Scott Carey

From: Gerald O. Barney <gerald.barney@groupoffice.ch>
Sent: Sunday, October 30, 2022 10:17 PM
To: Scott Carey
Subject: NTRPA Governing Board Meeting—November 3rd, 2022—Public Comment [Agenda# 2]
Attachments: NATURE—Radiofrequency EMF irradiation effects on pre-B lymphocytes.pdf; NATURE—Whole-body exposures to radiofrequency-electromagnetic energy can cause DNA damage via an oxidative mechanism.pdf; Expert-report-Christopher-J-Portier-Murray-v-Motorola-3-1-2021-1.pdf; TPC-CELL TOWER SAFETY_Disinformation Flyer.pdf; TPC-CELL TOWER SAFETY_Disinformation Flyer2.pdf; Tahoe Prosperity Center Lies.pdf; Rhetoric and frame analysis of ExxonMobil's climate change communications.pdf

Dear NTRPA Governing Board,

Microwave radiation causes cancer. The latest scientific study (*also attached*) published in the most prestigious journal NATURE all but ends any serious debate over whether cell phone radiation frequencies cause non-thermal DNA damage leading to cancer. For the last several decades, the wireless industry used the playbook of the Tobacco and Fossil Fuels industries to cloud the overwhelming science about the dangers of their technology (Exxon understood the science about global warming 40 years ago, and spent millions to promote misinformation). In a similar vein, the Tahoe Prosperity Center has spent thousands of dollars of City grant money in promoting disinformation on behalf of Verizon and AT&T locally (their flyers blatantly mischaracterize findings of the NIH, EPA, and the scientific community). We must stop this dangerous technology implementation now—just like global warming, we will not be able to go back in time to fix it. This time, we now know what we wish we knew 40 years ago: their sociopathic game.

Please sign the petition.

Click on the booklet below to access 3,300 pages of damning science on the City Council record:

The Current Science on
& Environmental Ef
Caused by Cell Tower R

See another collection here. This grave issue is now being taught in Nursing School textbooks.

Please protect us from this known **existential threat**, and Save Lake Tahoe. Don't forget to sign the petition!

The purpose of copyright law is "to Promote the Progress of Science and useful Arts" (U.S. Const. art. I, § 8, cl. 8). The House Committee on the Judiciary explicitly listed "reproduction of a work in legislative or judicial proceedings or reports" as an example of a fair use (H.R. Rep. No. 94-1476, 65 (1976)). Introducing entire copyrighted works in official governmental proceedings is generally fair use (*Sony Corp. of Am. v. Universal City Studios, Inc.*, 464 U.S. 417, 449-50 (1984) ("the fact that the entire work is reproduced…does not have its ordinary effect of militating against a finding of fair use"); *Jartech, Inc. v. Clancy*, 666 F.2d 403 (9th Cir. 1982) (holding that the city councils use of copyrighted material in the legal proceedings was not "the same intrinsic use to which the copyright holders expected protection from unauthorized use"); *Stern v. Does*, 978 F. Supp. 2d 1031, 1044-49 (C.D. Cal. 2011) (reproduction of copyrighted material for use in litigation or potential litigation is generally fair use, even if the material is copied in whole); *Ty, Inc. v. Publications Intern. Ltd.*, 292 F.3d 512 (7th Cir. 2002) (reproducing copyrighted works for litigation is an example of the fair use doctrine); *Healthcare Advocates, Inc. v. Harding, Earley, Follmer & Frailey*, 497 F.Supp. 2d 627, 638 (E.D. Pa. 2007) (holding that law firm's copying of an entire set of copyrighted web pages was justified where the web pages were relevant evidence in litigation); *Hollander v. Steinberg*, 419 Fed.Appx. 44 (2d Cir. 2011) (affirming dismissal of a copyright case by an attorney, where opposing counsel in an earlier civil action had appended that attorney's blog entries to a motion); *Religious Tech. v. Wollersheim*, 971 F.2d 364 (9th Cir. 1992) (holding that providing copies of the plaintiff's copyrighted documents to the defendant's expert witness was fair use); *Porter v. United States*, 473 F. 2d 1329 (5th Cir. 1973) (rejecting a claim by the widow of Lee Harvey Oswald that she was entitled to compensation because the publication of Oswald's writings in the Warren Commission Report diminished the value of the copyright in those works); *Kulik Photography v. Cochran*, 975 F. Supp. 812 (E.D. Va. 1997) (dismissing on jurisdictional grounds of a copyright infringement suit brought by the author of a photograph that was used without permission in the O.J. Simpson murder trial); *Levingston v. Earle*, No. 3:2012cv08165 (D. Ariz. 2014) (holding that appending a full copy of an author's book to a pleading, in a harassment proceeding against that author, was fair use); *Grundberg v. the Upjohn Co.*, 140 F.R.D. 459 (D. Utah 1991) (rejecting the defendant's attempt to register a copyright in its document production in order to restrict the plaintiff's use and public dissemination of those documents); *Shell v. City of Radford*, 351 F.Supp.2d 510 (W.D. Va. 2005) (dismissing a copyright infringement suit by a photographer whose photographs were copied and used by detectives investigating the murder of the photographer's assistant); *Denison v. Larkin*, 64 F. Supp. 3d 1127 (N.D. Ill. 2014) (dismissing with prejudice Plaintiff attorney's suit against defendants for using portions of her copyrighted Blog as evidence against her in an attorney disciplinary proceeding); *Carpenter v. Superior Court* (*Yamaha Motor Corp., USA*), 141 Cal.App.4th 249 (2006) (holding the plaintiff in a personal injury action could gain access to certain standardized neurological tests over an objection that the tests were protected by, *inter alia*, copyright law)).

Thank you for your consideration,

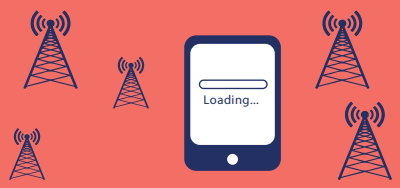
Gerald Barney

TAHOE WIRELESS BROADBAND AND YOU

REPORTED WIRELESS DATA TRAFFIC (MEGABYTES)

- **Wireless data use almost doubles in just one year.** Wireless data puts the internet in the palm of our hand and allows us to access nearly anything or anyone on the go, and its tremendous value to consumers shows no signs of slowing.
- This year, we saw mobile data grow by **12.89 trillion MBs** to a **total of 28.58 trillion.**
- That's an **82 percent increase** in the last year alone and is more data than was used in the first six and a half years of this decade combined.
- In fact, data use is up over **73 times since 2010.**[1]

NEED MORE TOWERS



Less Towers = Longer Wait

- **A fast wireless network is a critical resource for our community,** and failing to provide fast wireless networks is no different than failing to provide clean drinking water, natural gas, sewage service, or electricity.[3]
- When a disaster occurs people need to know about it. An increasingly large segment of the population use mobile devices instead of landlines. **Receiving alert on mobile devices is vital for emergency preparedness.**
- The World Health Organization (WHO) has classified radio frequency energy as "possibly carcinogenic to humans." **WHO also states that in the last twenty years no adverse health effects have been established as being caused by mobile phone use."**[2]
- The American Cancer Society, the International Agency for Research on Cancer and the National Toxicology Program claim that **cell towers are unlikely to cause cancer.**

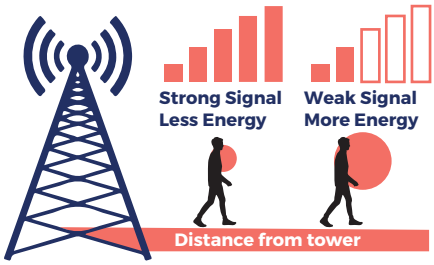
STUDIED FOR SAFETY

FDA FCC

Regulated Levels Are Safe to Humans

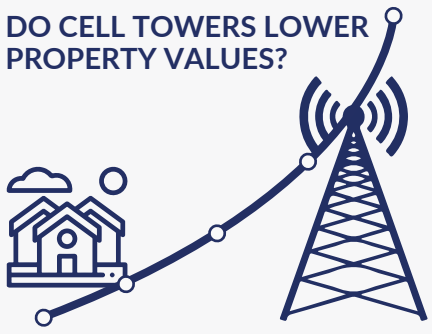
United States Environmental Protection Agency · American Cancer Society · World Health Organization

CELL TOWER SIGNAL



- **Using phones in areas of good reception *decreases* exposure as it allows the phone to transmit at reduced power.** More towers mean better coverage and hence less electromagnetic field radiation exposure from mobile phones.[2]

DO CELL TOWERS LOWER PROPERTY VALUES?



- The distance from a wireless facility has no apparent impact on the value or sale price of a home. The relationship between **the list and sale price remained the same no matter how close the property was to the wireless facility.**[5]

Disinformation

ARE CELLPHONE TOWERS DANGEROUS?

Research by organizations such as the National Institute for Occupational Safety and Health, the environmental Protection Agency (EPA), FCC and others have found **radio frequency energy within the regulated levels are not harmful to humans.**

Radio frequency waves, a form of energy, is released when a mobile device (phone, tablet or laptop) connects with a cell tower.

Different devices create different frequencies on the electromagnetic spectrum. **Some frequencies are harmful to humans while others are not**.

For instance, the frequencies that carry x-rays and gamma rays are on the radioactive end of the electromagnetic spectrum, and can cause harmful damage to the chemical bonds in our DNA.

Radio frequency energy from cell towers and mobile devices is "non-ionizing," similar to radio and television waves.

Tall cell towers keep radio frequency energy high above the ground. **At ground level, radio frequency energy from towers is thousands of times less than the FCC safe exposure limits.** Other antennas, such as those used for radio and television broadcast transmissions, use power levels that are generally much higher than those used for cellular antennas.[6]

DEFINITIONS

Mobile Broadband – The use of high speed internet via mobile devices (smart phone, tablet or laptop) that utilizes frequencies on the electro magnetic spectrum.

Electromagnetic Spectrum – The range of frequencies that emit electromagnetic energy. The lower end of the spectrum has low frequencies and longer waves of energy, while the higher end has high frequencies and shorter waves.

Electromagnetic Energy – Any energy emitted or absorbed by charged particles traveling through space, anything from visible light to nuclear reactions.

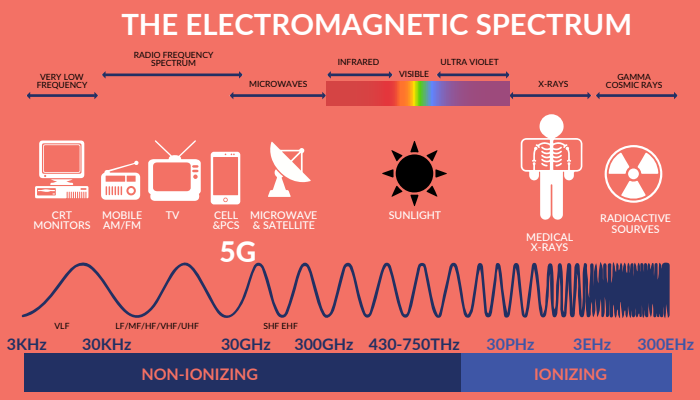
Ionizing and Non-ionizing Energy – Ionizing energy is energy on the high end of the spectrum that is harmful to human DNA. Energies that are on the low end of the spectrum are considered non-ionizing energy and are not harmful to humans.

Radio Frequency Energy - The range of frequencies on the non-ionizing end of the electromagnetic spectrum used for telecommunications devices such as mobile phones, laptops, radios and television.

WHAT THE EXPERTS SAY...

A systematic review of existing academic studies on the potential health risks of radio frequency emissions found that **the majority of research on the subject currently indicates no ill-health related to radio frequency energy exposure**.[7]

Research is ongoing. There is consensus that additional research is warranted to address gaps in knowledge, such as the effects of cell phone use over the long-term and on pediatric populations.[8]



The electromagnetic spectrum. CNET

REFERENCES

1. CTIA 2019 Annual Survey, www.ctia.org/news/2019-annual-survey-highlights
2. World Health Organization, Electromagnetic fields and public health: mobile Phones, WHO Fact Sheet #193. June, 2011. Reviewed October 2014
3. Wireless Emergency Alerts Report by the Department of Homeland Security, www.dhs.gov/sites/default/files/publications/Wireless%20Emergency%20Alerts%20Mobile%20Location%20Strategy.pdf
4. The American Cancer Society www.cancer.org/cancer/cancer-causes/othercarcinogens/atho me/cellular-phone-towers
5. Joint Ventures Wireless Communications Initiative Study - Wireless Facilities Impact on Property Values, November 2012 www.jointventure.org/images/stories/pdf/WirelessFacilitiesImpactOnPropertyValues.pdf
6. FCC Radio Frequency Safety, www.transition.fcc.gov/oet/rfsafety/rf-faqs.html
7. Martin Röösli et al., "Systematic Review on the Health Effects of Exposure to Radiofrequency Electromagnetic Fields from Mobile Phone Base Stations," Bulletin of the World Health Organization 88, no. 12 (December 1, 2010): 887–896F.
8. The Food and Drug Administration, www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/HomeBusinessandEntertainment/CellPhones/ucm116335.htm

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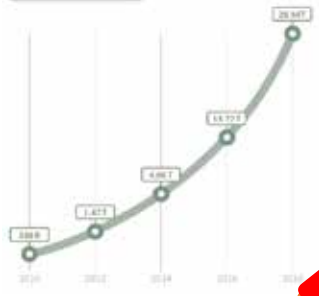

October 2019

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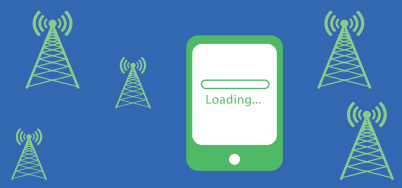

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Refe[illegible]ce [illegible]) Factsheet No 193. Reviewed October 2014

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FDA FCC

Regulated Levels Are Safe to Humans

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• A fast wireless network is a critical resources for our citizens, and failing to provide them is no different than failing to provide clean drinking water, natural gas, sewage service, or electricity.
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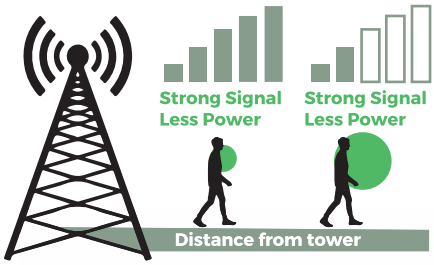
Reference 2. Wireless Emergency Alert[illegible]port by the Department of Homeland Security
www.dhs.gov/sites/default/files/publications/[illegible]eless[illegible]Emergency%20Alerts%20Mobile%20Penetration%20Strategy.p[illegible]

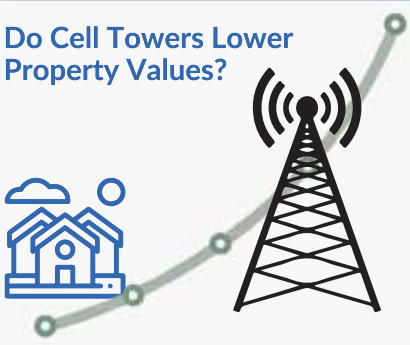
THIS IS NOT A 5G TOWER



• A 5G tower is different than a 4G tower both phy[illegible]ally and functionally: more 5G towers are needed to cover the same amount of space, they're much smaller, and they transmit data on an entirely different part of the radio spectrum.

Reference 4. 5G Cell Towers: Why You See Them and How They Work
https://www.lifewire.com/5g-cell-towers-4584192

Do Cell Towers Lower Property Values?



• The distance from a wireless facility has no apparent impact on the value or sale price of a home. The relationship between the list and sale price remained the same no matter how close the property was to the wireless facility.

Reference 5. Joint Ventures Wireless Communications Initiative Study Wireless Facilities Impact on Property Values November 2012
https://jointventure.org/images/stories/pdf/WirelessFacilitiesImpactOnPropertyValues.pdf

Are Cellphone Towers Dangerous?

Research by organizations such as the National Institute for Occupational Safety and Health, The Environmental Protection Agency (EPA), FCC and others have found **RF energy within the regulated levels are not harmful to humans.**

Radiofrequency (RF) waves, a form of energy, is released when a mobile device (phone, tablet or laptop) connects with a cell tower.

Different devices create different frequencies on the Electro Magnetic Spectrum. Some frequencies are harmful to humans while others are not.

For instance, the frequencies that create x-rays and gamma rays are on the radioactive range of the electromagnetic spectrum, and can cause harmful damage to the chemical bonds in our DNA.

RF energy from cell towers and mobile devices is "non-ionizing," similar to radio and television waves.

Tall cell towers keep RF energy high above the ground. **At ground level, RF energy from towers is thousands of times less than the FCC safe exposure limits.** Other antennas, such as those used for radio and television broadcast transmissions, use power levels that are gener-ally much higher than those used for cellular antennas.˝

What the Experts Say...

A systematic review of existing academic studies on the potential health risks of RF emissions found that the majority of research on the subject currently indicates no ill-health related to RF energy exposure.

The World Health Organization (WHO) has classified RF energy as "possibly carcinogenic to humans." WHO also states that in the last twenty years "no adverse health effects have been established as being caused by mobile phone use."

The American Cancer Society, the International Agency for Research on Cancer and the National Toxicology Program claim that cell towers are unlikely to cause cancer.

Research is ongoing. There is consensus that additional research is warranted to address gaps in knowledge, such as the effects of cell phone use over the long-term and on pediatric populations.

