disease in a population and relate this to a particular exposure that changes over time or space in the population. The main difference between an ecological epidemiology study and the studies discussed up to this point (case-control and cohort studies) is that the unit of observation is a population, not an individual. Thus, ecological studies do not ask the individuals about their exposures but instead infer that exposure based upon other information. All of the ecological studies regarding cellular telephone use are based upon the idea that cellular telephone use has been increasing over time and this would imply that glioma rates in a population will be increasing in time as well. To be able to do this type of analysis, one would need to know the statistics on the use of cell phones in this population; something that is seldom known and must be inferred from statistics on ownership of a cellular phone or from the control populations in the case-control studies or from the usage seen in the cohort studies.

Usage data from the cohort studies, if obtained in a timely manner, would be a good estimate of usage in the general population. Regretfully, the two cohort studies in adults obtained these data early on in the use of cellular telephones (1982-1995 in Denmark and 1999-2005 in the UK) and their usage has increased dramatically since that time. Thus, it is hard to extrapolate from the usage in these populations to usage today. In the case-control studies, one can make assumptions of how well the cases and controls represent the general population, but these assumptions generally cannot be tested and may be wrong.

It is also required to have accurate information on cancers in a population. This type of information is usually derived from routinely collected national or regional statistics from cancer registries. Cancer registries can be notoriously inaccurate in the actual diagnosis of the cancer, gaps in coverage of a region or time and other problems. Because of all of these problems, ecological epidemiology studies are often affected by confounding or ecological fallacy (this occurs when inferences about what is happening at the individual level are derived from correlations seen in groups or populations). For these reasons, ecological studies are considered very weak in identifying or excluding risk factors that might be important in a population.

The ecological studies relevant to this review can be broken down into three categories: ecological studies on brain tumors in general, ecological studies on specific types of malignant brain tumors, and ecological studies on acoustic neuromas. In this section, I will review ecological studies on brain tumors and gliomas.

Deltour et al. (2009) [129] investigated temporal trends in glioma incidence rates in Denmark, Finland, Norway and Sweden using data from the national cancer registries. These data are intended to cover the populations incidence for 100% of the Nordic population and there is no discussion about limitations of the data for gliomas. They restricted their analysis to the years 1974-2003. They did a change-point analysis and saw no statistically significant change in incidence rates from 1998-2003, when they claimed changes caused by cell phones would be visible. They concluded any increase in gliomas caused by cell phones, if it exists, is not observable in this population. This is an extension of an earlier paper [130].

Inskip et al. (2010) [131] examined temporal trends in brain cancer incidence rates in the United States using data from the Surveillance, Epidemiology, and End Results (SEER) Program. For this analysis, they used SEER data from 9 cancer-registries which cover about 10% of the US population, restricted their analysis to Caucasians, and covered the years 1992-2006. They only saw increases in the 20-29 year age group in females. They also looked at specific locations in the brain and saw increases in both males and females in frontal lobe tumors. They concluded these findings do not support the view that use of cellular telephones increase cancer risks.

de Vocht et al. (2011) [132] examined temporal trends in brain cancer incidence rates in England using data from the UK Office of National Statistics. These data should cover 100% of the UK population, but there are gaps maybe as high as 35%. They restricted their analysis to the years 1998-2007. They saw no increases in any age group. They also looked at specific locations in the brain and saw increases in both males and females in temporal lobe tumors and in men only, frontal lobe tumors. They concluded these findings do not indicate a pressing need to implement a precautionary principle to reduce RF exposures.

Ding and Wang (2011) [133] investigated temporal trends in brain and nervous tissue cancer incidence rates in Shanghai using data from the Shanghai Cancer Registry. These data should cover 100% of the Shanghai population; gaps were not discussed. They restricted their analysis to the years 1983-2007. They saw a doubling of brain cancer incidence in this period with no statistically significant changes in the increasing rate at any specific time. They concluded the study did not support an increase in brain and nervous system tumors due to RF exposures because the trend began before the widespread use of cellular phones.

Aydin et al. (2011) [109] compared hypothetical incidence trends generated from the ORs seen in their study of childhood brain tumors to incidence data on brain tumors in children and adolescents aged 5-19 years between 1990 and 2008 from the Swedish Cancer Registry. They concluded the patterns did not match and that this indicates that short-term mobile phone use does not cause an increase in brain cancers in children. **Soderqvist et al. (2011)** [112] had concerns regarding the interpretation of these findings and suggested there could still be an effect. **Aydin et al. (2012)** [134] responded, basically reiterating their original arguments.

Deltour et al. (2012) [135] investigated temporal trends in glioma incidence rates in Denmark, Finland, Norway and Sweden using data from the national cancer registries. These data are intended to cover the populations incidence for 100% of the Nordic population and there is no discussion about limitations of the data for gliomas. In this period, incidence rates have increased slightly in men and women, mostly in older populations. Using simulation studies, various relative risks and various induction periods, they simulated the results of a cohort study on the entire population of men aged 40-59 years over this period (with complete follow-up). They then looked to see if they had a significant RR change in that population and equated that to being able to see a change in the incidence rates in the data from the cancer registries. The probability of seeing the

change ranged from 2.9 % to 100% depending on the underlying simulation parameters. They concluded that many increased or decreased risks reported in case-control studies are implausible, implying that biases and errors in the self-reported use of mobile phone have likely distorted the findings. This conclusion is at best speculative because the simulations do not actually match the incidence data they are looking at or the analyses they did with the data.

Little et al. (2012) [136] examined temporal trends in brain cancer incidence rates in the United States using data from the Surveillance, Epidemiology, and End Results (SEER) Program. For this analysis, they used SEER data from 12 cancer-registries (coverage of the US population is unknown). They restricted their analysis to non-Hispanic white people and the years 1992-2008. Using the findings from **Interphone (2010)** and **Hardell et al. (2011)**, they predicted what the tumor incidence rates in 2008 should have been by using 1992-1996 as a baseline rate and US subscription data to drive the temporal change. They concluded that the results from **Hardell et al. (2011)** are not consistent with the US SEER data but that the results from the Interphone (2010) study are.

Barchana et al. (2012) [137] examined temporal trends in brain cancer incidence in Israel using data from the Israel National Cancer Registry. These data should cover 100% of the Israeli population and is 95% complete for brain tumors. They restricted their analysis to the years 1989-2009. They focused on high-grade versus low-grade gliomas in males and females. They also examined changes in laterality. They found a decrease in low-grade gliomas over this period and an increase in high-grade gliomas. They also saw an increase in laterality towards more left-sided tumors. They concluded the decrease in low-grade gliomas correlated with the introduction of mobile phone technology in Israel.

Hsu et al. (2013) [138] examined temporal trends in malignant brain cancer incidence rates and death rates in Taiwan using data from the Taiwan National Cancer Registry. There was no discussion of the quality of this cancer registry. They restricted their analysis to the years 2000-2009. Their entire evaluation consisted of a side-by-side comparison in a histogram of deaths, incidence and cell phone usage. No statistical evaluations were performed. They concluded there was no detectable correlation between morbidity/mortality of malignant brain tumors and cell phone use in Taiwan.

Kim et al. (2015) [139] investigated temporal trends in primary brain cancer incidence rates in New Zealand using data from the New Zealand Cancer Registry. These data should cover 100% of the NZ population and there is some discussion about changes in histological classification that could produce a false-negative finding. They restricted their analysis to the years 1995-2010. In general, they saw a decrease in brain tumors over this period with a larger decrease in women than in men. They saw a significant increase in all brain tumors in females aged 30-49, with increases in glioma of the parietal and temporal lobe. This finding was not consistent over other age groups or with the rates in men. They saw increases in the 70+ years group in most categories, but attributed that to better diagnosis, but with no justification. They concluded there has been no increase in primary brain tumors over this period.

Sato et al. (2016) [140] investigated temporal trends in malignant neoplasms of the central nervous system incidence rates in Japan using nationwide estimates of cancer incidence developed by the regional cancer registries. These estimates are intended to cover the populations incidence for 100% of the Japanese population and there is some discussion about limitations of the estimates. They restricted their analysis to the years 1993-2010. They focused on men and women in their 20s and 30s and used data from a survey of cellular phone use to determine if these increases could be due to cellular phone use using the highest response category from the **Interphone (2010)** study as

the expected change in risk ratio. In general, they saw an increase in brain tumors over this period with a larger increase in men than in women. They were able to show that the observed increases were greater than what would be predicted for only heavy users and the **Interphone (2010)** OR of 1.4. They then went on to show that using ORs of 6 for men and 12 for women in their 20s and 4 for men and 7 for women in their 30s came close to matching the data. They then concluded that increases in cancers by sex, age and period are inconsistent with sex, age and period usage of mobile phones and thus cannot be explained by the mobile phones.

Chapman et al. (2016) [141] examined temporal trends in brain cancer incidence rates in Australia using data from the Australian Institute of Health and Welfare. These data should cover 100% of the Australian population, but there is no discussion of the quality of the data. They restricted their analysis to the years 1982-2012. They suggested incidence has risen slightly in males and remained steady in females. They then used cellular phone usage data from Australia and created hypothetical curves for a RR of 1.5 for users and a 10-year lag and a second hypothetical curve with a RR of 2.5 for heavy users (defined as >896 hours of cumulative use and assumed for 19% of all users) and a 10-year lag. They concluded the hypothetical curves were significantly different from the observed curves. They cited **Dobes et al. (2011)** [142] as showing no rise in brain tumors in Australia, however, this study concluded there was a significant rise in glioblastoma in Australia from 2000-2008 at an annual rate of 2.5%.

de Vocht (2016) [143] examined temporal trends in brain cancer incidence counts (not standardized rates) in England using data from the UK Office of National Statistics. These data should cover 100% of the UK population, but there are gaps maybe as high as 35% and a 5-year lag in getting complete data. He restricted the analysis to the years 1985-2014. He obtained cellular phone subscription data from the ITU. He built a Bayesian counterfactual model of glioma, glioblastoma, parietal lobe tumors and temporal lobe tumors with covariates annual cancer incidence, population size, median age, cigarette smoking, urbanization rate and a factor to account for data quality in a specific period. The counterfactual model was compared to a model including cell phone subscription rates with several cut points to allow for lag times. He concluded that for glioma, glioblastoma and malignant tumors of the parietal lobe, cell phone usage did not differ from the counterfactual model. For malignant tumors of the temporal lobe, he found cell phone usage could be a causative factor for these tumors. There was a major error in the data used for this analysis and a correction was published [144]. The author claimed it had no impact on the findings although it changed the directions of the effects seen. **de Vocht (2019)** [145] repeated this analysis for glioblastoma in specific brain regions and for meningiomas and acoustic neuromas. Excess of the counterfactual were seen for glioblastomas in the frontal and temporal lobe, but were predominantly in the highest age groups. No excesses were seen for acoustic neuromas or meningiomas. He concluded cell phones are unlikely to be causative for these tumors.

Hardell and Carlberg (2017) [146] demonstrated that the rates of brain tumors of unknown type obtained from the Swedish Inpatient Register were increasing in the years from 1998-2015. In contrast, brain tumor diagnoses confirmed by cytology/histology increased in the Swedish Cancer Registry. Brain tumors diagnosed by MRI and CT are not always reported to the Swedish Cancer Registry. This suggests an under-reporting of brain cancers in the cancer registry and they suggest caution in using cancer registry data to understand any linkage between cellular phone usage and brain cancers. This was also suggested in an earlier evaluation by this group [147].

Phillips et al. (2018) [148] examined temporal trends in brain cancer incidence in England using data from the UK Office of National Statistics. These data should cover 100% of the UK population,

but there are gaps maybe as high as 2% and a multi-year lag in getting complete data. They restricted their analysis to the years 1995-2015. They looked at a number of different forms of brain tumors and locations. They saw an increase in glioblastomas for 2011-2015 relative to 1995-1999 by age groups, with the largest increases in the higher age groups. The greatest increases were tumors in the frontal and temporal lobes. They suggest that widespread environmental or lifestyle factors may be responsible, but did not draw any conclusions regarding cellular phones.

Keinan-Boker et al. (2018) [149] examined temporal trends in brain cancer incidence in Israel using data from the Israel National Cancer Registry. These data should cover 100% of the Israeli population and is 95% complete for brain tumors. They restricted their analysis to the years 1990-2015. They focused on benign versus malignant tumors by age and sex. In general, they saw a mixed set of effects that changed over these categories. In conclusion, they found the results to be not consistent with the penetrance of cellular phones in Israel over this period.

Karipidis et al. (2018) [150] examined temporal trends in brain and central nervous system tumor incidence rates in Australia using data from the Australian Institute of Health and Welfare. These data should cover 100% of the Australian population, but there is no discussion of the quality of the data. They restricted their analysis to the years 1982-2013 and cases aged 20-59 years. There is no discussion of standardizing the rates. Percent of the population with mobile phone subscriptions was obtained from the Australian Communications and Media Authority. They used a very simple model to predict incidence rates from subscription data using regular users and heavy users (19%) and various lag times. They concluded that there was no evidence that mobile phone use correlated with any brain tumor histological type or subtype.

Nillson et al. (2019) [151] examined temporal trends in glioma incidence rates in Sweden using data from the Swedish Cancer Registry. These data should cover 100% of the Swedish population. They restricted their analysis to the years 1980-2012 because problems with the registry starting in 2013. They saw no increases in age-standardized incidence rates over time and a significant decrease in low-grade gliomas. They concluded these findings do not indicate any effect of RF exposures on gliomas incidence.

Natukka et al. (2019) [152] examined temporal trends in glioma incidence rates in Finland using data from the Finnish Cancer Registry. These data should cover 100% of the Finnish population. They restricted their analysis to the years 1990-2016 with cases reclassified from 1990 to 2006 to match modern classifications. The data for 2007-2016 could not be classified by sex or age grouping. They discussed several major limitations of their analyses including misclassification, limitations to the analysis and small sample sizes. They saw no increases in age-standardized incidence rates for gliomas over 1990-2006 but could not do this analysis beyond then. There were no major changes in tumor locations over time.

These studies use a variety of different cancer registries and a variety of different methods to evaluate the relationship between temporal changes in brain cancer incidence and the use of mobile phones. Most studies find the relationship between increasing mobile phone use and incidence of brain tumors are inconsistent. However, all of these studies suffer from a variety of problems that are common with ecological studies. In most studies, the surrogate for individual exposure is derived from subscription data and not from actual cellular phone use data. Even in cases where exposure is used (such as high cumulative use), the exposure is simply expressed as a simple percentage of the population. The choice of tumor to examine can have a major impact on the trend as can the statistical model used to examine the data (this is clearly exemplified by the studies using the same UK data and seeing very different results). In many cases, the tumor

incidence rates are increasing, but there was insufficient statistical power to identify if the increase matches the increase in cellular phone usage and these were uniformly interpreted as showing no relationship. Finally, the cancer registries themselves have limitations and flaws that may also lead to ecological fallacies regarding their linkage to cellular phone usage.

4.1.5 Conclusions for Gliomas

The evidence on an association between cellular phone use and the risk of glioma in adults is quite strong. While there is considerable difference from study to study on ever versus never usage of cellular phones, 5 of the 6 meta-analyses in Figure 1 are positive and two are significantly positive. Once you consider latency, the meta-analyses in Figure 2 clearly demonstrate an increasing risk with increasing latency. The exposure response meta-regressions in Table 10 and Table 11 clearly indicate that risk is increasing with cumulative hours of exposure, especially in the highest exposure groups. There is a strong tendency toward gliomas appearing on the same side of the head as the phone is generally used and the temporal lobe is strongly suggested as a target. These findings do not appear to be due to chance. The cohort studies appear to show less of a risk than the case-control studies, but one study is likely to be severely impacted by differential exposure misclassification (Frei et al., 2007) and the other (Benson et al., 2012) is likely to have a milder differential exposure misclassification. The case-control studies are possibly impacted by recall bias although that issue has been examined in a number of different evaluations. Selection bias could have been an issue for the Interphone study, but their alternative analysis using different referent groups reduces that concern. Confounding is not an issue here. In conclusion, an association has been established between the use of cellular telephones and the risk of gliomas and chance, bias and confounding are unlikely to have driven this finding. The ecological studies are of insufficient strength and quality to fully negate the findings from the observational studies.

The data in children is insufficient to draw any conclusions.

4.2 Acoustic Neuromas

4.2.1 Studies in Adults

4.2.1.1 Case-Control Studies

Hardell et al. (1999) [85] did an analysis of acoustic neuromas in their study and saw an OR of 0.78 (0.14-4.20) based on 13 cases. No other information is provided. (Table 12)

Inskip et al. (2001) [44] saw no increases for acoustic neuromas in their study described on page 10. (Table 12, Table 13, Table 14, Table 15, Table 16, Table 17)

Muscat et al. (2002) [153] conducted a case-control study of acoustic neuromas from two hospitals in New York city as part of their larger study on brain tumors described on page 9. Cases were 18 years of age or older with histologically confirmed acoustic neuromas from 1997 to 1999. There were 90 cases (response rate appears to be 100%) and 86 hospital-based controls matched on age (5-years), sex, race and hospital. Interviewer-based structured questionnaires were used. Regular use was determined by simply asking the patient if they were a regular user. No OR was provided on regular users, but ORs were calculated for years of use, hours/month of use, and total hours. No obvious pattern existed for any of these categories. Ipsilateral use was evaluated using the **Inskip et al. (2001)** [44] method with an OR of 0.9, p=0.07. The main weakness in this study is the potential for recall bias, small sample size, and the short latency. (Table 13, Table 14, Table 15, Table 17)

Warren et al. (2003) [154] conducted a case-control study of intratemporal facial nerve tumors (age not given) in a tertiary care medical center from July 1, 1995 to July 1, 2000 in the United States. As matched controls, and to serve as an alternative case group, they chose 51 acoustic neuroma patients from the same facility. They also had rhinosinusitis controls, dysphonia or gastroesophageal reflux controls and two non-tumor control groups. Matching was based on age (+/- 6 years), sex and race. Cellular telephone usage was assessed via a detailed questionnaire. The study had 51 cases of acoustic neuroma matched with 141 rhinosinusitis, dysphonia or gastroesophageal reflux controls (participation rates were not provided). Ever use of a handheld cellular phone had an OR of 1.2 (0.6-2.2) and use of a handheld cellular phone for more than 1 call per week had an OR of 1.0 (0.4-2.2). They assessed use of tote phones and car phones as well. This is a very small study with limited details. (Table 12)

Baldi et al. (2011) [89] saw no increases for acoustic neuromas in their study. (Table 12)

The **Interphone Study Group (2011)** [67] also did a case-control study on acoustic neuromas using the same protocol as their brain cancer study [48] shown on page 11. As for brain tumors, there were a number of publications from individual countries and/or sub-groups of countries for acoustic neuromas [50, 53, 54, 57, 58, 60, 66, 155, 156]. The odds ratio (OR) of acoustic neuroma with ever having been a regular mobile phone user was 0.85 (95% confidence interval 0.69–1.04). The OR for ≥10 years after first regular mobile phone use was 0.76 (0.52–1.11). There was no trend of increasing ORs with increasing cumulative call time or cumulative number of calls, with the lowest OR (0.48 (0.30–0.78)) observed in the 9th decile of cumulative call time. In the 10th decile (≥1640 h) of cumulative call time, the OR was 1.32 (0.88–1.97); there were, however, implausible values of reported use in those with ≥1640 h of accumulated mobile phone use. With censoring at 5 years before the reference date the OR for ≥10 years after first regular mobile phone use was 0.83 (0.58–1.19) and for ≥1640 h of cumulative call time it was 2.79 (1.51–5.16), but again with no trend in the lower nine deciles and with the lowest OR in the 9th decile. In general, ORs were not greater in subjects who reported usual phone use on the same side of the head as their tumor than in those

who reported it on the opposite side, but it was greater in those in the 10th decile of cumulative hours of use. [partially copied from abstract] (Table 12, Table 13, Table 14, Table 16, Table 17)

Han et al. (2012) [157] conducted a case-control study on patients with acoustic neuromas who underwent surgery from 1997 to 2007 at the University of Pittsburgh medical center. The cases were sent questionnaires in 2009-2010 and then interviewed over the phone. Controls were from the outpatient clinic for degenerative spinal disorders at the same medical center, but during the years of 2009-2010. There were eventually 343 (59% response) cases and 343 (response rate not given) controls matched on sex and age (+/- five years). If age-matching was done based on the time of diagnosis for the case or at the time of the questionnaire administration, there should be no problem, but if age-matching was done as diagnosis for the patient matched to current age of the control, this would be a problem for the analysis of cell phone usage. Their main interest was in the relationship between dental x-rays and AN, but they asked about cell-phone usage as a side issue in order to adjust their main analyses on x-rays for cell phone usage. It is not clear exactly how exposure to cellular phones was assessed. If it was done right, regular usage was assessed at the time of the AN patient's diagnosis and the matching control was assessed the same way. The same would need to be true for the duration of use. Any other way in which exposure was assessed would render the interpretation of this study difficult. The questionnaire was not available to address these questions and the write-up does not explicitly make this clear. Assuming the case matching was done correctly and exposure was done correctly, they saw no increased OR [0.95 (0.58-1.58)] for regular use (defined as 1 call per week for 6 months or more) or for use ≤10 years [0.79 (0.45-1.37)] and saw an increased OR for ≥10 years of use [1.29 (0.69-1.63)]. Regular use of a cellular phone was a significant confounder (p=0.006) in their analysis of X-rays and AN. (Table 12, Table 13)

As for malignant brain tumors, **Hardell and colleagues** have published a number of studies on acoustic neuromas and cell phone usage [82, 158-160]. **Hardell et al. (2013)** [82] used data collected at the same time as their pooled case-control study on malignant brain tumors [88], described on page 16, to do a pooled case-control study on acoustic neuromas and cellular phone usage. ORs tended to increase with years of latency with the highest ORs in the longest latency group (>20 years), ORs tended to increase with cumulative use with the largest OR in the highest exposure quartile (>1486 hours cumulative use), ipsilateral ORs were larger than contralateral ORs and changes in tumor volume seemed to be associated with cumulative use. (Table 12, Table 13, Table 14, Table 16, Table 17)

Corona et al. (2012) [161] identified cases of unilateral AN in people ≥18 years of age residing in the municipalities of Salvador and Feira de Santana in Brazil from 2000 to 2010. For each case, they selected 3 controls from the same outpatient clinics as the cases and had visited the doctor "immediately after each case visit". They identified 85 AN patients and 181 controls of which 44 (51.8%) of the cases participated and 104 (57.4%) of the controls participated. There was no description of whether cases and controls were matched on any factor other than clinic. Exposure and demographic information was obtained by interview-administered questionnaire for both cases and controls. For regular use of a mobile phone (defined as one call per week for 6 months), the OR was 1.38 (0.61-3.14). For <6 years of phone use, the OR was 1.14 (0.42-3.08) and for ≥6 years it was 1.81 (0.73-4.47). They also looked at minutes of use per day (≤10, 11-30, >30) and saw increased ORs (1.49 [0.59-3.77], 1.77 [0.62-5.06], 1.15 [0.33-4.08]). Ipsilateral use showed an OR of 1.40 (0.65-3.04) and contralateral use showed an OR of 0.57 (0.23-1.43). (Table 12, Table 13, Table 15, Table 17)

Pettersson et al. (2014) [156] identified incident cases of acoustic neuroma (n = 542) between 20 and 69 years of age at diagnosis from September 2002 to August 2007 in Sweden. Controls (n=1095) were randomly selected from the Swedish population register, matched on age, sex and health-care region. Of these, 451 (83%) cases and 710 (65%) controls participated. The controls were assigned a reference date that corresponded to the date of diagnosis of their matched case. Self-reported exposure information was collected through postal questionnaires, sent to cases and their matched controls simultaneously, starting in October 2007. The referent group was regular users defined as having made or received on average at least one call per week over the last 6 months. Analyses were conducted on all cases and controls and then on cases and their matched controls for which the case was histologically confirmed (47% of cases). The OR for regular use is 1.18 (0.88-1.59). For duration of use, they saw an elevated OR for 5-9 years [1.40 (0.98-2.00)], but not for < 5 years [1.04 (0.72-1.52)] or ≥10 years [1.11 (0.76-1.61)]. Cumulative hours of use saw an exposure-response pattern with the highest OR [1.46 (0.98-2.17)] in the highest exposure group. Cumulative calls saw a similar pattern. When ORs are evaluated for any analog phone usage, the ORs generally increased and the pattern for time since first regular use began is decreasing with years. For digital phones, the pattern is the same as for all phones, with slightly larger ORs. The ORs for histologically-confirmed cases only generally has smaller ORs. ORs for ipsilateral use were generally lower than for contralateral use and near or below 1.0. Over half of the cases who were regular users noted they changed their preferred side of mobile use, mostly due to hearing loss. They attempted to evaluate this issue, but their definition of ipsilateral (having held the mobile phone on the tumor side or on both sides during any period before the reference date) would make it virtually impossible to see an increase in ipsilateral use [NOTE: most studies ask which is the usual hand for holding the mobile phone]. Contralateral was also defined using both sides (or opposite side). This problem is best seen when they looked at laterality over time; at the time of filling in the questionnaire, ipsilateral was 0.31 (0.18-0.53) and contralateral was 2.09 (1.45-3.00) whereas at five years before the reference date, ipsilateral was 0.97 (0.66-1.42) and contralateral was 1.33 (0.89-2.27). They evaluated the potential for recall bias for start year and found no systematic errors that were different between cases and controls [162]. (Table 12, Table 13, Table 14, Table 16, Table 17)

4.2.1.2 Case-Case Studies

Sato et al. (2011) [163] conducted a case-case study of mobile phone use and acoustic neuromas in Japan. Inclusion criteria were all verified cases occurring between January, 2000 and December, 2006 in 22 hospitals recruited to be in the study (32.4% of those asked). Phone usage and other information were obtained by written questionnaire sent to the patient. A total of 1589 cases met the inclusion criteria of which 787 (49.5%) eventually were included in the analysis. Reference dates were set at 1 year and 5 years before diagnosis. The case-case analysis is based upon three assumptions: (1) there was no risk from mobile phones to the contralateral side; (2) risk to the ipsilateral side was the same for left- and right-sided users; and (3) for non-users, incidence of left- and right-sided tumors was the same. Hence, contralateral cases served as controls. Weighted average number of calls per day, weighted average duration of one call and weighted average daily call duration at 5 years prior to diagnosis were all significantly increased (0.043, 0.017, and 0.004 respectively). In addition, patients with an age at diagnosis of <40 years (41 patients) had a significantly increased OR (1.72 [1.08-3.10]). Heavy users (>20 minutes per day) had increased ORs regardless of whether that heavy use was for 1 (2.7 [1.2-7.9]) or 5 (3.1 [1.5-7.4]) years or both (5.0 [1.4-24.8]) or only 5 years (1.9 [0.9-5.8]) before diagnosis, but not for only the period 1 year before diagnosis (0.9 [0.6-2.6]). Tumor sizes tended to be smaller with ipsilateral use compared to

contralateral use. The main weaknesses of this study are the potential for recall bias due to the mail-in questionnaire and the low response rate. (Table 17)