Disinformation

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World Health Organization, Electromagnetic fields and public health: mobile Phones, WHO Fact Sheet #193, June, 2011

FCC Radio Frequency Safety, http://transition.fcc.gov/oet/rfsafety/rf-faqs.html

The American Cancer Society, http://www.cancer.org/cancer/cancercauses/othercarcinogens/atho me/cellular-phone-towers

Martin Röösli et al., "Systematic Review on the Health Effects of Exposure to Radiofrequency Electromagnetic Fields from Mobile Phone Base Stations," Bulletin of the World Health Organization 88, no. 12 (December 1, 2010): 887–896F.

The Food and Drug Administration, http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/HomeBusinessandEntertainment/CellPhones/ucm116335.htm

CTIA 2019 Annual Survey, https://www.ctia.org/news/2019-annual-survey-highlights/

Wireless Emergency Alerts Report by the Department of Homeland Security, www.dhs.gov/sites/default/files/publications/Wireless%20Emergency%20Alerts%20Mobile%20Penetration%20Strategy.pdf

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TAHOE PROSPERITY CENTER

TAHOE PROSPERITY CENTER
tahoeprosperity.org

October 14, 2019

Dear Mayor and City Council Members,

As you know, the Lake Tahoe Basin Prosperity Plan, completed in 2010, created the Tahoe Prosperity Center and was focused on ways to improve the local community and economy. The top two issues in the original Lake Tahoe Basin Prosperity Plan that would improve prosperity in our community were:

1. Certainty in the marketplace and
2. Broadband and cell phone connectivity.

You have an opportunity to do both in the case of the cell tower located at 1360 Ski Run Boulevard and begin that process of improving prosperity. As stated in our previous email of August 5, 2019 the Tahoe Prosperity Center is very concerned about the public safety ramifications (and negative consequences) of reversing the approval of a previously approved cell tower that is desperately needed.

LIE We are also concerned about the misinformation being shared about potential negative impacts from cell towers and about the process they believe you should follow as you make a determination. We address each of those below using the "quoted language" of those who have not been named, but list themselves as "Concerned Citizens of South Lake Tahoe" as they have been emailing me.

1) **"We already get good coverage here."** Public safety is our number one priority. Provider maps have two primary levels of service and while coverage maps do show much of this region as "covered" that is simply one level of service. My house in Meyers is "covered" on both the Verizon and AT&T maps. However, I have to stand in my driveway to get one bar of service, and generally only mid-week on clear, sunny days. I am not able to use my phone inside my house or even outside on my back deck, so I have a land-line. In the Ski Run area, you can stand out on the sidewalk and probably get a bar or two of service, but in-building service is not consistent in much of the area this new cell tower will serve. Having service both inside and outside of buildings is needed for emergencies.

LIE

2) **"You are complicit in 'harming our children'."** As you will recall from the expert scientific testimony on April 2, 2019, there are no negative long-term health impacts related to cell towers and the radio frequencies they utilize. The American Cancer Society, World Health Organization and the Federal Drug Administration concur. Most of us drink coffee every day. Coffee and cell phones/towers are both listed as a "possible" 2b carcinogen according to the International Agency for Research on Cancer (IARC). In addition, baby monitors, WiFi routers and other electronic devices in our homes use the same radiofrequency waves. We are not suggesting banning coffee, baby monitors or Wifi, yet this group asks you to ban cell towers.

LIE F.U.

3) **"Just put them on public lands."** Some have suggested that cell towers can "easily be relocated to public lands" in the Tahoe Basin. That is simply untrue. Our Connected Tahoe project mapped all of the public land in the Tahoe Basin and the towers that are able to be placed on those lands have been evaluated. The few sites identified for public lands are moving forward through the normal permit processes, but one of those has been in process for nine years! Yes – nine years of permitting. Our evaluation found only a handful of sites determined as viable on public lands. We recognized that private property, such as the land at 1360 Ski Run Boulevard is a better solution for improving public safety and cell service and it will be co-located with multiple carriers.

LIE

Heavenly DAS used ski resort special use permit

4) **"This is not proper planning."** It has also been suggested that these sites are being proposed without thoughtful consideration and that providers should give up their "master plans" publicly. Not only does this fly in the face of "business competitive advantage", it is also factually incorrect. Tahoe Prosperity Center did map proposed cell tower sites in the region and this location is a priority site. Additionally, a significant amount of research, engineering, design and thought goes into the siting of a proposed cell tower. Each one of these proposed towers goes through an extensive (some might say exhaustive) permit process with the local jurisdiction and the Tahoe Regional Planning Agency. The Planning Commission did its thorough review and approved this site and we believe you should uphold their decision. The TRPA will also do its thorough review.

LIE: pretextual

5) **"Just create a new ordinance for cell towers."** Regarding certainty in the marketplace, Tahoe is already well-known as a place that is challenging to do business. We struggle with bringing private investment to our region due to the level of uncertainty in the market – whether for a cell tower, a housing development or retail and business opportunities. This exact site was approved six years ago for a mono-pine for AT&T, who chose to re-direct their investment into CAF-II (Connect America Funding) instead. Their approved permit expired as they redirected into CAF-II. It should be noted, there was no opposition by neighbors to the exact same location at that time. Verizon decided to apply for the same site and the City's Planning Commission unanimously approved it. While we agree a clear and concise City telecommunications policy makes sense, changing the rules halfway through a permit does not. We applaud the effort of the City Manager to try and find a suitable alternate location for this tower as a win-win solution, however, that effort is costing Verizon and the City - in terms of staff time, re-design studies and engineering. It should be fully accounted for and factored into any future permitting costs to Verizon.

BINGO

6) **"We don't really need another tower.** Another critical issue is capacity. Without adding some large co-located towers such as this one, along with small cell towers on utility or light poles, we run the risk of not being able to send texts or make calls in an emergency situation. Given our heavy population increases during holiday periods, as well as our winter and summer visitation seasons, we must add cell service capacity in order to serve both our residents who live here full-time, and our visitors when our population swells. We can see up to 250,000 visitors on busy holiday weekends, so both large and small cell towers are needed to cover that many people. You simply cannot protect the community with the existing cell tower infrastructure. Even your Police and Fire departments rely on cell phones to communicate – something that could greatly impact their ability to respond in emergencies without improved coverage.

LIE

BINGO

LIE

I would argue that those who oppose this cell tower would still like to see improved cell service, but just not in "their neighborhood." As stated earlier, these towers can't simply be located on US Forest Service (USFS) public lands. USFS lands have already been evaluated and the minimum number of sites that were determined feasible are moving forward, but those few sites will not be enough to improve coverage for all our residents, businesses and visitors in the community.

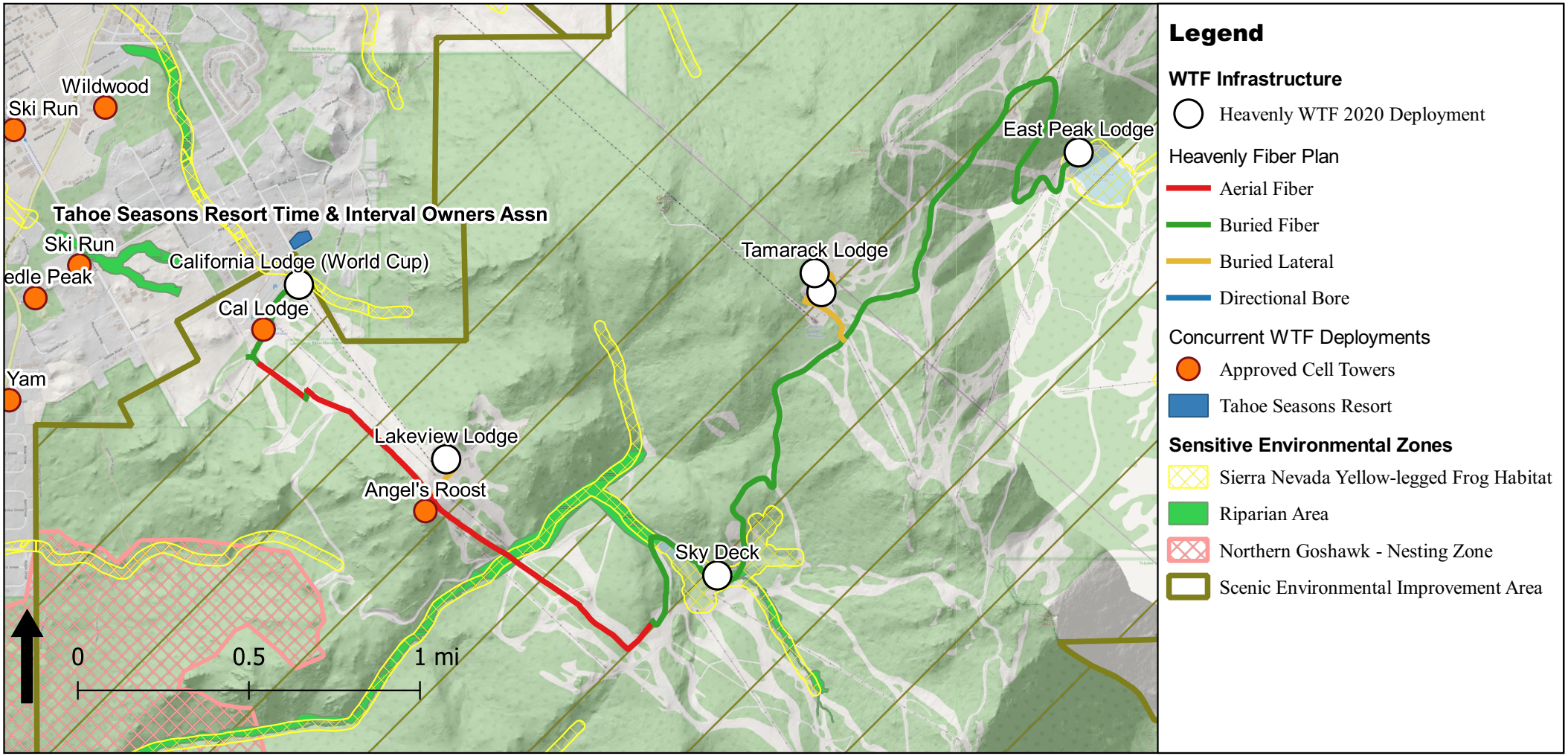
We hope that you support the City Planning Commission and the previous approval of the cell tower at 1360 Ski Run Blvd – for the safety of all the residents of the City of South Lake Tahoe.

Thank you,

Heidi Hill Drum
CEO, Tahoe Prosperity Center

Lie

Verizon's Unfair and Deceptive Business Practice: Concurrent National Forest Deployment



Unfair and Deceptive Business Practices

Verizon and the Tahoe Prosperity Center deceived City of South Lake Tahoe elected leaders, officials, staff, and residents into believing it was too burdensome to deploy towers in the adjacent National Forest lands, while simultaneously using existing special use permits to "fast-track" cell tower deployments and side-step non-discretionalry environmental review of which they had feigned as onerous. This constitutes Unfair and Deceptive Business Practices.

(*See* Business & Professions Code §§ 17200 *et seq.*):

In Real Time

Keeping It Real

by Peggy Bourland

WHO DOES THAT?

Just when you thought we'd heard the last from former city manager Nancy Kerry, she has resurfaced with a $50,000 liability claim against the city for comments posted on Facebook by Councilman Cody Bass that she claims have caused her "emotional distress."

She further proposed a public apology from the city and Councilman Bass in order to clear her sullied name. She set a deadline for the apology or an additional $5,000 would be added to the original claim.

Bass considers his comments regarding her receiving $300,000 after she was terminated, for what could possibly have been criminal behavior, to be valid. Will the Nancy Kerry soap-opera ever end?

NEXT:

We have a planning commissioner (Diana Madson) who has misplaced her ethical guidebook. A series of emails and text messages reveal her efforts to influence the city council concerning the approval of a 12-story cell tower on Ski Run Blvd. She refers to residents who opposed the cell tower as "crazies" and their well-documented health and property-value-loss objections as "junk science."

Heidi Hill Drum from the Prosperity Center and Jenna Palacio were party to this orchestrated campaign. Further, Ms. Madson provided scripted material for Cory Rich and Chris McNamara to read at the hearing.

Ms. Madson's removal from the planning commission should be certain and swift. Meanwhile, Jenna Palacio announced her departure from the planning commission citing work obligations related to the pandemic.

AND:

Mayor Jason Collin has become the subject of a smear campaign organized by a group of self-appointed "business leaders" who believe that his statements to the media about the governor-imposed travel restrictions have destroyed our local economy.

It would be fair to acknowledge that the economic fallout from the pandemic is worldwide and not unique to Tahoe. These "leaders" have created a fake news blog to disparage the mayor along with a GoFundMe account that falsely claims to be raising money to "Help Move Mayor Jason Collin out of Tahoe." Jason told KCRA News that he does not plan to run for reelection.

BETTER GOVERNMENT

At a time when we are witnessing pervasive civil unrest and demonstrations reminiscent of the turbulent 1960s, a level of dissatisfaction with previous and current local government decisions has been revived.

By promoting vacation rental businesses in neighborhoods, parking meters all over town and cell towers in residential areas, city government and city council members create distrust by their constituents. When the people stand up *en masse* to be heard, elected officials need to be paying attention. Another task force or paid consultant just delays the inevitable public outrage.

Proper management and good governance should be looking ahead to avoid these kinds of controversies and the civil discord that often follows when informed/organized citizens rise up and demand better.

FULL COURT PRESS

The citizen's vacation rental initiative (Measure T) passed in November of 2018. Designed to phase out VHRs in residential zones over three years, our "hoods" have already begun to feel more like real neighborhoods and less like motel districts. Michelle Benedict, Kathy Jo Liebhardt and others sought to overturn Measure T by filing a lawsuit against the city to challenge the measure, saying it was, among other things, unconstitutional.

When the lawsuit was first filed, "armchair attorney" Steve Teshara stated, "*Tahoe Chamber leaders have reviewed the initial legal complaint filed by the South Lake Tahoe Property Owners Group and we agree that Measure T is unconstitutional and unenforceable.*"

On June 1, 2020 the EDC Superior Court Judge Dylan Sullivan made a detailed and unambiguous tentative ruling that denied the plaintiff's claim that Measure T is unconstitutional.

The judge denied and eliminated the following claims from the case: whether Measure T interferes with vested rights; whether it exceeds the initiative power; whether the occupancy limits are unconstitutional; whether the permanent resident exception is unconstitutional; and whether Measure T is vague and ambiguous.

City Attorneys Heather Stroud and Beverly Roxas competently defended the voter initiative and prevailed with one claim still to be decided.

The ruling by the court confirms that VHR owners do not have a vested right to convert residential housing to commercial uses. It is a zoning issue that has been upheld in courts throughout California. People deserve to live without the disruption of tourism invading residential neighborhoods.

Even the TRPA in their recent housing report now identifies Measure T as part of the solution to Tahoe's housing crisis.

REPEAT:

Wash your hands, wear a mask in public and support local businesses.

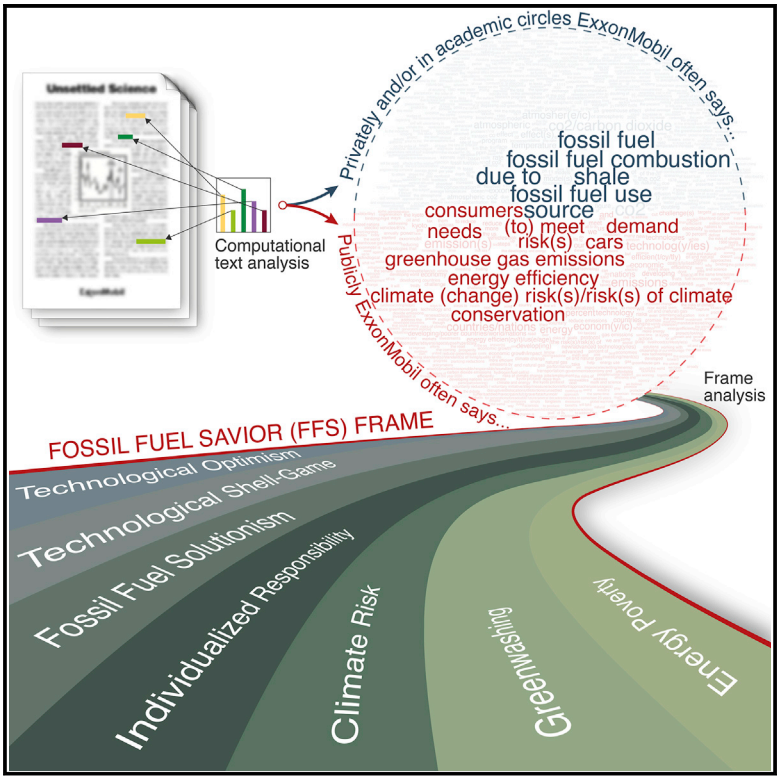
To be continued...

Article

One Earth

Rhetoric and frame analysis of ExxonMobil's climate change communications

Graphical abstract



Highlights

- ExxonMobil's public climate change messaging mimics tobacco industry propaganda
- Rhetoric of climate "risk" downplays the reality and seriousness of climate change
- Rhetoric of consumer "demand" (versus fossil fuel supply) individualizes responsibility
- Fossil Fuel Savior frame uses "risk" and "demand" to justify fossil fuels, blame customers

Authors

Geoffrey Supran, Naomi Oreskes

Correspondence

gjsupran@fas.harvard.edu

In brief

This is the first computational assessment of how ExxonMobil has used language to subtly yet systematically frame public discourse about climate change. We show that ExxonMobil uses rhetoric mimicking the tobacco industry to downplay the reality and seriousness of climate change, to present fossil fuel dominance as reasonable and inevitable, and to shift responsibility for climate change away from itself and onto consumers. Our work is relevant to lawsuits, policy proposals, and grassroots activism seeking to hold fossil fuel companies accountable for deceptive marketing.

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CellPress

CellPress
OPEN ACCESS

Gold Standard for the Global Goals
3 tons of CO_2 offset

One Earth

Article

Rhetoric and frame analysis of ExxonMobil's climate change communications

Geoffrey Supran[1,2,*] and Naomi Oreskes[1]
[1]Department of the History of Science, Harvard University, Cambridge, MA 02138, USA
[2]Lead contact
*Correspondence: gjsupran@fas.harvard.edu
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SCIENCE FOR SOCIETY A dominant public narrative about climate change is that "we are all to blame." Another is that society must inevitably rely on fossil fuels for the foreseeable future. How did these become conventional wisdom? We show that one source of these arguments is fossil fuel industry propaganda. ExxonMobil advertisements worked to shift responsibility for global warming away from the fossil fuel industry and onto consumers. They also said that climate change was a "risk," rather than a reality, that renewable energy is unreliable, and that the fossil fuel industry offered meaningful leadership on climate change. We show that much of this rhetoric is similar to that used by the tobacco industry. Our research suggests warning signs that the fossil fuel industry is using the subtle micro-politics of language to downplay its role in the climate crisis and to continue to undermine climate litigation, regulation, and activism.

SUMMARY

This paper investigates how ExxonMobil uses rhetoric and framing to shape public discourse on climate change. We present an algorithmic corpus comparison and machine-learning topic model of 180 ExxonMobil climate change communications, including peer-reviewed publications, internal company documents, and advertorials in *The New York Times*. We also investigate advertorials using inductive frame analysis. We find that the company has publicly overemphasized some terms and topics while avoiding others. Most notably, they have used rhetoric of climate "risk" and consumer energy "demand" to construct a "Fossil Fuel Savior" (FFS) frame that downplays the reality and seriousness of climate change, normalizes fossil fuel lock-in, and individualizes responsibility. These patterns mimic the tobacco industry's documented strategy of shifting responsibility away from corporations—which knowingly sold a deadly product while denying its harms—and onto consumers. This historical parallel foreshadows the fossil fuel industry's use of demand-as-blame arguments to oppose litigation, regulation, and activism.

INTRODUCTION

In previous work, we have shown that Exxon, Mobil, and ExxonMobil Corp misled the public about anthropogenic global warming (AGW) by contributing to climate science through academic and internal research, while promoting doubt about it in advertorials and other propaganda.[1–3] (We refer to Exxon Corporation as Exxon, Mobil Oil Corporation as Mobil, ExxonMobil Corporation as ExxonMobil Corp, and generically refer to all three as ExxonMobil.) We have also observed that, starting in the mid-2000s, ExxonMobil's statements of explicit doubt about climate science and its implications (for example, that "there does not appear to be a consensus among scientists about the effect of fossil fuel use on climate"[4]) gave way to implicit acknowledgments couched in ambiguous statements about climate "risk" (such as discussion of lower-carbon fuels for "addressing the risks posed by rising greenhouse gas emissions,"[5] without mention of AGW). This invites research as to how, beyond outright disinformation, ExxonMobil may have employed rhetoric and framing to construct misleading public narratives about AGW. Here, we take up this question.

"Framing" is a term of art in communications science that refers to how an issue is portrayed and understood.[6–9] Frames construct meaning by selecting "some aspects of a perceived reality" and making them "more salient in a communicating text, in such a way as to promote a particular problem definition, causal interpretation, moral evaluation, and/or treatment recommendation."[10] (Here and throughout, we strictly refer to "emphasis frames" rather than "equivalency frames.")[11] Analyzing which frames are present and absent in public discourse helps to reveal how actors have tried to shape policy debates by setting agendas and legitimating certain participants

and responses, while discouraging or precluding others.[12–15] Framing of responsibility, for example, can determine whether society calls upon individuals, industry, or government to take action.[16]

One of the fossil fuel industry's primary AGW frames has been scientific uncertainty.[17] Researchers have documented in detail industry's over-emphasis of uncertainty to deny climate science and delay action.[1,2,17–25] Subtler forms of rhetoric and framing, which dominate today's AGW discourse, are only just beginning to receive similar attention.[7,26–29] Fossil fuel interests have spent billions of dollars on AGW public affairs, yet their role in perpetuating these narratives is underexplored.[30,31]

In this paper, we analyze how ExxonMobil has publicly constructed AGW frames by selectively emphasizing some terms and topics while avoiding others. Our analysis compares the terms and topics between ExxonMobil's different AGW communications, including peer-reviewed publications, internal documents, and paid, editorial-style advertisements—known as advertorials—published on the Op-Ed page of *The New York Times* (NYT). We also identify frames in the latter. These well-defined, longitudinal corpora are conducive to a rigorous case study of fossil fuel industry messaging on AGW.

Our study offers the first computational assessment of how ExxonMobil has used language to frame public discourse about AGW. By bringing to bear the mixed-methods of computational linguistics and inductive frame analysis, our results add to (1) analyses of ExxonMobil's public affairs practices,[32–44] (2) qualitative accounts of the company's AGW communications,[23,45–49] and (3) the application of discourse and (algorithmic) content analysis to AGW communications by ExxonMobil and the wider climate countermovement.[1,2,17–19,26,27,29,50–57] A "distant"—that is, quantitative, statistical, and macroscopic—reading of ExxonMobil's AGW communications offers three practical advantages.[58] First, it complements the qualitative and/or manual methodologies previously applied to the AGW communications of ExxonMobil and other fossil fuel interests, and corroborates our prior work, which used manual coding to demonstrate systematic discrepancies between ExxonMobil's private and public AGW communications.[1,2] Second, automated methods of textual analysis allow detection of broad, sometimes subtle, patterns of language that would otherwise be unattainable. Third, by using existing corpora to establish the application of computational techniques to the analysis of AGW discourse, we help demonstrate the efficacy of these approaches, which researchers will be able to use to analyze the large numbers of documents that lawsuits against fossil fuel companies are anticipated to generate.

Our analysis is the first computational study illustrating how the fossil fuel industry has encouraged and embodied AGW narratives fixated on individual responsibility. Our findings corroborate the insights of qualitative discourse analyses about the role of fossil fuel interests, and add to what Kent[59] has called an "under-theorised" understanding "of why contemporary interest focuses on individual responsibility for climate change."[26,51] In so doing, this work helps to decrypt the fossil fuel industry's playbook of climate delay framings, illuminating how sense-making schema conveyed by subtle yet systematic deployments of language may have "penetrated public discourse to become naturalized as common sense or unfortunate realities."[13,26] Although misleading frames that deceive the public may be defended on First Amendment grounds, the history of tobacco litigation shows that a misleading framework may also be held in some circumstances to be part of a pattern of fraudulent activities. Our work may, therefore, be relevant to ongoing lawsuits against ExxonMobil alleging "deceptive marketing" and "greenwashing," as well as to calls for policymakers to ban fossil fuel industry advertisements or require that they come with tobacco-style warning labels.[60–65] Our research also adds to an expanding scholarly and journalistic AGW literature—spanning emissions accounting and extreme weather attribution;[66,67] supply-side policy analysis;[68–70] decarbonization theory;[71,72] the history of climate denial, lobbying, and propaganda by fossil fuel interests;[73–83] ethical philosophy;[84,85] and climate litigation[86,87]—challenging the zeitgeist of individualized responsibility. Finally, this study contributes to broader literatures on discourse and content analysis;[88–91] corporate issue management and advocacy marketing;[56,92–96] and the cross-pollination of corporate strategies of public affairs, litigation, and deceit.[13,86,97–100]

We adopt a mixed-method, computational approach to rhetorical frame analysis of 180 ExxonMobil documents previously compiled for manual content analysis[1,2]: 32 internal company documents (1977–2002; from ExxonMobil Corp,[101] *InsideClimate News*,[102] and Climate Investigations Center),[103] 72 peer-reviewed publications (1982–2014; from ExxonMobil Corp),[104] and 76 advertorials in the NYT expressing any positions on AGW (real and human caused, serious, or solvable) (1972–2009; from PolluterWatch and ProQuest).[105,106] To our knowledge, these constitute all publicly available internal and peer-reviewed ExxonMobil documents concerning AGW, including those made available by the company. They also include all discovered ExxonMobil advertorials in the NYT taking any positions on AGW. These corpora thus offer bound sets reflecting ExxonMobil's internal, academic, and public AGW communications, respectively.

Following text pre-processing and vectorization into document-term matrices, we first use frequency score (FS) and Dunning log-likelihood (LL) ratio corpus comparison algorithms to identify statistically distinctive keywords ("divergent terms") that help locate rhetorical frames.[107–110] The FS indicates how often a given term appears in corpus A versus corpus B (accounting for corpus sizes), and ranges from 0 (only in corpus A) to 1 (only in corpus B). The LL ratio (G^2) indicates the statistical significance of the relative frequencies of a given term between corpora A and B, and ranges from large and negative (term is disproportionately common in corpus A) to large and positive (disproportionately common in corpus B). Second, we complement this approach with latent Dirichlet allocation (LDA) topic modeling to identify statistically distinctive, thematically connected texts and vocabularies ("divergent topics"), which are commonly equated to either frames or frame elements.[111–115] Third, we integrate these quantitative tools into an inductive, qualitative approach to constructing frames as "frame packages" in advertorials.[17,116–118] In the discussion, we examine the congruence of our findings with the tobacco industry's rhetorical strategies in public relations and litigation.[13,109,119,120]

Table 1. Rhetorical tropes and taboos: Highly divergent terms in (left) ExxonMobil Corp advertorials versus (right) Mobil advertorials, by LL ratio (G^2) and FS

ExxonMobil Corp advertorials often say:					Mobil advertorials often say:				
	ExxonMobil Corp	Mobil	G^2	FS		ExxonMobil Corp	Mobil	G^2	FS
energy	279	99	110.51	0.76	*nations*	4	79	−74.90	0.05
challenge(s)	52	4	54.33	0.94	plan	0	21	−26.84	0.00
(to) meet	51	14	26.70	0.80	senate	0	16	−20.45	0.00
demand	32	8	18.22	0.82	treaty	0	14	−17.89	0.00
use	60	27	16.78	0.71	in kyoto	0	13	−16.61	0.00
needs	27	9	11.53	0.77	the us [United States]	18	51	−12.99	0.28
risk(s)	46	3	50.30	0.94	*co2/carbon dioxide*	33	105	−31.90	0.26
climate (change) risk(s)/risk(s) of climate	26	0	39.02	1.00	emission(s)	97	197	−24.48	0.35
longterm	37	3	38.05	0.93	greenhouse gases	8	39	−18.96	0.19
research	75	21	38.53	0.80	effect	1	18	−16.67	0.06
gcep [Global Climate and Energy Project]	17	0	25.51	1.00	global warming	2	21	−16.25	0.10
technologies	55	18	24.00	0.77	evs [electric vehicles]	0	12	−15.34	0.00
solar	24	3	21.02	0.90					
stanford	14	0	21.01	1.00					
policies	27	5	19.17	0.86					
wind	18	3	13.62	0.87					

Terms that appear to be thematically related have been grouped (asterisked, high-scoring terms identify each group). ExxonMobil Corp advertorials often say terms ("tropes") with large positive G^2 scores and rarely say terms ("taboos") with FS scores near 0. Mobil advertorials often say terms with large negative G^2 scores and rarely say terms with FS scores near 1. p values < 0.001 for all G^2 and FS scores.

RESULTS

In the section entitled "divergent terms and topics," we compare divergent terms and topics between pairs of document categories. In "rhetorical frames," we summarize the findings of frame package analysis of advertorials: three dominant frames communicated by 11 constituent discourses. Other sections then focus on two of these complementary discourses, "discourse of climate risk" and "discourse of individualized responsibility," and analyze how they work alongside other discourses to construct one specific frame, Fossil Fuel Savior (FFS) ("FFS frame").

Divergent terms and topics

Table 1 presents a selection of highly divergent terms in ExxonMobil Corp advertorials versus Mobil advertorials, as identified by LL and FS. Likewise, Tables 2 and 3 compare highly divergent terms between all advertorials (Mobil plus ExxonMobil Corp) and, respectively, Exxon internal documents (Table 2) and Exxon/ExxonMobil Corp peer-reviewed publications (Table 3). In all three tables, the highest $|G^2|$-scoring terms, marked with asterisks, are suggestive of distinctive themes around which we group other relevant terms. These themes closely resemble the divergent topics shown in Table 4, which emerge from LL analysis of our LDA topic model solutions in all advertorials (top half of Table 4) and in combined internal and peer-reviewed documents (bottom half). The top 20 words associated with each topic are listed, together with assigned topic labels.

Mobil versus ExxonMobil Corp advertorials

We have previously shown that both Mobil and ExxonMobil Corp advertorials often promoted doubt about climate science.[1,2] Terms conveying explicit doubt are therefore common to both corpora, and so do not appear in Table 1 (for examples, see S2.1, supplemental information). This undercuts ExxonMobil Corp's suggestion that only Mobil, not ExxonMobil Corp, promoted doubt.[2,3] Both did. Moreover, when Exxon and Mobil merged in 1999, ExxonMobil Corp inherited legal and moral responsibility for both parent companies.

Comparison of advertorials over time can nevertheless be insightful in revealing other rhetorical trends. In this regard, Mobil and ExxonMobil Corp advertorial corpora serve as well-defined longitudinal proxies.

Table 1 shows, for example, that earlier, Mobil advertorials disproportionately contested climate science head-on, discussing emission(s) of CO_2/carbon dioxide and the global warming effect (terms exhibiting statistically significant divergence are underlined throughout). Mobil advertorials also notably engaged in climate policy debates concerning the role of the US (and Senate) compared with other nations as part of the Kyoto treaty plan. By contrast, ExxonMobil Corp advertorials no longer referred to "global warming": the term became taboo (FS = 0.10). Relative usage of "climate change" versus "global warming" went from 3-to-1 pre-merger to 34-to-1 post merger. Indeed, ExxonMobil Corp mostly sidestepped detailed discussions about climate science, acknowledging only the long-term risks of climate change before reframing it as a challenge to meet the public's energy demand and needs. ExxonMobil

Table 2. Rhetorical tropes and taboos: Highly divergent terms in (left) advertorials versus (right) internal documents, by LL ratio (G^2) and FS

Advertorials often say:					Internal documents often say:				
	Advertorials	Internal	G^2	FS		Advertorials	Internal	G^2	FS
emission(s)	294	97	293.80	0.86	*co2/carbon dioxide*	138	1,053	−291.63	0.21
risk(s)	49	7	72.48	0.93	atmosher(e/ic)	36	458	−187.01	0.14
greenhouse gas emissions	42	7	58.90	0.92	fossil fuel	9	144	−66.26	0.11
climate (change) risk(s)/risk(s) of climate	26	0	57.89	1.00	ppm [parts per million]	0	78	−62.12	0.00
climate change	124	103	45.39	0.71	co2 concentration	1	61	−40.57	0.03
dont [don't]	24	2	40.93	0.96	fossil fuel combustion	1	48	−30.69	0.04
know	32	8	37.59	0.89	co2 increase	0	28	−22.30	0.00
longterm	40	17	33.14	0.83	source	6	39	−9.08	0.24
doom(sday/sdayers)/ apocalypse/hype/scare	11	0	24.49	1.00	*effect(s)*	27	359	−150.31	0.13
debate	26	12	20.05	0.82	temperature	15	270	−130.89	0.10
(un)know(/n/ing/ledge)	57	66	9.63	0.64	doubling	2	83	−51.60	0.05
energy	378	222	227.73	0.78	greenhouse effect	10	119	−46.69	0.15
(to) meet	65	2	128.34	0.99	ocean	15	135	−43.38	0.19
challenge(s)	56	5	94.08	0.96	due to	5	89	−42.94	0.10
energy efficiency	30	1	58.76	0.98	ph [pH]	0	44	−35.04	0.00
electricity	29	1	56.60	0.98	radiation	1	44	−27.68	0.04
consumers	21	0	46.76	1.00	co2 greenhouse	0	33	−26.28	0.00
oil and natural gas	18	0	40.08	1.00	sea	6	65	−23.99	0.16
energy use	23	4	31.75	0.92	global temperature	0	30	−23.89	0.00
demand	40	21	27.24	0.80	2050	0	30	−23.89	0.00
needs	36	22	20.69	0.77	temperature increase	3	50	−23.44	0.11
for generations/foreseeable future/several decades/ decades to come/next 25 years	12	3	14.10	0.89	polar	1	28	−15.83	0.07
countries/nations	157	17	251.77	0.95	*program*	12	195	−90.37	0.11
developing/poorer countries/ world/nations	53	3	97.01	0.97	natuna [Natuna Island, Indonesia]	0	67	−53.36	0.00
kyoto	59	7	92.31	0.95	doe [Department of Energy]	0	38	−30.26	0.00
targets	26	4	37.52	0.93	tanker	1	35	−20.96	0.06
econom(y/ic)	148	22	216.08	0.93	*model(s)*	30	309	−110.12	0.17
economic growth/impact	29	2	51.34	0.97	figure	0	112	−89.19	0.00
prosperity	15	0	33.40	1.00	rate	2	122	−81.13	0.03
jobs	13	0	28.95	1.00	data	10	98	−33.68	0.17
prices	12	0	26.72	1.00	vugraph	0	41	−32.65	0.00
cost	33	17	22.92	0.80	scenario	1	42	−26.17	0.05
tax	15	2	22.68	0.94					
living standard(s)/standard(s) of living/quality of life	10	0	22.27	1.00					
steps	36	1	71.76	0.99					
reduce emissions	23	0	51.21	1.00					
voluntary	18	0	40.08	1.00					
wise(r)/prudent/reasonable/ responsible/sound(er)	39	21	25.87	0.79					
technolog(y/ies)	198	40	257.20	0.91					
vehicles	33	0	73.48	1.00					

(*Continued on next page*)

Table 2. *Continued*

Advertorials often say:					Internal documents often say:				
	Advertorials	Internal	G^2	FS		Advertorials	Internal	G^2	FS
natural gas	48	18	43.87	0.85					
trees	24	2	40.93	0.96					
invest(ing/ment(s))	27	4	39.46	0.93					
gcep [Global Climate and Energy Project]	17	0	37.85	1.00					
evs [electric vehicles]	16	0	35.63	1.00					
gasoline	20	2	32.72	0.95					
innovat(e/ion(s))	17	1	30.93	0.97					
solutions	26	7	29.36	0.88					
renewables	13	0	28.95	1.00					
wind	21	5	25.29	0.90					

Terms that appear to be thematically related have been grouped (asterisked, high-scoring terms identify each group). Advertorials often say terms ("tropes") with large positive G^2 scores and rarely say terms ("taboos") with FS scores near 0. Internal documents often say terms with large negative G^2 scores and rarely say terms with FS scores near 1. p values < 0.001 for all G^2 and FS scores.