4.2.1.3 Cohort Studies

Schuz et al. (2011) [99] used the same cohort as **Frei et al. (2011)** [96] to evaluate the incidence of acoustical neuromas in humans associated with mobile telephone use (description of the cohort on page 19). The cohort was updated to include follow-up to 2006. The results pertain only to people who used phones for greater than 11 years (because of the 1995 cut-off for knowledge of who had a cellular phone subscription) and the referent group is all non-users and people who got phones after 1995. They saw no association (men 0.88, 0.52-1.48, no observed tumors in female users). They also saw no impact of long-term mobile phone use on the size of the tumors. This study has the same limitations of other evaluations with this cohort. There are earlier publications on this cohort [94, 95]. (Table 12)

Benson et al. (2013) [102] also studied acoustic neuromas in their cohort study described on page 19. Relative risks (RRs) for phone use were ever/never 1.44 (0.91-2.28), daily use 1.44 (0.91-2.28)), <5 years 1.0 (0.54-1.82), 5-9 years 1.80 (1.08-3.03) and 10+ years of use 2.46 (1.07-5.64) (all adjusted for socioeconomic status, region, age (in 3-year groupings), height, BMI, alcohol intake, exercise and hormone therapy). In a letter responding to a letter by **de Vocht (2014)** [105], **Benson et al. (2014)** [106] updated their follow-up to 2011 but did not update cellular phone usage (still relying on the 1999-2005 response) and saw OR for acoustic neuroma for ever/never users of 1.19 (0.81-1.75). Note that with 7 years average follow-up, they saw 96 acoustic neuromas or 13.7/year but adding 2010 and 2011 increased the acoustic neuromas by 15 per year. The same limitations mentioned on page 19 also apply here. (Table 12, Table 13)

Table 12: Results from epidemiology studies for ever versus never or regular versus non-regular use of a cellular telephone and the risk of acoustic neuroma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Sample Size for all endpoints (% resp.)	Exposed (%) Cases	OR (95% CI)	Comparison group
Hardell et al. (1999)	CC	1994-1996 ,Sweden	20-80, Both	Acoustic Neuroma	13 (ND) Cases ND (ND) Controls	ND (ND)	0.78 (0.14-4.20)	>1 year
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Acoustic neuroma	782 (92%) Cases 799 (86%) Controls 96 Acoustic Neuromas	40 (41.7%) 30 (31.2%)	0.8 (0.5-1.4) 1.0 (0.5-1.9)	Any use >5 times use
Warren et al. (2003)	Case-Control	1995-2000	ND	Acoustic Neuroma	51 (ND) Cases 141 (ND) Controls	21 (41.2%) 11 (21.6%) 6 (11.8%) 7 (13.7%) 5 (9.8%)	1.2 (0.6-2.2) 1.0 (0.4-202) 1.0 (0.4-2.7) 1.2 (0.5-3.8) 2.1 (0.6-7.0)	Ever use >1 call per week “tote” phone Automobile phone Automobile phone >1 call/week
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Acoustic neuroma	1105 (82%) Cases 2145 (53%) Controls	643 (58.2%) 304 (27.5%)	0.85 (0.69-1.04) 0.95 (0.77-1.17)	Avg 1 call per week for 6 mo (lag 1 yr) Avg 1 call per week for 6 mo (lag 5 yr)
Han et al. (2012)	CC	1997-2007, US	Age not given, Both	Acoustic Neuroma	343 (59%) Cases 343 (ND) Controls	203 (59.2%)	0.95 (0.58-1.58)	Avg 1 call per week for 6 mo
Corona et al. (2012)	CC	2006-2010, Brazil	18, Both	Acoustic Neuroma	44 (51.8%) 104 (57.4%)	34 (77.3%)	1.38 (0.61-3.14)	Avg 1 call per week for 6 mo
Pettersson et al. (2014)	Case-Control	Sweden	20-69, Both	Acoustic Neuroma	451 (83%) 710 (65%)	302 (67.0%) 143 (70.8%)	1.18 (0.88-1.59) 0.99 (0.65-1.52)	All, Once per week ≥6 months Histopathologically confirmed, Once per week ≥6 months
Hardell et al. (2013)	CC	1997-2003, 2007-2009, Sweden	20-80, Both	Acoustic neuroma	316 (93%) Cases 3530 (87%) Controls	200 (63.3%)	1.6 (1.2-2.2)	>1 year
Schuz et al. (2011)	Cohort	1998-2006, Denmark	≥30 at time of entry	Acoustic neuroma	2,883,665 404 cases	15 (0.38) Male 0 (0) Female	0.87 (0.52-1.46)	Subscription > 11 years prior Phone use only for before 1995
Benson et al. (2013) Benson et al. (2014)	Cohort	1999-2009, UK 1996-2011, (UK)	Middle-aged women	Acoustic neuroma	791,710 (65%) 2009 – 96 cases 2011 – 126 cases	67 (69.8) Ever use 8 (8.3) Daily use Exclude first 3 years 31 (32.3)	1.44 (0.91-2.28) 1.37 (0.61-3.07) 1.96 (0.96-4.02) 1.19 (0.81-1.75)	Ever used (asked 1999-2005) Every day (asked 1999-2005) Ever used (asked 1999-2005) Ever used (asked 1999-2005)

Table 13: Results from epidemiology studies for time (years) since first use of a cellular telephone and the risk of Acoustic Neuroma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Duration	Exposed Cases	OR (95% CI)	P Trend	Comments
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Acoustic Neuroma	<0.5 years	4	0.3 (0.1-1.3)	ND	Any use
					0.5-3 years	8	1.8 (0.7-4.5)		2+ calls/w
					≥3 years	10	1.4 (0.6-3.4)		
					≥5 years	5	1.9 (0.6-5.9)		
Muscat et al. (2002)	CC	1997-1999, New York City	≥18, Both	Acoustic neuroma	1-2 years	7	0.5 (0.2-1.3)	0.84	Referent was asked if they were a regular user
					3-6 years	11	1.7 (0.5-5.1)		
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Acoustic neuroma	1-1.9years	63	0.73 (0.49-1.09)	ND	Avg 1 call per week for 6 mo (lag 1 yr),
					2-4 years	276	0.87 (0.69-1.10)		no hands-free
					5-9 years	236	0.90 (0.69-1.16)		
					≥10 years	68	0.76 (0.52-1.11)		
					Exposure up 5 years				
					5-9 years	236	0.99 (0.78-1.24)		Excludes hands-free usage
					≥10 years	68	0.83 (0.58-1.19)		
Han et al. (2012)	CC	1997-2007, US	Age not given, Both	Acoustic Neuroma	<10 years	111	0.79 (0.45-1.37)		Avg 1 call per week for 6 mo
					≥10 years	92	1.29 (0.69-2.43)		
Corona et al. (2012)	CC	2006-2010, Brazil	18, Both	Acoustic Neuroma	<6 years	12	1.14 (0.42-3.08)	ND	Avg 1 call per week for 6 mo
					≥6 years	23	1.81 (0.73-4.47)		
Pettersson et al. (2014)	Case-Control	Sweden	20-69, Both	Acoustic Neuroma	<5 years	81	1.04 (0.72-1.52)		Avg 1 call per week for 6 mo (lag 1 yr),
					5-9 years	119	1.40 (0.98-2.00)		weighted hands-free
					≥10 years	102	1.11 (0.76-1.61)		
					Histologically confirmed				
					<5 years	47	0.96 (0.58-1.61)		
					5-9 years	55	1.10 (0.65-1.84)		
					≥10 years	41	0.93 (0.54-1.60)		
Hardell et al. (2013)	CC	1997-2003, 2007-2009, Sweden	20-80, Both	Acoustic Neuroma	1-5 years	65	1.3 (0.9-1.8)	ND	>1 year
					5-10 years	77	2.3 (1.6-3.3)		
					10-15 years	34	2.1 (1.3-3.5)		
					15-20 years	12	2.1 (1.02-4.2)		
					>20 years	12	4.5 (2.1-9.5)		
					Per year of latency		1.060 (1.031-1.089		
Benson et al. (2013)	Cohort	1999-2009, UK	Middle-aged women	Acoustic Neuroma	<5 years	19	1.0 (0.54-1.82)	0.03	Ever used (asked 1999-2005)
					5-9 years	38	1.80 (1.08-3.03)		
					≥10 years	8	2.46 (1.07-5.64)		
					Excluding first 3 years				
					<5 years	4	1.80 (0.55-5.90)		
					5-9 years	20	1.89 (0.87-4.08)		
					≥10 years	6	3.11 (1.08-8.95)		
Benson et al. (2014)		1999-2011, UK			<5 years	No data	0.94 (0.53-1.66)	0.30	Ever used (asked 1999-2005)
					5-9 years		1.46 (0.94-2.27)		
					≥10 years		1.17 (0.60-2.27)		

Table 14: Results from epidemiology studies for duration (cumulative hours) of use of a cellular telephone and the risk of acoustic neuroma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Cumulative use	Exposed Cases	OR (95% CI)	P Trend	Comparison group
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Acoustic neuroma	<13 hours	5	0.7 (0.2-2.3)	ND	Any use
					13-100 hours	8	1.2 (0.5-3.1)		2+ calls/w
					>100 hours	9	1.4 (0.6-3.5)		
					>500 hours	1	0.4 (0.0-3.3)		
Muscat et al. (2002)	CC	1997-1999, New York City	≥18, Both	Acoustic neuroma	1-60 hours	9	0.9 (0.3-3.1)	0.53	Referent was asked if they were a regular user
					>60 hours	9	0.7 (0.2-2.6)		
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Acoustic neuroma	1-year lag				Avg 1 call per week for 6, no hands-free
					<5 hours	58	0.77 (0.52-1.15)		
					5-12.9 hours	63	0.80 (0.54-1.18)		
					13-30.9 hours	80	1.04 (0.71-1.52)		
					31-60.9 hours	66	0.95 (0.63-1.42)		
					61-114.9 hours	74	0.96 (0.66-1.41)		
					115-199.9 hours	68	0.96 (0.65-1.42)		
					200-359.9 hours	50	0.60 (0.39-0.91)		
					360-734.9 hours	58	0.72 (0.48-1.09)		
					735-1639.9 hours	49	0.48(0.30-0.78)		
					≥1640 hours	77	1.32 (0.88-1.97)		
					5-year lag				
					<5 hours	42	1.07 (0.69-1.68)		
					5-12.9 hours	30	1.06 (0.60-1.87)		
					13-30.9 hours	40	1.32 (0.80-2.19)		
					31-60.9 hours	36	0.86 (0.52-1.41)		
					61-114.9 hours	21	0.63 (0.35-1.13)		
					115-199.9 hours	22	0.71 (0.39-1.29)		
					200-359.9 hours	29	0.83 (0.48-1.46)		
					360-734.9 hours	26	0.74 (0.42-1.28)		
					735-1639.9 hours	22	0.60 (0.34-1.06)		
					≥1640 hours	36	2.79 (1.51-5.16)		
Pettersson et al. (2014)	Case-Control	Sweden	20-69, Both	Acoustic Neuroma	<38	70	1.09 (0.73-1.62)		Avg 1 call per week for 6 mo (lag 1 yr), weighted hands-free
					38-189	73	1.12 (0.74-1.69)		
					190-679	66	1.13 (0.75-1.70)		
					≥680	89	1.46 (0.98-2.17)		
					Histologically confirmed				
					<38	30	0.97 (0.55-1.71)		
					38-189	39	0.91 (0.51-1.60)		
					190-679	34	1.03 (0.57-1.87)		
					≥680	37	1.14 (0.63-2.07)		
Hardell et al. (2013)	CC	1997-2003, 2007-2009, Sweden	20-80, Both	Acoustic Neuroma	Per 100 cumulative hours of use	NA	1.009 (1.001-1.017)		>1 year
					Quartiles				
					1-122 hours	91	1.6 (1.1-2.2)	0.052	
					123-511 hours	37	1.5 (0.9-2.3)		
					512-1,486 hours	42	2.4 (1.5-3.8)		
					>1,486 hours	30	2.6 (1.5-4.4)		

Table 15: Results from epidemiology studies for average daily or monthly use of a cellular telephone and the risk of acoustic neuroma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Measure	Exposed Cases	OR (95% CI)	P Trend	Comparison group
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Acoustic neuroma	Average daily				
					<3 minutes	7	1.0 (0.4-2.9)	ND	Any use
					3 to 15 minutes	10	1.4 (0.6-3.2)		2+ calls/w
					≥15 minutes	5	0.9 (0.3-2.8)		
					≥60 minutes	1	0.3 (0.0-2.7)		
Muscat et al. (2002)	CC	1997-1999, New York City	≥18, Both	Acoustic neuroma	Average monthly				
					1-2.5 hours	11	1.1 (0.4-2.9)	0.40	Referent was asked if they were a regular user
					>2.5 hours	7	0.6 (0.2-1.7)		
Corona et al. (2012)	CC	2006-2010, Brazil	18, Both	Acoustic Neuroma	Minutes/day				
					≤10	19	1.49 (0.59-3.77)	ND	Avg 1 call per week for 6 months
					11-30	11	1.77 (0.62-5.06)		
					>30	5	1.15 (0.33-4.08)		

Table 16: Results from epidemiology studies for other use measures of a cellular telephone and the risk of acoustic neuroma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Measure	Exposed Cases	OR (95% CI)	P Trend	Comments
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Acoustic neuroma	Year use began 1995-1998 1993-1994 ≤1992 <1990	 7 9 6 2	 0.7 (0.3-2.0) 1.5 (0.6-3.6) 1.2 (0.4-3.4) 1.3 (0.2-6.6)	ND	Any use 2+ calls/w
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Acoustic neuroma	Cumulative use by recency of starting use *1-4 years before reference date* <5 hours 5-114.9 hours 115-359.9 hours 360-1639.9 hours ≥1640 hours *5-9 years before reference date* <5 hours 5-114.9 hours 115-359.9 hours 360-1639.9 hours ≥1640 hours *≥10 years before reference date* <5 hours 5-114.9 hours 115-359.9 hours 360-1639.9 hours ≥1640 hours	 54 198 57 26 4 4 77 55 64 36 0 8 6 17 37	 0.81 (0.53-1.24) 0.92 (0.71-1.20) 0.74 (0.49-1.13) 0.55 (0.29-1.03) 0.63 (0.14-2.80) 0.84 (0.21-3.40) 0.97 (0.67-1.41) 0.95 (0.62-1.45) 0.74 (0.49-1.12) 1.05 (0.62-1.78) - 0.81 (0.30-2.14) 0.28 (0.09-0.86) 0.39 (0.20-0.74) 1.93 (1.10-3.38)	ND	Avg 1 call per week for 6 mo (lag 1 yr), no hands-free
Pettersson et al. (2014)	Case-Control	Sweden	20-69, Both	Acoustic Neuroma	Cumulative # calls <1,100 1,100-4,400 4,400-13,850 ≥13,850	 72 71 79 75	 1.21 (0.82-1.78) 1.07 (0.71-1.61) 1.22 (0.83-1.80) 1.20 (0.79-1.82)		Avg 1 call per week for 6 mo (lag 1 yr), weighted hands-free

Table 17: Results from epidemiology studies for laterality of cellular telephone use and the risk of acoustic neuroma in adults

Author (year)	Study Type	Years, Country	Age (years), sex	Tumor Type	Location or laterality	Ipsilateral OR (95%CI)	Contralateral OR (95% CI)	Inskip P.value	Comparison group
Inskip et al. (2001)	CC	1994-1998, US	≥18, Both	Acoustic neuroma	Inskip method	0.9		0.63	2 or more calls/week + 6 months latency
Muscat et al. (2002)	CC	1997-1999, New York City	≥18, Both	Acoustic neuroma	Inskip Method	0.9		0.07	Asked if they were a regular user
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Acoustic neuroma	1-year lag				Avg 1 call per week for 6 mo (lag 1 yr)
					Regular use	0.77 (0.59-1.02)	0.92 (0.70-1.22)		
					≥10 years since start	1.18 (0.69-2.04)	0.69 (0.33-1.42)		
					≥1640 hours cumulative	2.33 (1.23-4.40)	0.72 (0.34-1.53)		
					≥270 calls (hundreds)	1.67 (0.90-3.09)	0.52 (0.21-1.26)		
					5-year lag				
					Regular use	0.98 (0.73-1.30)	0.93 (0.68-1.27)		
					≥10 years since start	1.05 (0.65-1.68)	0.58 (0.30-1.11)		
					≥1640 hours cumulative	3.53 (1.59-7.82)	1.69 (0.43-6.69)		
					≥270 calls (hundreds)	2.00 (0.89-4.51)	1.40 (0.43-4.53)		
Corona et al. (2012)	CC	2006-2010, Brazil	18, Both	Acoustic Neuroma	Regular Users	1.40 (0.65-3.04)	0.57 (0.23-1.43)		Avg 1 call per week for 6 mo
Pettersson et al. (2014)	Case-Control	Sweden	20-69, Both	Acoustic Neuroma	Regular users	0.98 (0.68-1.43)	1.33 (0.89-1.99)		Avg 1 call per week for 6 mo (lag 1 yr), weighted hands-free
					Duration of use (years)				
					<5	1.05 (0.62-1.78)	1.41 (0.80-2.48)		
					5-9	0.95 (0.57-1.58)	1.51 (0.92-2.49)		
					≥10	1.01 (0.61-1.68)	1.09 (0.63-1.88)		
					Cumulative hours of use				
					<38	0.78 (0.45-1.38)	1.69 (0.94-3.05)		
					38-189	1.18 (0.63-2.20)	1.05 (0.56-1.95)		
					190-679	0.98 (0.52-1.84)	1.31 (0.74-2.32)		
					≥680	1.20 (0.69-2.08)	1.26 (0.70-2.25)		
Sato et al. (2011)	Case-Case	2000-2006, Japan	Any age, Both	Acoustic neuroma	l/l & r/r (97 cases)	1.08 (0.93-1.28)			Avg 1 call per week for 6 mo (lag 1 yr)
					l/l & r/r (86 cases)	1.14 (0.96-1.40)			Avg 1 call per week for 6 mo (lag 5 yr)
					Duration				
					≤5 years	1.06 (0.88-1.31)		0.240	Avg 1 call per week for 6 mo (lag 1 yr)
					5-10 years	1.05 (0.82-1.45)			
					>10 years	1.62 (0.79-4.77)			
					≤5 years	1.11 (0.92-1.38)		0.300	Avg 1 call per week for 6 mo (lag 5 yr)
					5-10 years	1.56 (0.90-3.34)			
					>10 years	1.00 (0.59-3.23)			
					Weighted average daily call				
					≤3 minutes	1.18 (0.93-1.57)		0.230	Avg 1 call per week for 6 mo (lag 1 yr)
					1-3 minutes	0.89 (0.72-1.21)			
					10-20 minutes	0.82 (0.65-1.19)			
					>20 minutes	2.74 (1.18-7.85)			
					≤3 minutes	1.11 (0.85-1.55)		0.004	Avg 1 call per week for 6 mo (lag 5 yr)
					1-3 minutes	0.89 (0.71-1.21)			
					10-20 minutes	0.84 (0.62-1.44)			
					>20 minutes	3.08 (1.47-7.41)			
					Weighted avg duration 1 call				
					≤1 minute	1.13 (0.89-1.51)		0.230	Avg 1 call per week for 6 mo (lag 1 yr)
					1-3 minutes	0.91 (0.75-1.21)			
					3-5 minutes	1.11 (0.76-1.95)			
					>5 minutes	1.51 (0.95-2.75)			
					≤1 minute	1.02 (0.79-1.43)		0.017	Avg 1 call per week for 6 mo (lag 5 yr)
					1-3 minutes	1.04 (0.81-1.44)			
					3-5 minutes	1.37 (0.83-2.74)			
					>5 minutes	1.68 (1.00-3.28)			
Hardell et al. (2013)	CC	1997-2003, 2007-2009, Sweden	20-80, Both	Acoustic Neuroma	Regular users	1.8 (1.3-2.6)	1.5 (0.98-2.2)		>1 year usage

4.2.2 Studies in Children

I could not identify any studies on acoustic neuromas in children and exposure to RF or cellular telephones.

4.2.3 Discussion

As for gliomas, I will focus on three areas of interest from the epidemiology studies of acoustic neuromas (AN); consistency of the association, the existence of an exposure-response relationship, and the strength of the association.

4.2.3.1 Consistency of the Association

The studies to be considered are listed in Table 12 and **Muscat et al. (2002)** in Table 13. All of these studies did a reasonable job of addressing confounders in their analyses and so this problem will not be discussed further. First, we should consider timing of the study. As mentioned earlier, for studies in the 1990s, we are looking at a rare exposure and trying to associate it with a rare disease (AN) and probably with very little time from the beginning of exposure to disease onset. Thus, it is unlikely that **Hardell et al. (1999)** [85], **Inskip et al. (2001)** [44], **Muscat et al. (2002)** [153], **Warren et al. (2003)** [154], and **Baldi et al. (2011)** [89] would show much of an association. And that is basically the case, with these studies producing ORs of approximately 1.0. The later studies are more likely to show an effect if one exists than these early studies and these should be given greater weight.

The size of a study will also matter since studies with greater numbers of cases and controls (especially exposed cases) will generally have smaller confidence bounds and have a greater chance of seeing an effect if one exists. Thus, the studies by **Hardell et al. (1999)** [85], **Inskip et al. (2001)** [44], **Muscat et al. (2002)** [153], **Warren et al. (2003)** [154], **Baldi et al. (2011)** [89], **Corona et al. (2012)** [161], **Benson et al. (2013)** [102] and **Schuz et al. (2011)** [94] will carry less weight in an overall evaluation.

There are also studies where the referent group was "never used a mobile phone" versus studies where the referent group was "not a regular user of mobile phones" defined by different measures. Less weight should be given to studies with comparisons to "never used" simply because the "ever used" group could include people who used a phone only a few times.

Given these caveats, there are five case-control studies that should carry the greatest weight: **Interphone (2010)** [67], **Hardell et al. (2013)** [160], **Han et al. (2012)** [157], **Corona et al. (2012)** [161], and **Pettersson et al. (2014)** [162]. Three of these 4 studies have ORs greater that 1.0 for regular usage of a cellular phone with 1 (**Hardell et al. (2013)** [160]) being significantly >1 [1.6 (1.2-2.2)].

The largest study, **Interphone (2010)** [67] has an OR for regular use of 0.85 (0.69-1.04). The difference in the response rate for cases (82%) versus controls (53%) could lead to problems with selection bias as was suggested for the brain tumor data from the Interphone study [74]. This study demonstrated no increases in OR with duration of use, even with a 5-year latency. (Table 12, Table 13)

The next largest study, and **Pettersson et al. (2014)** [162], had approximately half the number of exposed cases as **Interphone (2010)** [67] and showed an OR for regular use of

1.18 (0.88-1.59). They saw an increased OR for 5-9 years duration of use [1.39 (0.97-1.97)] which dropped for ≥10 years durations [1.09 (0.75-1.59)]. They had a non-responder questionnaire which was answered by 93 controls and 7 cases. Of the 93 control non-responders, 62 (67%) were regular mobile phone users compared to 442 (69%) out of 643 responding controls. There were only 7 non-responder cases who replied to the questionnaire and 4 were regular phone users. Thus, even though there are a larger number of non-responders in controls, there is no obvious suggestion of selection bias. (Table 12, Table 13)

Hardell et al. (2013) [160] was the next largest study with roughly 1/3 of the number of exposed cases as **Interphone (2010)** [67]. They saw an OR for regular use of 1.6 (1.2-2.2) and an increasing risk with increasing duration of use. In addition, all of the 5-year groupings of duration of use were greater than 1 and all usage longer than 5-years was significantly greater than 1 (Table 13). Only living cases were included. Their response rate was high enough that participation bias is unlikely to have lowered the OR values. Recall bias could have increased the ORs. In one of the original case-control studies [117] used in their pooled analysis, they evaluated this issue and saw little indication of recall bias with regard to malignant brain tumors (no information on AN). (Table 12, Table 13)

Han et al. (2012) [157] also was about 1/3 of the number of exposed cases as **Interphone (2010)** [67]. They saw an OR for regular use of 0.95 (0.58-1.58) and an increasing risk with increasing duration. It is impossible to judge the potential for selection bias since they gave no indication of the response rates for controls. In addition, it is also impossible to judge the quality of the exposure metrics since there was insufficient detail to understand how they related controls to cases in obtaining this information. (Table 12, Table 13)

Corona et al. (2012) [161] had 34 exposed cases or about 20x smaller than **Interphone (2010)** [67]. They saw increased ORs (non-significant) for all categories of usage. The response rates for cases and controls were moderate but not remarkably different suggesting no problem with selection bias although there was no follow-up with non-respondents. It is not possible to judge recall bias in this small study. (Table 12, Table 13)

Sato et al. (2014) [163] is the next largest study; but being a case-case study, it is more relevant to the issue of laterality and will be discussed later.

Schuz et al. (2011) [99], with only 15 exposed cases, is a cohort study with limitations due to potential differential exposure misclassification (discussed earlier). They saw an OR for subscriptions from 11 years prior to reference date of 0.86 (0.52-1.46). (Table 12)

Benson et al. (2013) [102], with only 8 cases that are daily users, saw an OR of 1.37 (0.61-3.07). They had 67 ever users in the cases and these had an OR of 1.44 (0.91-2.28). Using never use as the reference category, they looked at duration of use and saw clearly increasing ORs with increasing duration. This study may also have problems with exposure misclassification (discussed earlier). (Table 12, Table 13)

Roosli et al. (2019) [118] also did a meta-analysis of AN and cellular phones. They give mRRs for the analyses of studies showing ORs for ≥10 years exposure. For the case-control studies, they get an mRR of 1.29 (0.74-2.23). For the Cohort studies, they show an mRR of 0.98 (0.65, 1.48) and for all studies combined they get 1.19 (0.80-1.79). Entering their numbers into Stata (v 16.2 for MAC), I can reproduce their findings. They also did a meta-analysis of ever versus never use for all 9 case-control studies (1.05 [0.84-1.32]) and the

cohort studies (0.93 [0.57-1.50]) with a combined mRR of 1.02 (0.84-1.24). They show a number for regular use from **Muscat et al. (2002)** [153] which is not in the paper and appears to be the unadjusted crude OR. They give no reason for using **Shuz et al. (2006)** [94] instead of **Schuz et al. (2011)** [99] for this analysis although they used **Frei et al. (2011)** [96] for their analysis of gliomas. I am also unable to match the number they use for **Benson et al. (2013)** [102] which they list as 1.19 (0.81-1.75) but the paper lists as 1.37 (0.61-3.07). They also conducted a cumulative meta-analysis of the studies with ≥10 years of use. They also did several other analyses of ever versus never use with no appreciable changes in the results. One problem with these meta-analyses is that they give very little weight to the largest studies. They did not consider laterality or tumor location in the brain.

The remaining meta-analyses are older and use fewer and fewer of the individual studies.

To provide a better evaluation of the results, Figure 3 is a forest plot of all of the ORs from individual publications that evaluated regular use versus minimal or never use or ever use versus never use (if both were given in a study, regular use is shown). The column labeled "Study" provides the reference to the publication and the years in which cases and controls were collected for case control studies and the years when phone use information was collected for cohort studies and the year in which follow-up ended. Some studies are pooled evaluations of multiple other studies, so the other studies are indented. The column labeled "RR" is the risk ratio (OR, RR or mRR) from the study, "Lower" and "Upper" are the lower and upper bound on a 95% confidence interval around the RR. The graphic on the right simply plots the RR as a square or diamond with the "whiskers" (blue line running through the box) showing the width of the 95% confidence interval. The vertical line passing through 1 represents no effect. If the box and both whiskers are to the right of this line (greater than 1) and not touching it, this finding is statistically significant with a positive effect; if they fall completely to the left of the vertical line (below 1), then the risk is significantly reduced. The blue boxes that are filled in are major studies, the blue boxes that are white in the middle are the sub-studies and the red diamonds are all meta-analyses.