Corp advertorials emphasized the need for more climate and energy technologies research, such as the company's sponsorship of the GCEP (Global Climate and Energy Project) at Stanford University. Current solar and wind technologies were presented as inadequate.

Advertorials versus internal documents

Comparing divergent terms in all advertorials against those in internal documents, a combination of the above advertorial themes emerges (Tables 2 and 4). Numerous Mobil and ExxonMobil Corp advertorials promoted explicit doubt about whether AGW is real and human caused. They emphasized debate and focused on what scientists "do and don't know" [*Climate science uncertainty*] (topic labels from Table 4 are indicated in bracketed italics throughout). This eventually gave way to rhetoric about potential long-term risks of AGW (after several years of overlap in ~2000–2005 and 2007), juxtaposed against the challenge to meet demand [*Energy/emissions challenge*]. The energy use and needs of consumers, such as electricity and oil and natural gas, are presented as necessitating greater energy efficiency and new technologies [*Energy/emissions challenge*; *Vehicles*]. The public is told about how ExxonMobil Corp is partnering with GCEP at Stanford to develop solutions such as more efficient gasoline vehicles and "clean…natural gas" [*Vehicles*; *Energy technologies*]. ExxonMobil Corp touts its efforts to plant trees, but renewables such as wind and electric vehicles/EVs are given short shrift [*Conservation*; *Energy technologies*]. Algorithmic analysis also documents Mobil's public rhetoric on the Kyoto Protocol: targets that exempt developing countries threaten American jobs, prosperity, and economic growth; instead, governments and industry should pursue market-based, voluntary steps to reduce emissions [*Climate policy*].

Compared with Mobil advertorials, which promoted debate about climate science, and ExxonMobil Corp advertorials, which did the same or ignored it, Exxon's internal conversations focused on it. Internal documents are notable for their detailed articulation of the causes and consequences of AGW. The source of the observed CO_2 increase in the atmosphere was fossil fuel combustion [*AGW science/projections*]. Effects of the resulting greenhouse effect would include a global temperature increase. Internal discussions adopted a rigor absent from the company's public communications, including reference to climate models, scenarios, and rates of change [*Climate modeling*]. One scenario they examined—the doubling of atmospheric CO_2 concentration by 2050—threatened melting of the polar icecaps, a decrease in ocean pH, and rising sea levels [*AGW science/projections*]. ExxonMobil advertorials disputed or remained silent about not just this early knowledge of climate science and its implications but also Exxon's "CO_2 program" that helped acquire and apply that knowledge [*AGW science/projections*]. Internal memos report that this program included measuring CO_2 with a tanker, monitoring DOE (US Department of Energy) climate science, and evaluating the CO_2 emissions from their natural gas project in Natuna, Indonesia [*Climate research programs*].

Advertorials versus peer-reviewed publications

Table 3 compares divergent terms in all advertorials against those in peer-reviewed publications. Advertorials are distinguished by the same rhetorical themes as in "advertorials versus internal documents"; indeed, the contrast against academic articles is more pronounced. Independently and collectively, Mobil and ExxonMobil Corp advertorials offset the risks of manmade climate change by also promoting debate about complex science [*Climate science uncertainty*]. Advertorials are again seen to frame AGW as a challenge to meet the needs of consumers for more energy from fossil fuels, while seeking to allay concerns by publicizing the promise of advanced technology innovation (including cogeneration) [*Energy/emissions challenge*; *Energy technologies*]. In comparison with peer-reviewed papers, advertorials stand out for their emphasis of corporate environmental programs to reduce emissions through energy efficiency and conservation [*Conservation*].

While advertorials talk about the scientific process—research, science, and the extent of scientists' knowledge are disproportionately discussed—peer-reviewed publications

Table 3. Rhetorical tropes and taboos: Highly divergent terms in (left) advertorials versus (right) peer-reviewed documents, by LL ratio (G^2) and FS

Advertorials often say:					Peer-reviewed documents often say:				
	Advertorials	Peer reviewed	G^2	FS		Advertorials	Peer reviewed	G^2	FS
energy	378	1,777	500.41	0.82	et al	0	4,001	−372.50	0.00
(to) meet	65	98	191.64	0.93	model	5	3,000	−236.23	0.03
challenge(s)	56	100	151.75	0.92	figure	0	1,475	−137.32	0.00
needs	36	71	92.45	0.91	table	1	909	−75.18	0.02
more energy	21	12	87.65	0.97	rate	2	823	−60.90	0.05
consumers	21	33	60.70	0.93	estimates	5	978	−59.17	0.10
energy use	23	83	39.00	0.85	observed	1	715	−57.60	0.03
energy efficiency	30	152	36.65	0.81	scenario	1	562	−43.84	0.04
for generations/foreseeable future/several decades/ decades to come/next 25 years	12	28	27.91	0.90	noise	0	311	−28.95	0.00
fossil fuels	24	149	22.89	0.77	projections	0	273	−25.42	0.00
gasoline	20	117	20.61	0.78	ipcc [Intergovernmental Panel on Climate Change]	4	505	−25.00	0.14
demand	40	422	14.35	0.67	error	1	317	−22.17	0.06
research	96	209	232.87	0.91	*co2*	69	5,161	−172.61	0.22
science	61	74	198.02	0.95	ocean	15	2,412	−134.77	0.12
scientists	39	25	157.74	0.97	transport	0	825	−76.81	0.00
dont [don't]	24	0	148.34	1.00	carbon cycle	0	462	−43.01	0.00
greenhouse gas emissions	42	60	126.97	0.94	ghg [greenhouse gas]	0	446	−41.52	0.00
carbon dioxide	69	227	126.15	0.86	ppm [parts per million]	0	397	−36.96	0.00
know	32	25	121.96	0.96	atmospheric co2	1	480	−36.52	0.04
climate (change) risk(s)/risk(s) of climate	26	10	119.09	0.98	ch4	0	272	−25.32	0.00
debate	26	30	86.15	0.95	gt [gigaton]	0	243	−22.62	0.00
manmade	15	2	80.58	0.99	*temperature*	15	1,836	−89.31	0.15
climate change	124	1,122	63.41	0.70	anthropogenic	0	609	−56.70	0.00
(un)know(/n/ing/ledge)	57	330	59.52	0.78	effect(s)	27	1,727	−48.70	0.25
risk(s)	49	261	56.56	0.80	due to	5	731	−39.08	0.13
longterm	40	282	31.82	0.75	radiative forcing	0	338	−31.47	0.00
gap(s)	11	39	18.93	0.86	climate sensitivity	0	219	−20.39	0.00
better science/understanding	6	10	16.85	0.93	temperature change	0	198	−18.43	0.00
complex	14	120	7.97	0.71	*mitigation*	4	880	−55.49	0.09
technolog(y/ies)	198	1,016	238.49	0.80	injection	0	443	−41.24	0.00
gcep [Global Climate and Energy Project]	17	1	97.44	1.00	ccs [carbon capture and storage]	0	374	−34.82	0.00
promise	20	12	82.39	0.97	dissolution	0	270	−25.14	0.00
evs [electric vehicles]	16	11	63.42	0.97	alkalinity	0	260	−24.21	0.00
trees	24	48	61.15	0.91	caco3	0	251	−23.37	0.00
cars	24	59	54.00	0.90	budget	0	180	−16.76	0.00
solutions	26	78	51.00	0.87	cement	1	237	−15.31	0.08
nuclear	26	82	49.12	0.87					
renewables	13	18	39.86	0.94					
wind	21	82	33.25	0.84					
cogeneration	12	26	29.19	0.91					
innovat(e/ion(s))	17	93	19.02	0.79					
invest(ing/ment(s))	27	243	13.96	0.70					

(*Continued on next page*)

Table 3. *Continued*

Advertorials often say:					Peer-reviewed documents often say:				
	Advertorials	Peer reviewed	G^2	FS		Advertorials	Peer reviewed	G^2	FS
steps	36	36	126.05	0.95					
programs	28	14	120.90	0.98					
reduce emissions	23	25	78.03	0.95					
wise(r)/prudent/reasonable/ responsible/sound(er)	39	119	75.54	0.87					
environmental	56	384	46.45	0.75					
conservation	15	66	21.23	0.83					
nations	83	110	259.48	0.94					
kyoto	59	182	113.35	0.87					
governments	36	62	99.41	0.92					
senate	16	0	98.89	1.00					
developing/poorer countries/ world/nations	53	196	88.01	0.85					
econom(y/ic)	148	714	190.67	0.81					
prosperity	15	1	85.32	1.00					
economic growth/impact	29	74	63.68	0.89					
living standard(s)/standard(s) of living/quality of life	10	0	61.81	1.00					
voluntary	18	32	48.89	0.92					
jobs	13	11	48.27	0.96					

Terms that appear to be thematically related have been grouped (asterisked, high-scoring terms identify each group). Advertorials often say terms ("tropes") with large positive G^2 scores and rarely say terms ("taboos") with FS scores near 0. Peer-reviewed documents often say terms with large negative G^2 scores and rarely say terms with FS scores near 1. p values < 0.001 for all G^2 and FS scores.

actually engage in it. As expected, academic articles—even more so than internal documents—are distinguished by their articulation of AGW science. Observed atmospheric CO_2 concentrations are reported in ppm (parts per million), anthropogenic temperature change due to radiative forcing by GHG (greenhouse gases) such as CO_2 and CH_4 is acknowledged, and AGW model projections are run for different scenarios based on climate sensitivity [*AGW science/projections*]. The academic language of estimates and noise and references to the IPCC (Intergovernmental Panel on Climate Change) are commonplace [*Climate modeling*]. While advertorials offer unfocused representations of technologies such as renewables, nuclear, and EVs as variously promising, hypothetical, or insufficient, Exxon/ExxonMobil Corp supported peer-reviewed studies that squarely centered AGW mitigation around approaches consistent with continued reliance on fossil fuels: CCS (carbon capture and storage); and the injection of CO_2 into oceans through dissolution of minerals such as $CaCO_3$ to increase alkalinity [*CO_2 disposal/storage*; *Carbon cycles*]. As a recent literature review observed, the "use of enhanced ocean alkalinity for C storage was first proposed by [chief Exxon climate scientist Haroon] Kheshgi."[122]

Like internal documents, peer-reviewed publications attribute GHG emissions and/or AGW to fossil fuels significantly more often than advertorials ($p < 0.01$–0.03). Common terms include fossil fuel emissions, fossil fuel CO_2, and fossil fuel combustion [*AGW science/projections*] (see Table 5).

Rhetorical frames

Frame package analysis leads us to identify three dominant frames in ExxonMobil's advertorials, which we name (1) Scientific Uncertainty, (2) Socioeconomic Threat, and (3) Fossil Fuel Savior (FFS) (for details, see S4, supplemental information). The Scientific Uncertainty frame presents AGW as unproven and advocates additional climate science research. The Socioeconomic Threat frame argues that binding climate policies (such as the Kyoto Protocol) are alarmist and threaten prosperity, urging voluntary measures instead. The FFS frame describes AGW as the inevitable (and implicitly acceptable) risk of meeting consumer energy demand with fossil fuels for the foreseeable future, and presents technological innovation as the long-term solution.

These frames are constructed of reasoning and framing devices variously communicated by the 11 discourses listed in Figure 1. Figure 1 is a Venn diagram representing the chain of logic (i.e., reasoning devices) of each frame as defined by Entman:[10] problem, cause, moral evaluation, and solution (as indicated, these reasoning devices are the logical bases challenged by denials that AGW is real, human caused, serious, and solvable, respectively).[10] Discourses are manifest in one or more framing devices (e.g., lexical choices, catchphrases, depictions), and their positions in Figure 1 depict their contributions to the reasoning devices of each frame (definitions and examples of each frame's reasoning and framing devices are provided in S4 and S5, supplemental information). For example, discourses of Technological

Table 4. Topical tropes: Highly divergent topics in (top) advertorials versus (bottom) internal and peer-reviewed documents, by LL ratio (G^2) of topics identified by LDA topic modeling

Category	Topic labels	G^2	Top terms
Advertorials	energy/ emissions challenge	10,271.93	*energy, *technolog(y/ies), *emission(s), *efficien(t/tly/cy), *world, *global, fuel(s), *improv(e/es/ed/ing/ements), *develop(ing), *environment(/al/ally), *econom(y/ic), *need(s), *challenge(s), *percent, *demand, *risk(s), *gas, *reduce, *invest(/ing/ment/ments), future, [*meet, *longterm]
	climate policy	6,045.82	*countries/nations, *kyoto, *emission(s), *econom(y/ic), *protocol, *targets, *gases, *agree(ment)/consensus, *industrialized, *administration, *reduction*, *participat(e/tion/ing), *senate, *plan, *measures*, *governments, *developed, *develop(ing), *public, *treaty [*jobs/*employment, *cost(/s/ly/lier/liest)*, *bind(ing), lifestyle(s), *voluntary]
	vehicles	1,992.81	*vehicles, *evs/electric vehicles, *vehicle*, *gasoline, *cars, *diesel*, *citizenship, *math, corporate, *engine, *performance, *road, *engines, *social, car, *science, *education, balancing, dieselpowered, spills
	energy technologies	1,627.41	nuclear, *power, solar/photovoltaic(s), *oil, *renewable(s), trillion, *natural*, cell, brooklyn, reserves, barrels, turbine, *wind, generate, *gas, petroleum, fine, hydropower, inexhaustible, vote [*offshore*, onshore, ethanol, biofuels]
	conservation	304.39	*tree(s), forest(s), *plant(/ing), *helped, buildings, lands, sequestration, star, *protect(/ion/ing), acres, eco(logical/system), enhance, conservancy, epas [EPA's], habitat, planted, threat, *conservation, agricultural, carefully [diversity, eagle, indigenous, preservation, restoring, wildlife]
	climate science uncertainty	201.47	climate, *change*, research, scientific, science, human, uncertain(/ty/ties), (un)*know(/n/ing/ledge), national, *scientists, earths, predict, *debate, underst(and/anding/ood), variability, weather, impacts, consequences, ability, *development* [program(s), *policy, compl(ex/exity/icated), *universit(y/ies)]
Internal and peer reviewed	AGW science/ projections	−4,554.30	*co2/carbon dioxide, atmospher(e/ic), *effect(s), *fossil*, *temperature, fuel(s), *concentration, *increase*, *concentrations, carbon, *rate, global, *ocean, *ppm, *average*, level, *due, *oceans, combust(ion)/burn(ing), *biosphere [*scenarios, impact]
	climate modeling	−3,897.21	*model(s), results, *forc(e/ed/ing)*, climate, *data, *estimates, response, variability, *temperature, *shown, *flux, anthropogenic, range, *projections, emission(s), detection, parameter, *estimated, studies, based
	CO_2 disposal/ storage	−2,668.42	*co2/carbon dioxide, *ph [pH], *figure, *time*, *seawater, *depth, *km*, *vertical, *retention*, *model(s), seafloor, *sparger*, *degassing*, diffusive, *natuna*, release, flow, *mixed, *surface, fraction [*injection]
	mitigation assessments	−1,917.80	*transport, mitigation, price, cost(/s/ly/lier/liest), biomass, *waste*, *al [et al.], infrastructure, china, usa, wastewater, reduction, potentially, forestry, losses, sector, availability, capture, direct, sectors
	climate research programs	−1,259.86	*dr* [Dr.], *program(s)*, *exxon*, *tanker*, *ere* [Exxon Research and Engineering Company], *phase*, federal, fund(/ed/ing), plan, division, *weinberg* [Harold Weinberg], additional, mass, academy, interface, underway, wines, organization, *shaw* [Henry Shaw], engineering [*committee*, funds, scoping]
	carbon cycles	−1,215.66	*al [et al.], *ocean, deep, carbon, broecker [Wallace Broecker], upwelling, bbsr [Bermuda Biological Station for Research], stocks, uptake, land, gt [gigaton], vegetation, bermuda, landuse, *cycles*, jain [Atul Jain], station, transient, biospheric, column [dissolved, *water, inventory]
	oil and gas production	−1,034.26	*ccs [carbon capture and storage], hs [HS], gas, acid, cement, n2 [N_2], processing, date, *natuna* [Natuna Island, Indonesia], park, project, earliest, eor [enhanced oil recovery], field, oil, mw [megawatt], recovery, describes, liquid, substantial [pipeline]

For each emergent topic, a topic label and its corresponding top 20 terms are listed (additional informative terms are in brackets at the end of each list). Top 20 terms are ordered according to the relevance metric proposed by Sievert and Shirley,[121] which accounts for both per-term (w)-per-topic (k) probabilities ($\varphi_{w,k}$) and the marginal probability of each term in the corpus (p_w). We indicate divergent terms, as identified earlier by G^2 and FS, between advertorials versus (italics) internal documents, (underlining) peer-reviewed publications, and (asterisks) internal and peer-reviewed documents. p values < 0.001 for all G^2 and FS scores.

Shell Game, which, as Schneider et al.[27] define them, use "misdirection that relies on strategic ambiguity about the feasibility, costs, and successful implementation of technologies," serve to downplay the need for public and political concern by trivializing the seriousness and solvability of AGW. Technological Shell Game discourse is therefore placed in the overlapping areas of Moral evaluation ("Serious") and Solutions ("Solvable") in Figure 1.

The frame of Scientific Uncertainty—and its underlying taxonomy of explicit doubt about climate science and its

Table 5. Rhetoric of individualized responsibility: Highly divergent terms in (top) advertorials and (bottom) internal and/or peer-reviewed documents, by LL ratio (G^2) and FS

	Advertorials	Internal	Peer reviewed	G^2 (Int./P.r.)	FS (Int./P.r.)	Example
Advertorials often say:						
(to) meet	65	2	98	128.34/191.64	0.99/0.93	"To meet this demand, while addressing the risks posed by rising greenhouse gas emissions, we'll need to call upon broad mix of energy sources."[5]
vehicles	33	0	240	73.48/25.02	1/0.74	"[T]he cars and trucks we drive aren't just vehicles, they're opportunities to solve the world's energy and environmental challenges."[123]
greenhouse gas emissions	42	7	60	58.9/126.97	0.92/0.94	"We're supporting research and technology efforts, curtailing our own greenhouse gas emissions and helping customers scale back their emissions of carbon dioxide."[124]
energy efficiency	30	1	152	58.76/36.65	0.98/0.81	"We have invested $1.5 billion since 2004 in activities to increase energy efficiency and reduce greenhouse gas emissions. We are on track to improve energy efficiency in our worldwide refining and chemical operations."[125,126]
cars	24	0	59	53.44/54	1/0.9	"By enabling cars and trucks to travel farther on a gallon of fuel, drivers not only spend less money per mile, they also emit less carbon dioxide (CO_2) per mile."[127]
reduce emissions	23	0	25	51.21/78.03	1/0.95	"During the fact-finding period, governments should encourage and promote voluntary actions by industry and citizens that reduce emissions and use energy wisely. Governments can do much to raise public awareness of the importance of energy conservation."[128]
consumers	21	0	33	46.76/60.7	1/0.93	"We also are developing new vehicle technologies that can help consumers use energy more efficiently."[125,126]
world	91	64	338	43.45/150.55	0.74/0.85	"By 2030, experts predict that the world will require about 60 percent more energy than in 2000 …. As a result, greenhouse gas emissions are predicted to increase too."[129]
developing countries	27	3	162	43/26.94	0.95/0.78	Through 2030, "developing countries … will rely on relatively carbon-intensive fuels like coal to meet their needs."[5]
transportation	23	2	121	38.87/26.93	0.96/0.8	"Ongoing advances in vehicle and fuel technology will be critical to meeting global demand for transportation fuels. They will also help address the risk posed by rising greenhouse-gas emissions."[123]
energy use	23	4	83	31.75/39	0.92/0.85	"Central to any future policy should be the understanding that man-made greenhouse gas emissions arise from essential energy use in the everyday activities of people, governments and businesses."[130]
people	30	11	61	27.87/75.73	0.85/0.91	"Thus, we're pleased to extend our support of … American Forests … whose 'Global Releaf 2000' program is mobilizing people around the world to plant and care for trees."[131]
demand	40	21	422	27.24/14.35	0.8/0.67	"[I]n the electric power sector, growing demand will boost CO_2 emissions."[132]

(*Continued on next page*)

Table 5. *Continued*

	Advertorials	Internal	Peer reviewed	G^2 (Int./P.r.)	FS (Int./P.r.)	Example
needs	36	22	71	20.69/92.45	0.77/0.91	"[F]ossil fuels must be relied upon to meet society's immediate and near-term needs."[133]
conservation	15	5	66	14.89/21.23	0.86/0.83	"Prudent measures such as conservation and investment in energy-efficient technology make sense, but embarking on regulatory [climate/energy] policies that may prove wasteful or counterproductive does not."[134]
energy demand	15	14	59	4.38**/23.59	0.69**/0.84	"[I]ncreasing prosperity in the developing world [is] the main driver of greater energy demand (and consequently rising CO_2 emissions) over the coming decades."[135]
Internal and/or peer-reviewed documents often say:						
fossil fuel	9	144	359	−66.26/−4.48**	0.11/0.34***	"Release of this amount of CO_2 to the atmosphere raises concern with respect to its effect on the CO_2 greenhouse problem. Global fossil fuel emissions of CO_2 currently amount to about 1.8×10^{10} metric tons per year."[136]
						"Arrhenius put forth the idea that CO_2 from fossil fuel burning could … warm the Earth. … fossil fuel greenhouse warming … fossil fuel greenhouse effect …"[137]
natuna	0	67	NA	−53.36/NA	0/NA	"This would make Natuna the world's largest point source emitter of CO_2 and raises concern for the possible incremental impact of Natuna on the CO_2 greenhouse problem."[136]
due to	5	89	731	−42.94/−39.08	0.1/0.13	"The CO_2 concentration in the atmosphere has increased …. The most widely held theory is that: the increase is due to fossil fuel combustion."[138]
						"About three-quarters of the anthropogenic emissions of CO_2 to the atmosphere during the past 20 years is due to fossil fuel burning."[139]
fossil fuel combustion	1	48	NA	−30.69/NA	0.04/NA	"[T]here is the potential for our [climate] research to attract the attention of the popular news media because of the connection between Exxon's major business and the role of fossil fuel combustion in contributing to the increase of atmospheric CO_2."[140]
shale	1	41	NA	−25.43/NA	0.05/NA	"The quantity of CO_2 emitted by various fuels is shown in Table 1 …. They show the high CO_2/energy ratio for coal and shale … ["Shale oil"] is not predicted to be a major future energy source due to … rather large amounts of CO_2 emitted per unit energy generated (see Table 1)."[138]
ccs	0	NA	374	NA/−34.82	NA/0	"CCS includes applying technologies that capture the CO_2 whether generated by combustion of carbon-based fuels or by the separation of CO_2 from natural gas with a high CO_2 concentration."[141]
source	6	39	322	−9.08*/−7.16**	0.24*/0.28**	"[F]ossil fuel combustion is the only readily identifiable source [of CO_2] which is (1) growing at the same rate, (2) large enough to account for the observed increases …"[142]

(*Continued on next page*)

Table 5. *Continued*

	Advertorials	Internal	Peer reviewed	G^2 (Int./P.r.)	FS (Int./P.r.)	Example
						Table 1 presents "coal combustion" and "natural gas combustion" as the "source[s]" of CO_2, CH_4, and SO_2[143]
fossil fuel use	0	13	NA	−10.35*/NA	0**/NA	"[F]or scenarios with higher fossil fuel use (hence, higher carbon dioxide emissions …"[139]
fossil fuel CO_2	0	NA	64	NA/−5.96**	NA/0***	"This long tail on the fossil fuel CO_2 forcing of climate may well be more significant to the future glacial/interglacial timescale evolution of Earth's climate."[144]
fossil fuel emissions	0	NA	54	NA/−5.03**	NA/0***	"We use our Integrated Science Model to … estimate the time variation fossil fuel emissions of CO_2 … required to match the [IPCC] concentration stabilization scenarios."[145]

Divergent terms in advertorials are identified by frame package analysis as framing devices of individualized responsibility discourse. Example quotations illustrate how advertorials use divergent terms to disproportionately present: (1) consumer demand for energy as the cause of—and culpable for—fossil fuel use, greenhouse gas emissions, and/or AGW; and (2) individual/demand-side actions as accountable for mitigating AGW. By contrast, divergent terms in internal and/or peer-reviewed documents often articulate the causality and culpability of fossil fuel combustion. p values < 0.001 for all G^2 and FS scores except: * <0.005; ** <0.05; *** ≥ 0.05. NA, not available.

implications—has previously received detailed scrutiny and is here discussed further only in S4.1, supplemental information.[1,2,17–24] By contrast, frames of Socioeconomic Threat and FFS—and the subtler discourses of delay that underpin them—are underexplored.[17,26–28] For further discussion of the Socioeconomic Threat frame, see S4.2, supplemental information. In the remainder of this paper, we focus on the role of two specific, complementary discourses, Climate Risk and Individualized Responsibility, in constructing the FFS frame. As Figure 1 suggests, these discourses serve as rhetorical gateways connecting the problem and cause of the FFS frame to its moral evaluation and solution.

Discourse of climate risk

We have previously noted that, accompanying the emergence in the mid-2000s of implicit acknowledgments by some ExxonMobil Corp advertorials that AGW is real and human caused, there appeared to be a rhetorical framework focused on risk.[2] Algorithmic analyses here demonstrate that this was part of a wider trend in which, following the merger of Exxon and Mobil at the end of 1999, "risk" was incorporated into advertorials communicating explicit doubt. Specifically, LL and FS results in Table 1 show that "risk(s)" is among the terms that most statistically distinguish Mobil advertorials from ExxonMobil Corp advertorials. Within all advertorials published prior to the merger and expressing any positions on AGW (as real and human caused, serious, or solvable), "risk(s)" appears three times, only once in reference to the risk(s) of AGW or greenhouse gases. By contrast, from 2000 onwards, such "risk(s)" are cited 46 times: an average of once per advertorial; 10 times higher than an average NYT article.[146] Permutations include "risk," "risks," "potential risks," "long-term risk," "long-term risks," "legitimate long-term risk," "legitimate long-term risks," and "potential long-term risks."

In 2000, for instance, ExxonMobil Corp's first post-merger advertorial in our corpus promoted "scientific uncertainty" that AGW is real, human caused, serious, and solvable, acknowledging only that it "may pose a legitimate long-term risk, and that more needs to be learned about it."[147] By the time the company took out its last advertorial expressing a position on AGW in 2009, its tune had changed but "risk" rhetoric remained. The advertorial was entitled, "Tackling climate risks with technology," followed by the subtitle, "Support for oil and natural gas innovation can reduce emissions."[148]

The function of "risk" rhetoric in moderating the conveyed status of AGW or greenhouse gases is unambiguous. First, "risks" is among the top terms characterizing the LDA-generated topic of *Energy/Emissions Challenge*, which is the primary topic that introduces readers to AGW (and compares it with energy demand; see "discourse of individualized responsibility") (Table 4). Second, "climate (change) risk(s)/risk(s) of climate" is, like "risk(s)" itself, a statistically distinctive term of ExxonMobil Corp advertorials versus Mobil advertorials, internal documents, and peer-reviewed publications (Tables 1, 2, and 3). Indeed, automated collocation analysis reveals that the highest scoring collocate of "climate change" and "global warming" in ExxonMobil Corp advertorials is "risk(s)." By contrast, in Mobil advertorials, it is "science" (followed by "gases" and "debate") (Table S18).

Discourse of individualized responsibility

Table 5 (top half) collates terms that are (1) identified by frame package analysis as framing devices communicating Individualized Responsibility in advertorials, and (2) highly divergent between all advertorials and internal and/or peer-reviewed documents according to LL and FS analyses. Two patterns emerge.

First, we observe that advertorials disproportionately employ terms that present consumer demand for energy (rather than corporate supply of oil, coal, and gas) as the cause of fossil fuel production, greenhouse gas emissions, and/or AGW. A characteristic example of this "(energy) demand" rhetoric is a 2008 ExxonMobil Corp advertorial stating: "By 2030, global

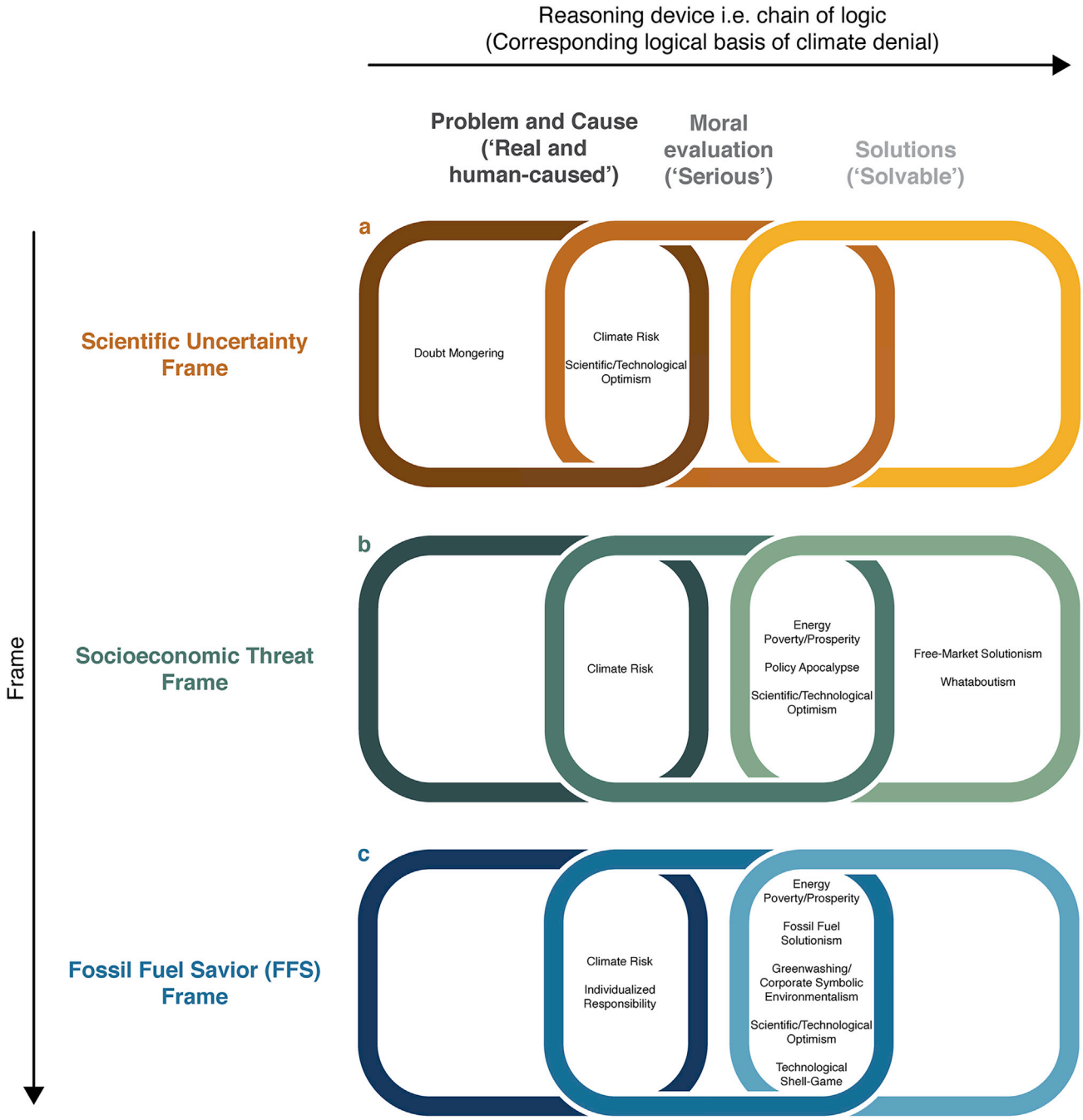

Figure 1. Typology of discourses of climate denial and delay

Using frame package analysis, we identify three dominant frames in ExxonMobil's advertorials: (a, top) Scientific Uncertainty; (b, middle) Socioeconomic Threat; and (c, bottom) Fossil Fuel Savior (FFS). For each frame, a Venn diagram is presented corresponding to the reasoning devices (i.e., chains of logic) defined by Entman:[10] (left) problem and cause; (middle) moral evaluation; and (right) solution (as indicated, these reasoning devices are the logical bases challenged by denials that AGW is real, human caused, serious, and solvable, respectively). Each reasoning device is communicated by one or more of the 11 discourses of climate denial and delay listed within each chain of logic. Although not shown, these discourses are manifest in one or more framing devices (e.g., lexical choices, catchphrases, depictions), as identified in S4, supplemental information. As an example, discourses of Technological Shell Game, which, as Schneider et al.[27] define them, use "misdirection that relies on strategic ambiguity about the feasibility, costs, and successful implementation of technologies," serve to downplay the need for public and political concern by trivializing the seriousness and solvability of AGW. Technological Shell Game discourse is therefore placed in the overlapping areas of Moral evaluation ("Serious") and Solutions ("Solvable") in the diagram. For definitions and examples of all reasoning devices, framing devices, and discourses, see S4 and S5, supplemental information.

energy demand will be about 30 percent higher than it is today … oil and natural gas will be called upon to meet … the world's energy requirements."[149] Another, in 2007, says that "increasing prosperity in the developing world [will be] the main driver of greater energy demand (and consequently rising CO_2 emissions)."[135] A 1999 Mobil advertorial is even blunter: "[G]rowing demand will boost CO_2 emissions."[132] In other words, they present growing energy demand as inevitable, and imply that it can only be met with fossil fuels.