The graphic in Figure 3 is very useful for examining these types of data in a single view. Looking just at the filled in blue blocks (Studies A,B,C,D,E,F,G,H,I,J,K), 5 studies have their ORs below 1, two are equal to 1 and four are above 1. One study (I) shows a significant increase in risk. The first meta-analysis (Meta Analysis A,B,C,D,E,F,G,H,I,J,K) combines the information from all of the studies to produce an mRR of 1.06 (0.88-1.29) suggesting that all of the positives and negatives balance out to a small, non-significant increased risk. However, as mentioned earlier, the newer, larger studies represent longer exposures, so I have also done meta-analyses on the five case-control studies that collected cases after 2002 (E,F,G,H,I) and the two cohort studies (J,K). Combining the five case-control studies (Meta Analysis E,F,G,H,I) results in a mRR of 1.13 (0.87-1.48), a slight increase in risk from the use of a mobile phone, but heterogenous across studies. The combined cohort studies yield a mRR of 0.99 (0.64-1.53) suggesting no risk, and no heterogeneity (p=0.35). Combining the 5 case-control studies and the 2 cohort studies (Meta Analysis E,F,G,H,I,J,K) yields an mRR of 1.11 (0.88-1.39) again suggesting marginal risk but with significant heterogeneity (p=0.04).

Figure 4 is a forest plot of all of the ORs from individual publications that reported on duration of use ≥5 years or more. There are 8 studies; 5 of these studies show groupings of 1-4 years, 5-9 years and ≥10 years, one study with groupings of <6 years, and ≥6 years, one study with ≥5 years and one study with <10 years and >10 years. For the study by **Hardell et**

al. (2013) [160], groupings of 10-14, 15-19 and ≥20 years were combined by meta-analysis to get a single mRR for ≥10 years. There are 2 groups of meta-analyses each with three separate meta-analyses for 1-4 years, 5-9 years and ≥10 years (combined with only ≥10 years for **Han et al. (2012)** [157] and <6 years for **Corona et al. (2012)** [161]). The first group of 3 meta-analyses combines the case-control studies and the second group of 3 meta-analyses adds in the cohort studies. In order to accommodate the study by **Inskip et al. (2001)** [44] with only a ≥5 year grouping and the study by **Corona et al. (2012)** [161] with ≥6 years, all studies with 5-9 and ≥10 years were combined in the last 2 meta-analyses to yield mRRs for ≥5-6 years for the case-control studies and all of the studies. The mRRs for <5 years are all near 1. The mRRs for 5-10 years are all elevated and close to statistical significance. The mRRs for ≥10 years are elevated, but less than for 5-10 years. Finally, both of the mRRs for ≥5 years are significantly elevated.

The studies in adults of an association between cellular phone use and acoustic neuroma are consistent enough to conclude an association exists.

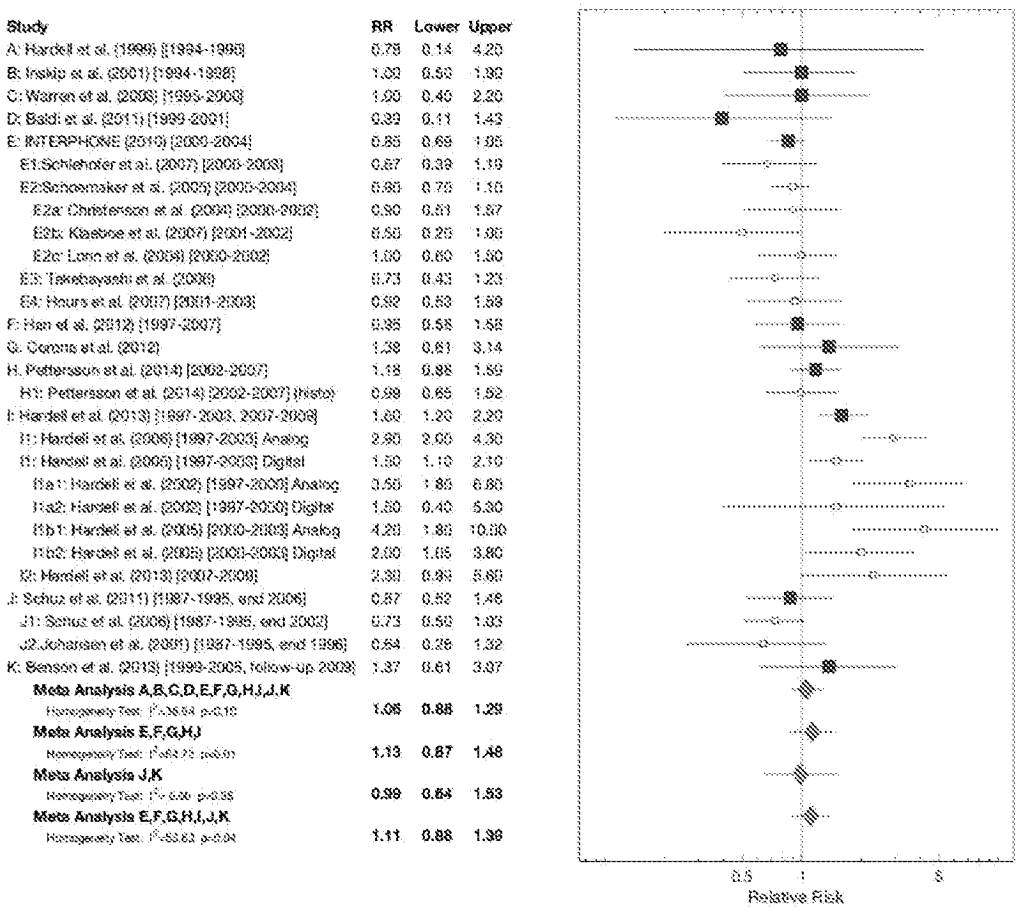


Figure 3: Forest plot and meta-analyses of regular use or ever use of cellular telephones and the risk of acoustic neuroma [studies with a solid blue square either single studies that stand alone or pooled studies that encompass numerous single studies; open squares are individual studies or smaller pooled studies; red diamonds are meta-analyses][a]

[a] - The column labeled "Study" provides the reference to the publication and the years in which cases and controls were collected for case control studies and the years when phone use information were collected for cohort studies and the year in which follow-up ended. Some studies are pooled evaluations of multiple other studies, so the other studies are indented. The column labeled "RR" is the risk ratio (OR, RR or mRR) from the study, "Lower" and "Upper" are the lower and upper bound on a 95% confidence interval around the RR. The graphic on the right simply plots the RR as a square or diamond with the "whiskers" (blue line running through the box) showing the width of the 95% confidence interval. The vertical line passing through 1 represents no effect. If the box and both whiskers are to the right of this line (greater than 1) and not touching it, this finding is statistically significant with a positive effect; if they fall completely to the left of the vertical line (below 1), then the risk is significantly reduced. The blue boxes that are filled in are major studies, the blue boxes that are white in the middle are the sub-studies and the red diamonds are all meta-analyses. "Homogeneity Test" provides the I^2 statistic and the p-value for the Q-test.

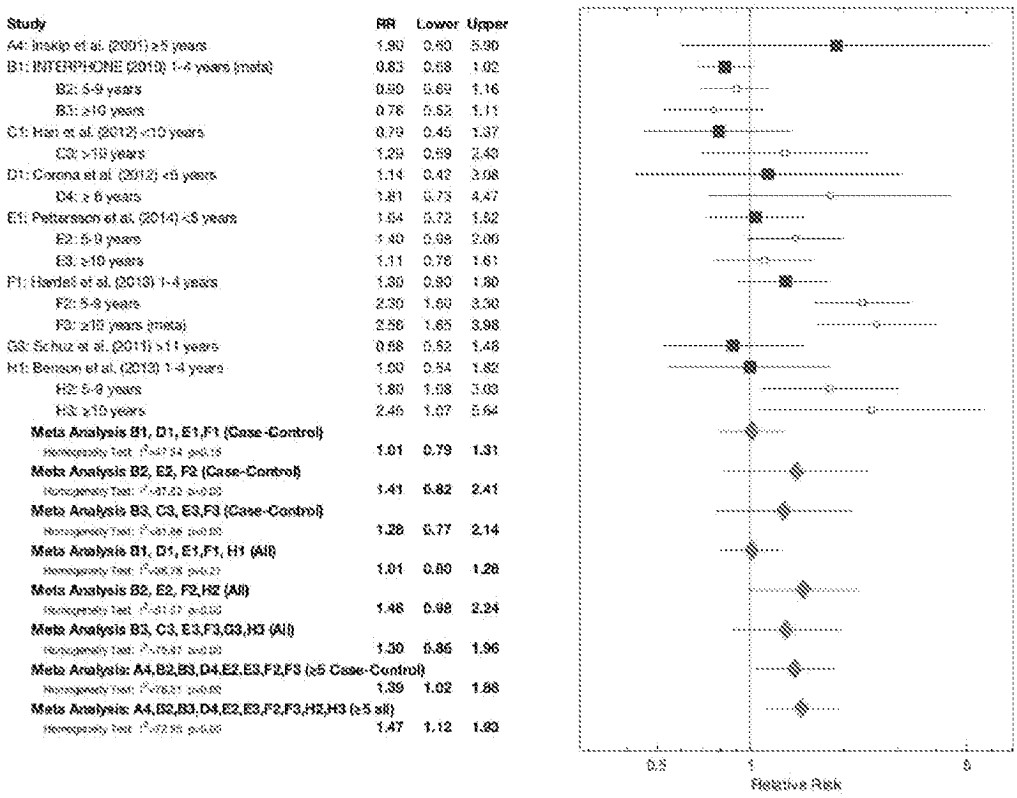


Figure 4: Forest plot and meta-analyses of duration of use of cellular telephones and the risk of acoustic neuroma [studies with a solid blue square are stand alone; red diamonds are meta-analyses, the columns and the figure are as in Figure 1]

4.2.3.2 Exposure-Response

As for gliomas, the best measure for exposure-response relationships is the cumulative hours of use of a cellular telephone since it includes both the frequency of use and the duration of use. While duration of use is also a form of exposure-response, it is more likely that, similar to ionizing radiation, RF is likely to have an association between total accumulated exposure and the risk of AN if a relationship exists. Table 14 provides the results for all of the epidemiology studies with estimates of the cumulative use of cellular phones.

Inskip et al. (2001) [44] shows consistent exposure-response and has two of the three ORs above 1. **Muscat et al. (2002)** [153] shows no increased risk. **Interphone (2010)** [67] basically shows flat exposure-response for the entire study until the largest exposure category, that is elevated in risk with an OR of 1.32 (0.88-1.97). The same pattern holds with a 5-years lag although the highest exposure group is now statistically significant with an OR of 2.79 (1.51-5.16). **Pettersson et al. (2014)** [162] saw a clearly increasing exposure-response pattern with ORs above 1 in all exposure categories and becoming almost significant in the highest exposure category [1.46 (0.98-2.17)]. **Hardell et al. (2013)** [160] saw a pattern of increasing risk with increasing exposure with 3 of their 4 categories statistically significant. They also did a regression resulting an OR of 1.009 (1.001-1.017) per hundred cumulative hours.

It is not possible from the published results to find categories of exposure that match across the various studies in order to do a simple meta-analysis by category. However, it is possible to do a meta-regression where the exposure categories are turned into a single exposure and the meta-regression tests to see if the slope of the data from the various studies is increasing with exposure. As for glioma (Section 1.3.2, page 41), I set the exposure for each category equal to the center of the interval defined for the category and or the last category, which is generally expressed as ≥ some number of hours, I used the difference between the middle of the second largest category and the lower bound of that category and added it to the upper end of the second highest category to get the exposure for the highest category. The exposures for all of the categories of the studies entering into the meta-regression are shown in Table 18. As a check, a meta-regression was performed of just the **Hardell et al. (2013)** [160] study; the mRR is 1.015 (1.000-1.030) per 100 hours with p=0.05 compared to 1.009 (1.001-1.016) per 100 hours seen by **Hardell et al. (2013)** [160] using the original data.

Table 19 provides the results of the meta-regression for the 5 case-control studies with duration of exposure where all of the ORs are a comparison against non-regular users. There is a significant association between exposure and risk with a mRR of 1.007 (1.001-1.013, p=0.017). This is almost identical to what was seen by Hardell et al. (2015) [1.009 (1.001-1.016)]. The test of heterogeneity is significant (pQ<0.001) and an I^2 of 57.31. Removing **Interphone (2010)** [67] doubles the mRR to 1.014 (1.066-1.024) and reduces heterogeneity. Removing **Pettersson et al. (2014)** [162] results in no change in the mRR and slightly wider confidence intervals that barely include 1. Removing **Hardell et al. (2013)** [160] cuts the mRR in half and leads to a non-significant risk (1.003 [0.998-1.009; p=0.250) and reduces heterogeneity. The alternative high dose yielded the same pattern but higher mRRs per 100 hours, larger confidences bounds, less statistical significance and less heterogeneity (not shown). (Table 19)

There were other measures of exposure used in the various studies that are worth mentioning. **Inskip et al. (2001)** [44] used average minutes/day and saw no exposure-response relationship (Table 15). **Corona et al. (2012)** [161] also used average minutes/day and saw an increasing exposure response in the first 2 groupings and a lower OR in the highest grouping, all increased but with lower confidence bounds below 1 (Table 15). **Muscat et al. (2002)** [153] used hours/month and saw no pattern (Table 15). **Inskip et al. (2001)** [44] also considered the year that cellular telephone use began and again saw no exposure-response (Table 16). **Interphone (2010)** [67] considered cumulative use by years of duration of use (1-4 years, 5-9 years and ≥10 years). In 1-4 years and 5-9 years duration categories, they saw flat exposure-response. The highest cumulative use, ≥1640 hours, in the highest duration of use category, ≥10 years, was significantly increase (1.93 [1.10-3.38]) (Table 16). **Pettersson et al. (2014)** [162] considered cumulative number of calls and saw a flat exposure-response with all ORs above 1.0 (Table 16).

Table 18: Meta-Regression Exposure Values for Table 19

Author (year)	Exposures (times 100 hrs)
Inskip et al. (2001)	0.065, 0.57, 1.435
Muscat et al. (2002)	0.30, 3 (0.90[a])
Interphone (2010)	0.025, 0.09, 0.22, 0.46, 0.88, 1.575, 2.80, 5.475, 11.875, 82 (20.925[a])
Pettersson et al. (2014)	0.19, 2.08, 4.345, 34 (9.245[a])
Hardell et al. (2013)	0.615, 3.17, 9.99, 74.3 (19.73[a])

[a] alternative exposure for highest exposure group

Table 19: Meta-Regression Analysis with Sensitivity Analysis of ORs for Five Case-Control Studies using Cumulative Hours of Use as the Exposure Metric and the Original Referent Groups

Meta Regression Studies[a]	Per 100 hours Use	P>|Z|	95% Confidence Interval		I^2	pQ
All	1.007	0.017	1.001	1.013	57.31	<0.001
drop Inskip et al. (2001)	1.007	0.021	1.001	1.013	62.4	<0.001
drop Muscat et al. (2002)	1.007	0.019	1.001	1.013	60.91	<0.001
drop Interphone (2010)	1.014	0.001	1.006	1.022	42.36	0.053
drop Petterson et al. (2014)	1.007	0.053	1.000	1.014	64.21	<0.001
drop Hardell et al. (2013)	1.003	0.25	0.998	1.009	29.45	0.111

4.2.3.3 Strength of the Association

The strength of the association is tied to the magnitude of the response and the statistical significance of that response. For all of these studies, the actual magnitude of the RRs seen in the studies are small, in many cases falling below 1. It is clear from Figure 4, that the longer the duration, the larger the mRR and the more statistical significance to the risk.

Laterality matters for addressing the strength of the association. For regular users versus non-regular users, **Interphone (2010)** [67] and **Pettersson et al. (2014)** [162] saw ipsilateral ORs smaller than the contralateral ORs [Note that **Pettersson et al. (2014)** [162] define ipsilateral differently, including people who used both hands in the ipsilateral category]. In contrast, **Corona et al. (2012)** [161] and **Hardell et al. (2013)** [160] saw ipsilateral ORs greater than the contralateral ORs. Laterality seems to become more pronounced with a longer duration of exposure or greater cumulative hours of use in **Interphone (2010)** [67] but not in **Pettersson et al. (2014)** [162].

In the case-case study by **Sato et al. (2014)** [163], they calculated ORs for the grouping left-handed users with left side ANs (l/l) and right-handed users with right-side ANs (r/r) against all miss-matched tumors (l/r and r/l). For a 1-year lag they saw an OR of 1.08 (0.93-1.28) and for a 5-year lag they saw an OR of 1.14 (0.96-1.40). When they examined this for duration of use, they saw generally increasing ORs that were >1, but not statistically significant. For weighted average minutes per day of use, they saw significant ORs for 1-year lag (2.74 [1.18-7.85]) and 5-year lag (3.08 [1.47-7.41]) and significantly increasing ORs for the 5-year lag group (p=0.004). For the average duration of a call, they saw the same basic pattern.

4.2.4 Ecological Epidemiology Studies of Acoustic Neuroma

Benson et al. (2013) [102] examined temporal trends in acoustic neuroma incidence rates in England using data from the UK Office of National Statistics. They restricted their analysis to the years 1998-2008. They provided no analysis of these data, only a plot of incidence over time.

Several studies are also mentioned in Section 1.4.

4.2.5 Conclusions for Acoustic Neuromas

The evidence on an association between cellular phone use and the risk of acoustic neuromas in adults is strong. While there is considerable difference from study to study on ever versus never usage of cellular phones, 3 of the 4 meta-analyses in Figure 3 are above 1 although none-significantly. The meta-analyses in Figure 4 demonstrate an increased risk in the highest 2 latency groups for the case-control studies that gets slightly higher when the cohort studies are added. For latency ≥5 years, the mRRs are significantly elevated for the case-control studies and the combined case-control and cohort studies. The exposure response meta-regressions in Table 19 indicates that risk is increasing with cumulative hours of exposure, especially in the highest exposure groups. This finding, however, is sensitive to the inclusion of the **Hardell et al. (2013)** [160] study. There is a strong tendency toward ANs appearing on the same side of the head as the phone is generally used, especially as the exposure increases. These findings do not appear to be due to chance. The cohort studies appear to show less of a risk than the case-control studies, but one study is likely to be severely impacted by differential exposure misclassification (**Schuz et al. (2011)** [99]) and the other (**Benson et al. (2013)** [102]) is likely to have a milder differential exposure misclassification. Both studies have very few cases. The case-control studies are possibly impacted by recall bias and this cannot be ruled out for the ANs. Selection bias could have been an issue for **Interphone (2010)** [67], and, unlike their analysis of the glioma data, they have not looked at an alternate referent population for their analyses of AN. Confounding is not an issue here. In conclusion, an association has been established between the use of cellular telephones and the risk of ANs and chance and confounding are unlikely to have driven this finding. Potential recall bias and selection bias may still be an issue with some of these findings.

Laboratory Cancer Studies

There is sufficient evidence from laboratory studies to conclude that RF can cause tumors in experimental animals with strong findings for gliomas, heart Schwannomas and adrenal pheochromocytomas in male rats and harderian gland tumors in male mice and uterine polyps in female mice.

5.1 Chronic Carcinogenicity Studies

5.1.1 Mice

Tillmann et al. (2007) [164] Exposed groups of 50 male and female B6C3F$_1$ mice to four exposure levels (whole body averaged specific absorption rates (SAR) of 0.0, 0.4, 1.3 and 4.0 mW/g) of two different radiofrequency radiation (RF) exposures (902 MHz GSM and 1747

MHz DCS modulated frequencies) for 2 hours per day, 5 days per week for 2 years using head-only exposure in a Ferris wheel/tube-restrained exposure system. The two hours of exposure was done in three phases imitating exposures classified as "basic", "talk" and "environment". All test animals were given a full necropsy and both gross and microscopic lesions identified and characterized. They reported no increases in tumor incidences for any lesion. They did report a significant exposure-related decrease in hepatocellular adenomas in males in the highest exposure group for both GSM (p=0.048) and DCS (p=0.015) exposures. Tumor count data was provided for Pituitary gland, Harderian gland, lungs, liver, adrenals, uterus and hematopoetic/lymphoreticular tissues. Brain tumor data was described as negative but counts were not provided. They reported no difference in survival by treatment group. All data presented were reanalyzed using a one-sided Fisher's exact test for pairwise comparisons and the one-sided exact Armitage linear trend test for increasing or decreasing risk with exposure [165]. The reanalysis showed a decrease in the GSM data in all three treated groups in females in Harderian gland adenomas (p=0.045, <0.01, 0.011; trend test p=0.047), in alveolar/bronchiolar carcinomas at the two lowest exposures (p=0.008, 0.008) and adenomas at the highest exposure (p=0.045), and increased trend in liver adenomas (p=0.033) and a significant increase in uterus endometrial stromal polyps at the two lowest exposures (p=0.004, 0.046) with no increased trend. In the DCS data for females, there was significant effect at the highest exposure for uterus glandular polyps (p=0.013) with a significant trend (p=0.002). In the male GSM exposure groups, Harderian gland adenomas were increased in all groups (p=0.027, 0.003, 0.001) with a significant trend (p=0.004) and a significant decreased trend in liver adenomas (p=0.001) and decreases at all three exposures (p=0.014, 0.014, <0.01). In the male DCS exposure groups, Harderian gland adenomas were decreased for all exposure groups (p=0.001, 0.001, 0.001) with a significant decreased trend (p=0.018), a decrease in liver adenomas at the two highest groups (p=0.03, <0.01) with significant negative trend (p<0.01), and a significant increase in lymphomas in all exposure groups (p=0.004, 0.046, 0.046) with no trend. The increases in Harderian gland adenomas in the male GSM studies may be due to the exposure, but this was not explored by the authors. The large control response for Harderian gland adenomas in males in the DCS exposure studies suggests the incidence for this tumor in these studies is highly variable.

National Toxicology Program (2018) [166] exposed groups of 90 5-6 week old male and female B6C3F1/N mice to sham, GSM-modulated RF (2.5, 5 or 10 W/kg 9 hours/day, 7 days/week) or CDMA-modulated RF (2.5, 5 or 10 W/kg 9 hours/day, 7 days/week) for 106 (males) or 108 (females) weeks. The 9 hours and 10 minutes of exposure was achieved by cycling the fields 10 minutes on and 10 minutes off for 18 hours and 20 minutes each day. The mice exposed GSM-modulated and CDMA-modulated RF used the same sham controls. Exposures were conducted in reverberation chambers and animals were housed in individual cages. Full pathology was conducted on all animals. GSM Study: Survival was significantly higher for the 5 W/kg males than the sham controls; all other groups were not different from controls. There were no body weight differences between exposed animals and controls. They saw a marginal increase in skin fibrosarcoma, sarcoma or malignant fibrous histiocytoma in male mice (p=0.093) (mostly occurring in the tails of these animals), a significant increase in alveolar/bronchiolar adenomas and carcinomas in male mice (p=0.040) but not for adenomas and carcinomas separately, and significant increases in malignant lymphomas in the two lowest exposure groups for females, but the trend test was not significant and the control numbers were substantially smaller than historical

controls. To clarify the significance of the lung tumors in males, the NTP historical control data described in the technical report [166] was obtained electronically online, and using Tarone's test for historical controls [167], yields p=0.072. CDMA Study: Survival was significantly higher for the 2.5 W/kg females than the sham controls; all other groups were not different from controls. There were no body weight differences between exposed animals and controls. There were sporadic positive pairwise comparisons that were significant for liver tumors in male mice, but none of these demonstrated any pattern of exposure-response. Also, significant increases in malignant lymphomas in the lowest exposure group for females with increases in all groups, but the trend test was not significantly increased and the control numbers were substantially smaller than historical controls. Two adenomas and 1 carcinoma of the pars distalis in the pituitary gland occurred in the 5 W/kg group but not the other groups (these tumors were not seen in the historical controls). After 14 weeks of exposure, **Smith-Roe et al (2020)** [168] evaluated genotoxicity in several tissues of mice included in these studies for this purpose using the alkaline comet assay (three brain regions, liver, peripheral blood) and the micronucleus assay (peripheral blood). Significant increases in DNA damage were seen in the frontal cortex of male mice (DCMA and GSM) and leukocytes of female mice (CDMA only). NTP uses 5 levels of evidence for classifying the findings of carcinogenicity studies. Equivocal evidence is defined as "*Equivocal evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be test agent related.*" In this study, for GSM-exposed mice, they labeled the skin tumors and lung tumors in males as equivocal and the malignant lymphomas in females as equivocal. For CDMA-exposed mice, they labeled the liver hepatoblastomas in males and the malignant lymphomas in females as equivocal. All of these conclusions seem reasonable. (Note: some text copied directly from **NTP (2018)** [166]).

5.1.2 Rats

Chou et al. (1992) [169] exposed groups of 100 male Sprague-Dawley rats to pulsed microwave radiation at 2450 MHz at 800 pulses per second with a pulse width of 10 μs for 21.5 hours per day, 7 days per week, for 25 months with an appropriate sham control. The exposure was intended to match a military-grade radar system and provide a whole body SAR of about 0.4 w/kg. They saw no changes in survival, body weight, or a number of other measures in the exposed animals and no increased tumor risk in any one organ. They did see a statistically significant increase in total tumors ($p<0.001$), but it is not clear if this evaluation included multiple findings from the same animal or not (the statistical method used may have been incorrect).

La Regina et al. (2003) [170] exposed groups of 80 male and female Fisher 344 rats (aged 6 weeks) to sham, 835.6 MHz FDMA RF (SAR 1.3 W/kg) or 847.7 MHz CDMA RF (SAR 1.3 W/kg) for 4 hours/day, 5 days/week for 24 months in a tube-restrained Ferris-wheel exposure system. The exposure was predominantly to the head, but all tissues were examined. There were no differences in survival or body weight across appropriate comparison groups. They reported no significant tumor findings.

Anderson et al. (2004) [171] exposed groups of pregnant Fischer 344 rats to RF at 1620 MHz for 2 hours per day, 5 days per week from day 19 of gestation to weaning. At approximately 5 weeks of age, groups of 90 male and female offspring were exposed to the same RF using tubes with predominantly head only exposure for 2 hours per day, 5 days per weeks for 24

months. Targeted head exposure was sham, 0.16 and 1.6 mW/g. They reported no statistically increased differences in reproductive index, litter size, body weight or other clinical signs. There was a slight increase in survival in the highest exposure group in females relative to the sham exposed group. They noted there were no exposure-related significant increases in any tumors and that the highest exposure group of males had a significant increase in mesothelioma of the testis, but that this was within the range of historical controls. A reanalysis of the data presented results in the same findings as those presented by **Anderson et al. (2004)** and also showing a significant trend for mesothelioma of the testis (p=0.003). **Anderson et al. (2004)** compared the oligodentroglioma data in males to the NTP historical control data presented by **Haseman et al. (1990)** [172], however, NTP has a set of controls more closely linked in time to this study that is more appropriate [173] showing the same range of responses (0-2%). Using the range of historical controls is inappropriate in this type of analysis [32, 33, 174] and a direct method of testing, Tarone's historical control test [167], is more appropriate; this test yields a p-value of $p<0.001$ for the oligodentrogliomas in males. For the mesotheliomas in the testes, the NTP database contains no entries and the source cited by **Anderson et al. (2004)** has a range of 0-2% while the observed response in the highest exposure group was 6/90=6.7%, so well outside the range.