Synonyms for "(energy) demand" include "needs" ("fossil fuels must be relied upon to meet society's immediate and near-term needs") and "energy use" ("man-made greenhouse gas emissions arise from essential energy use in the everyday activities of people, governments and businesses"). Fossil fuels are either presented as passively responding "to meet this demand" of consumers, developing countries, and the world; or they are left out of the equation entirely: "[A]s populations and economies have grown, energy use has increased, and so have greenhouse gas emissions."[150]

Second, we observe that, to the extent that advertorials admit the need for AGW mitigation, they disproportionately introduce terms conveying individual and/or demand-side actions as the appropriate response. Even while promoting explicit doubt about the reality of AGW, advertorials focus on downstream energy efficiency and greenhouse gas emissions, rather than upstream supply of fossil fuels, as the appropriate target of mitigation efforts. "During the [climate science] fact-finding period," a 1997 advertorial states, "governments should encourage and promote voluntary actions by industry and citizens that reduce emissions and use energy wisely. Governments can do much to raise public awareness of the importance of energy conservation."[128] Twelve years later, advertorials continued to equate the "global environmental challenge" with "curbing greenhouse gas emissions," but not with constraining fossil fuel supply.[151] As one 2000 advertorial put it: "Prudent measures such as conservation and investment in energy-efficient technology make sense, but embarking on regulatory [energy] policies that may prove wasteful or counterproductive does not."[134]

Advertorials repeatedly highlighted ways the public could, as one in 1998 put it, "show a little voluntary 'can do.'"[152] A 2008 advertorial suggested that the "cars and trucks we drive aren't just vehicles, they're opportunities to solve the world's energy and environmental challenges."[123] A 2007 advertorial offered readers "simple steps to consider": "Be smart about electricity use"; "Heat and cool your home efficiently"; "Improve your gas mileage"; "Check your home's greenhouse gas emissions" using an online calculator.[153] Mobil and ExxonMobil Corp presented themselves as facilitating, and participating in, such demand-side AGW mitigation. A 1997 advertorial laid the groundwork: "We're supporting research and technology efforts, curtailing our own greenhouse gas emissions and helping customers scale back their emissions of carbon dioxide."[124] In 1999, Mobil announced that "we're pleased to extend our support of … American Forests … whose 'Global Releaf 2000' program is mobilizing people around the world to plant and care for trees."[131] This narrative was echoed by advertorials a decade later: "By enabling cars and trucks to travel farther on a gallon of fuel, drivers…emit less carbon dioxide (CO_2) per mile," said a 2008 advertorial.[127] "We also are developing new vehicle technologies that can help consumers use energy more efficiently," said two more the following year.[125,126]

By contrast, Exxon and ExxonMobil Corp's internal and/or academic communications recognized AGW and/or greenhouse gases as also an upstream problem caused by fossil fuel supply and burning (see also S2.2, supplemental information). "[F]ossil fuel combustion is the only readily identifiable source [of CO_2 consistent with the rate and scale of] observed increases…," observed Exxon scientist James Black[142] in a 1978 presentation to the Exxon Corporation Management Committee. Other internal (1979) and peer-reviewed (2001) documents likewise attributed CO_2 accumulation in the atmosphere as "due to fossil fuel burning" and "fossil fuel combustion."[138,139] A 1984 internal report and a 1994 academic article spoke of "fossil fuel emissions of CO_2," while a 1998 paper referred to "fossil fuel CO_2 forcing of climate."[136,144,145] A 1982 internal memo went further, acknowledging "the connection between Exxon's major business and the role of fossil fuel combustion in contributing to the increase of atmospheric CO_2."[140] The 1979 and 1984 internal documents discuss the CO_2 emissions of specific fossil fuel sources such as shale oil and Exxon's natural gas reservoir off Natuna Island in Indonesia.[136,138]

In sum, ExxonMobil's advertorials statistically overuse terms that reduce AGW to a downstream problem caused by consumer energy demand, to be solved primarily by energy efficiency to reduce greenhouse gas emissions. In contrast, their private and academic documents disproportionately recognize that AGW is an upstream problem caused by fossil fuel supply.

As we show in S6.2, supplemental information, this statistical dichotomy extends throughout all of ExxonMobil Corp's flagship reports concerning AGW spanning 2002–2019 compared with the firm's internal and academic publications.

FFS frame

In addition to Climate Risk and Individualized Responsibility, the FFS frame comprises the five other discourses shown in Figure 1 and defined in S5, supplemental information. Together, they establish the frame's chain of logic (i.e., reasoning devices, see Table S4).

First, as shown in the previous two sections, discourses of Climate Risk and Individualized Responsibility present AGW as the inevitable "risk" of meeting consumer energy demand.

In response to this problem definition and causal attribution, discourses of Scientific/Technological Optimism (which gives primacy to scientific or technological breakthroughs as the solutions to AGW) and Greenwashing/Corporate Symbolic Environmentalism (which is when companies make changes for environmental reasons that, in the case of greenwashing, are merely and deliberately symbolic) lend what Plec and Pettenger[52] (2012) call "an aura of scientific and technical authority," which "resigns us to putting our faith in the power of industry, technology, and science" (see also Schneider et al.[26]). "[W]e believe that technology provides the key avenue to solutions that manage long-term risk and preserve prosperity," says the voice of reason presented by a 2002 advertorial entitled "A responsible path forward on climate." "[This] will almost certainly require decades."[154] ExxonMobil asserts its leadership in this challenge with advertorials citing "our industry-leading investments in research and

development,"[149] such as "supporting climate-related research efforts at major universities, including Stanford and MIT."[155] Visual images such as graphs, charts, and science iconography reinforce this impression.

This technocratic authority helps legitimize accompanying discourses of Fossil Fuel Solutionism and Technological Shell Game, which join the dots between energy demand and continued reliance on fossil fuels. An example of Fossil Fuel Solutionism (which presents fossil fuels and their industry as an essential and inevitable part of the solution to AGW) is a 2007 advertorial that unequivocally depicts the future: "Coal, oil, and natural gas will remain indispensable to meeting total projected energy demand growth" through 2030.[156] "Oil and gas will be essential to meeting demand," reiterates another in 2008.[5] "Meeting this growing long-term demand requires that we develop all economic sources of energy – oil, natural gas, coal, nuclear and alternatives," says a third in 2009.[151]

The non-fossil fuel alternatives are then dismissed by Technological Shell Game discourse promoting doubt and confusion about AGW's technological solvability, such as three advertorials in 2005 depicting, again unequivocally, how "Wind and solar … meet about 1% of total world demand by 2030."[157–159] Another, 3 years later, updates the figure to "only 2 percent" (including biofuels).[5] ExxonMobil also takes aim at clean energy subsidies and renewable energy's "highly variable output" and "enormous land-use requirements."[133,154,160] Meanwhile, the three 2005 advertorials, and another in 2009, falsely promote natural gas as "clean-burning" and "clean," respectively.[157–159]

In a 2009 advertorial, ExxonMobil acknowledges that there is "a dual challenge" to "provide energy" and "protect the environment" (notably, they say that this challenge concerns energy rather than fossil fuels, and that it applies to "all of us").[150] But then they tip the scales by pitting concrete, unequivocal benefits ("[Energy] lights our homes. Fuels our transportation. Powers our industries. … [D]riv[es] our economy and rais[es] living standards") against amorphous, uncertain costs (the "risks of climate change"). Two 2007 advertorials similarly compare "economic growth and human development" against undefined "risks of climate change."[161,162]

In cases such as these, discourses of Energy Poverty/Prosperity and Policy Apocalypse (which respectively articulate social justices of energy access and alleged socioeconomic tolls of decarbonization—the latter strictly assigned to the socioeconomic threat frame), contrasted against that of Climate Risk, work to affirm the moral evaluation of the FFS frame that fossil fuel lock-in is righteous and reasonable.

DISCUSSION

The patterns observed in "results" are similar to those documented in the tobacco industry. In "risk rhetoric facilitates ExxonMobil's have-it-both-ways position on AGW" and "energy demand rhetoric individualizes AGW responsibility," we discuss the strategic functions of AGW "risk" rhetoric and individualized responsibility framings, respectively, in comparison with the history of the tobacco industry. "Energy demand rhetoric individualizes AGW responsibility" distinguishes how consumer energy demand is presented in public ("demand as fossil fuel lock-in in public relations") versus in legal defense ("demand as blame in litigation"). "Historical contexts, ramifications, and trajectories of ExxonMobil's communication tactics" explores the historical contexts, ramifications, and trajectories of ExxonMobil's "risk" rhetoric ("risk") and individualized responsibility framings ("individualized responsibility").

Risk rhetoric facilitates ExxonMobil's have-it-both-ways position on AGW

Our identification of ExxonMobil's discursive shift to "risk" rhetoric (see "discourse of climate risk") is broadly consistent with independent findings. Jaworska[51] observes the emergence of "risk" as one of the most frequent collocations of "climate change" in the late 2000s within the corporate social responsibility reports of the world's major oil corporations, including ExxonMobil. Grantham and Vieira,[44] examining "welcome letters" from ExxonMobil's CEO in the company's Corporate Citizenship Reports, note that "risk" is one of the most influential words coinciding with emphasis on the "planet." Schlichting[17] concludes that, over the course of the 2000s, industry actors increasingly adopted the framing that "climate change [might be/is] a risk."

ExxonMobil's rhetorical pattern of stressing "risk" is consistent with the company's effort in the mid-2000s, chronicled by journalist Steve Coll,[48] "to reposition ExxonMobil's arguments about warming to more fully account for consensus scientific opinion, without admitting that any of the corporation's previous positions had been mistaken, for that might open a door to lawsuits."

This approach resembles the tobacco industry's well-documented response to the scientific consensus on the harms of tobacco use, described by historian Allen Brandt[163] as a "shift" in focus from scientific "uncertainty" to "(alleged) risks" of smoking (see also Proctor[164,165]). This scientific hedging strategy was made explicit in a 1996 Reynolds training manual instructing new employees to tell reporters that smoking was "a risk factor" but "not a proven cause."[165] In 1998, for example, Philip Morris's CEO Geoffrey Bible conceded a "possible risk" but not a "proven cause," the distinction being in what historian Robert Proctor[165] calls "a kind of legal having-it-both-ways: an admission strong enough to ward off accusations of having failed to warn, yet weak enough to exculpate from charges of having marketed a deadly product." This carefully parsed conclusion became the industry's new official position.[163]

"Risk" facilitates ExxonMobil's have-it-both-ways position on AGW. It is a "'good' candidate to serve various rhetorical purposes," Jaworska[51] notes, because it "opens up many semantic slots." Fillmore and Atkins'[166] work on the conceptual meaning of risk, for example, shows that "risk" has two dominant sub-frames, "Chance" and "Harm," and many optional valence description categories. "Chance" is defined as "uncertainty about the future," such that risk rhetoric (1) implies inherent uncertainty and (2) is subject to temporal discounting heuristics.[167–169] "The essence of risk is not that it *is* happening, but that it *might* be happening."[170,171]

"Risk" is never clearly or consistently defined by ExxonMobil. The presence and absence of risk's various sub-frames introduce so-called strategic ambiguity—and therefore flexibility—in contemporaneous and retrospective interpretations of what ExxonMobil wants us to see as a "risk" rather than a "reality."[27,172] For instance, does the "Chance" sub-frame of "risk"—and

therefore the implication of uncertainty—apply to whether AGW is happening, human caused, serious, or solvable? Sub-frames of Harm, Actor, Victim, and Valued Object are also rarely articulated: who assumes the risk(s) of AGW: the public, the company, its shareholders, or others? What might be the consequences, and when? In contrast, the "Gain," "Beneficiary," and "Motivation" sub-frames of risk taking, manifest in discourse of Policy Apocalypse, are stated explicitly, as discussed in "demand as fossil fuel lock-in in public relations."

Like its weaponized rhetorical cousins—such as "uncertainty," "sound science," and "more research" and the hedging words "may," "potential," etc.—"risk" has the strategic advantage of not necessarily implying intent to deny or delay, because it is coopted from common academic, regulatory, journalistic, and colloquial parlance (S1.4.2, Supran and Oreskes[1]).[15,146,167,173,174] It can be used correctly (for example, to refer to expected *future* damages and stranded fossil fuel assets—a risk that we have previously shown ExxonMobil was publicly silent about) or incorrectly (for example, to describe AGW and past/present climatic changes such as sea level rise as risks rather than realities).[1]

ExxonMobil employs almost identical "risk" language in advertorials promoting explicit doubt about AGW as in those that implicitly acknowledge it. For example, they refer to "the risk of global warming" in 1989 (accompanied by explicit doubt); the "risk(s)" "that climate changes may pose" in 2000 (alongside explicit doubt); and "the risks of climate change" in 2009 (which, in the absence of doubt, is coded as an implicit acknowledgment).[150,175,176] This is not limited to advertorials (for wide-ranging examples, see table 3 of Supran and Oreskes[2]). In ExxonMobil Corp's *2005 Corporate Citizenship Report*, for instance, which extensively questions whether AGW is human caused and serious, a member of the public asks: "Why won't ExxonMobil recognize that climate change is *real* …?" The company replies: "ExxonMobil recognizes the *risk* of climate change and its *potential* impact" (emphases added).[177] By shifting the conversation from the semantics of reality to the semantics of risk, they inject uncertainty into the AGW narrative, even while superficially appearing not to.

Energy demand rhetoric individualizes AGW responsibility

Two dimensions of issue responsibility are commonly identified in communications and psychological research: causality and treatment.[16,178] Causality responsibility addresses the source of a problem—who or what causes it. Treatment responsibility identifies who or what has the power to alleviate the problem, and should be held responsible for doing so. Studies of responsibility framing and attribution theory argue that attribution of these responsibilities broadly takes two conflicting forms: individual versus social.[16,179,180] Expressing our findings in "discourse of individualized responsibility" through this analytical lens, ExxonMobil's public advertorials are biased toward individualist framings of both causality and treatment responsibilities for AGW as compared with their private and academic representations.

Jaworska[51] has observed similar appeals to energy demand as the driving force behind greenhouse gas emissions in the corporate citizenship reports of ExxonMobil Corp and other fossil fuel companies, noting that they are "an example of differentiation, which shifts the responsibility to other constituencies." Princen et al.[72] similarly argue that a focus on carbon and greenhouse gases—and away from fossil fuels—is reductionist. "This chemical framing," they note, "implies that the problem arises after a chemical transformation, after fuels are burned. It effectively absolves of responsibility all those who organize to extract, process, and distribute…So constructed…the burden of harm and responsibility for amelioration falls on governments and consumers rather than extractors."

"The most effective propaganda," Parenti[181] contends, "is that which relies on framing rather than on falsehood." As with the language of risk, a rhetorical power of narratives that individualize responsibility is that they do not require the statement of outright falsehoods. After all, consumer demand is one valid and universally recognized aspect of the AGW problem and its solution, and not all advertorials entirely disregard the role of fossil fuels. On balance, however, the disproportionate public fixation of ExxonMobil, a supplier company, on demand-side causation and accountability (as shown in "discourse of individualized responsibility") fulfills the fundamental function of emphasis frames to "call attention to some aspects of reality while obscuring other elements."[10] It is in this selection process that the individualized responsibility framing device creates a false dichotomy, leading readers toward AGW problem definitions, evaluations, and solutions skewed toward consumer demand and away from industry supply.[11,16,178]

ExxonMobil's framing is reminiscent of the tobacco industry's effort "to diminish its own responsibility (and culpability) by casting itself as a kind of neutral innocent, buffeted by the forces of consumer demand."[165] It is widely recognized that the tobacco industry used, and continues to use, narrative frames of personal responsibility—often marketed as "freedom of choice"—to combat public criticism, influence policy debates, and defend against litigation and regulation.[13,100,119,164,182–184] Friedman et al.[13] recently demonstrated that tobacco companies use "freedom of choice" to imply two distinct concepts: liberty and blame. In their public relations messaging, industry asserts smokers' rights as individuals who are at liberty to smoke. In the context of litigation, industry asserts that those who choose to smoke are solely to blame for their injuries.

In the following two subsections, we further explore the congruence between ExxonMobil's public responsibility framing and these tobacco tactics ("demand as fossil fuel lock-in in public relations"; "demand as fossil fuel lock-in in public relations"). We discuss how this Individualized Responsibility discourse is rationalized and reinforced by the semantic duality of "risk."

Demand as fossil fuel lock-in in public relations

In "FFS frame," we showed that ExxonMobil's FFS frame insists—typically as self-fulfilling fact rather than opinion—upon society's inevitable and indefinite reliance on fossil fuels. Rather than asserting that demand is a personal choice and liberty, ExxonMobil's public "(energy) demand" rhetoric inverts the tobacco industry's "freedom of choice" messaging. Liberty becomes lock-in.

Within this frame, discourses of Energy Poverty/Prosperity and Policy Apocalypse contrast against that of Climate Risk ("FFS frame"). The role of "risk" rhetoric here is to downplay the downside, namely AGW, of this alleged dichotomy: fossil

fuels are essential, whereas the potential effects—indeed realities—of AGW are uncertain.[26] Such assertions, St. John III[35] notes, extend Mobil's messaging in its "Observations" columns "about what constitutes reasonable risk." Observations were "pithy, easy-to-read" advertorials that Mobil ran in Sunday newspaper supplements between 1975 and 1980.[35,185] In a 1980 "Observations" column, for example, Mobil lamented that "the country seems to be afflicted with the Chicken Little Syndrome" of "cry[ing] that 'The sky is falling!'"[186] "Hardly a day passes," they said, without "fresh perils" like "harmful rain" or "cancerous sunshine." But a "risk-free society" through government regulation is impossible, the advertorial reasoned, because "everything people do everyday involves a slight measure of risk" (emphasis in original). The company concluded with the warning that to "avoid risk, fight change" may be a short-term solution, "but for the long pull, it's a way to certain stagnation." Tobacco industry apologists made the same arguments, calling it "the menace of daily life."[187]

To the extent that advertorials concede AGW may be a problem, the "risk" angle helps frame AGW as unpredictable, positioning the oil industry "not as a contributor but as a victim" alongside consumers.[51] As a 2009 advertorial put it, "[we'll need] a global approach to managing the risks of climate change. Everyone has a role to play – industry, governments, individuals."[150] This complemented Mobil's broader use of advertorials to rhetorically reframe itself as what Kerr[42] terms a "corporate citizen." "A citizen of many lands" is how Mobil described itself in a 1999 advertorial.[131] "Climate change: we're all in this together," another was titled in 1996.[188] With this narrative of an "empathetic fellow traveler," St. John III[35] argues, "Mobil offers up the reasonable, risk-taking corporate persona who is willing to take the initiative to provide a beneficial product to all Americans…[B]y appealing to Americans' penchant for valorizing the self-starting individual, such a message of energy harvesting as never being 100% safe could well explain how a significant amount of Americans today do not see fossil fuel-induced climate change as a significant risk."[35]

ExxonMobil's advertorials say almost nothing about the seriousness of AGW.[1,2] Nor do they mention the concepts of carbon budgets and stranded fossil fuel assets, which are part of the argument for the fundamental incompatibility of unrestricted fossil fuel supply with climate mitigation.

Overall, the didactic framing of demand as fossil fuel lock-in communicates what Plec and Pettenger[52] describe as "a rhetoric of resignation, naturalizing consumption of resources and teaching us to put our trust in industry solutions to energy problems." Or as Schneider et al.[27] and Cahill[26] put it, quoting the neoliberal bromide: "There is no alternative" to the *status quo*.

Demand as blame in litigation

Although the tobacco industry sells "freedom of choice" as *liberty* in public relations, in litigation they equate it with *blame* toward individuals who exercised their choice to smoke.[13,164,183,184] Climate litigation is nascent, yet the fossil fuel industry has already successfully repackaged demand as *lock-in* to instead impute *blame* on customers for being individually responsible.

In 2018, arguing in defense of five oil companies (including ExxonMobil Corp) against a lawsuit brought by California cities seeking climate damages, Chevron lawyer Theodore Boutrous Jr. offered his interpretation of the IPCC's latest report: "I think the IPCC does not say it's the production and extraction of oil that is driving these emissions. It's the energy use. It's economic activity that creates demand for energy." "It's the way people are living their lives."[189] The judge's dismissal of the case accepted this framing: "[W]ould it really be fair to now ignore our own responsibility in the use of fossil fuels and place the blame for global warming on those who supplied what we demanded?"[190]

Even if plaintiffs prove their case, fossil fuel companies can invoke "affirmative defenses"—as tobacco companies often have—such as "common knowledge" and "assumption of the risk."[164,183] These respectively argue (1) "that the plaintiff had engaged in an activity [such as smoking] that involved obvious or widely known risks," and (2) "that the plaintiff knew about and voluntarily undertook the risk."[13] As Brandt[163] explains it, "If there was a risk, even though 'unproven,' it nonetheless must be the smoker's risk, since the smoker had been fully informed of the 'controversy.' The industry had secured the best of both worlds."

By way of the FFS frame, ExxonMobil appears to have constructed an ability to do the same. On the one hand, "risk" rhetoric is weak enough to allow the company to maintain a position on climate science that is ambiguous, flexible, and unalarming ("risk rhetoric facilitates ExxonMobil's have-it-both-ways position on AGW"). On the other, it is strong enough—and prominent enough, in NYT advertorials and elsewhere—that ExxonMobil may claim that the public has been well informed about AGW. This duality has been a cornerstone of the tobacco industry's legal position on the "risks" of smoking: "Everyone knew but no one had proof."[163,164] Akin to early, tepidly worded warning labels on cigarette packages, ExxonMobil's advertorials in America's newspaper of record help establish this claim, sometimes explicitly: "*Most people acknowledge* that human-induced climate change is a long-term *risk*," a 2001 advertorial states[13,130] (emphases added). "The *risk* of climate change and its *potential* impacts on society and the ecosystem are *widely recognized*," says another the following year.[191] As Baker[192] has pointed out about the socialization of risk, "a transfer of risk is also a transfer of responsibility …. [R]isk *creates* responsibility."

The fossil fuel industry's use of demand-as-blame framing is not limited to its legal defenses. As Schneider et al.[27] describe, fossil fuel interests have likewise sought to delegitimize AGW activism, such as the fossil fuel divestment movement, by deploying a rhetorical "hypocrite's trap [that] performs the disciplinary work of individualizing responsibility" (see also Ayling[193]).

Historical contexts, ramifications, and trajectories of ExxonMobil's communication tactics

ExxonMobil's selective use of rhetoric and discourse to frame AGW epitomizes the first "general principle" of effective public affairs according to Herbert Schmertz,[185] Mobil Oil's Vice President of Public Affairs (1969–1988) and the pioneer of their advertorials: "Grab the good words – and the good concepts – for yourself."[185] "[B]e sensitive to semantic infiltration, the process whereby language does the dirty work of politics…Be sensitive to these word choices, and be competitive in how you use them. Your objective is to wrap yourself in the good phrases while sticking your opponents with the bad ones."

Risk

ExxonMobil Corp's systematic introduction of "risk" rhetoric into its doubt-mongering advertorials coincided with the 1999 merger of Exxon and Mobil, suggestive of a strategic shift in public relations.

A second shift, in the mid-2000s, from explicit doubt to implicit acknowledgment confused by "risk" rhetoric, coincides with what one ExxonMobil Corp manager saw as "an effort by [then CEO Rex] Tillerson to carefully reset the corporation's profile on climate positions so that it would be more sustainable and less exposed."[48]

To this day, ExxonMobil Corp's (also Chevron's and ConocoPhillips') refrain on AGW, and the primary basis on which the company is now widely perceived to accept basic climate science, is that it is a "risk."[26,194,195] Across all of ExxonMobil Corp's flagship reports concerning AGW, by far the highest scoring collocate of "climate change" and "global warming" is "risk(s)" (S6.1, supplemental information). Compared with internal and peer-reviewed documents, terms in flagship reports invoking "risks of climate change" are highly divergent (S6.1). As with advertorials, none say that climate change is real and human caused.

Individualized responsibility

The findings in the results section lead us to conclude that ExxonMobil advertorials used frames of individualized responsibility and the rhetoric of "risk" to construct what St. John III[35] calls a "sense-making corporate persona" that appealed to the enduring principles of "rugged individualism" and self-reliance that pervade US culture and ideology.[35,196–201] Their public affairs campaign coincided with solidifying, intertwined notions of distributed risks and individualized responsibility in western public policy debates since the 1970s, which have been driven by the global embrace of neoliberalism and globalization[27,197,202,203] and encouraged by reductive, episodic news framings[16,179] (and which are conceptualized by social theories[59,204,205] such as Beck et al.'s "risk society,"[170,206,207] Douglas et al.'s "risk culture,"[208] and Foucault et al.'s "governmentality").[209,210] ExxonMobil tapped into this trend toward the individualization of social risks, and brought it to bear on AGW.[59,208,211]

ExxonMobil is part of a lineage of industrial producers of harmful commodities that have used personal responsibility framings to disavow themselves.[212–214] Among them: tobacco companies;[13,119,120] the National Association of Manufacturers;[215] plastics producers (including Exxon, Mobil, and ExxonMobil Corp), packaging and beverage manufacturers, and waste companies;[197,216–222] and purveyors of sugar-sweetened beverages and junk food,[98,99,214] leaded products,[223,224] motor vehicles,[94,225] alcohol,[12,226] electronic gambling,[227] and firearms.[228]

Among, in particular, the public AGW communications of major fossil fuel companies, individualized responsibility framings—and the accompanying narrative of fossil fuel lock-in—have become seemingly ubiquitous.[26,51] The very notion of a personal "carbon footprint," for example, was first popularized in 2004–2006 by oil firm BP as part of its $100+ million per year "beyond petroleum" US media campaign.[229–235] Discourse analysis of this campaign led Doyle[236] to conclude that "BP places responsibility for combatting climate change upon the individual consumer." Smerecnik and Renegar[57] have shown that subsequent BP branding activities similarly "plac[e] participatory emphasis on consumer conservation behavior as opposed to corporate responsibility." This industry framing continues to dominate today.[26,81] In 2019, for instance, BP launched a new "Know your Carbon Footprint" publicity campaign.[237] In 2020, the CEO of Total said that "Change will not come from changing the source of supply. You have to reduce demand."[238] Until 2020, all major oil and gas companies disregarded or disavowed accountability for all Scope 3 greenhouse gas emissions resulting from the use of their products. ExxonMobil Corp, Chevron, and ConocoPhillips continue to do so.[239]

The result is that fossil fuel industry discourse on AGW appears to have encouraged and embodied what Maniates[197] describes as "an accelerating individualization of responsibility" that "is narrowing, in dangerous ways, our 'environmental imagination'" by "ask[ing] that individuals imagine themselves as consumers first and citizens second."[197,26,27,52,56] This depoliticized "capitalistic agency," Smerecnik and Renegar[57] argue, works to "prohibit fundamental social change that would disrupt the fossil fuel industry."[57,59] Experimental evidence appears to support this conclusion. Palm et al.,[240] for example, observe that messages framed in terms of individual behavior not only "decreased individuals' willingness to take personal actions" but also "decreased willingness to [take collective action such as to] support pro-climate candidates, reduced belief in the accelerated speed of climate change, and decreased trust in climate scientists." Illustrations of how narratives of individualized responsibility have protected fossil fuel interests from climate action are widespread. One is Yale University's 2014 refusal to divest from fossil fuel companies, which was "predicated on the idea that consumption of fossil fuels, not production, is the root of the climate change problem."[241] Another is the Republican Party's 2020 legislative agenda on AGW, whose premise was that "fossil fuels aren't the enemy. It's emissions."[242,243] A third is that the Paris Agreement "is silent on the topic of fossil fuels."[68]

Summary and conclusion

Available documents show that, during the mid-2000s, ExxonMobil's public AGW communications shifted from explicit doubt (a Scientific Uncertainty frame) to implicit acknowledgment couched in discourses conveying two frames: a Socioeconomic Threat frame, and a Fossil Fuel Savior (FFS) frame. According to the FFS frame:

(1) Everything about AGW is uncertain: a "risk," as contrasted with a reality.
(2) Fossil fuel companies are passive suppliers responding to consumer energy demand.
(3) Continued fossil fuel dominance is (1) inevitable, given the insufficiency of low-carbon technologies; and (2) reasonable and responsible, because fossil fuels lead to profound, explicit benefits and only ambiguous, uncertain climate "risk(s)."
(4) Customers are to blame for demanding fossil fuels, whose "risk(s)" were common knowledge. Customers knowingly chose to value the benefits of fossil fuels above their risks.

Ignored and obscured by these perspectives are fossil fuel interests' pervasive marketing, disinformation campaigns, and lobbying against climate and clean energy policies, all of which

have served to establish and reinforce infrastructural, institutional, and behavioral carbon lock-ins, thereby undercutting consumer choice and agency.[244,245]

Propaganda tactics of the fossil fuel industry such as these have received less scrutiny than those of their tobacco counterparts. Further attention is needed, because although individualized narratives of risk, responsibility, and the like are less blatant than outright climate science denial, such "discursive grooming" is now pervasive in structuring the agenda of scholars, policymakers, and the public.[59,68,69,197,246]

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and reasonable requests for resources by qualified researchers should be directed to and will be fulfilled by the lead contact, Geoffrey Supran (gjsupran@fas.harvard.edu).

Materials availability

This study did not generate new unique materials.

Data and code availability

Raw data (original PDF internal documents, peer-reviewed publications, and advertorials) for this study cannot be reproduced due to copyright restrictions. However, a catalog of all 180 analyzed documents, and links to public archives containing these data, are provided in S7, supplemental information. Additionally, raw searchable .txt versions of all documents, as well as post-processed flattened text and document term matrices, are deposited on Harvard Dataverse: https://doi.org/10.7910/DVN/XXQUKJ. The datasets and code generated during this study are provided in the same repository. Access will be granted upon reasonable request by qualified researchers.

Corpora

For detailed descriptions of how we previously compiled the 180 ExxonMobil documents analyzed in this study, see Supran and Oreskes.[1,2] For a catalog of all 180 documents, and links to their public archives, see S7, supplemental information. In summary, the 32 internal company documents (1977–2002) were collated from public archives provided by ExxonMobil Corp,[101] *InsideClimate News*,[102] and Climate Investigations Center.[103] The 72 peer-reviewed publications (1982–2014) were obtained by identifying all peer-reviewed documents among ExxonMobil Corp's lists of Contributed Publications, except for three articles discovered independently during our research. All 72 publications were (co-)authored by at least one ExxonMobil employee.[104] The 76 advertorials (1972–2009) expressing any positions on AGW (real and human caused, serious, or solvable) were identified by manual content analysis of 1,448 ExxonMobil advertorials (1924–2013) collated from PolluterWatch and ProQuest archives.[105,106]

Pre-processing

To enable computational analysis, scanned documents were converted to searchable text files using optical character recognition. Text was stripped of formatting details and punctuation, tokenized, and lowercased (for details, see S1.1, supplemental information). This yielded internal, peer-reviewed, and advertorial corpora comprising 69,802 words, 716,477 words, and 34,141 words (16,121 in Mobil advertorials and 18,020 in ExxonMobil Corp advertorials), respectively.

For divergent term (topic) analysis, we added (substituted) several synthetic tokens that combine: terms of identical cognate form (e.g., "effect" and "effects" became "effect(s)"); and terms judged by the authors to be near-synonyms (e.g., "co2" and "carbon dioxide" became "co2/carbon dioxide"; "countries" and "nations" became "countries/nations")—for all synthetic tokens, see vectorize.R script.[109,247] Document collections were transformed into document-term matrices comprising all: 1- to 5-grams (unique, contiguous word strings of 1–5 tokens in length) for divergent term analysis; and 1-grams for divergent topic analysis.[248]

Divergent term analysis (FS and LL ratio)

Internal, peer-reviewed, and advertorial corpora were compared pairwise to identify rhetorical distinctiveness (or divergence) between the terms communicated in each text. (We combine all (Mobil plus ExxonMobil Corp) advertorials before comparing them against internal and peer-reviewed documents from Exxon and Exxon/ExxonMobil Corp, respectively. This simplifies the presentation of results without substantively affecting our findings.) To capture different forms of divergence, we applied two algorithms: FS and Dunning LL ratio (G^2) score.[108–110] FS and LL are established, complementary tools for word frequency analysis in computational linguistics and digital humanities.[110,249,250]

The FS indicates how often a given term appears in one corpus versus another. The score ranges from 0 (when only corpus A features the term) to 1 (when only corpus B includes the term). To account for the difference in word counts between corpora, we normalized scores by using relative frequencies. For example, a score of 0.8 means that 80% of all normalized instances of a term appear in corpus B. As Risi and Proctor observe, "FSs are useful for identifying taboos: terms generally avoided by one side or the other."[109]

FSs produce immediately interpretable results, yet their reliance on multiplicative ratios—versus additive differences—tends to over-represent rare words.[108] To identify subtle patterns that might otherwise escape notice, we also use the LL (G^2) statistic proposed by Dunning (1993), which is a parametric analysis that primarily identifies "surprising," additively over-represented words, while also giving some weight to multiplication.[108,110,251] Large $|G^2|$ scores indicate terms that have statistically significant relative frequency differences between two corpora. LLs are therefore useful for identifying tropes: terms used disproportionately by one side.

Divergent topic analysis (LDA)

In the field of automated text summarization, divergent terms identified by LL are referred to as "topic signatures."[249,252] In order to identify the topics represented by such terms, and to better understand the roles these terms play in framing each topic, we also examine the documents using topic modeling with LDA.[111] LDA is a computational, unsupervised machine-learning algorithm for discovering hidden thematic structure in collections of texts.[253] *A priori* coding schemes are not supplied. Rather, 'topics' (clusters of words associated with a single theme) emerge inductively based on patterns of co-occurrence of words in a corpus.

We are specifically interested in identifying the topical distinctiveness (or divergence) between document categories. In the main text, we compare topics between (α) all advertorials and (β) combined internal and peer-reviewed documents.

To do so, we first model the distribution of topics over all document categories, by inputting to LDA an aggregated corpus comprising all advertorials, internal documents, and peer-reviewed publications (for details of LDA model selection, topic validation, and labeling, see section S1.2, supplemental information). Once topic-word distributions are obtained, we then take an approach analogous to that for finding divergent terms above, noting that just as LL ratios of term frequencies identify divergent terms, LL ratios of topic weights identify divergent topics. We compute LL ratios of topic weights by constructing document-topic matrices for each of sub-corpora α and β.

Although they are run independently, analyses of divergent terms (by FS and LL) and topics (by LL of LDA) are complementary. The former identifies the distinctive usage of individual n-grams by one corpus versus another. The latter helps contextualize the thematic role that these words together play in communicating and framing topics.