Smith et al. (2007) [175] duplicated the exposure system of **Tillmann et al. (2007)** [164] for groups of 50 male and female Wistar rats. They reported no survival differences and no significant increases in tumors in any tissue evaluated. For the tissues they reported in the paper, a re-analysis using the Armitage linear trend test shows an increase in the incidence of C-cell adenomas in female rats for both GSM (p=0.025) and DCS (p=0.043) exposures, but not for c-cell carcinomas (p=0.50 and p=0.37) and it remains significant for the combined adenomas and carcinomas (p=0.028 and p=0.044).

Bartsch et al. (2010) [176] conducted four separate RF studies in female Sprague-Dawley rats; two long-term (I and II) and two life-long (III and IV) experiments were conducted exposing animals to a low-intensity GSM-like signal (900 MHz pulsed with 217 Hz, 100 µW/cm. average power flux density, 38–80 mW/kg mean specific absorption rate for whole body). Health and survival of unrestrained female Sprague-Dawley rats kept under identical conditions was evaluated. Radiofrequency (RF)-exposure was started at 52–70 days of age and continued for 24 (I), 17 (II) and up to 36 and 37 months, respectively (III/IV). In the first two experiments 12 exposed and 12 sham-exposed animals each were observed until they were maximally 770 or 580 days old (animals either died of natural causes or were sacrificed because they were moribund). In experiment I, no adverse health effects of chronic RF-exposure were detectable, neither by macroscopic nor detailed microscopic pathological examinations. In experiment II no apparent macroscopic pathological changes due to treatment were apparent and microscopic analyses were not conducted. Reductions in pituitary tumors were seen for both experiment I and II but no increases were reported. In experiments III and IV, 30 animals per group showed a significant reduction in survival in the RF-exposed groups relative to the sham-exposed groups and both groups in experiment III showed a significant reduction in survival compared to experiment IV. A reduction in mammary tumors were seen in the RF-exposed animals compared to sham, but this may be due to the survival differences (authors did not evaluate this issue). This study did not perform full pathology, had limited sample sizes and presents very little tumor data.

NTP (2018) [177] exposed groups of 56 time-mated F_0 female Sprague-Dawley rats, housed in specially designed reverberation chambers, to whole-body exposures GSM-modulated cell phone RF or CDMA-modulated RF at power levels of 0 (sham control), 1.5, 3, or 6 W/kg for 7 days per week, continuing throughout gestation and lactation. Exposure was up to 18 hours and 20 minutes per day with continuous cycling of 10 minutes on and 10 minutes off during the exposure periods. At weanling, groups of 90 5-6 week old male and female Sprague-Dawley rats were exposed the same exposures as their F_0 dams for 105 weeks. The rats exposed to GSM-modulated and to CDMA-modulated RF used the same sham controls. Exposures were conducted in reverberation chambers and animals were housed in individual cages. Full pathology was conducted on all animals. GSM Exposures: In F_0 females, there were no exposure-related effects on pregnancy status, maternal survival, or the percentage of animals that littered. During gestation, mean body weight gains of 6 W/kg females were significantly lower than those of the sham controls from GD 15 through 18 and during the overall gestation period (GD 6 through 21). During lactation, the mean body weights of 3 and 6 W/kg females were significantly lower than those of the sham controls for the period of PND 4 through 21. In F_1 offspring, there was no effect on litter size, pup mortality or survival. During lactation, mean pup weights were significantly lower at most timepoints in the 3 W/kg groups and at all timepoints in the 6 W/kg groups. At the end of 2 years, survival of all exposed male groups was significantly greater than that of the sham control group due to the higher severity of chronic progressive nephropathy in the kidney of sham control males (note, almost all male rats had chronic progressive nephropathy). Survival of exposed female groups was similar to that of the sham controls. The mean body weights of all exposed males and females were similar to those of the sham control groups. There were no exposure-related clinical observations. In the heart at the end of the 2-year studies, malignant schwannoma was observed in all exposed male groups and the 3 W/kg female group, but none occurred in the sham controls. Endocardial Schwann cell hyperplasia also occurred in a single 1.5 W/kg male and two 6 W/kg males. There were also significantly increased incidences of right ventricle cardiomyopathy in 3 and 6 W/kg males and females. In the brain of males, there were increased incidences of malignant glioma and glial cell hyperplasia in all exposed groups, but none in the sham controls. There was also increased incidences of benign or malignant granular cell tumors in all exposed groups. There were significantly increased incidences of benign pheochromocytoma and benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla in males exposed to 1.5 or 3 W/kg. In the adrenal medulla of females exposed to 6 W/kg, there were significantly increased incidences of hyperplasia. In the prostate gland of male rats, there were increased incidences of adenoma or adenoma or carcinoma (combined) in 3 W/kg males and epithelium hyperplasia in all exposed male groups. In the pituitary gland (pars distalis), there were increased incidences of adenoma in all exposed male groups. There were also increased incidences of adenoma or carcinoma (combined) of the pancreatic islets in all exposed groups of male rats, but only the incidence in the 1.5 W/kg group was significant. In female rats, there were significantly increased incidences of C-cell hyperplasia of the thyroid gland in all exposed groups, and significantly increased incidences of hyperplasia of the adrenal cortex in the 3 and 6 W/kg groups. CDMA Exposures: In F_0 females, there were no exposure-related effects on pregnancy status, maternal survival, or the percentage of animals that littered. During gestation, the mean body weights and mean body weight gains of exposed groups were similar to those of the sham controls. During lactation, mean body weights were significantly lower than those of the sham controls at

most time points in the 6 W/kg group, at several time points in the 1.5 and 3 W/kg groups, and the mean body weight gains for the period as a whole (PND 1 through 21) were significantly lower in the 3 and 6 W/kg groups. In F_1 offspring, there were no effects on litter size on PND 1. On PND 7 through 21, there were significant decreases in live litter size in the 6 W/kg group when compared to the sham controls. Throughout lactation, the male and female pup mean body weights in the 6 W/kg groups were significantly lower than those of the sham controls. At the end of 2 years, survival in all exposed male groups was greater than that of the sham control group due to the effects of chronic progressive nephropathy in the kidney of the sham control males. In females, there was a small, but statistically significant increase in survival in the 6 W/kg group. Although there were some differences in mean body weights in exposed male groups, at the end of the study, the mean body weights of exposed male and female groups were similar to those of the sham controls. There were no exposure-related clinical observations. At the end of the 2-year study, malignant schwannoma of the heart occurred in all exposed male groups and the incidence in the 6 W/kg group was significantly increased; this neoplasm did not occur in the sham controls. There was also an increased incidence of endocardial Schwann cell hyperplasia in 6 W/kg males. In females, malignant schwannoma occurred in two animals each in the 1.5 and 6 W/kg groups. In the brain, malignant glioma occurred in 6 W/kg males and 1.5 W/kg females; none occurred in the sham control groups. Glial cell hyperplasia also occurred in 1.5 and 6 W/kg males and 3 and 6 W/kg females. In males, there was a significantly increased incidence of pituitary gland (pars distalis) adenoma in the 3 W/kg group, and increased incidences of hepatocellular adenoma or carcinoma (combined) in the liver of all exposed groups. In the adrenal medulla of females, there were increased incidences of benign, malignant, or complex pheochromocytoma (combined) in all exposed groups, but only the incidence in the 1.5 W/kg group was significantly increased compared to the sham controls. In the prostate gland of male rats, there were increased incidences of epithelial hyperplasia in all exposed groups, but only the incidence in the 6 W/kg group was significantly increased compared to the sham control group. After 14 weeks of exposure, **Smith-Roe et al (2020)** [168] evaluated genotoxicity in several tissues of rats included in these studies for this purpose using the alkaline comet assay (three brain regions, liver, peripheral blood) and the micronucleus assay (peripheral blood). Significant increases in DNA damage were seen in the hippocampus of male rats (CDMA-only). For the NTP, clear evidence of carcinogenic activity is "*demonstrated by studies that are interpreted as showing a exposure-related (i) increase of malignant neoplasms, (ii) 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.*" For GSM exposures in males, NTP classified the malignant schwannomas of the heart, the malignant gliomas and the pheochromocytomas of the adrenal medulla as "clear evidence of carcinogenicity" and the granular cell tumors of the meninges, prostate gland tumors, pituitary gland tumors and pancreas islet-cell tumors as "equivocal findings". In females, the NTP classified the malignant schwannomas of the heart as equivocal. For the CDMA exposures in males, NTP classified the malignant schwannomas of the heart and the malignant gliomas as "clear evidence of carcinogenicity" and the pituitary tumors and liver tumors as "equivocal evidence". In females, the NTP classified the malignant schwannomas of the heart, the malignant gliomas and the pheochromocytomas of the adrenal medulla as equivocal. Given the glial hyperplasia, cardiomyopathy in the right ventricle and the magnitude of the effect in the adrenal gland, I

agree with the calls by the NTP. It is also worth noting that, when compared to the historical controls (Tarone's test), the lowest exposure CDMA group had a significant (0.016) increase in malignant gliomas. (Note: some text copied from **NTP (2018)** [177]).

Falcioni et al. (2018) [178] exposed groups (number not given) of F_0 female Sprague-Dawley rats, housed in specially designed cages, to whole-body exposures 1.8 GHz GSM-modulated cell phone RF at power levels of 0 (sham control), 5, 25 and 50 V/m for 7 days per week, from PD-12 continuing throughout gestation and lactation. Exposure was for 19 hours per day. At weanling, groups of approximately 200 (highest 2 exposures) or 400 (sham controls and low exposure) 5-6 week old male and female Sprague-Dawley rats were exposed the same exposures as their F_0 dams for 105 weeks (equivalent to 0.001, 0.03 and 0.1 W/kg SAR). Exposures were conducted in circular cage array with an antenna in the middle and animals were housed in individual chambers (5 per cage). Full pathology was conducted on all animals. This report only details the findings in the brain and the heart. They noted non-significant increases in Schwann cell hyperplasia at the high exposure for both males and females and an increase in malignant Schwannomas of the heart in males in the highest treatment group ($p=0.037$) and, using the Armitage linear trend test, yielded a significant trend ($p=0.037$). They noted that the rate of schwannomas in untreated males from their historical controls was 19/3160 (0.6%) and they observed 3/207 (1.4%). Heart schwannomas in females showed no trend. There were no increases in premalignant or malignant lesions in the brain for males or females in this study. The females had a slight positive trend in gliomas ($p=0.118$) but it was clearly not significant.

5.2 Transgenic and Tumor-Prone Models

5.2.1 Eμ-pim1 transgenic mouse

The Eμ-pim1 transgenic mice are prone to getting lymphomas.

Repacholi et al. (1997) [179] exposed groups of 100 to 101 female heterozygous Eμ-pim1 mice to GSM modulated RF at 900 MHz for up to 18 months with SAR values ranging from 0.13 to 1.4 W/kg depending upon animal sizes and the number in a cage. Mice were exposed for 30 minutes twice a day in cages grouped around a central antenna There were no differences in weight by exposure, but there was a difference in deaths prior to study termination with 44/100 sham animals terminated early and 70/101 exposed animals terminated early. They reported a significant increase in the incidence of all lymphomas ($p<0.001$) and of non-lymphoblastic lymphomas ($p=0.002$) as a function of exposure. The statistical analysis of the data were unusual with analysis of only animals that died during the course of the study (terminal sacrifice animals were not examined histopathologically) and using a competing risk logistic regression model that is not fully explained in addition to the standard Fisher's exact test. The assumption that animals that did not die prior to terminal sacrifice were free of lymphomas makes this study difficult to interpret.

Utteridge et al. (2002) [180] attempted to replicate the study of Repacholi et al. (1997) [179] but with several differences. They used 120 animals per group, they included groups of wild-type C57BL/6N female mice, their GSM signal was 898.4 MHz, they used a restrained Ferris wheel design, exposed for 1 hour per day, 5 days per week for 104 weeks, and did full histopathological analysis on all mice regardless of survival. They used four different exposure groups at 0.25, 1.0, 2.0 and 4.0 W/kg. No exposure-related differences in body weight or survival were seen. They reported no exposure-related increases in any tumors

from this study. The longer duration of this study makes the direct comparison to Repacholi et al. (1997) difficult since most animals in this study had lymphomas at 104 weeks.

Oberto et al. (2007) [181] used the same exposure system as Utteridge et al. (2002) [180] to repeat the study of Repacholi et al. (1997) [179] by exposing groups of 50 male and female heterozygous Eμ-pim1 mice to 900 MHz pulsed RF fields for 18 months at whole-body SAR levels of 0.5, 1.4 and 4.0 W/kg. Exposures were for 30 minutes, twice daily, 7 days per week. Survival was reduced for male mice in all exposures and for female mice exposed at 0.5 W/kg; there were no significant differences in body weights. They reported no significant changes in lymphomas in males or females and a significant increase in Harderian gland adenomas in males that was exposure-dependent (p=0.028). Using the Armitage linear trend test, the data show the change in Harderian gland adenomas in males (p=0.007), liver vascular tumors in males (p=0.015) and lung alveolar/bronchiolar adenomas (p=0.045) in males. The largest difference between Repacholi et al. (1997) (22%) and Oberto et al. (2007) (44%) was in the number of sham controls with lymphomas and this was not due to only looking at decedents since Oberto et al. (2007) provided this analysis as well.

5.2.2 Patched1$^{+/-}$ Mice

The Patched1 heterozygous (Ptc1+/-) knockout mice are prone to getting tumors of the brain and are hypersensitive to ionizing radiation.

Saran et al. (2007) [182] exposed groups of 23-36 male and female Ptc1+/- mice and groups of 22-29 male and female wildtype CD1 mice to 900 MHz RF at whole-body SAR of 0.4 W/kg from postnatal days 2-6 for 30 minutes, twice per day and then followed for their lifespan with full necropsy at death or moribund sacrifice. Exposures were done in a system that constrained the mice during exposure. There were no survival differences with regard to exposure. The authors reported no increases in any tumors as a function of exposure. They reported an increase in Rhabdomyosarcoma in male and female combined in exposed versus sham which was marginally significant when evaluated using the one-sided trend test (p=0.053). This study used a fairly low exposure for a very short exposure window.

5.2.3 AKR/j Mouse

The AKR/j mouse is known to rapidly develop hematopoietic tumors, especially thymic lymphoblastic lymphoma, in the first year of life.

Sommer et al. (2004) [183] exposed groups of 160 female AKR/j mice to either sham or 900 MHz GSM-like RF (0.4 W/kg) for 24 hours/day, 7 days/wk until 46 weeks of age. Mice were housed 6-7 per cage in a Ferris wheel design. There was a significant difference in relative weight change but not in absolute change. There were no survival differences. There were no differences in death from lymphoblastic lymphoma between the sham and RF exposed groups. In a second study using the same design, **Sommer et al. (2007)** [184] used 1966 MHz UMTS RF (0.4 W/kg). There were no significant weight changes, no changes in survival or the incidence of lymphomas although there was a marginal reduction in the number of animals surviving to study end in the RF exposed group (p=0.055).

Lee et al. (2011) [185] exposed groups of 40 male and 40 female AKR/j mice to sham or a combination of 848.5 MHz CDMA (2 W/kg) and 1950 MHz WCDMA (2 W/kg) RF for 45

min/day, 5 days/week for up to 42 weeks. Animals were housed 5 per cage during exposure in a reverberation chamber. No differences in body weight, survival or tumor incidence were observed.

5.2.3 C3H Mice

The C3H mouse carries a virus passed through breast milk that induces tumors of the mammary gland.

Szmigielski et al. (1982) [186] exposed groups of 40 female C3H/HeA mice to 2450 MHz RF from 6 weeks to 12 months at levels of 0, 2-3 W/kg and 6-8 W/kg. Exposure was carried out in an anechoic chamber for 2 hours per day, 6 days per week. The presence of mammary gland tumors was determined by palpation every two weeks. The authors noted a exposure-related increase in the number of mammary tumors ($p<0.01$) and a exposure-related decrease in the time to onset of mammary tumors ($p<0.05$) in their experiments. By their analysis, no other tumors were significantly increased as a function of exposure to the RF.

Toler et al. (1997) [187] exposed groups of 200 female C3H/HeJ mice for 21 months (22 h/day, 7 days/week) to a horizontally polarized 435 MHz pulse-wave (1.0 microsecond pulse width, 1.0 kHz pulse rate) RF environment with an SAR of 0.32 W/kg. An additional 200 mice were sham-exposed. All animals were necropsied and subject to full histpathological analysis. The exposure facility used 50 single housing cages around a central antenna facility to produce uniform circular fields. No survival differences were observed between the groups. There were no significant differences between the two groups with respect to latency to tumor onset, tumor growth rate and overall tumor incidence for mammary tumors. The only significant difference between groups for tumors in other organs was for bilateral ovarian epithelial stromal tumors ($p=0.03$ by their analysis, $p=0.023$ by mine) but became nonsignificant when all animals with stromal tumors were considered ($p=0.24$ by their analysis, $p=0.12$ by mine).

Frei et al. (1998) [188] exposed groups of 100 female C3H/HeJ mice for 18 months to 2450 MHz microwave radiation for 20 hours per day, 7 days per week. Exposure was via the CWG system with 2 animals per cage distributed around a circular field. The SAR targeted in this study was 0.3 W/kg. There were no differences in body weight or survival in the two groups. There were no significant differences between the two groups with respect to latency to tumor onset, tumor growth rate and overall tumor incidence for mammary tumors. There were no significant increases in tumors at any site but they also saw a slight increase in bilateral ovarian stromal tumors. **Frei et al. (1998)** [189] repeated this study using an SAR of 1 W/kg, again seeing no increases in any tumor as a function of exposure. In this second study, mammary tumors in sham-treated animals were much lower (30%) than in the previous study (54%).

Jauchem et al. (2001) [190] exposed groups of 100 female C3H/HeJ mice to pulses composed of an ultra-wideband (UWB) of frequencies, including those in the RF range (rise time 176 ps, fall time 3.5 ns, pulse width 1.9 ns, peak E-field 40 kV/m, repetition rate 1 kHz) at an SAR of 0.0098W/kg for 2 minutes per week for 12 weeks with a follow-up of 64 weeks. They saw no neoplastic changes associated with exposure. [This study uses an incredibly small SAR for a very short period.]

5.3 Initiation-Promotion Studies

In general, initiation promotion studies use two stages of exposure to determine if a particular exposure starts the cancer process (initiates tumors) or makes tumors grow faster or appear more readily (promotion). In most cases in the literature that follows, researchers are testing for the promotional impacts of RF using a known initiator (chemical that starts the cancer process).

5.3.1 Skin Models

The usual initiation-promotion study in skin involves the application of an initiator chemical (7,12-dimethylbenz[a]anthracene (DMBA) or benzo[a]pyrene (BAP)) once to the shaved skin of a mouse followed by frequent exposures to a promotor (in this case RF) for a long period of time. The studies also typically use a known promotor as a positive control (e.g. 12-O-tetradecanoylphorbol-13-acetate or TPA) to demonstrate the experimental setting is working appropriately. The tumors that appear on the back of the animals are tracked over time and the endpoints of interest (tumor frequency and multiplicity) recorded daily.

Chagnaud et al. (1999) [191] exposed groups of 8-18 female Sprague-Dawley rats to GSM 900 MHz RF at an SAR of 75 mW/kg starting 20, 40 or 75 days after initiation by BaP (2 mg) for 2 hours per day, 5 days per week for two weeks. In addition, GSM 900 MHz RF at an SAR of 270 mW/kg was administered 40 days after exposure to BaP (2 mg) for 2 hours per day, 5 days per week for two weeks. The study was terminated approximately 160 days after the BaP exposure. There was no impact of any RF exposure on the survival or time to tumor in these experiments.

Mason et al. (2001) [192] exposed groups of 27-55 female Sencar rats to DMBA (initiator, 2.56 µg) followed by a single 10 second exposure to 94 GHz RF at 1 W/cm^2 or to infrared radiation (IR) at 1.5 W/cm^2, both designed to raise skin temperature by 13-15˚ C. The animals were followed for 23 weeks and there was no indication of a promotion affect on these animals. In a second experiment using the same basic protocol, exposures of 10 seconds twice per week for 12 weeks to RF at 333 mW/cm^2 and IR at 600 mW/cm^2 (designed to raise skin temperature by 4-5˚ C) and followed to 25 weeks. There was no indication of a promotion effect of RF in this experiment. The authors also conducted a co-promotional study where the RF and IR exposures were given along with TPA to see if the RF enhanced the TPA promotional effect; this study was also negative.

Imaida et al. (2001) [193] exposed exposed groups of 48 female ICR mice to DMBA (initiator, 100 µg) followed by a TDMA RF field at 1.49 GHz (50 pulse per second) for 90 minutes per day, 5 days per week for 19 weeks at an SAR of 2 W/kg. There was no promotion of tumors by RF in this study.

Huang et al. (2005) [194] exposed a group of 20 male ICR mice to DMBA (initiator, 100 µg) followed by a CDMA signal at 849 MHz for 45 minutes twice per day, 5 days per week for 19 weeks at an SAR of 0.4 W/kg. They exposed a second group of 20 males to CDMA signal at 1763 MHz for 45 minutes twice per day, 5 days per week for 19 weeks at an SAR of 0.4 W/kg. There was no promotion of tumors by RF in this study.

Paulraj and Behari (2011) [195] exposed groups of 10 male Swiss albino mice to DMBA (initiator, 100 µg) to 112 MHz amplitude modulated (AM) at 16 Hz (power density 1.0 mW/cm^2, SAR 0.75 W/kg) or to 2.45 GHz radiation (power density of 0.34 mW/cm2, SAR,

0.1 W/kg), 2 h/day, 3 days a week for a period of 16 weeks. There was no promotion of tumors by RF in this study. In a second experiment, mice were transplanted intraperitoneally (ip) with ascites $8x10^8$ (Ehrlich-Lettre ascites, strain E) carcinoma cells per mouse followed by the same 2 radiation exposures for 14 days. They saw a non-significant increase in the number of ascites in the treated groups compared to the appropriate controls. This study suffers from a very small sample size.

5.3.2 Lymphoma Models

Here, the initiator is ionizing radiation.

Heikkinen et al. (2001) [196] exposed groups of 50 female CBA/S mice to Xrays (initiation, 4-6 MV, 3 weekly exposures of 1.333 Gy) followed by exposure to NMT900-type frequency-modulated RF at 902.5 MHz and a nominal SAR of 1.5 W/kg for 1.5 hours/day, 5 days per week, for 78 weeks. A second group with the same initiation was exposed to GSM-type RF at 902.5 MHz (pulse frequency 217 Hz) at an SAR of 0.35 W/kg with the same exposure pattern. They saw a increase in the median corpuscular hemoglobin concentration in both RF exposure groups (p=0.008 NMT900 and p=0.026 GSM). There were no survival differences. There were several changes in preneoplastic hyperplastic markers related to RF exposure, but no significant increases in tumors related to RF. There was a significant reduction in pheochromocytomas in the adrenal glands in both RF exposure groups. There were no changes in lymphoma incidence.

5.3.3 Mammary-gland Tumor Model

This model typically involves female Sprague-Dawley rats initiated by DMBA.

Bartsch et al. (2002) [197] sequentially conducted three identical studies where groups of 60 female Sprague-Dawley rats were given DMBA as an initiator (50 mg/kg/day) followed by either sham exposure or exposure to GSM RF at 900 MHz (pulse 217 Hz) for 23 hours per day, 7 days per week for 259-334 days. Exposures were in group-housed cages and ranged from 15 to 130 mW/kg depending upon the age of the animals. There were no differences between sham and exposed animals in terms of numbers of benign or malignant tumors at study termination in all three experiments although the experiments themselves differed significantly in overall tumor incidence. In the first experiment, malignant mammary tumors appeared much more rapidly in sham-exposed animals, but this was not reproduced in the two replicates.

Anane et al. (2003) [198] conducted 2 experiments using a GSM signal at 900 MHz with female Sprague-Dawley rats in cages in a chamber for 2 hours/day, 5 days/week for 9 weeks and followed without exposure for 2 more weeks. Initiation was done using DMBA (10 mg) and RF exposures began 10 days after initiation. In the first exposure, 16 animals per group were exposed to 0, 1.4, 2.2 or 3.5 W/kg SAR RF and in the second were exposed to 0, 0.1, 0.7 and 1.4 W/kg SAR RF. The first experiment saw a reduction in time to tumor for the 1.4 W/kg group, a lesser, but still significant reduction in time to malignant tumor for the 2.2 W/kg group and no difference from sham-exposed for the 3.5 W/kg group. This was not seen in the second experiment. The second experiment also saw substantially reduced tumor counts in the treated groups compared to the first experiment.

Yu et al. (2006) [199] exposed four groups of 99-100 female Sprague-Dawley rats to DMBA (initiator, 35 mg/kg) followed by sham exposure or exposure to 900MHz GSM signal RF for 4 hours/day, 5 days/week for 26 weeks in a Ferris wheel tube-restrained exposure system. The four exposures were 0, 0.44, 1.33 and 4.0 W/kg SAR. No differences in body weight, incidence, latency, multiplicity or size of mammary gland tumors was seen in this experiment as a function of RF exposure.

Hruby et al. (2008) [200] conducted an experiment almost identical to that of Yu et al. (2006). Four groups of 100 female Sprague-Dawley rats were exposed to DMBA (initiator, 17 mg/kg) followed by sham exposure or exposure to 900MHz GSM signal RF for 4 hours/day, 5 days/week for 26 weeks in a Ferris wheel tube-restrained exposure system. The four exposures were 0, 0.4, 1.3 and 4.0 W/kg SAR. The results showed a significant shift from benign mammary tumors to malignant mammary tumors for animals with exposure to RF. The highest exposure group saw a significant increase in malignant tumors relative to the sham controls and all three RF exposure groups saw a significant reduction in benign tumors compared to the sham exposure group. No differences in volume or time-to-palpable tumor were seen.

5.3.4 Brain tumor models

Brain tumor initiation-promotion studies generally use rats (Fischer 344 or Sprague-Dawley) initiated for brain tumors using N-ethyl-N-nitrosourea (ENU) in-utero using a single intravenous exposure to the dam.

Adey et al. (1999) [201] exposed two groups of 9 pregnant Fisher 344 rats to ENU (4 mg/kg) on day 18 of gestation and two groups of 9 to sham exposure. Starting on day 19 of gestation to post-natal day (PND) 21, two groups of dams and offspring (one with ENU [denoted EF for ENU-Field] and the other without [denoted SF for Sham-Field]) were exposed in cages to far field TDMA (836.55 MHz) for 2 hours/day, 7 days/week (SAR not provided) and two groups (no enu [denoted SS] and with ENU [denoted ES]) were given smam exposure to RF. Starting on PND 33 until two years of age, groups of 30 male and 30 female mice were exposed to near-field TDMA exposures at 836.55 MHz in the same groups as with the dams (SS, ES, SF, EF). Near field exposures (animals held in tubes with predominantly head exposure) had an SAR from 1.1-1.6 W/kg. Animals administered ENU had a reduction in survival in all groups and animals with RF exposure survived longer than their respective controls in all groups (not statistically significant). All RF exposed groups had reduced central nervous system tumors relative to their appropriate controls except for meningiomas (without ENU there was 1 tumor in RF exposed and no tumors in control and with ENU there were 2 tumors in RF exposed and none in control) and granular cell tumors (without ENU there was 1 tumor in RF exposed and no tumors in control). A reanalysis of the data using the exact trend statistic (one-sided) shows a significant reduction in CNS tumors with RF exposure with ($p=0.036$) and without ($p=0.016$) ENU, almost entirely due to glial tumors. No numbers were provided for any differences by sex.

Adey et al. (2000) [202] repeated this study with a larger number of offspring (45 males and 45 females) in each of the exposure groups and using an FM signal (836.55 MHz). The survival patterns were the same as for their previous study. Unlike the previous study, RF exposure yielded approximately the same incidence as sham exposure for all CNS and brain tumors. Differences between sexes were not provided.

Zook and Simmens (2001) [203] exposed pregnant female Sprague-Dawley rats to ENU at a exposure of 0, 2.5 or 10 mg/kg on day 15 of gestation. At 8 weeks of age, groups of 30 male and 30 female rats with in-utero ENU exposure were exposed to sham, pulsed-wave RF exposure (860 MHz) at a brain SAR of 1 W/kg or pulsed-wave RF exposure (860 MHz) at a brain SAR of 1 W/kg for 6 hours per day, 4 days per week for 22 months. The exposure was 'head only' and used a tube-restrained system in a Ferris wheel design. Results were presented for males and females combined. There were no significant findings in the brain or central nervous system. There was a significant increase in thyroid tumors in males (p=0.016, all sham controls grouped and all ENU exposures grouped) and a marginal increase in female mammary tumors (p=0.057).

Zook and Simmons (2006) [204] repeated this experiment where they exposed pregnant female Sprague-Dawley rats to ENU at a exposure of 6.35 or 10 mg/kg on day 15 of gestation. At 8 weeks of age, groups of 90 male and 90 female rats with in-utero ENU exposure were exposed to sham or pulsed-wave RF exposure (860 MHz) at a brain SAR of 1 W/kg for 6 hours per day, 4 days per week for 22 months. The exposure was 'head only' and used a tube-restrained system in a Ferris wheel design. Results were presented for males and females combined. There were no significant findings in the brain or central nervous system.

Shirai et al. (2005) [205] exposed pregnant female Fisher 344 rats to ENU as done in Adey et al. (1999). At 5 weeks of age, groups of 50 male and 50 female rats with in-utero ENU exposure were exposed to sham, TDMA RF exposure (1439 MHz) at a brain SAR of 0.67 W/kg or at a brain SAR of 2 W/kg for 90 minutes per day, 5 days per week until age 104 weeks. The exposure was "head only" as in **Adey et al. (1999)**. In females, there was a non-significant increase in survival with RF exposure but not in males. The authors reported no significant changes in any CNS tumors in the RF-exposed animals relative to sham-exposed animals. However, a reanalysis of the data using the Armitage linear trend test shows a marginal decrease in any type of brain tumor in females (p=0.057) that is driven by a reduction in astrocytomas (p=0.032). This was not seen in males. They noted a significant reduction in pituitary tumors in the highest exposure group for males, but tumor numbers were not provided.

Shirai et al. (2007) [206] used the exact same exposure scenario to examine the effects of WCDMA RF at 1.95 GHz at SAR 0.67 W/kg and 2.0 W/kg. There were no obvious survival differences among the treated groups and the sham controls and some mild organ weight differences in females but none in males. The authors reported no significant changes in tumor rates for any organ however they did not do trend tests. Using the Armitage linear trend test, female rats saw a significant increase in any brain tumor (p=0.030) driven primarily by an increase in astrocytomas (p=0.027). Males saw an increase in astrocytomas that was not statistically significant (p=0.181).

5.3.5 Liver Tumor Models

Imaida et al. (1998) [207] exposed groups of 48 five-week old male Fisher 344 rats to a single exposure of 200 mg/kg diethylnitrosamine (DEN) followed two-weeks later by exposure to 1.439 GHz TDMA RF at a whole body SAR of 0.453-0.680 W/kg 90 minutes a day, 5 days/week for six weeks. At three weeks the rats received a 2/3 partial hepatectomy and at the end of the six weeks of RF exposure, the study was terminated and all rats

examined in their liver for the number and size of glutathione S-transferase placental form positive focal lesions that are considered precursors for liver cancer. They saw significant increases in corticosterone ($p<0.001$), melatonin ($p<0.05$) and adrenocorticotropic hormone ($p<0.001$) and a significant reduction ($p<0.05$) in the number of GST-positive foci/cm2. Similar findings were seen for the exact same experimental design using 929.2 MHz TMDA RF with whole body SARS between 0.58-0.80 W/kg [208].

5.4 Co-Carcinogenesis

Co-carcinogenesis studies are conducted by administering RF exposure along with another substance already known to be carcinogenic to see if the RF exposure enhances the carcinogenic findings. Usually, these models are targeted to a specific type of cancer.

Szmigielski et al. (1982) [186] exposed groups of 40 6-week old male Balb/c mice to 5% solution of 3,4-benzopyrene (BP) on depilated skin every second day for 5 months. Groups of these mice were exposed to 2450 MHz microwaves for 2 hours/day for the same 5 months at exposure of 5 mW/cm2 or 15 mW/cm2. Two other groups of mice were exposed to 1 or 3 months of the same RF exposure of 5 mW/cm2 followed by exposure to BP until 5 months. All animals were observed until 10 months. Exposures were in anechoic chamber. The target of these exposures was skin tumors. There were clear exposure-related and age-related increases in skin tumors in all RF-exposed groups compared to their sham-exposed groups. It is not clear if the sham-exposed controls in the 1- and 3-month RF exposure experiments were properly done. In addition, the presentation of the results from this study are sufficiently confusing that misinterpretation of the findings is possible.

Szudzinski et al. (1982) [209] performed a similar experiment to that done by Szmigielski et al. (1982) (they are in the same research group). They exposed groups of 100 6-week old male Balb/c mice to 1% solution of 3,4-benzopyrene (BP) on depilated skin every second day for 6 months. Groups of these mice were exposed to 2450 MHz microwaves for 2 hours/day for the same 6 months at exposures of 2 mW/cm2 or 6 mW/cm2. Three other groups of mice were exposed to 1, 2 or 3 months of the same RF exposure of 4 mW/cm2 followed by exposure to BP until 6 months. All animals were observed until 10 months of age. Exposures were in anechoic chambers. The target of these exposures was skin tumors. There were clear exposure-related and age-related increases in skin tumors in all RF-exposed groups compared to their sham-exposed groups. It is not clear the sham-exposed controls in the 1-, 2- and 3-month RF exposure experiments were properly done. In addition, the presentation of the results from this study are sufficiently confusing that misinterpretation of the findings is possible.

Wu et al. (1994) [210] exposed two groups of 26-32 male and 26-32 female BALB/c mice to dimethylhydrazine for 14 weeks (15 mg/kg subcutaneous injection oncer per week) and then an additional 8 weeks (20 mg/kg subcutaneous injection oncer per week). Three weeks after the first injection, one groups of mice was sham exposed and the other exposed to 2450 MHz RF (10-12 W/kg SAR) for 3 hours/day, 6 days/week for 5 months. The focus was on colon tumors and there was no difference between groups.

Heikennen et al. (2003) [211] exposed groups of female K2 transgemic mice (overexpressing human ornithine decarboxylase gene) and their wild-type littermates (strain not provided) were exposed to UV radiation (240 J/m2) 3 times per week for 52 weeks. The separate groups were exposed to sham RF, D-AMPS RF (849 MHz, 0.5 W/kg SAR) or GSM RF (902.4

MHz, 0.5 W/kg SAR) 1.5 hours/day, 5 days/week for 52 weeks. The target of the experiment was skin lesions. There were no survival differences when compared to appropriate controls in transgenic or wild-type RF-treated animals and no changes in skin lesion incidence was observed.

Heikennen et al. (2006) [212] exposed groups of 72 female Wistar rats (age 7 weeks) to 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) via drinking water at a exposure of 1.7 mg/kg/day for 104 weeks. Separate groups were exposed to pulsed RF at 900 MHz (pule frequency 217 Hz) in a circular array of small cages for 2 hours per day, 5 days per week, for 104 weeks at whole body SARs of 0 (sham), 0.3 or 0.9 W/kg. There were no survival differences, body weight gain differences or MX consumption differences between sham-exposed and RF-exposed rats. By Peto's test, the combined incidence of vascular tumors in the mesenteric lymph nodes was significantly increased in trend (p=0.036). Using the Armitage linear trend test, the combined incidence was also significant (p=0.001, one-sided) driven by the increase in hemangiomas (p=0.023). The authors argued this was not significant since the incidence in the cage controls was higher than the sham controls. There was a significant increase in vacuolated foci in the liver by the Armitage linear trend test (p=0.002) but no increases in tumors in the liver.

Tillmann et al. (2010) [213] exposed pregnant B6C3F1 mice and 54-60 of their female offspring to whole-body UMTS RF at 1966 MHz (4.8 W/m2 or 48 W/m2) from GD6 to 2 years of age. The dams exposed to 4.8 W/m2 also received a exposure of 40 mg/kg ENU on GD 14 as did a group with sham exposure to the RF. A full necropsy was performed on each animal. No differences in survival were seen between RF-exposed groups and their appropriate controls. The 48 W/m2 group did not show any increases in tumors relative to the appropriate controls although they did see a significant increase in liver focal lesions (p=0.002 one-sided). The ENU-treated groups were terminated after 75 weeks due to mortality and all animals necropsied. The RF-exposed group saw an increase in bronchiolar-alveolar carcinomas (p=0.005), adenomas (p=0.032), adenomas or carcinomas combined (0.017) and a marginal increase in hyperplasias (p=0.098). They also saw an increase in liver adenomas (p<0.001), not carcinomas or blastomas, but an increase in combined adenomas/carcinomas/blastomas (p=0.023) and an increase in liver foci (p=0.005). There were no increases in brain tumors in any treated groups. Tumor multiplicity in both the lung and the liver was increased as was the incidence of metastasizing lung tumors.

5.5 Summary and Conclusions for Laboratory Cancer Studies

The central question to ask of animal cancer studies is "Can RF increase the incidence of tumors in laboratory animals?" The answer, with high confidence, is yes. Table 20 summarizes the findings from the chronic exposure carcinogenicity studies for RF.

For rats, the **NTP (2018)** [177] chronic exposure bioassay in male Sprague-Dawley rats, including in-utero exposure, is clearly positive for acoustic neuromas of the heart, malignant gliomas of the brain and pheochromocytomas of the adrenal gland. These findings are further supported by the presence of preneoplastic lesions and tissue toxicity in the heart, brain glial cells and adrenal glands. The less convincing findings in the study by **Falcioni et al. (2018)** [178] of heart acoustic neuromas in male Sprague-Dawley rats and a marginal increase in malignant gliomas in females provides additional support for this finding. The study by **Anderson et al. (2004)** [171] with a significant increase in oligodentrogliomas in

male Fischer 344 rats when compared against historical controls provides additional strong support for an increase in gliomas from exposure to RF. This study also saw an increase in testis mesothelioma which may have been due to exposure. The lack of any brain pathology or tumors in any organ or tissue within the study by **La Regina et al. (2003)** [170], which was also in Fischer 344 rats, weakens the findings from the Anderson et al. (2004) study, but cannot fully negate them since these are different exposures at different frequencies. The **Bartsch et al. (2010)** [176] study, done using Sprague-Dawley rats, is too limited to challenge the findings of the **NTP (2018)** study. Finally, the lack of brain and heart tumors in the **Smith et al. (2007)** [175] study, done in Wistar rats, could easily be due to the different strain of rat. This study did see an exposure-related increase in thyroid C-cell tumors that was not seen in the other studies in rats.

In B6C3F_1 mice (the only strain tested for chronic exposure), the strongest findings are for the Harderian gland tumors in males for GSM but not DCS RF and the increase in uterine polyps in females for both GSM and DCS in the **Tillmann et al. (2007)** study [164] and the increase in rare tumors of the pars distalis in the pituitary of females in the **NTP (2018)** [166] study which were also seen for the male rats in the other NTP study [177]. The variability of the Harderian gland increases and decreases between males and females and the different types of RF in the **Tillmann et al. (2007)** study suggest that the Harderian gland is a sensitive target in these animals or that the response is highly variable in these mice for these tumors. The NTP historical controls [214] for Harderian gland tumors for this period include 29 studies and range between 6% and 26% with a mean of 16% for adenomas and carcinomas combined; the exposed groups in the **Tillmann et al. (2007)** GSM study showed responses of 24%, 32% and 36% for the low, medium and high male exposure groups, beyond the range of the historical control data supporting the conclusion this is a real, exposure-related finding. The **NTP (2018)** study did not see an increase in Harderian gland tumors in males nor an increase in uterine polyps in females. However, this study used a very different exposure system and this may have contributed to the differences.

The studies in transgenic and tumor-prone mice show mixed results. The initial positive finding of lymphomas in Eμ-pim1 transgenic mice by **Repacholli et al. (1997)** [179] were not seen in two subsequent studies [180, 181] that used better designs and better methods. It is interesting to note that the **Oberto et al. (2007)** study [181] saw an increase in Harderian gland tumors in male mice, supporting the finding from **Tillmann et al. (2007)** [164]. The one study in Patched1+/- transgenic mice was negative for brain tumors but saw a marginal increase in Rhabdomyosarcomas. The two studies in AKR/j mice were negative. The study with the highest SAR exposure levels in C3H mice [186] was positive for mammary tumors, but the remaining four [187-190] were not. It is of note that two of these studies [187, 188] saw increases in uterine stromal polyps supporting the findings from **Tillmann et al. (2007)** [164].

The initiation-promotion studies in skin [191-195] were uniformly negative as was the one study using a lymphoma model [196]. The initiation-promotion studies using a mammary tumor model [197-200] were also uniformly negative although the study by **Hruby et al. (2006)** [200] saw an exposure-related shift from benign mammary tumors to malignant tumors. The initiation-promotion studies using ENU-based brain tumor models [201-206] were negative for brain tumors with the exception of one study [206] showing an increase in brain tumors driven by an increase in astrocytomas. One of these studies [203] saw an increase in thyroid tumors in males as a function of exposure that supports the one finding

in the chronic study by **Smith et al. (2007)** [175] who saw an increase in thyroid tumors in females. The one initiation-promotion study using a liver tumor model [207] saw increases in liver foci and several changes in endocrine hormones, but no liver tumors.

Four of the co-carcinogenesis studies were positive [186, 209, 212, 213] and two were negative [210, 211]. Two of the positive studies [186, 209] showed skin tumors (not surprising since the co-carcinogen was BP applied to the skin) and another positive study [212] showed increases in lymph nodes and blood vessel tumors. Another positive study [213] saw increases in lung tumors and liver tumors in female mice exposed in-utero supporting findings seen in the **Tillmann et al. (2007)** [164] study and the **NTP (2018)** [166] study.

In conclusion, there is sufficient evidence from these laboratory studies to conclude that RF can cause tumors in experimental animals with strong findings for gliomas, heart Schwannomas and adrenal pheochromocytomas in male rats and harderian gland tumors in male mice and uterine polyps in female mice. There is also some evidence supporting liver tumors and lung tumors in male and possibly female mice.

Table 20: Summary of Chronic Exposure Carcinogenicity Studies for Radiofrequency Radiation

Study	Species/Strain	RF Exposure	Sex	Tumor Finding	Notes
Tillmann et al. (2007) [164]	Mouse $B6C3F_1$	GSM 902 MHz	M	Harderian Gland ↑ Liver Adenoma ↓	
			F	Harderian Gland ↓ Lung Tumors ↓ Liver adenomas ↑ Uterus polyps ↑	All exposures, no trend Two lowest exposures, no trend
		DCS 1747 MHz	M	Harderian Gland ↓ Liver Adenoma ↓ Lymphomas ↑	All exposure groups, no trend
			F	Uterus polyps ↑	
National Toxicology Program (2018) [166]	Mouse $B6C3F_1$	GSM 1.9 GHz	M	Lung tumors ↑	
			F	Malignant lymphomas ↑	Lowest 2 exposures, no trend
		CDMA 1.9 GHz	M	Liver tumors ↑	Sporadic, no trend or pattern
			F	Malignant lymphomas ↑ Pituitary pars distalis ↑	Low group, increased in all, no trend Rare tumor
Chou et al. (1992) [169]	Rats S-D	Pulsed 2450 MHz	M	Total tumors ↑	No individual tumor findings
La Regina et al. (2003) [170]	Rats F344	FDMA 835.6 MHz	M		No tumor findings
			F		No tumor findings
		CDMA 847.7 MHz	M		No tumor findings
			F		No tumor findings
Anderson et al. (2004) [171]	Rats F344	Iridium 1.62 GHz	M	Testis mesothelioma ↑ Oligodentroglioma ↑	Using HC, $p<0.001$
			F		No tumor findings
	Rats	GSM	M		No tumor findings

Smith et al. (2007) [175]	Wistar	902 MHz	F	C-cell tumors ↑	Adenomas & combined, not carc.
		DCS 1747 MHz	M		No tumor findings
			F	C-cell tumors ↑	Adenomas & combined, not carc.
Bartsch et al. (2010) [176]	Rats S-D	GSM 900 MHz	F		No tumor findings (four separate experiments, small sample sizes, not full pathology)
NTP (2018) [177]	Rats S-D	GSM 900 MHz	M	Heart schwannoma ↑ Brain glioma ↑ Adrenal pheochromocytoma ↑ Brain meninges ↑ Prostate gland ↑ Pituitary pars distalis ↑ Pancreas islets ↑	Rare tumor, biological call Lowest 2 exposures, no trend Biological call Rare tumor, biological call No trend, extensive hyperplasia Low exposure group, no trend
			F	Heart schwannoma ↑	One exposure only, rare tumor
		CDMA 900 MHz	M	Heart schwannoma ↑ Brain glioma ↑ Pituitary pars distalis ↑ Liver tumors ↑F	Rare tumor, biological call One exposure, no trend Rare tumor, increased but not significant
				Heart schwannoma ↑ Brain glioma ↑ Adrenal pheochromocytoma ↑	Marginal finding Rare tumor, 3 in lowest group, no sig, no trend Low exposure only, no trend
Falcioni et al. (2018) [178]	Rats S-D	GSM 1.8 GHz	M	Heart schwannoma ↑	
			F		No tumor findings (slight ↑ in malignant gliomas)

6. Mechanisms Related to Carcinogenicity

There is sufficient evidence to suggest that both oxidative stress and genotoxicity are caused by exposure to RF and that these mechanisms could be the reason why RF can induce cancer in humans.

6.1 Introduction

Many human carcinogens act via a variety of mechanisms causing various biological changes, taking cells through multiple stages from functioning normally to becoming invasive with little or no growth control (carcinogenic). **Hanahan and Weinberg (2011)**[215] identified morphological changes in cells as they progress though this multistage process and correlated these with genetic alterations to develop what they refer to as the "hallmarks of cancer." These hallmarks deal with the entire process of carcinogenesis and not necessarily with the reasons that cells begin this process or the early stages in the process where normal protective systems within the cells remove potentially cancerous cells from the body. While tumors that arise from a chemical insult to the cell may be distinct from other tumors by mutational analysis, they all exhibit the hallmarks as described by **Hanahan and Weinberg (2011)**.

Systematic review of all data on the mechanisms by which a chemical causes cancer is complicated by the absence of widely accepted methods for evaluating mechanistic data to arrive at an objective conclusion on human hazards associated with carcinogenesis. Such systematic methods exist in other contexts [216], but are only now being accepted as a means of evaluating literature in toxicological evaluations [32, 217-220].

In this portion of the report, I am focusing on the mechanisms that can cause cancer. **Smith et al. (2015)** [39] discussed the use of systematic review methods in identifying and using key information from the literature to characterize the mechanisms by which a chemical causes cancer. They identified 10 "Key Characteristics of Cancer" useful in facilitating a systematic and uniform approach to evaluating mechanistic data relevant to carcinogens. These 10 characteristics are presented in Table 21 (copied from Table 1 of **Smith et al. (2015)** [39]). While there is limited evidence on RF exposure for most of the key characteristics, genotoxicity (characteristic two) and oxidative stress (characteristic five) have sufficient evidence to warrant a full review.

Table 21: Key characteristics of carcinogens, Smith et al. (2016)[65]

Characteristic	Examples of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei)

3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Abbreviations: AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the 10 characteristics in this table could interact with any other (e.g., oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.

6.2 Oxidative Stress

6.2.1 Introduction

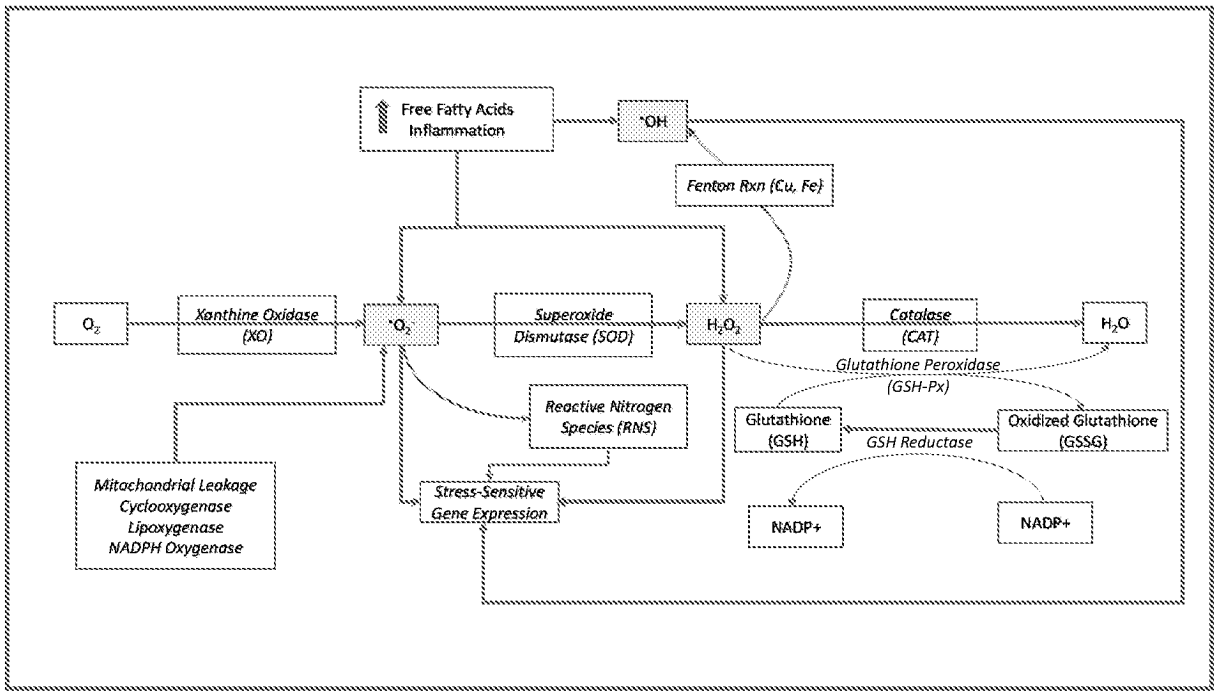
Oxidative stress refers to an imbalance between the production of reactive oxygen species (free radicals) in a cell and the antioxidant defenses the cell has in place to prevent this. Oxidative stress has been linked to both the causes and consequences of several diseases [221-226] including cancer [39, 227-231]. Multiple biomarkers exist for oxidative stress; the most common being increased antioxidant enzyme activity, depletion of glutathione or increases in lipid peroxidation. In addition, many studies evaluating oxidative stress used antioxidants following exposure to RF to demonstrate that the effect of the oxidative stress can be diminished.

Measuring oxidative stress can be difficult due to redundant pathways of a highly interconnected system. Molecular oxygen is essential to the proper function of a cell. During the course of normal oxidative phosphorylation, between 0.4 and 4% of all oxygen consumed is converted into the free radical superoxide ($^{\bullet}O_2$). This $^{\bullet}O_2$ can be converted into other ROS and reactive nitrogen species (RNS) and is normally eliminated by antioxidant defenses. $^{\bullet}O_2$ molecules are quickly converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD). H_2O_2 is then either detoxified to H_2O and O_2 by glutathione peroxidase or diffuses into the cytosol and is detoxified by catalase. However, in the presence of reduced transition metals such as copper (Cu) or iron (Fe), H_2O_2 can be converted to the highly reactive hydroxyl radical ($^{\bullet}OH$). These linkages are illustrated in Figure 5.

The three reactive oxygen species (ROS) in the cell ($^{\bullet}O_2$, $^{\bullet}OH$, H_2O_2) can be measured directly, changes in the activity of the major enzymes (XO, SOD, CAT, GSH-Px, GSH

reductase) can be measured, changes in GSH or GSSG can be measured, changes in gene expression can be measured, changes in nitrogen oxide (NO) can be measured and changes in other enzymes (e.g. cyclooxygenase) can be measured. No one study measures all of these components. Most studies measure two or more components of this system in animals or cells exposed to RF to see if they have changed due to the RF exposure.

Figure 5: Exogenous and endogenous stimuli leading to ROS generation and activation of stress-sensitive gene expression. (modified from [232])



6.2.2 International Agency for Research on Cancer (IARC)

The IARC reviewed the potential for carcinogenicity from RF in 2011 [35]. They evaluated the scientific literature prior to 2011 and concluded "there was weak evidence that exposure to RF radiation affects oxidative stress and alters the levels of reactive oxygen species." This conclusion was driven by methodological shortcomings in the studies, lack of a sham-controlled group in some studies, use of mobile phones for exposures and poor dosimetry. Having looked over the IARC review (I was an *Invited Specialist*[4] for this review), I agree with their assessment of these data and will not discuss any studies prior to 2010.

6.2.3 *In vivo* Studies in Mammals, 2011-2020

6.2.3.1 Humans

Five studies evaluated the effects of RF on humans, two studies using blood, two using saliva and one using seminal plasma. Gulati et al. (2018) [232] compared 116 individuals in India living near cellular towers to 106 controls living more than 800 meters from towers. They saw significant decreases in SOD, CAT and a significant increase in lipid-peroxidation

[4] *Invited Specialists* are experts who have critical knowledge and experience 3 but who also have a conflict of interest that warrants exclusion from 4 developing or influencing the evaluations of carcinogenicity.

(LP) in plasma associated with being close to cellular towers. **Zothansiama et al. (2017)** [233] studied 40 people living close to cellular towers (<80 meters) with people living further away (>300 meters) in a different population in India and measured RF power-density in the bedrooms of all of the participants. They saw the same changes in SOD, CAT and LP. In addition, increasing power-density measurements were associated with increased micronuclei (MN) in peripheral blood lymphocytes. **Khalil et al. (2014)** [234] and **Abu et al. (2015)** [235] reported on the same set of 12 individuals whose saliva was sampled before and after 15 and 30 minutes of use of a specific cellular phone (1800 MhZ Nokia with an SAR of 1.09). They saw an increase in SOD, but no change in malondialdehyde (MDA) or 8-hydroxydeoxyguanosine (8-OHdG, a measure of oxidative damage). **Malini (2017)** [236] compared usage in 47 males in India in groupings of 1-5 hours/day (20 men), 5-10 hours/day (22 men) and >10 hours/day (5 men) and saw no changes in ROS, ROS scavengers or DNA damage in semen.

6.2.3.2 Mouse

In the discussion that follows, unless otherwise mentioned, SAR values used in the studies are generally less than 1 W/kg either whole body or tissue specific. Details can be found in Supplemental Table 1.

6.2.3.2.1 BALB/c Mice

Khalil et al. (2011) [237] saw no changes in oxidative stress in brain, spleen or serum in BALB/c mice exposed for 30 days to 900 MHz RF at 1 W/kg SAR. **Bahreyni et al. (2018)** [238] saw changes in reactive oxygen species (ROS) and/or ROS-scavenging enzymes in heart, liver, kidney, cerebellum and hippocampus in the dams and heart, liver, kidney, and cerebellum of their offspring from pregnant female BALB/c mice exposed for 20 days to joint 900/1800 MHz RF for which the SAR was not provided.

6.2.3.2.2 Parkes Mice

Shahin et al. (2013) [239] saw the expected changes in ROS and ROS-scavenging enzymes (SOD, CAT, GST) in the liver, kidney ovaries and blood of pregnant Parkes mice exposed for 45 days to 0.023 W/kg of 2450 MHz RF and saw associated DNA damage in the brains from the same exposure.

6.2.3.2.3 Swiss Mice

Shahin et al. (2014) [240] saw an increase in ROS and associated changes in ROS scavengers in the hypothalamus, liver, kidney and testis of male Swiss mice exposed for 30 days to 0.018 W/kg 2450 MHz RF and saw significant tissue toxicity in the testis. **Shahin et al. (2017)** [241] also saw an increase in ROS and associated changes in ROS scavengers in the hypothalamus, uterus and ovaries of female Swiss mice exposed for 100 days to an unknown SAR from a 1800 MHz cellular phone. They also saw significant tissue changes in the uterus and a modification of reproductive hormones. **Shahin et al. (2018)** [242] saw changes in stress-related hormones and associated markers in the hippocampus and blood of male Swiss mice exposed for 15, 30 or 60 days to 0.0146 W/kg 2450 MHz RF. These stress changes, probably associated with induced nitrous oxide, led to reductions in learning and spatial memory in these mice. **Shahin et al. (2018)** [243] saw an increase in ROS and

associated changes in ROS scavengers , increased apoptosis, and tissue toxicity in the testis of male Swiss mice exposed for 120 days to 0.05 W/kg 1800 MHz (using a mobile phone). **Pandey et al. (2017)** [244] saw mitochondrial damage, other cellular damage and DNA damage in spermatocytes of male Swiss mice exposed for 35 days to 0.0045-0.0056 W/kg 900 MHz RF; they attributed these changes to oxidative stress.

Esmekaya et al. (2016) [245] exposed Swiss mice with chemically-induced epileptic seizures (induced by pentylenetetrazole) for 15 or 30 minutes to a 900 MHz cellular phone with a head SAR of 0.301 W/kg and saw changes in ROS and ROS scavengers in the brain.

6.2.3.2.4 ICR Mice

Zong et al. (2016) exposed male ICR mice for 7 days to 0.05 W/kg 900 MHz RF and saw no changes in ROS in liver, lung and blood. **Zong et al. (2015)** [246] exposed male mice to 0.05 W/kg 900 MHz RF for 4 hours/day for 7 days and saw no significant changes in ROS, ROS scavengers or DNA damage in liver, lung and blood.

6.2.3.2.5 C57BL/6 Mice

Jeong et al. (2018) exposed 14-month-old female C57BL/6 mice for 8 months to 5 W/kg 1950 MHz RF and saw no changes in ROS, apoptosis or DNA damage in the brain and no change in locomotor activity.

6.2.3.2.6 Summary in Mice

The best-studied strain of mouse is the Swiss-albino mouse and all studies using these mice demonstrated indications of oxidative stress induced by RF in multiple studies in the brain and testis and in single studies to the uterus, ovaries, liver and kidney at multiple frequencies and very low SARs. Three of the seven studies in Swiss mice used cellular phone exposure systems. In BALB/c mice, there is one negative study in brain, serum and spleen at 1 W/kg SAR, 900 MHz and 1 positive study in brain, heart, liver and kidney at 900/1800 MHz but an unknown SAR. One study in Parkes mice shows clear oxidative stress in liver, kidney and ovaries, DNA damage in the brain and changes in blood chemistry for a low SAR at 2450 MHz. In ICR mice, there is one study showing no changes in oxidative stress in liver, lung and blood at a low SAR at 900 MHz. Finally, in C57BL/6 mice, there is one study with no indication of oxidative stress in the brain at a much higher SAR at 1950 MHz.

In summary, RF can cause oxidative stress in the brain, testis, liver, kidney, uterus, heart and ovaries of Swiss-albino mice and the liver, kidney, ovaries and brain of ICR mice. There is insufficient data to support a causal linkage between RF exposure and oxidative stress in other strains of mice.

6.2.3.3 Rats

In the discussion that follows, unless otherwise mentioned, SAR values used in the studies are generally less than 1 W/kg either whole body or tissue specific. Details can be found in Supplemental Table 1.

6.2.3.3.1 Wistar Rats

There are 60 studies of RF in Wistar rats of which 35 used laboratory exposure systems

and 23 used cellular phones. These can be further divided by frequency and by organ to provide a summarized view of the findings. Fifteen (15) studies with laboratory exposure systems used 900-915 MHz RF, 1 used 1500 MHz, 11 used 1800 MHz, 4 used 2100 MHz, 18 used 2450 MHz, 1 used 2600 MHz and 1 used 2856 MHz (NOTE, this adds up to more than 33 studies because some studies used multiple frequencies). Seven (7) of the studies using cell phones or wifi devices used 900 MHz, 2 used cell phones with joint 900/1800 MHz, 2 used cell phones with joint 900/1800/1900 MHz, 1 used 1910.5 MHz, 3 used a 2450 MHz device, 1 used 2115 MHz and one used 2437 MHz.

All of the 8 studies in Wistar rats using laboratory systems at 900-915 MHz that evaluated oxidative stress in the brain showed changes in both ROS and ROS scavengers [247-254] with three examining and demonstrating tissue changes in the brain [250, 251, 253] (none examined DNA damage) and 2 examining and demonstrating behavioral changes [252, 253]. All 3 of the studies at only 900 MHz using a cellular phone showed changes in both ROS and ROS scavengers [255-257] with one examining and demonstrating tissue changes in the brain [256] but no significant change in DNA damage. One study at 1500 MHz showed decreases in SOD in the brain, changes in learning and spatial memory and brain tissue toxicity [258].

All of the 5 studies in Wistar rats using laboratory systems at 1800 MHz that evaluated oxidative stress in the brain showed changes in ROS and/or ROS scavengers [249-251, 259, 260] with three examining and demonstrating tissue changes in the brain [250, 251, 260] (none examined DNA damage). The one study at 900/1800 MHz using a cellular phone showed changes only in catalase activity with no other changes in either ROS or ROS scavengers [261] although they did see changes in animal behavior. Two studies in Wistar rats using laboratory systems at 2450 MHz that evaluated oxidative stress in the brain showed changes in ROS but not ROS scavengers [262, 263], one saw both change [254], one saw both change with brain toxicity [251], and one study showed no changes in ROS but used an unusual marker that appears to be focused entirely on nitrous oxides [264]. Two studies using 2450 MHz devices (wifi) were positive for both ROS and ROS scavengers with one showing changes in spatial memory from prenatal exposure [265] and the other not showing behavioral changes using adult exposure [266]. Studies were also clearly positive for the brain at 2100 MHz [267], 2115 MHz [268, 269] and 2856 MHz [258].

Sixteen (16) studies in Wistar rats looked at oxidative stress in the testis or sperm. Four (4) studies using laboratory-created 900 MHz saw changes in ROS and/or ROS scavengers (depending on what was measured) [270-273] and one saw changes in ROS but not ROS scavengers [274], two measured and demonstrated changes in tissue [272, 273] and one measured and demonstrated damage to DNA [272]. The two studies using 900 MHz cellular phones saw changes in ROS and ROS scavengers [275, 276] with one measuring and demonstrating both tissue damage and DNA damage [275]. One study with laboratory-generated 1800 MHz RF had no statistically significant change in ROS, but did see changes in ROS scavengers and apoptosis [277] and one study saw both ROS and ROS scavengers changed [271]. The one study using a 900/1800 MHz cellular phone saw changes in ROS and ROS scavengers and tissue toxicity [278]. One study with a combined 900//1800/1900 MHz cellular phone examined only ROS scavengers and saw changes and tissue toxicity [279]. The one study with a laboratory generated 2450 MHz signal saw changes in both ROS and ROS scavengers [271]. Single studies at 1950 MHz [280], 2100 MHz [281] and 2437 MHz

[282] saw changes to both ROS and ROS scavengers with two examining and demonstrating tissue toxicity [280, 282].

Heart tissue was examined in 4 studies. One, using 2450 MHz saw changes in ROS and ROS scavengers, tissue toxicity and apoptosis [283]. Another, also at 2450 MHz, saw changes in ROS and ROS scavengers, but not for all markers examined [284], and another at 2450 MHz saw changes in ROS but not ROS scavengers. The final study used laboratory generated 900 MHz and saw changes in ROS and ROS scavengers [270].

Liver tissue was examined in 7 studies in Wistar rats. Two studies using laboratory-created 900 MHZ [249, 270] and one using a 900 MHz cellular phone [285] saw changes in ROS and ROS scavengers. One study at 1800 MHz saw changes in ROS and ROS scavengers [249] while another showed no significant changes [286]. The one study using laboratory-created 2450 MHz showed an increase in ROS and tissue toxicity but did not look for changes in ROS scavengers [287] and another using laboratory-created 2600 MHz saw no significant change in ROS or ROS scavengers but did see tissue changes [288]. The one study using 1910.5 MHz saw an increase in ROS (scavengers not evaluated) and increased DNA damage.

Kidney tissue was examined in 3 studies; two were positive for changes in both ROS and ROS scavengers, one using 2450 MHz [289] and the other examining the frequencies of 900, 1800 and 2450 MHz [271]. One study showed no change in ROS (ROS scavengers not examined) using 1800 MHz [286].

Three studies evaluated the effect of RF in the eye epithelium of Wistar rats and all were effectively negative [290-292].

One study using laboratory-generated 2450 MHz saw increased ROS in the spleen (ROS scavengers were not examined) [287]. One study using laboratory-generated 900 MHz saw changes in ROS and ROS scavengers in the lung [270]. The Laryngotracheal mucosa was examined in one study using 2450 MHZ showing increased ROS but no significant change in ROS scavengers [293]. The ovary was examined in one study using 2450 MHZ showing increased ROS (ROS scavengers were not examined) [294]. One study using the three frequencies 900, 1800 and 2450 MHz saw changes in ROS for all three frequencies but no significant changes in ROS scavengers [295] in uterus and blood. A single study using 900 MHz saw changes in ROS and ROS scavengers in lymphoid tissues and blood [296]. A cell phone at 900 MHz only was used for one study and at a combined 900/1800/1900 MHz phone for one other study. Finally, one study used a combined 848.5/1950 MHz signal that was laboratory generated.

6.2.3.3.2 Sprague-Dawley Rats

There are 37 studies in Sprague-Dawley (SD) rats. Laboratory-generated RF at 900 MHz was used in 21 studies, 1800 MHz in 4 studies, 2100 MHz in 2 studies, and 2450 MHz in 5 studies [297-301].

Five studies evaluated oxidative stress in the brain using a laboratory-generated 900 MHz signal, and all of them demonstrated some degree of stress. Three studies demonstrated changes in both ROS and ROS scavengers [297, 299, 301] with 2 also demonstrating tissue changes in the brain [299, 301]. One study [298] saw no significant change in ROS but changes in ROS scavengers and tissue toxicity and one only examined a single ROS scavenger (significantly decreased) and saw changes in learning, spatial memory and the

blood-brain barrier. One study [302] using laboratory-generated 900, 1800 and 2100 MHZ saw changes in ROS and ROS scavengers at all three frequencies in the brain and significant DNA damage at 2100 MHz. One last study [303] using laboratory-generated 2450 MHz RF saw changes in gene expression and protein levels in the brain linked to oxidative stress and tissue response.

Three studies [304-306] examined oxidative stress in the testis or sperm using a laboratory-generated 900 MHz signal with all showing changes to ROS and ROS scavengers and 2 examining and demonstrating tissue changes and increased apoptosis [304, 306]. One study using a 900 MHz cellular phone demonstrated changes in ROS, ROS scavengers, tissue toxicity and apoptosis [307], whereas another using a 900/1800/1900 MHz cellular phone failed to demonstrate any significant changes in ROS, ROS scavengers or tissue toxicity [308]. A single study using a laboratory-generated 2450 MHZ signal with a moderate SAR (3.21 W/kg) demonstrated increases in ROS, decreases in ROS scavengers and increased tissue toxicity [309]. The final study evaluating oxidative stress in the testis used a combined 848.8/1950 MHz signal and a moderate SAR (4 W/kg) and failed to see any changes in ROS or tissue toxicity (ROS scavengers were not evaluated) [310].

Four studies examined oxidative stress in the kidney using laboratory-generated 900 MHz signals, 2 saw changes in ROS, ROS scavengers and tissue toxicity [299, 311], one saw increased ROS, tissue toxicity and apoptosis (ROS scavengers not examined) [312], and one saw no significant changes in ROS or ROS scavengers although they did see kidney toxicity [313]. One other study in the kidney used 2100 MHz and demonstrated changes in ROS, ROS scavengers, tissue toxicity and apoptosis [314]. **Turedi et al. (2017)** [312] also examined the bladder and saw clear changes in oxidative stress.

Four studies examined oxidative stress in the liver using laboratory-generated 900 MHz signals, 2 saw changes in ROS, ROS scavengers and tissue toxicity [299, 315], one saw increased ROS and decreased ROS scavengers (tissue toxicity not examined) [316], and one saw no significant changes in ROS, some changes in ROS scavengers and kidney toxicity [317]. One other study in the liver used 1800 MHz demonstrated changes in ROS, ROS scavengers and tissue toxicity [318].

Two studies looked at ovaries, one using 900 MHZ [319] and one using 2450 MHZ [320], saw changes in ROS and tissue toxicity but no changes in ROS scavengers. **Saygin et al. (2018)** [320] also looked at uterus and fallopian tubes and saw no significant changes in any oxidative stress markers.

Two studies in SD rats examined oxidative stress in the heart using laboratory-generated 900 MHz signals. One study, using in-utero exposure, saw clear increases in ROS and decreases in ROS scavengers with tissue toxicity and apoptosis [321]. The other study, using young rats, saw increased ROS, increased apoptosis, but no changes in ROS scavengers or in tissue toxicity [322].

Two studies in SD rats examined oxidative stress in the spinal cord using laboratory-generated 900 MHz signals with almost identical protocols. Both studies saw clear increases in ROS and weak or non-significant changes in ROS scavengers with tissue toxicity and apoptosis[323, 324]. One study using laboratory-generated RF looked at the sciatic nerve and saw changes in ROS and ROS scavengers, apoptosis and tissue toxicity [325].

Single studies evaluated the ear (increased ROS, no other changes) [326], pancreas (ROS, ROS scavengers and tissue changes) [327], spleen and thymus (ROS, ROS scavengers and tissue changes) [328] and eyes (ROS, ROS scavengers) [305].

6.2.3.3.3 *Other* Rat Strains

Three studies examined RF oxidative stress in Fischer rats. One study used laboratory-generated signals at 900, 1800 and 2450 MHz and saw changes in ROS and ROS scavengers, DNA damage and inflammation in the brain [329]. A second study evaluated blood using a 900 MHz signal and saw changes in ROS and ROS scavengers in blood and changes in learning and spatial memory [330]. The final study used 900 and 1800 MHz signals and recorded changes in ROS, ROS scavengers, and tissue changes in the brain with associated learning and spatial memory deficits [331].

Two studies listed their rats as albino; these could have been Wistar rats. One study evaluated serum exposed to a 900 MHz laboratory-derived field and saw a decrease in ROS scavengers (ROS was not evaluated) [332]. The second examined parotid glands in rats exposed to a 900 MHz cellular phone and observed an increase in ROS and a decrease in ROS scavengers with associated tissue changes [333].

The only study in Long-Evans rats used a laboratory-generated 900 MHz signal and saw changes in stress hormones in the brain but no significant changes in learning or spatial memory [334].

One study appears to have used locally-caught wild rats, exposed them to a 2100 MHz mobile phone and demonstrated an increase in creatinine kinase-MB (indicator of oxidative stress in the heart) and a decrease in cardiomyocytes [335].

Four studies failed to identify the strain of rat [336-339].

6.2.3.3.4 Summary in Rats

The best-studied strains of rat are the Wistar and SD rats and these show clear indications of oxidative stress induced by RF in multiple studies in the brain and testis and some indication of oxidative stress in the heart. The SD rats also seem to have consistent evidence of oxidative stress in the liver and kidney. Other findings in female reproductive organs, spinal cord, eye and other tissues are shown in 1 or 2 studies each. In other strains of rat, the most prominent findings are in the brain where there is generally increased oxidative stress. Most of these findings are at SARs below 1 W/kg and seem to occur regardless of the frequency used.

In summary, RF can cause oxidative stress in the brain, testis, and heart of SD and Wistar rats and the liver and kidney of SD rats. Brain appears to be a target for oxidative stress in Fischer rats. There is insufficient data to support a causal linkage between RF exposure and oxidative stress in other strains of rat.

6.2.3.4 Other Laboratory Species

Three studies looked at the effects of RF on oxidative stress in New Zealand White rabbits. **Guler et al. (2016)** [340] used laboratory-generated 1800 MHz signals and saw increases in brain ROS (ROS scavengers were not examined) in male rabbits exposed both in-utero and

after birth but not in females. **Guler et al. (2012)** [341] used the same laboratory set up and study design and saw changes in liver ROS and ROS scavengers and an increase in 8-OHdG in females, but no direct DNA damage. **Ogur et al. (2013)** [342] in an earlier study used the same exposure and saw increased ROS in blood for males and females with in-utero exposure and for females (not males) with exposure 1 month after birth. This same research group had done an earlier study with a similar design and saw no significant changes in blood [343].

One study examined laboratory-generated 900 MHz signals in Guinea pigs and saw a reduction in ROS scavengers in the liver but no significant change in ROS.

There is insufficient data to support a causal linkage between RF exposure and oxidative stress in laboratory species other than rats and mice.

6.2.4 *In Vitro* Studies in Mammalian Cells

6.2.4.1 Human Cells

6.2.4.1.1 Primary Cells

In vitro studies in primary cells refer to the use of cells taken directly from humans, then exposed in a laboratory to RF where oxidative stress is evaluated. Three studies exposed human sperm to RF and evaluated oxidative stress. Using a 900 MHZ mobile phone led to changes in ROS (ROS scavengers not examined) and DNA damage [344]. Using a laboratory-generated 1950 MHz signal resulted in no significant changes in ROS [345]. Using a 2450 MHz cellular phone resulted in clear oxidative stress with changes in both ROS and ROS scavengers [346].

Three studies used peripheral blood. Monocytes showed changes in ROS, ROS scavengers and apoptosis after being exposed to a laboratory-generated 900 MHz signal [347]. In another study, monocytes, but not lymphocytes, saw an increase in ROS (ROS scavengers not evaluated) after exposure to a laboratory derived 900 MHz signal [348]. The third study, both monocytes and lymphocytes exposed to a laboratory-derived 1800 MHz signal showed changes in ROS scavengers (ROS was not directly measured) [349]. A single study used umbilical cord blood exposed using a 900 MHz cellular phone resulting in an increase in ROS [350].

A single study used astrocytes from human brains exposed to 918 MHz RF and saw a decrease in ROS (ROS scavengers not examined) [351] (Note, this study was aimed at RF as a therapy for Alzheimer's).

Human stem cells exposed to 900, 1950 or 2535 MHz RF saw no significant changes in ROS apoptosis or DNA damage except for DNA damage that was shown at 900 MHz [352].

One study used primary cells from human skin, umbilical veins and amniotic fluid and saw no increase in ROS, saw binucleated nuclei in skin but no DNA damage via comet assay [353]

The final study of human primary cells used thyroid gland cells exposed to 900 or 895 MHz RF and saw no significant increase in oxidative stress [354].

Three (3) of these studies used SAR above 1 W/kg.

6.2.4.1.2 HEK293 Embryonic Kidney Cell Line

Two studies using the same basic design of 1 hour exposure to 2450 MHz RF saw a significant change in ROS and ROS scavengers [355, 356]. The only other study used a 940 MHz signal and also resulted in significant change in ROS and ROS scavengers [357].

6.2.4.1.3 HL-60 Leukemia Cell Line

Two studies, one at 900 MHz [358] and the other at 2450 MHz [359] both demonstrated increases in ROS and changes in ROS scavengers. The 900 MHz study [358] also saw damage to mitochondrial DNA. Finally, HL-60 cells exposed to 900, 1950 or 2535 MHz RF saw no significant changes in ROS or apoptosis [352]. Only 1 study used SARs above 1 W/kg.

6.2.4.1.4 SH-SY5Y Human Neuroblastoma Cell Line

Two studies, one with 935 MHz [360] and the other with 1800 MHz [361], saw no changes in oxidative stress. Two studies, one with 837 and 1950 MHz [362] and the other with 1800 MHz wifi device [363], saw changes in ROS only (changes in ROS scavengers were not evaluated). Finally, two studies, one with 935 MHz [364] and the other with 1800 MHz [365], saw changes in both ROS and ROS scavengers. Five of these studies used SARs greater than 1 W/kg.

6.2.4.1.5 Other Human Cell Lines

Studies in ACS cells (adipose tissue), Huh7 cells (liver), and U87 cells (glioma) all studied only ROS and demonstrated a significant increase in ROS [362, 366]. Studies in U-87 MG cells (glioma), MCF-7 cells (breast cancer), MDA-MB-231 cells (breast cancer) and HLE B3 cells (lens epithelium) studied a full spectrum of ROS and ROS scavengers and saw significant indications of oxidative stress [361, 362, 367-369]. A single study in MCF10A cells (breast) so no increase in ROS or ROS scavengers[370].

6.2.4.2 Cells Derived From Mice

6.2.4.2.1 Primary Cells

One study in Leydig cells saw changes in ROS and ROS scavengers after exposure to RF [371]. Another study of preantral follicles (ovaries) also saw changes in ROS and ROS scavengers after exposure to RF [372]. A study of spermatocytes saw an increase in ROS associated with an increase in DNA damage [373].

6.2.4.2.2 NIH/3T3 Mouse Embryonic Fibroblast Cells

Three studies used NIH/3T3 cells. All three saw increases in ROS but did not study ROS scavengers [362, 374, 375] with two also showing an increase in apoptosis [374, 375].

6.2.4.2.3 GC1 and GC2 Mouse Spermatocyte Cell Lines

Four studies evaluated the effects of RF on mouse-derived spermatocyte cell line GC1 and/or GC2. All four saw increases in ROS [373, 376-378], 2 of these showed increases in DNA damage [376, 377], 2 saw increases in 8-OhdG [373, 377] and one saw an increase in apoptosis [378].

6.2.4.2.4 N9 Mouse Microglia Cells

Two studies in N9 cells saw significant changes in ROS and ROS scavengers [364, 379] and one study demonstrated an increase in NO [380].

6.2.4.2.5 Other Mouse Cell Lines

One study with Neuro-2A cells (neuroblastoma) saw an increase in ROS (did not study ROS scavengers), but no significant change in DNA damage [381]. Two studies in the same laboratory evaluated RF and HT22 cells (hippocampus), neither study evaluated ROS scavengers, one saw a significant increase in ROS and a change in cell cycle [382] while the other with lower SAR values and two frequencies combined saw no significant change in ROS [383]. One study in RAW 264.7 cells (macrophage) saw an increase in ROS but did not study ROS scavengers [384]. Finally, one study using TM3 cells (leydig) saw changes in ROS and ROS scavengers but no change in apoptosis [385].

6.2.4.3 Cells Derived from Rats

Two studies used rat primary cells from the brain. One saw a decrease in ROS (scavengers not evaluated) in astrocytes when exposed to 918 MHz RF and challenged with hydrogen peroxide [351]. One study of rat neonatal spinal ganglia and neurons exposed to 1800 MHz RF saw an increase in ROS but no DNA damage [386].

One additional study used PC12 cells (rat derived pheochromocytoma cell line) exposed simultaneously to 837 MHz and 1950 MHz RF saw significant increased ROS at 12 hours but not at other times in a 24-hour window.

6.2.4.4 Cells Derived from Hamsters

Two studies exposed V79 cells (hamster lung cells) to 1800 MHz with one seeing increased ROS (nothing else studied) [387] and the other showing increased ROS and ROS scavenger activity [388]. A final study using CHO cells (ovaries) exposed to 900 MHz saw increased ROS (scavengers not evaluated) that remained 12 hours after exposure stopped [389].

6.2.5 Summary for Oxidative Stress

Most of the in-vivo and in-vitro studies of oxidative stress saw significant increases in ROS. Most of the studies that evaluated ROS scavengers saw significant changes in these markers that is associated with oxidative stress, the tissue or cells. Nineteen (19) in-vivo studies, 18 done in rats or mice and one in rabbits, evaluated oxidative stress as well as DNA damage, about half with SARs below 1 and a mix of exposure durations and almost all of them showed an increase in DNA damage.

Although reactive oxygen species can potentially cause damage to cellular function and structure and thereby impair its functionality, their presence and production cannot be immediately considered as harmful because changes in the levels of ROS and ROS scavengers is a normal part of cellular metabolism and physiology. Thus, many of the studies in this section simply demonstrate a change and not necessarily harm. However, tissue toxicity, increased DNA damage and changes in apoptosis do indicate that the changes in ROS are sufficient to impair cellular function and damage cellular components.

Many of the studies presented in this section did address these issues. With respect to cancer, of greatest concern would be damage to DNA. Twelve (12) of these in-vivo studies showed an increase in DNA damage associated with oxidative stress [239, 244, 256, 268, 272, 275, 302, 329, 338, 390-392], seven (7) did not see a significant change in DNA damage [236, 246, 256, 337, 341, 393, 394] and one saw a significant decrease in DNA damage after 15 days of exposure and an increase after 30 days of exposure [336]. Eight (8) in-vitro studies evaluated some aspect of oxidative stress as well as DNA damage, all of them with rather short exposure periods and most with SARs greater than 1. Five (5) of these studies demonstrated increases in DNA damage [344, 346, 352, 376, 377] and three (3) saw no significant increase in DNA damage [353, 381, 386].

There is sufficient evidence in the literature to conclude that oxidative stress is a possible mechanism by which RF causes cancer in humans.

6.3 Genotoxicity

6.3.1 Introduction

Genotoxicity refers to the ability of an agent (chemical or otherwise) to damage the genetic material within a cell, thus increasing the risks for a mutation. Genotoxic agents interact with the genetic material, including DNA sequence and structure, to damage cells. DNA damage can occur in several different ways, including single- and double-strand breaks, cross-links between DNA bases and proteins, formation of micronuclei and chemical additions to the DNA.

Just because a chemical can damage DNA does not mean it will cause mutations. So, while all chemicals that cause mutations are genotoxic, all genotoxic chemicals are not necessarily mutagens. Does that mean that the genotoxicity of a chemical can be ignored if all assays used for identifying mutations in cells following exposure to a chemical are negative? The answer to that question is no and is tied to the limitations in tests for mutagenicity (the ability of a chemical to cause mutations in a cell). It is unusual to see an evaluation of the sequence of the entire genome before exposure with the same sequence after exposure to determine if the genome has been altered (mutation). There are assays that can evaluate a critical set of genes that have previously been associated with cancer outcomes (e.g. cancer oncogenes), but these are seldom applied. In general, mutagenicity tests are limited in the numbers of genes they actually screen and the manner in which these screens work.

Because screening for mutagenicity is limited in scope, any genetic damage caused by chemicals should raise concerns because of the possibility of a mutation arising from that genetic damage. In what follows, the scientific findings available for evaluating the genotoxic potential of RF will be divided into four separate sources of data based on the biological source of that data: (1) data from exposed humans, (2) data from exposed human cells in a laboratory setting, (3) data from exposed mammals (non-human), and (4) data from exposed cells of mammals (non-human) in the laboratory. These four areas are based upon the priorities one would apply to the data in terms of impacts. Seeing genotoxicity in humans is more important than seeing genotoxicity in other mammals. In addition, seeing genotoxicity in whole, living organisms (*in vivo*) carries greater weight than seeing responses in cells in the laboratory (*in vitro*). Basically, the closer the findings are to real, living human beings, the more weight they should be given.

6.3.2 International Agency for Research on Cancer (IARC)

The IARC reviewed the potential for carcinogenicity from RF in 2011 [35]. They evaluated the scientific literature prior to 2011 and concluded "*there was weak evidence that RF radiation is genotoxic, and no evidence for the mutagenicity of RF radiation .*" This conclusion was driven by methodological shortcomings in the studies, lack of a sham-controlled group in some studies, use of mobile phones for exposures, poor dosimetry and contradictory results. Having looked over the IARC review, I agree with their assessment of these data and will not discuss any studies prior to 2010.

6.3.3 *In Vivo* Studies in Mammals

6.3.3.1 Humans

Several studies have addressed the presence of DNA damage directly in humans using the duration or frequency of cellular phone usage and comparing easily obtained human tissues (e.g. buccal swaps, sperm/semen, peripheral blood). **Vanishree et al. (2018)** [395] examined buccal swabs from 86 18-30 year-old cell phone users (46 M, 40 F) for micronuclei (MN). They compared low mobile phone users (<5 years and <4-5 hr/week) to high mobile phone users (>5 years and more than 10 hr/week) and saw an increase in MN in the high exposure group. They also saw an increase in MN on the side of the mouth where the mobile phone is used (ipsilateral) and in those who failed to use a headphone. **de Oliviera et al. (2017)** [396] examined buccal swabs from 30 male and 30 female 20-28 year-old cell phone users for MN. They saw no increase in MN by duration of use, frequency of use or ipsilateral vs. contralateral exposure. The categories for duration of use were unbalanced and they found no relationship with smoking (which is a known risk factor). Gulati et al. (2016) [397] examined buccal swabs from 116 people (68 M, 48F) residing near mobile towers (not defined but Table 1 suggests ≤400 meters) to 106 people living >800 meters from mobile towers (age range not provided). They found an increase in MN in buccal cells associated with distance to the cell tower and duration of use but saw no association with tobacco use. **Bannerjee et al. (2016)** [398] examined buccal swabs from 300 male 20-30 year-old cell phone users for MN. They compared low mobile phone users (<5 years and <3 hr/week) to high mobile phone users (>5 years and more than 10 hr/week). They saw an increase in MN in the high exposure group, an increase in MN on the ipsilateral side and in those who failed to use a headphone; they did not adjust for other risk factors. **Daroit et al. (2015)** [399] examined oral mucosa swabs from 3 different regions of the mouth of 60 people (24 M, 36 F) aged 19-33 years for MN and other genetic damage markers (broken eggs, binucleated cells, karyorrhexis). They saw increased MN on the whole mucosa and lower lip and increased binucleated cells (BN) on the border of the tongue for those using cellular phones for >60 minutes per week and increased broken eggs (BE) on the border of the tongue for those using cell phones for >8 years; all other comparisons were non-significant and no other risk factors were evaluated. **Sousa et al. (2014)** [400] examined ipsilateral-only oral mucosa cells in three groups (> 5 hr/week, >1 and ≤5 hr/week, ≤ 1 hr/week) of 15 individuals (sexes not specified) for the presence of MN, BE and degenerative nuclear anomalies (DN). They saw no changes in MN or DN but did see an increase in BE as a function of duration of usage per week (no other risk factors were examined). **Ros-Lior et al. (2012)** [401] examined buccal swabs from 50 (16 M, 34 F)

Caucasian 20-40 year-old cell phone users for MN. They compared short-term mobile phone users (<10 years) to long-term mobile phone users (>10 years). They saw no increase in MN, BN or DN in the long-term users nor did they see any relationship to ipsilateral use; they did not adjust for other risk factors and saw no relationship with smoking.

Radwan et al. (2016) [402] studied the effect of stress on sperm DNA damage in 286 males. They saw no indication of an increase in DNA fragmentation in sperm as a function of years of cell phone use (≤5, >5 to ≤10, > 10 years). In an earlier study from the same group using 344 men (286 in the 2016 study are included here) **Jurewicz et al. (2014)** [403] had a similar finding.

Gulati et al. (2016) [397] also examined peripheral blood lymphocytes (PBL) from 116 people (68 M, 48F) residing near mobile towers (not defined but Table 1 suggests ≤400 meters) to 106 people living >800 meters from mobile towers (age range not provided). They found an increase in tail moment (TM) (comet assay) associated with distance to the cell tower and duration of use but saw no association with tobacco use. **Gandhi et al. (2015)** [404] used the comet assay to evaluate DNA damage in PBL from 63 (38 M, 25 F) people with residences near (50-300 meters) a mobile phone tower and 28 controls (15 M, 13 F) with no nearby towers at home or work. All evaluations of DNA damage regarding distance to towers as well as mobile phone usage were significantly higher in the high exposure categories.

Cam and Seyhan (2012) [405] examined the hair roots of 8 individuals (6 women, 2 men) before and after 15 minutes exposure to a cellular phone and then 2 weeks later, before and after exposure for 30 minutes to a cellular phone. The comet assay showed a clear increase in single strand breaks after both 15 and 30 minutes of use with 30 minutes of use showing the greatest amount of damage.

6.3.3.2 Mice

In the NTP Study [166] using B6C3F1 mice, after 14 weeks of exposure, **Smith-Roe et al (2020)** [168] evaluated genotoxicity in several tissues of mice included in these studies for this purpose using the alkaline comet assay (three brain regions, liver, peripheral blood) and the micronucleus assay (peripheral blood). Significant increases in DNA damage were seen in the frontal cortex of male mice (DCMA and GSM) and leukocytes of female mice (CDMA only).

Jiang et al. (2013) [406] exposed groups of 10 male ICR mice to 900 MHz RF, SAR 0.548 W/kg, for 4 hr/day for 7 days and examined for MN in erythrocytes and bone marrow. They saw no significant changes in MN in either tissue, however, they did not use a sham control group. **Jiang et al. (2012)** [407] exposed groups of 5 male ICR mice to 900 MHz RF, SAR 0.548 W/kg, for 4 hr/day for 1,3,5,7 or 14 days and examined for general DNA damage (comet assay) in leukocytes. They saw no significant changes for any duration of exposure, however, they also did not use a sham control.

Chaturvedi et al. (2011) [408] exposed groups of 5 male Parks mice to 2450 MHz, SAR 0.0356 W/kg RF for 2 hr/day for 5 days. They saw an increase in tail moment, tail DNA and tail length in brain tissue using the comet assay.

6.3.3.3 Rats

In the NTP Study [166] using Sprague-Dawley rats, after 14 weeks of exposure, **Smith-Roe et al (2020)** [168] evaluated genotoxicity in several tissues of rats included in these studies for this purpose using the alkaline comet assay (three brain regions, liver, peripheral blood) and the micronucleus assay (peripheral blood). Significant increases in DNA damage were seen in the hippocampus of male rats (CDMA-only). **Usikalu et al. (2013)** [409] exposed groups of 2 male and 2 female Sprague-Dawley rats to 2450 MHz RF at SARs of 0, and 2.39 W/kg for 10 minutes and evaluated the induction of DNA damage by comet assay in the ovaries (F) and testis (M). Both tissues showed a significant increase in DNA damage as a function of exposure.

Akdag et al. (2016) [410] exposed groups of 8 male Wistar rats to 2450 MHz RF for 24 hr/day for 12 months at SARs of 0 or $1.41 \bullet 10^{-4}$ W/kg. Using the comet assay, they examined DNA damage in the brain, liver, kidney and testis and only saw increased DNA damage in the testis. **Gurburz et al. (2014)** [411] exposed groups of 6 male Wistar rats to 1800 MHz, SAR 0.23 or 2100 MHz, SAR 0.23 for 1 or 2 months. They examined only the urinary bladder and saw no increases in MN. **Atli et al. (2013)** [412] exposed groups of 2-week old and 10-week old Wistar rats (sex not provided) to 900 MHz RF, SAR 0.76 (2-week old) or 0.37 (10-week old) W/kg for 2 hr/day, 45 days with and without a recovery period of 15 days. Significant DNA damage (chromosomal aberrations, MN, and polychromatic erythrocytes) in bone marrow was seen for all of the experimental groups. Using the same experimental design with 1800 MHz RF, SAR 0.37 (2-week) and 0.49 (10-week), **Sekeroglu et al. (2012)** [413] saw the same significant DNA damage. **Trosic et al. (2011)** [414] exposed groups of 9 male Wistar rats to 915 MHz RF, SAR 0.6 W/kg, for 1 hr/day, 7 d/week, 2 weeks. They saw increases in DNA damage (comet assay) in liver and kidney, but not in brain.

Gouda et al. (2013) [415] exposed groups of 15 male albino (probably Wistar) rats to 1800 MHz RF, SAR 0.3 W/kg, from a cellular phone for 2 h/day either continuous or discontinuous (30 min on, 30 min off) for 2, 4 or 6 weeks. Using genomic DNA from the liver, they saw a significant increase in mutations to two genes (TP53 and BRCA1) after 6 weeks of exposure in the continuous group and a significant increase in DNA fragmentation at all durations for continuous exposure.

In a series of 3 studies, **Deshmukh et al. (2013, 2015, 2016)** exposed groups of 6 male Fischer rats to 900 MHz RF, SAR $5.95 \bullet 10^{-4}$ W/kg, 1800 MHz RF, $5.83 \bullet 10^{-4}$ W/kg, or 2450 MHz RF, $6.67 \bullet 10^{-4}$ W/kg, for 2 h/day, 5 d/week, 30 days [416], 90 days [417] or 180 days [418]. Increases in DNA damage in the brain in the 30-day study and hippocampus in the other two studies were seen using the comet assay.

6.3.3.4 Summary for DNA Damage In-Vivo

DNA damage was seen from exposure to RF in humans (5 studies of oral mucosa cells, 2 in PBL and 1 in hair follicles), mice (2 studies) and in rats (8 studies). Four studies in humans (2 oral mucosa cells, 2 sperm cells), 2 studies in mice which failed to use sham controls, and 1 study in rats saw no increases in DNA damage. In laboratory animals, 2 studies at 900 MHz saw no DNA damage while 6 were positive, one study using 1800 and 2100 MHz RF was negative while 5 using 1800 MHz were positive and all 6 studies using 2450 MHz were positive. In humans, most studies failed to control for confounders and failed to find an

association with smoking that should have been apparent. The strongest study, using hair follicles, used the individuals as their own control and this study was positive.

6.3.4 *In Vitro* Studies in Mammalian Cells

6.3.4.1 Humans

6.3.4.1.1 Primary Cells

Five studies exposed human PBL to RF. One study using laboratory-generated 900 MHz for 30 minutes with 60 minutes recovery saw no change in DNA repair [419]. One multi-laboratory study using laboratory-generated 1800 MHz RF for 28 hours saw no changes in MN, sister-chromatid exchange, chromosomal aberrations or comet assay tail moment [420]. Two studies with laboratory-generated 1950 MHz RF and 20 or 24-hr exposure with a 28-hr recovery saw no changes in micronuclei [421, 422]. One study with laboratory-generated 2450 MHz RF for 72 hr and a high SAR (10.9 W/kg) saw no change in MN or binucleated DNA [423].

Both studies using semen/sperm, one using an 850 MHz phone for 60 minutes and the other using a 900/1800 MHz phone for 1 to 5 hours saw an increased DNA fragmentation index.

The final human primary cell study using amniotic cells exposed to 900 MHz RF for 24 hours at 4 different SAR values and saw no change in aneuploidy in chromosomes 1 and 17.

6.3.4.1.2 Human Cell Lines

One study using SH-SY5Y neuroblastoma cells exposed to laboratory-generated 1950 MHz RF for 20 hours saw no change in tail behavior using the comet assay [424]. In contrast, a second study using the same cell line and exposure for 16 hours saw a non-significant increased tail length in the comet assay for not only SH-SY5Y cells, but also U87, U251 and U373 glioma cells and NCH421K glioblastoma cells [425]. They also observed an increase in DNA repair but no change in double strand breaks. Another study using A172 and U251 glioblastoma cells and SH-SY5Y neuroblastoma cells using 1800 MHz for 1, 6 or 24 hours saw no increase in DNA repair [426].

Two studies used HepG2 liver cells, one at 1950 MHz for 16 hours exposure saw no changes [425] while the other using 900 or 1800 MHz RF for 1-4 hours saw morphological changes in DNA at 4 hours [427].

One study used HMy2.CIR lymphoblastoma cells exposed to laboratory-generated 1800 MHz RF for 24 hours and observed changes in DNA repair proteins [428].

A study in HL-60 leukemia cells exposed to laboratory-generated 1800 MHz RF for 24 hours saw no changes in MN or DNA damage via the comet assay [429].

One study in HaCat skin cells exposed to 900 MHz RF for 30 minutes with a 4 or 24 hour recovery saw no change in MN [430].

Two studies in human/hamster AL hybrid ovary cells exposed to 900 MHz RF for 30 minutes saw different responses; one saw aberrant spindles [431] and the other saw no changes in MN but waited at least 4 hours after exposure before evaluation [430].

6.3.4.2 Mouse

6.3.4.2.1 Mouse Primary Cells

Three studies from the same laboratory exposed bone marrow cells extracted from bone marrow stromal cells from male Kumming mice and exposed them to 900 MHz RF. In the first study, the cells were exposed for 3 hours/day for 5 days and poly(ADP-ribose) polymerase-1 mRNA expression (*PARP-1*) was shown to be significantly elevated for 10 hours after the final exposure (this is an indication of breaks in strands of DNA) [432]. The second study exposed the cells for 4 hr/day for 5 days, allowed the cells to recover for 4 hours and then, after measuring DNA damage (comet assay, γ-H2AX foci) saw no differences between sham controls and the RF-exposed cells [433]. The final study exposed cells for 3 hours/day for 5 days, had a three-hour recovery then measured DNA damage (comet assay, *PARP-1*) and found a large, time-dependent change in both measures but did not provide statistical p-values [434].

Another study used oocytes and spermatozoa from $B6D2F_1$ mice, exposed for 60 minutes to 1950 MHz RF, combined to allow fertilization, and then allowed 17 to 20 hours to recover. They saw no chromosomal aberrations in the resulting one-cell embryos [435].

6.3.4.2.2 Mouse Cell Lines

One study exposed GC-2 mouse spermatocyte cells to 1800 MHz RF for 24 hours at SARs of 1,2 and 4 W/kg and saw an increase in DNA damage (comet assay, 4 W/kg) but no change in DNA double strand breaks (g-H2AX foci) [436]. A second study exposed GC-2 cells to a 900 MHz cellular phone signal for 24 hours to four different modes of cell phone use and saw DNA damage (comet assay) for three of the modes [437].

One study exposed ataxia telangiectasia mutated (Atm-/-) and Atm+/+ mouse embryonic fibroblast cells to 1800 MHz RF for 1 to 36 hours, SAR 4 W/kg, and saw increased DNA damage (comet assay) and DNA fragmentation in the Atm-/- cells at multiple times [438].

6.3.4.3 Rat

6.3.4.3.1 Primary Cells

One study exposed astrocytes extracted from Wistar rats to 872 MHz RF, SAR 0.6 or 6 W/kg, for 24 hours and saw no significant increase in micronuclei or DNA damage (comet assay) [439].

One study exposed femur and tibia lymphocytes extracted from Sprague-Dawley rats to 900 MHz RF for 30 minutes and saw no significant increase in DNA damage (comet assay) [440].

6.3.4.3.2 Rat Cell Lines

One study exposed PC12 rat pheochromocytoma cells to 1950 MHz, SAR 10 W/kg, for 24 hours and saw no significant DNA damage (comet assay) [441]

6.3.4.4 Hamster

6.3.4.4.1 Primary Cells

There were no studies of hamster primary cells.

6.3.4.4.2 Hamster Cell Lines

One study using V79 hamster lung fibroblast cells exposed to laboratory-generated 2450 MHz RF for 15 minutes saw an increase in aberrant spindles and apoptosis [442]. Another study using V79 cells exposed to 1950 MHz RF for 20 hours, SAR 0.15, 0.3, 0.6 and 1.25 W/kg, saw an increase in micronuclei at the two lowest SAR values [443].

6.3.4.4 Summary for DNA Damage In-Vitro

About half of the in-vitro studies showed some form of DNA damage and about half demonstrated no significant effects. There was no pattern by cell type, species, SAR or frequency. Very few of the studies used the same cell and frequency so it is difficult to give greater weight to the positive findings or the negative findings.

6.3.5 Summary for Genotoxicity

In addition to the many studies cited above and in the IARC Monograph [35], Lai (2021) [444] has compiled literature on other genetic effects (e.g. changes in gene expression) and downstream changes (e.g. cell-cycle arrest) that also point toward RF having an impact on cellular genetics and their control of cellular function.

A majority of the *in vivo* studies evaluating genotoxicity and RF, either with oxidative stress or independent of evaluating oxidative stress, showed a significant increase in DNA damage. In contrast, only about half of the *in vitro* studies of genotoxicity and RF were positive with no obvious pattern of why this might have happened.

Overall, there is sufficient evidence to suggest that genotoxicity, probably due to oxidative stress, is caused by RF and could be a mechanism by which cancer is induced by RF.

6.3. Summary for Mechanisms of Carcinogenicity

There is sufficient evidence to suggest that both oxidative stress and genotoxicity are caused by exposure to RF and that these mechanisms could be the reason why RF can induce cancer in humans.

There is the possibility of publication bias in this body of literature on mechanism. Publication bias occurs when studies that are positive tend to get published whereas negative studies are either never submitted for publication or they are rejected because they are negative (rejection is less of a problem since journals are now very aware of problems with publication bias). This potential problem cannot be resolved with the data in hand. There is also a possible bias in these results based upon a small collection of laboratories providing a majority of the studies; this could also create a small amount of bias in the direction of the positive results since scientists seldom pursue negative findings but will generally continue to pursue reasons for positive findings.

7. Summary of Bradford Hill Evaluation

RF exposure probably causes gliomas and acoustic neuromas and, given the human, animal and experimental evidence, I assert that, to a reasonable degree of scientific certainty, the probability that RF exposure causes these cancers is high.

Table 22 summarizes the information for each of Hill's aspects of causality. For these data, causality is strengthened because the available epidemiological studies show a **consistent positive association** between brain tumors and RF exposure. Analyzed collectively with meta-analyses using the most reasonable combinations of studies show positive responses. And, in answer to Hill's question, the relationship between brain tumors and RF exposure has been observed by different persons, in different places, circumstances, and times. Using meningiomas as controls in some case-control studies suggests recall bias is minimal.

Causality is strengthened for these data because **the strength of the observed associations**, when evaluated simultaneously in meta-analyses, are statistically significant and the results are unlikely to be due to chance. Even though only one of the individual studies provides odds ratios that are large and precise, the meta-analyses have objectively shown that the observed association across these studies is significant and supports a positive association between brain tumors and RF.

Biological plausibility is strongly supported by the animal carcinogenicity data and the mechanistic data on genotoxicity and oxidative stress. When addressing biological plausibility, the first question generally asked is "Can you show that RF causes cancers in experimental animals?" In this case, the answer to that question is clearly yes. RF can cause tumors in experimental animals with strong findings for gliomas, heart Schwannomas and adrenal pheochromocytomas in male rats and harderian gland tumors in male mice and uterine polyps in female mice. There is also some evidence supporting liver tumors and lung tumors in male and possibly female mice. Thus, it is biologically plausible that RF can cause cancer in mammals.

The next question generally asked is "Does the mechanism by which RF causes cancer in experimental animals also work in humans?" The best understood mechanism by which agents cause cancer in both humans and animals is through damaging DNA that leads to mutations in cells that then leads to uncontrolled cellular replication and eventually cancer. It is absolutely clear from the available scientific data that RF causes oxidative stress in humans and experimental mammals. This has been amply demonstrated in humans that were exposed to RF, in human cells *in vitro*, and in experimental animal models and their cells *in vitro* and *in vivo*. One possible consequence of oxidative stress is damage to DNA and potentially mutations. RF induces DNA damage as measured in multiple ways, in humans, animals and cells, providing additional support for a biological mechanism that works in humans.

Table 22: Summary conclusions for Hill's nine aspects of epidemiological data and related science

Aspect	Conclusion	Reason
Consistency of the observed association	Strong	Multiple studies, many are positive, meta-analyses with little heterogeneity show positive findings at higher exposures, different research teams, different continents, different questionnaires, no obvious bias in case-control studies, no obvious confounding, laterality is significant
Strength of the observed association	Strong	Significant meta-analyses

Biological plausibility	Very Strong	Multiple cancers in multiple species, same tumors as humans in male rats, not due to chance, increased risk of rare tumors, convincing evidence for genotoxicity and oxidative stress
Biological gradient	Strong	Clearly seen in some case-control studies, clearly seen in the meta-analyses and met-regressions, not seen in the cohort studies, clearly seen in animal studies
Temporal relationship of the observed association	Satisfied	Exposure clearly came before cancers
Specificity of the observed association	Strong	The only cancers linked to RF exposure are gliomas and acoustic neuromas
Coherence	Strong	Cancers seen in the rats have strong similarity to human gliomas and acoustic neuromas, laterality and brain location support coherence
Evidence from human experimentation	No data	No studies are available
Analogy	No data	No studies available in the literature

In general, there is support that a **biological gradient** exists for the epidemiological data and thus support from this aspect of the Bradford-Hill evaluation. RF mRRs increased with duration of cellular phone use and with cumulative hours of exposure when studies are combined in both meta-analyses and meta-regressions. In addition, laterality is strengthened when duration of use of a cellular phone increases. The animal studies clearly demonstrate dose-response.

The proper **temporal relationship** exists with the exposure coming before the cancers.

The human evidence is **coherent**. The cancer findings in humans agree with the cancer findings in rats. Also, studies focused on the temporal lobe appear to support this area as a target for cellular phone usage. Finally, laterality, when evaluated in meta-analyses shows that tumors are more closely associated with the predominant side of the head used by people with their cellular phones.

Glioma and acoustic neuroma are not **specific** to RF exposure; however, RF exposure is specific to these two tumors. There is no **experimental evidence** in humans and I did not find any references where researchers looked for analogous exposures with similar toxicity.

Hill (1965)[34] asks "*is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?*" There is no better way of explaining the scientific evidence relating RF exposure to an increase in gliomas and acoustic neuromas in humans than cause and effect.

In my opinion, RF exposure probably causes gliomas and neuromas and, given the human, animal and experimental evidence, I assert that, to a reasonable degree of scientific certainty, the probability that RF exposure causes gliomas and neuromas is high.

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mobile communication frequency range signal. *Bioelectromagnetics* 2011, **32**(4):291-301.

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433. Ji Y, He Q, Sun Y, Tong J, Cao Y: **Adaptive response in mouse bone-marrow stromal cells exposed to 900-MHz radiofrequency fields: Gamma-radiation-induced DNA strand breaks and repair**. *J Toxicol Environ Health A* 2016, **79**(9-10):419-426.

434. He Q, Zong L, Sun Y, Vijayalaxmi, Prihoda TJ, Tong J, Cao Y: **Adaptive response in mouse bone marrow stromal cells exposed to 900MHz radiofrequency fields: Impact of poly (ADP-ribose) polymerase (PARP)**. *Mutation research* 2017, **820**:19-25.

435. Suzuki S, Okutsu M, Suganuma R, Komiya H, Nakatani-Enomoto S, Kobayashi S, Ugawa Y, Tateno H, Fujimori K: **Influence of radiofrequency-electromagnetic waves from 3rd-generation cellular phones on fertilization and embryo development in mice**. *Bioelectromagnetics* 2017, **38**(6):466-473.

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437. Liu C, Gao P, Xu SC, Wang Y, Chen CH, He MD, Yu ZP, Zhang L, Zhou Z: **Mobile phone radiation induces mode-dependent DNA damage in a mouse spermatocyte-derived cell line: a protective role of melatonin**. *Int J Radiat Biol* 2013, **89**(11):993-1001.

438. Sun C, Wei X, Fei Y, Su L, Zhao X, Chen G, Xu Z: **Mobile phone signal exposure triggers a hormesis-like effect in Atm(+/+) and Atm(-/-) mouse embryonic fibroblasts**. *Sci Rep* 2016, **6**:37423.

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441. Zeni O, Sannino A, Sarti M, Romeo S, Massa R, Scarfi MR: **Radiofrequency radiation at 1950 MHz (UMTS) does not affect key cellular endpoints in neuron-like PC12 cells**. *Bioelectromagnetics* 2012, **33**(6):497-507.

442. Ballardin M, Tusa I, Fontana N, Monorchio A, Pelletti C, Rogovich A, Barale R, Scarpato R: **Non-thermal effects of 2.45 GHz microwaves on spindle assembly, mitotic cells and viability of Chinese hamster V-79 cells**. *Mutation research* 2011, **716**(1-2):1-9.

443. Sannino A, Zeni O, Romeo S, Massa R, Scarfi MR: **Adverse and beneficial effects in Chinese hamster lung fibroblast cells following radiofrequency exposure**. *Bioelectromagnetics* 2017, **38**(4):245-254.

444. Lai H: **Genetic effects of non-ionizing electromagnetic fields**. *Electromagn Biol Med* 2021:1-10.

Appendix I: Current CV: Christopher J. Portier

CURRICULUM VITAE
Christopher J. Portier, Ph.D.

Personal Data: Birth Date April 3, 1956
Birthplace Houma, Louisiana

Addresses: 4224 Midvale Ave N.
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United States
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Scheibenstrasse 15
CH-3600 Thun
Switzerland
Ph: +41-79-605-7958

Email: cportier@mac.com

Education:

1981	Ph.D.	(Biostatistics), University of North Carolina, Chapel Hill
1979	M.S.	(Biostatistics), University of North Carolina, Chapel Hill
1977	B.S.	(Mathematics), summa cum laude, Nicholls State University

Employment:

2018-present	**Scientific Advisor**, World Health Organization, Environment Program - Europe
2016-present	**Scientific Advisor on Pesticide Policies**, multiple European Non-Government Organizations
2013-present	**Consultant** to various governmental agencies (multiple countries) and law firms
2013-2014	**Senior Visiting Scientist**, International Agency for Research on Cancer, Lyon, France
2013-present	**Senior Contributing Scientist**, Environmental Defense Fund, New York City, NY
2010-2013	**Director**, National Center for Environment Health, Centers for Disease Control and Prevention, Atlanta, GA
2010-2013	**Director**, Agency for Toxic Substances and Disease Registry, Atlanta, GA
2009 – 2010	**Senior Advisor to the Director**, National Institute of Environmental Health Sciences and National Toxicology Program, Research Triangle Park, North Carolina.
2009 – 2010	**Visiting Scientist**, National Research Centre for Environmental Toxicology (EnTox), Queensland, Australia
2006 - 2009	**Associate Director,** National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

2006 - 2009	**Director, Office of Risk Assessment Research,** National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.
1993 – 2010	**Head, Environmental Systems Biology** (originally Stochastic Modeling), Laboratory of Molecular Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.
2000 - 2006	**Associate Director, National Toxicology Program**, National Institute of Environmental Health Sciences, Division of Intramural Research, Research Triangle Park, North Carolina.
2000 - 2006	**Director, Environmental Toxicology Program**, National Institute of Environmental Health Sciences, Division of Intramural Research, Research Triangle Park, North Carolina.
2006-2007	**Scientific Advisor to the Director**, Public Health and the Environment Department, World Health Organization, Geneva, Switzerland (detail from NIEHS – four months)
1993 - 2005	**Chief, Laboratory of Computational Biology and Risk Analysis** (originally the Laboratory of Quantitative and Computational Biology), National Institute of Environmental Health Sciences, Division of Intramural Research, Research Triangle Park, North Carolina.
1996 - 2000	**Associate Director for Risk Assessment**, Environmental Toxicology Program National Institute of Environmental Health Sciences, Division of Intramural Research, Research Triangle Park, North Carolina.
1990 - 1993	**Head, Risk Methodology Section**, National Institute of Environmental Health Sciences, Division of Biometry and Risk Assessment, Research Triangle Park, North Carolina.
1987, 1992, 1990	**Guest Scientist**, German Cancer Research Center, Heidelberg, Germany.
1978 - 1990	**Principal Investigator**, National Institute of Environmental Health Sciences, Division of Biometry and Risk Assessment, Research Triangle Park, North Carolina.
1977	**Mathematician**, Computer Sciences Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee.
1976	**Undergraduate Research Trainee**, Neutron Physics Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

University Affiliations:

2014 – present	Visiting Professor, Department of Toxicogenomics, Maastricht University, The Netherlands
2013 – 2016	Honorary Professor, National Research Centre for Environmental Toxicology, University of Queensland, Brisbane, Australia
2011 – present	Adjunct Professor, Department of Environmental Health, Emory University, Atlanta, GA, USA
2009 – 2010	Visiting Professor, University of Queensland, Brisbane, Australia
1986 - 2007	Adjunct Professor of Biostatistics, University of North Carolina, School of Public Health, Chapel Hill, North Carolina.
1990-1992	Adjunct Professor of Statistics, University of Waterloo, Waterloo, Ontario, Canada

Honors & Awards:

- 2016 Elected Fellow, Collegium Ramazzini
- 2013 President's Dream Green Team Award for "A Human Health Perspective on Climate

Change"
- Fellow, World Innovation Foundation, 2006
- Society of Toxicology, Risk Assessment Specialty Section, Paper of the Year, 2006
- Society of Toxicology, Risk Assessment Specialty Section, Paper of the Year, 2005
- Outstanding Risk Practitioner Award, International Society for Risk Analysis, 2000.
- Elected Fellow, International Statistical Institute, 2000.
- Outstanding Performance Award, National Institute of Environmental Health Sciences, numerous dates.
- Commendation for Sustained High Quality Work Performance, National Institute of Environmental Health Sciences, numerous dates.
- Merit Award, National Institute of Health, 1998.
- Board of Publications, Best Paper Award, Society of Toxicology, 1995.
- Distinguished Achievement Award, Section on Statistics and the Environment, American Statistical Association, 1995.
- Spiegelman Award presented by the American Public Health Association to the most outstanding public health statistician under the age of 40, 1995.
- Best-applied statistics paper, Centers for Disease Control, 1993.
- Elected Fellow, American Statistical Association, 1992.
- Elected Foreign Correspondent, Russian National Academy of Natural Sciences, 1992.
- First recipient of the James E. Grizzle Distinguished Alumnus Award, The Department of Biostatistics, The University of North Carolina, 1991.

Professional Societies Membership:

Society of Toxicology, American Public Health Association, International Statistics Institute, Bioelectromagnetics Society

Editorial Activities:

- Editor in Chief - The Open Environmental Journal (2008 to 2010)
- Associate Editor – Frontiers in Predictive Toxicity (2010 to present)
- Associate Editor - Environmental Health Perspectives (1987-2006)
- Associate Editor - Risk Analysis: An International Journal (1989-2003)
- Editorial Board – Environmental and Ecological Statistics (2004-2007)
- Associate Editor – Statistics in Medicine (1998-2002)
- Associate Editor - Biometrics (1997-99)
- Editorial Board Member/Reviewer (different dates): Biometrika, Cancer Research, Communications in Statistics, Fundamental and Applied Toxicology, Journal of Applied Toxicology, Journal of the American Statistical Association, Journal of Toxicology and Environmental Health, Science, Mathematical Biosciences, Journal of Mathematical Biology, Carcinogenesis, Science, PNAS, Toxicological Sciences and others

Advisory & Review Committees:

2019-present	Member, UCSF PHRE Science Response Network
2016-2020	Member, World Health Organization Regional Office Europe, Setting research priorities in environment and health
2015 – 2016	Member, Committee to Review the Draft Interagency Report on the Impacts of Climate Change on Human Health in the United States, National Research Council, National Academy of Sciences, USA
2010 – 2016	Member, Science Advisory Group on Electromagnetic Fields and Health, Netherlands Organisation for Health Research and Development

2009 – 2010	Coordinating Lead Author, Interagency Working Group on Climate Change and Health
2009 – 2013	Member, Institute of Medicine Roundtable on Environmental Health Sciences Research and Medicine
2009 – 2012	Member, National Academies of Science Roundtable on Science and Technology for Sustainability
2009	Member, WHO Advisory group on the health implications of the use of DDT to reduce risks of malaria.
2005 – 2010	Chair, Subcommittee on Toxics and Risk, President's National Council on Science and Technology
1997 - 2012	Advisor, *World Health Organization*, International Program on Chemical Safety, EMF Project.
2008 – 2010	Member, Environmental Protection Agency, Science Advisory Board
2007 – 2010	Member, International Life Sciences Institute, Health and Environmental Sciences Institute, Subcommittee on Susceptible Populations
2008	Center Review Committee, Canadian National Science and Engineering Research Council Chair in Risk Assessment
2008	Chair, International Agency for Research on Cancer Monographs Advisory Group, Lyon, France
2008	Advisory Group, Center for Environmental Oncology, University of Pittsburgh Cancer Institute
2007.	Chair, WHO Workshop on Low Cost Options for Reducing Exposures to ELF-EMF, Geneva
2007.	Invited Participant, International Program on Chemical Safety Workshop on Aggregate and Cumulative Risk Assessment, Washington, DC.
2006	Rapporteur, International Agency for Research on Cancer, Scientific Advisory Group to Plan Volume 100 of the IARC Monograph Series
2005	Chair, International Agency for Research on Cancer, Scientific Advisory Board on the Preamble to the Cancer Monograph Series
2005	Chair, World Health Organization Expert Panel on Health Criteria Document for Extremely Low Frequency Electric and Magnetic Fields
2003 – 2005	Co-Chair, Subcommittee on Health and Environment, President's National Council on Science and Technology
2003	Ad-Hoc member, EPA Science Advisory Board, Review of Children's Cancer Risk Assessment Supplement to Cancer Guidelines
2002 – 2006	Co-Chair, Subcommittee on Mercury, President's National Council on Science and Technology
2000 – 2007	Member, Finish Academy of Sciences Centers of Excellence Program Science Advisory Committee
2000	Reviewer, *Congressional Research Service, Library of Congress*; Research needs relevant to children's environmental health risks.
1998 - 2004	Member and Chair, *Environmental Protection Agency*, FIFRA Science Advisory Panel.
1997 - 2006	Member, National Occupational Research Agenda Team, *National Institute of Occupational Safety and Health.*
1995 - 2000	Advisor, *Australian Health Council,* Risk Assessment Methodology, Member *NHMRC* Steering Committee on Cancer Risk Assessment Guidelines.
1992 - 2000	Member, *EPA* Dioxin Reassessment Working Group.

1985 - 2007	Thesis director for graduate students, Department of Biostatistics, *University of North Carolina - Chapel Hill, North Carolina.*
1997	Advisor, *Netherlands National Health Council,* Risk Assessment Methodology.
1997	Reviewer, *Air Force Office of Scientific Research.*
1996 - 1997	Temporary Advisor, *World Health Organization,* Expert Committee on Food Additives.
1996	Advisor, *Environmental Protection Agency;* Evaluation of the benchmark dose methodology.
1996	Advisor, *Environmental Protection Agency;* Evaluation of risks from exposure to PCBs.
1996	Expert Review Committee, *Environmental Protection Agency;* Cancer dose-response for PCB's.
1995 - 1996	Member, *California Environmental Protection Agency,* Risk Assessment Advisory Committee.
1994 - 1997	Science Advisory Panel, *Public Broadcasting System Production* "Poisons in the Womb".
1991 - 1995	Ad-Hoc Member, *Environmental Protection Agency,* Science Advisory Panel.

Legislative Hearings:

- Glyphosate Hearing, European Parliament, Brussels, October, 2017
- Glyphosate Carcinogenicity, European Parliament, Brussels, December 2015
- Glyphosate Carcinogenicity, German Parliament, Berlin, July 2015
- Lead and Children's Health, Senate Committee on Environment and Public Works, July, 2012
- Asthma and Children's Health, Senate Committee on Environment and Public Works, May, 2012
- Contaminated Drywall, Senate Committee on Commerce, Science and Transportation, December, 2012.
- Camp Lejeune Contaminated Drinking Water, House Committee on Science and Technology, September, 2010.
- Autism and Vaccines, House Committee on Government Reform, December, 2002.

US Government Service Activities:

- Member, President's Task Force on Environmental Justice 2010-2013
- Member, President's Task Force on Children's Environmental Health 2009-2013
- Member, National Toxicology Program Executive Committee 2010-2013
- Financial Support and International Press Conference for research on "The Health Benefits of Tackling Climate Change" appearing as a series in Lancet, November 25, 2009
- Organizing Committee, White House Stakeholder briefing on Climate Change and Human Health, Old Executive Office Building, November 2009.
- Member, US Delegation, World Climate Congress, Geneva (September 2009)
- Member, US Delegation, Global Risk Communication Dialogue (2008-2009)
- Member, NIEHS Corrective Action Plan Management Committee (2008-2009)
- Primary focus, all interagency activities on hazards and risk (2006 to present)
- Co-Organizer, NIEHS/EPA Workshop on Children's Environmental Health, RTP, NC, January, (2007)
- Co-Organizer, NIEHS/NTP Workshop on the Identification of Targets for the HTS Roadmap Project (2007)
- Coordinator, NIEHS/EPA Review of the Children's Environmental Health Centers Program (2006-2007)
- Organizing Committee, Global Environmental Health Initiative, NIEHS (2006 to 2009)

- NIEHS Leadership Council (2005 to 2009)
- Organizer, formal collaborative agreements between NTP and Ramazzini Foundation (2001 to 2006)
- Organizer, formal collaborative agreements between NTP and Korean NTP (2002 to 2006)
- NIEHS Title 42 Review Committee (2003 to 2004)
- NIEHS Executive Committee and Operations Update Committee (2000 to 2005)
- NIEHS Leadership Retreats, DERT Retreats, DIR Retreats (all years since 1997)
- Presenter, NIEHS-sponsored National Academy of Sciences Committee on Emerging Issues in Environmental Health, November, 2001
- Organizer and presenter, National Toxicology Program Executive Committee Meetings (multiple dates since 2000)
- Organizer and presenter, National Toxicology Program Board of Scientific Counselors (multiple dates since 1998)
- Organizer, Joint NIEHS/US Geological Survey Interagency Program on Exposure Assessment, April 2001 to present)
- Organizer, US-Vietnam Scientific Conference on the Health and Environmental Effects of Agent Orange/Dioxin in Vietnam, March, 2002
- Organizing Committee, National Toxicology Program/EPA/FDA Scientific Conference on the Allergenicity of Genetically Modified Food, November, 2001
- NIEHS Town Hall Meeting, Los Angeles California, November, 2001
- NTP Research Directions, NAEHSC, Research Triangle Park, NC. May, 2001.
- NCI Study Section Center Presite Meeting, Seattle, Washington, January, 2001.
- Program committee member, *NIEHS/Colorado State University* conference on the Application of Technology to Chemical Mixture Research, 2001.
- Coordinating Core Committee, National Center for Toxicogenomics, NIEHS, 2000 to present
- Organizer, Joint US-Vietnam Consultation on Research on Agent Orange Health Effects in Vietnam. Singapore, 2000
- *ICCVAM/NICEATM*, Up-and-Down Procedure Peer Review Meeting, 2000.
- Chairman, *NIEHS* Risk Assessment Research Committee, 1995-present.
- Discussant, *NIEHS/PNNL* Workshop on Human Biology Models for Environmental Health Effects, 2000.
- Risk Assessment Coordinator, *NIEHS* US *RAPID* Program for the Evaluation of Health Risks from Exposure to Electric and Magnetic Fields, 1996-99.
- Organizer and Chair, Four Public Comment Sessions on the report of the *NIEHS/DOE* Working Group on the Health Effects of Exposure to Electric and Magnetic Fields, 1998.
- Organizer and Co-Chair, *NIEHS/DOE* Working Group on the Health Effects of Exposure to Electric and Magnetic Fields, 1998.
- Scientific Organizing Committee, *NIEHS* Workshop on Risk Assessment Issues Associated with Endocrine Disrupting Chemicals, 1998.
- Organizer, *NIEHS/DOE* Science Research Symposium on the Health Effects of Exposure to Electric and Magnetic Fields I: Biophysical Mechanisms and *In Vitro* Experimentation, 1998.
- Organizer, *NIEHS/DOE* Science Research Symposium on the Health Effects of Exposure to Electric and Magnetic Fields II: Epidemiological Findings, 1998.
- Organizer, *NIEHS/DOE* Science Research Symposium on the Health Effects of Exposure to Electric and Magnetic Fields III: *In Vitro* and Clinical Research Findings, 1998.
- Head, Toxicokinetics Faculty, *NIEHS,* 1994-97.
- Coordinator/Director, *NIEHS/ATSDR* Interagency Course on Mechanistic Modeling in Environmental Risk Assessment, 1996.
- Organizer, *NIEHS/EPA* Workshop on Research Priorities for New Risk Assessment Guidelines,

1996.

- Co-Organizer, *National Institute of Statistical Sciences*, *NIEHS/EPA* Workshop on Mechanistic Modeling in Risk Assessment, 1995.
- Scientific Coordinator and Mission Director, *NIEHS* "Mission to Vietnam" to assess the potential for scientific collaboration on the impact of Agent Orange on the Vietnamese Population, 1995.
- Chairman, *NIEHS* Computer Science Focus Group, 1995.
- Discussant, National Toxicology Program Workshop on Mechanistic Modeling in Toxicology, *NIEHS*, 1995.
- Discussant, National Toxicology Program Workshop on Mechanisms of Carcinogenesis, *NIEHS*, 1995.
- Co-Organizer, International Conference on The Role of Cell Proliferation in Carcinogenesis, co-sponsored by *NIEHS*, *The Chemical Industry Institute of Toxicology*, *The International Life Sciences Institute* and *The American Industrial Health Council*, 1992.
- Organizer and Director, Scientific Basis of Animal Carcinogenicity Testing, Moscow, Russia, co-sponsored by the *International Agency for Research on Cancer*, *NIEHS, Health and Welfare Canada* and *The All-Union Cancer Research Center*, 1991.
- Chairman, Computer Technology Advisory Forum, *NIEHS*, 1989.
- Organizer and Director, Design and Analysis of Long-Term Animal Carcinogenicity Experiments, Lyon, France, co-sponsored by the *International Agency for Research on Cancer* and the *NIEHS*, 1988.

Non-Governmental (US) Activities:

- Member, NRC Committee to review the Draft Interagency Report on the Impacts of Climate Change on Human Health in the United States, Washington, DC, 2015
- Expert Scientist, International Agency for Research on Cancer Monograph Meeting on Some Organophosphate Pesticides and Herbicides, Lyon, France, March, 2015
- Overall Chair, International Agency for Research on Cancer Monograph Meeting on Diesel and Gasoline Engine Exhausts and related compounds, Lyon, France, June, 2012
- Advisor to Wellcome Trust at "International Research Futures Symposium on Global Change, Economic Sustainability, and Human Health", London, England, March, 2012.
- Expert Panel Member for review of Hollings Marine Laboratory, National Oceanographic and Atmospheric Agency, Charleston, USA, February, 2012.
- Chair, Mechanism Subgroup, International Agency for Research on Cancer Monograph Meeting on Radiofrequency Electric and Magnetic Fields, Lyon, France, May, 2011
- Advisor, Greek Ministry Health, Working group on hexavalent chromium in the environment, January, 2011
- Member, WHO Consultation on Human Health Risks from DDT, Geneva, Switzerland, November, 2010
- Associate Editor, Frontiers in Predictive Toxicity, 2010 – 2011
- Scientific Advisor, Health Investigation Levels Workshop, Canberra, Australia, January, 2010
- Chair, IARC Working Group, IARC Monograph 100-G, Lyon, France, October, 2009
- Scientific Organizing Committee, VII World Congress on Alternatives and Animal Use in Life Sciences, Rome, Italy, September, 2009
- Chair, Research Directions Working Group, World Health Organization Consultation on Global Research on Climate Change and Health, October, 2008.
- Editor-in-Chief, The Open Environment Journal, May 2008-August, 2010
- Member, EPA Science Advisory Board, July, 2008-present
- Working Group Member, IARC Monograph 98 - Fire-fighting, Painting and Shift-work, Lyon, France, November, 2007

- Chair, WHO Extremely Low Frequency Magnetic and Electric Fields Workshop on Intervention Strategies, June, 2007
- Special Advisor to the Director, Program on Public Health and the Environment, WHO, Geneva, May-July, 2007
- Member, International Life Sciences Institute Working Group on Susceptible Populations, March, 2007 – present
- Special Advisor to the Director, Program on Public Health and the Environment, WHO, Geneva, November, 2006-January, 2007
- Breakout Group Chair, International Workshop on Uncertainty and Variability in PBPK Modeling, RTP, NC USA, October, 2006
- Member, Health Effects Sciences Institute Committee on Sensitive Subpopulations and Groups, Washington, DC, 2006 to present
- Rapporteur, Steering Committee for developing the 100th Monograph of the International Agency for Research on Cancer, Lyon, France, September, 2006
- Co-Organizer, parallel workshops on the advancement of PBPK modeling in risk assessment, Research Triangle Park, November, 2006, Corfu, Greece, April, 2007.
- Organizer, Alternative Models in Developmental Neurotoxicity, Alexandria, Virginia, March, 2006.
- Organizer, NTP High Throughput Screening Workshop, Washington, DC, December, 2005
- Organizer, ISRTP Meeting on Alternative Methods in Toxicology, Baltimore, Maryland, November, 2005
- Organizer, NTP 25th Anniversary Meeting, Washington, DC, May, 2005
- Organizer, IPCS/WHO Workgroup on Dose-Response Modeling, Geneva, Switzerland, September, 2004
- Organizer, Consultation on harmonization of toxicological research between the NTP, Ramazzini Foundation and the European Union, European Congress of Toxicology, Florence, Italy, September, 2003.
- Member, WHO Workgroup on the epidemiology of cellular phone toxicity, Tskuuba, Japan, September, 2003.
- Program Committee, 12th International Conference on Global Warming, Boston, Massachusetts, May 2003
- Program Committee, International Conference on Cancer Risk Assessment, Athens, Greece, August, 2003
- Chair, WHO Public Consultation on Risk Communication, Luxembourg, February, 2003.
- Chair, WHO Committee on Establishing a Plan for Implementation of the Precautionary Principle in Risk Management. Luxembourg, February, 2003.
- Presenter (on behalf of US Government), National Academy of Sciences Panel on the Use of Third Party Toxicity Research with Human Research Participants, December, 2002
- Member, US Science Delegation, United Nations Environmental Program Consultation on Organic Mercury, September, 2002
- Science Panel Member, IARC Carcinogenicity Review of ELF-EMF, Lyon, France, June, 2001.
- Reviewer, Finish Ministry of Health Centers of Excellence Program, Helsinki, April, 2001.
- *EPA* dioxin reassessment peer review workshop and public comment session, Washington, DC, 2000.
- Organizer: Dioxin Dose-Response Working Group Meeting, Fort Collins, Colorado, February, 2000.
- Chair, Spiegelman Award Committee, *American Public Health Association,* 1998.
- Chair, *Bioelectromagnetics Society* Symposium on the use of Transgenic Animals in Evaluating Health Risks from Exposure to Cellular Phones, St. Petersburg, Florida, 1998.

- Member, *World Health Organization* International Program on Chemical Safety, Workshop on Issues in Cancer Risk Assessment, 1998.
- Advisor, *Joint Committee on Food Additives, World Health Organization/Food and Agriculture Organization*. Evaluation of certain food additives and contaminants
- Member, US Government Methylene Chloride Risk Characterization Science Committee, 1996-1998.
- Scientific Organizing Committee, *Colorado State University* Workshop on Biomedical Advances on Chemical Mixtures, 1997.
- *National Academy of Sciences*, Institute of Medicine, Committee on Funding Future Agent Orange Research in Vietnam, 1996.
- Discussant, Workshop on the role of Endocrine Disruptors in Human Health, 1995.
- Advisor to *Australian Health Council* on Risk Assessment Methodology, Member *NHMRC* Steering Committee on Cancer Risk Assessment Guidelines
- Participant, International Program on Chemical Safety of the *World Health Organization* Workshop on Chemical Risk Assessment, London, England, 1995.
- Participant, *IARC* Workshop on Receptor-Mediated Carcinogenesis, Lyon, France, 1994.
- Co-Organizer, Symposium on Quantitative Risk Assessment, *German Cancer Research Center*, Heidelberg, Germany, 1993.
- Participant, *IARC* Monograph on Risk Assessment Methodology, *International Agency for Research on Cancer*, Lyon, France, 1993.
- Thesis advisor for graduate student, *University of Waterloo*, Waterloo, Ontario, Canada. 1991-93.
- Co-Organizer, *Russian Academy of Sciences* Informatics and Cybernetics Research Award, 1992.
- Official Observer, IARC Monograph on the Biological Effects of Ultraviolet Radiation, *International Agency for Research on Cancer*, Lyon, France, 1992.
- Member, *International Life Sciences Institute*, Dose-Response Working Group, 1991.
- Participant in Banbury Conference on Human Health Risks from Exposures to Dioxins, Banbury Conference Center, Cold Spring Harbor, New York, 1990.
- Co-Chairman, Session on Biostatistical Developments in Cancer Research, *15th International Cancer Congress*, Hamburg, Germany, 1990.
- Participant in *Environmental Protection Agency* Workshop on Risk Assessment Guidelines, Virginia Beach, Virginia, 1989.

Direction of Ph.D. Theses:

A Bailer. *The effects of treatment lethality on tests of carcinogenicity*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1986.

P Williams. *Estimating tumor incidence rates using the method of moments and maximum likelihood estimation combined*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1989.

G Carr. *The analysis of data on adverse reactions to chemicals in developmental toxicology*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1989.

S Liu. *Estimating parameters in a two-stage model of carcinogenesis using information on enzyme-altered foci from initiation-promotion experiments*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1993.

CD Sherman. *Multipath/multistage models of carcinogenesis*. Department of Statistics and Actuarial Sciences, University of Waterloo, Waterloo, Ontario, Canada, 1994.

C Lyles. *Cell labeling data: Models and parameter estimation*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1995.

F Ye. *The equal slopes test for benchmark doses*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 2001

S Whitaker. *Development of a biologically-based mathematical model of fetal development*. Department of Mathematics, North Carolina State University, Raleigh, North Carolina, 2000.

R Helms. *Homeostatic feedback control of growth on multistage cancer models*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 2001.

Journal Articles: (peer reviewed)

1. Portier CJ: A comprehensive analysis of the animal carcinogenicity data for glyphosate from chronic exposure rodent carcinogenicity studies. *Environmental Health* 2020, 19(1):18.

2. Robinson, C., Portier, C., Čavoški, A., Mesnage, R., Roger, A., Clausing, P., Whaley, P., Muilerman, H., Lyssimachou, A.: **Achieving a High Level of Protection from Pesticides in Europe: Problems with the Current Risk Assessment Procedure and Solutions,** *European Journal of Risk Regulation* 2020, 1-31

3. Krewski D, Rice JM, Bird M, Milton B, Collins B, Lajoie P, Billard M, Grosse Y, Cogliano VJ, Caldwell JC *et al*: **Concordance between sites of tumor development in humans and in experimental animals for 111 agents that are carcinogenic to humans**. *Journal of toxicology and environmental health Part B, Critical reviews* 2019, **22**(7-8):203-236.

4. Alexeeff, S. E., A. Roy, J. Shan, X. Liu, K. Messier, J. S. Apte, C. Portier, S. Sidney and S. K. Van Den Eeden (2018). "High-resolution mapping of traffic related air pollution with Google street view cars and incidence of cardiovascular events within neighborhoods in Oakland, CA." Environ Health **17**(1): 17-38.

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Appendix II: Previous Cases Resulting in Depositions and Court Appearances

Glyphosate multidistrict litigation under Judge Vince Chhabria. MDL 2741, Case 3:16-md-02741-VC, US District Court, Northern District of California

Edwin Hardeman (plaintiff) v. Monsanto Company (defendant), MDL 2741, Case 3:16-cv-00525-VC, US District Court, Northern District of California

Edwin Hardeman (plaintiff) v. Monsanto Company (defendant), MDL 2741, Case 3:16-cv-00525-VC, US District Court, Northern District of California

Alva and Alberta Pilliod (plaintiffs) v. Monsanto Company (defendant), Alameda County Superior Court, Case A158228

Walter Winston et al. (plaintiffs) v. Monsanto Company (defendant), Circuit Court of the City of St. Louis, State of Missouri, Case No. 1822-CC00515

Depositions from Winston v. Monsanto were also to be used for the following

Bellah v. Monsanto, Lake C., CA
Caballero v. Monsanto, Alameda County, CA
Bargas v. Monsanto, Alameda County, CA
Wade v. Monsanto, St. Louis City, MO
Stevick v. Monsanto, San Francisco, CA

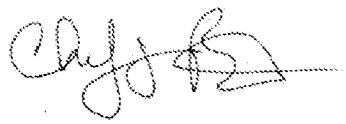
Seitz v. Monsanto, St. Louis City, MO
Kane v. Monsanto, St. Louis City, MO
Bogner v. Monsanto, St. Louis County, MO
Neal v. Monsanto, St. Louis CCity, MO

Appendix III: Compensation

Billing is at $500.00 per hour in 30-minute increments for all activities including depositions and trial testimony with the exception of travel time which will be billed at $200.00 per hour with a maximum of 8 hours per day. Reasonable expenses incurred including transportation costs, hotels and meals will be reimbursed.

Certification

I hereby certify that this report is a complete and accurate statement of all of my opinions, and the basis and reasons for them, to which I will testify under oath.



3/1/2021

Christopher J. Portier — Date