Frame package analysis

Van Gorp[117] argues that the "strongly abstract nature of frames implies that quantitative research methods should be combined with the interpretative prospects of qualitative methods." To this end, we use the distinctive terms and topics identified using computational techniques to then inform an inductive, qualitative approach to constructing frames as frame packages in advertorials. Van Gorp[117] defines frame packages as an integrated structure of framing devices (manifest textual elements that function as indicators of a frame) and reasoning devices (logical chains of causal reasoning), and proposes Strauss and Corbin's[254] three-step coding scheme for identifying frame packages and

assembling them into a so-called "frame matrix."[6,10,17,116–118,254] We adopt this approach.

Open coding

The first step is to compile what Van Gorp[116] calls an "inventory of empirical indicators that may contribute to the readers' interpretation of the text," comprising feasible framing or reasoning devices identified in each document. We used FS, LL, and LDA to systematize this process of locating frames and detecting how they are shaped by lexical composition (for details, see S1.3, supplemental information). We further investigated these discursive constructs by performing collocation searches.[51] The logDice statistic was computed to measure collocational association because it permits meaningful comparison of different sized corpora.[255,256]

Axial coding

The second step is to arrange coded devices along "axes of meaning" by comparing and contrasting open-coding results between documents and then reducing the results to broader meanings or dimensions.[113,116] We do so with reference to an inventory of discourses that we assembled based on a literature review of past studies of AGW communications by fossil fuel interests (see S3, supplemental information).[116]

Selective coding

The last step is to enter axial codes into a "frame matrix" that summarizes the framing and reasoning devices of each frame package.[116]

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.oneear.2021.04.014.

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AUTHOR CONTRIBUTIONS

Conceptualization, G.S.; methodology, G.S.; validation, G.S. and N.O.; formal analysis, G.S.; investigation, G.S.; writing – original draft, G.S.; writing – review & editing, G.S. and N.O.; visualization, G.S.; supervision, G.S. and N.O.; funding acquisition, G.S. and N.O.

DECLARATION OF INTERESTS

The authors have received speaking and writing fees (and N.O. has received book royalties) for communicating their research, which includes but is not limited to the topics addressed in this paper. The authors have no other relevant financial ties and declare no competing interests.

INCLUSION AND DIVERSITY

While citing references scientifically relevant for this work, we also actively worked to promote gender balance in our reference list.

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One Earth, Volume *4*

Supplemental information

Rhetoric and frame analysis of ExxonMobil's climate change communications

Geoffrey Supran and Naomi Oreskes

SUPPLEMENTAL INFORMATION

SUPPLEMENTAL FIGURES

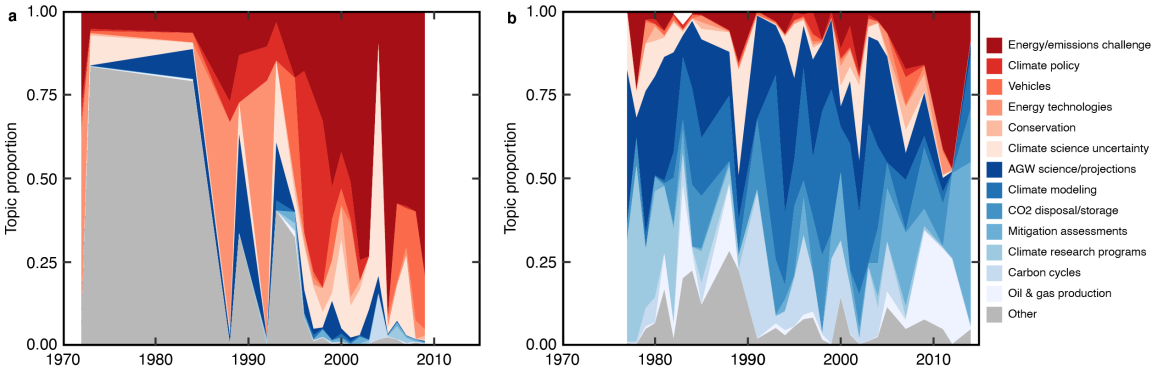

Figure S1. Topic prevalence over time in (a) advertorials and (b) internal and peer-reviewed publications. Topic proportions are calculated as the normalized sum of LDA per-document (d)-per-topic (k) probabilities ($\theta_{d,k}$) of all documents published each year. Note that, as documented in table S20, our corpus comprises only three advertorials published prior to 1988.

SUPPLEMENTAL TABLES

Table S1. Fossil fuel industry AGW discourses, based on a meta-analysis of existing academic literature. In some cases, discourses from individual studies straddle two or more discourses in our classification.

Author	**Rowlands (2000)** [38]	**Livesey (2002)** [39]	**Smerecnik & Renegar (2010)** [40]	**Doyle (2011)** [41]	**Plec & Pettenger (2012)** [42]	**Schlichting (2013)** [29]
Corpus	Exxon and BP's public statements on AGW	Four advertorials in The New York Times	BP's "Helios Power" campaign	BP advertising campaigns	ExxonMobil's "Energy Solutions" TV advertisements	38 studies on industry actors' AGW communications
Time period	Unspecified (~1997-2000)	March-April 2000	2007	2005-06	2009, 2011	1990-2010
Focus	Positions of Exxon and BP Amoco on AGW	How ExxonMobil's public discourses construct social "reality"	Discourses in green marketing	Discursive strategies to create an environmental brand image	(Didactic) frames and discourses in green marketing	Strategic frames of industry actors
Analytic method	Review (not specifically defined)	Rhetorical and discourse analyses	Rhetorical analysis	Discourse analysis	Frame analysis	Frame meta-analysis
Discourses						
Climate Risk				"Risk" rhetoric channelling Beck's risk society. AGW as a future event rather than a present reality.		"Climate change might be/is a risk"
Doubt Mongering	Scientific uncertainty	Demonize most climate scientists		Scientific doubt-mongering		"Scientific uncertainty"
Free-Market Solutionism	Support "voluntary market-driven efforts"	Primacy of "the market", private sector, and economists. Governments sidelined, regulatory controls rejected	Individual, capitalistic agency	Late capitalism economic discourse: global capitalism equals expanding global environmental good. Citizen as consumer. Blame on consumers for not buying BP's ostensibly environmentally friendly products. Responsibility for combating AGW placed on individual consumer.		
Individualized Responsibility		Re-constitute citizen as consumer ExxonMobil as responsible citizen ExxonMobil as vulnerable human entity in complex natural scene				"Industry is responsible for the climate. Consumers must also take responsibility".
Energy Poverty/Prosperity		"Lifestyle" protection	"Utopian fantasy world where fossil fuel-based transportation and a clean environment are harmoniously united"	Prioritization of human needs and economic growth over the environment		
Energy Utopia						
Fossil Fuel Solutionism		Responsible corporate actor pursuing "prudent", rationalist approach		BP as solution, rather than contributor, to AGW. Environmental leadership: Highlighting progressive and green values and investments.		"Fossil energy sources can be used sustainably"
Greenwashing/Corporate Symbolic Environmentalism	Reducing scope-1 GHG emissions				Alternative energy leader/expert solving environmental problems; Green energy	"Industrial leadership": "Corporate achievements in climate protection"; Green "visionaries"
Scientific/Technological Optimism	Support "continued research"	Scientific powerhouse and technological leader. Entrepreneurship and technology will provide solutions.		Technology as the solution	Technocratism: Scientific & technological solutions; authoritarian values	"Technological innovations are the solution"
Policy Apocalypse	Socioeconomic harm of "premature" climate policies (e.g. Kyoto Protocol)					"Socioeconomic consequences"
Technological Shell-Game				"Clean" natural gas presented as equivalent to renewable energy		
Whataboutism	Developing countries must participate in climate policies					
Other						

Table S1, continued.

Author	**Robinson (2014)** [43]	**Gaither & Gaither (2016)** [44]	**Schneider *et al.* (2016)** [45]	**Cahill (2017)** [46]	**Ayling (2017)** [47]
Corpus	Marketing campaigns of oil majors	Advertisements on APCCCE (coal) and API (petroleum) trade group websites	Five US coal industry corporate advocacy campaign case studies	Corporate websites, blogs, and social media channels of five oil and gas majors	Australian coal industry (Minerals Council of Australia) statements
Time period	N/A (Case studies span ~1998-present)	Spring 2014	N/A (Case studies span ~2008-present)	2016	2013-16
Focus	Brand lessons from oil industry image marketing campaign case studies	Discourses in trade group marketplace advocacy	Rhetorical strategies of US coal industry	Discourse and framing by oil and gas companies	Coal industry discourse in response to fossil fuel divestment activism
Analytic method	Review (not specifically defined)	Circuit of culture discourse analysis	Critical approaches from environmental communication, rhetoric, cultural studies	Critical discourse analysis	Content analysis
Discourses					
Climate Risk				"Risk management lens that downplays the material impact of climate change while foregrounding the economic impacts of mitigation"	
Doubt Mongering			"Corporate ventriloquism": "corporations transmit messages through other entities, usually of their own making, in order to construct and animate an alternative ethos, voice, or identity that advances their interests".		
Free-Market Solutionism				"Free markets = fair and efficient solutions"	
Individualized Responsibility	Employees as global citizenry present corporations as citizens		"Hypocrite's trap": "set of interrelated arguments that attempts to disarm critics of industries…based on the critics' own consumption of or reliance on those goods".	"The world needs more energy (increasing energy demand inevitable)". "Corporations as citizens vs Citizens as consumers". "Supplying energy is a humanitarian project".	Divestment activists are "hypocritical"
Energy Poverty/Prosperity			"Energy utopia": "particular energy source as the key to providing a "good life" that transcends the conflicts of environment, justice, and politics".		"Contribution to the Australian community through exports, wages, jobs, investment, taxes, and royalties, as well as its provision of reliable and affordable electricity for Australian households and businesses". "Concern for the overseas poor".
Energy Utopia					
Fossil Fuel Solutionism				"Fossil fuels must continue to play an integral role in the global economy for the foreseeable future".	Coal is "essential to Australia's past and future development"
Greenwashing/Corporate Symbolic Environmentalism	Green rebranding: showcase investments in clean energy, climate research; conservation grants; scope-1 GHG emissions reductions			"Increasing efficiency and innovating new technologies".	"Support for indigenous youth through employment opportunities"
Scientific/Technological Optimism				"Scientific knowledge and technical expertise".	Innovation: "progress is being made on carbon capture and storage (CCS) and new-generation technologies"
Policy Apocalypse		Industry supporter (America's everyman/everywoman) adversely impacted by environmental regulations. Industry as paternal caretaker for American citizens, under threat by regulation.	"Industrial apocalyptic": "imminent demise of a particular industry, economic, or political system and the catastrophic ramifications associated with that loss".		"Lack of support [for industry] will result in job losses, higher electricity bills, and loss of government revenues"
Technological Shell-Game	Natural gas as "climate-friendly"		"Technological shell game": "misdirection that relies on strategic ambiguity about the feasibility, costs, and successful implementation of technologies in order to deflect attention from environmental pollution and health concerns".	"Renewable energy is expensive and unreliable". "Natural gas is the new coal".	Australian coal "is the cleanest coal in the world"
Whataboutism					
Other					

Table S1, continued.

Author	**Scanlan (2017)** [48]	**Grantham & Vieira Jr. (2018)** [49]	**Jaworska (2018)** [25]	**Lamb *et al.* (2020)** [50]
Corpus	Oil and gas industry advertisements	12 CEO/President welcome letters	Corporate social responsibility and environmental reports of major oil companies	N/A (Theorized taxonomy of discourses of climate delay)
Time period	2000-15	2002 to 2013	2000-13	N/A
Focus	Frames in industry rhetoric on fracking	ExxonMobil's social responsibility communication	Discourses in corporate social responsibility	Discourses of climate delay
Analytic method	Content analysis	Text network analysis	Corpus-linguistic and discourse analyses	Expert elicitation
Discourses				
Climate Risk		"Planet" theme introduces keyword of "risk"	Industry as victim of unpredictable climate "risk"	
Doubt Mongering			Scientific doubt-mongering	
Free-Market Solutionism				"No sticks, just carrots": "we should only pursue voluntary policies ('carrots'), in particular those that expand consumer choices"
Individualized Responsibility			Differentiation: shifting responsibility to other stakeholders (consumers, governments)	"Individualism": "redirects climate action from systemic solutions to individual actions"
Energy Poverty/Prosperity	Natural gas offers "economic development and jobs"; "energy independence and security"		Downplay AGW urgency by foregrounding the economy and energy demand	"Appeal to social justice": "moves social impacts to the forefront of policy discussions, framing a transition to renewable energy as burdensome and costly to society
Energy Utopia				
Fossil Fuel Solutionism			Non-radical changes proposed	"Fossil fuel solutionism": "the fossil fuel industry is "part of the solution to the scourge of climate change""
Greenwashing/Corporate Symbolic Environmentalism			Industry as technological leader of breakthrough solutions. Enthusiasm for breakthrough technological solutions.	"All talk, little action": "points to recent advances in lowering emissions or in setting ambitious climate targets, thus downplaying the need for more stringent or new types of additional action"
Scientific/Technological Optimism	"Faith in science and American ingenuity"			"Technological optimism": "technological progress will rapidly bring about emissions reductions in the future"
Policy Apocalypse				"Appeal to well-being": "climate policy threatens fundamental livelihoods and living standards"
Technological Shell-Game	Natural gas offers "environmental protection and sustainability"			
Whataboutism				"Whatboutism": "Actors [point to] their own small contribution to global emissions"
Other				"'Free rider' excuse": "others will actively take advantage of those who lead on climate change mitigation". "Policy perfectionism": "argues for disproportional caution in setting ambitious levels of climate policy in order not to lose public support". "Change is impossible": "Reifies the current state of things and denies the ability of societies to organize large socio-economic transformations". "Doomism": "any actions we take are too little, too late. Catastrophic climate change is already locked-in"

S1. SUPPLEMENTAL EXPERIMENTAL PROCEDURES

S1.1. Corpora

The 180 ExxonMobil documents analyzed in this study were previously compiled in refs. [1,2]. One 1989 advertisement, however, was here omitted because, as noted in ref. [2], it is not in fact an advertorial, but an advertisement in *The New York Times Magazine* that may or may not have actually included Exxon among its industry sponsors[3].

Unlike advertorials in the *NYT*, peer-reviewed publications disclosed by ExxonMobil Corp, and internal documents recovered to date, all three of which are bound sets, 'non-peer-reviewed' documents analyzed in our original study are virtually limitless in potential number and scope and so are excluded in this study. Indeed, as noted in ref. [1], there are countless additional climate change communications from ExxonMobil that could be included in future work, including as yet undiscovered internal documents, advertorials and advertisements published in outlets beyond the *NYT*, and non-peer-reviewed materials such as speech transcripts, television advertisements, social media posts, patent documents, shareholder reports, and third-party communications (for example, from lobbyists, think-tanks, and politicians funded by ExxonMobil). These documents are potentially important, but are not the focus of the present study.

See section S6, however, for algorithmic analysis of all ExxonMobil Corp flagship reports concerning AGW.

S1.2. Pre-processing

To enable computational analysis in *R*, scanned documents were converted to searchable text files using *Readiris Corporate 17* optical character recognition (OCR) software[4,5]. We then used regular expression search algorithms and manual cleaning to strip out formatting details such as boilerplate archive timestamps and copyright statements; column breaks and whitespaces; author, journal, and publisher information; publication dates; and page numbers. Bibliographies, contents pages, disclosure and acknowledgment statements, appendices, and forewords (unless written by ExxonMobil representatives) were also removed from internal and peer-reviewed documents. In the case of advertorials, company logos and graphics (except for pullout quotations) were removed. Spellcheck was used to identify and correct common OCR-generated errors.

We did not use a stemmer or lemmatiser to reduce related words to their base forms, but we added several synthetic tokens that combine terms of similar cognate form (e.g. "co2" and "carbon dioxide" became "co2/carbon dioxide"; "effect" and "effects" became "effect(s)").

For divergent term analysis (section 2.3), stopwords were not removed. For divergent topic analysis (section 2.4), stopwords were removed, after which word counts of internal and peer-reviewed corpora were respectively scaled down – by randomly sampling the same fraction of words from each document of each corpus – to match one another and to collectively match the word count of advertorials.

Only terms appearing at least 10 times in a corpus were included in document-term matrices.

S1.3 Topic Modeling

S1.3.1 Model selection

LDA topic modeling is performed using the *R* 'topicmodels' package by Grün and Hornik (2011) [6,7]. The units of analysis were individual words. These words were itemized for LDA into 'documents' (as defined by Maier *et al.* (2018)) comprising the original 180 articles[8]. As prescribed by Maier *et al.*, hyperparameter α {0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1} was optimized

by maximizing *intrinsic topic coherence* (as defined by Mimno *et al.* (2011)) for fixed $\beta = 1/K$ and for a range of K values {10, 11,…, 30}[8–10]. For each value of K, models corresponding to the two top-scoring α values were retained. The most appropriate model was then selected based on intersubjective qualitative author judgment, using what Maier *et al.* (2018) term a *substantive search in coherence-optimized candidates*[8]. This involved assessing the interpretability and relative efficacy of the optimized models for each value of K (and two α values) in terms of (a) per-term-per-topic probability distributions ($\phi_{w,k}$) and (b) reordered lists of the top words assigned to each topic using Sievert and Shirley (2014)'s *relevance* metric[11]. Models with $K < 15$ led topics to blur together, while $K > 20$ yielded diminishing returns due to excessive granularity. Final parameters based on this recursive process were $K = 16$, $\alpha = 0.1$, $\beta = 1/K = 10$.

S1.3.2 Topic validation and labeling

The semantics of each topic solution were examined on the basis of (a) authors' expert knowledge about climate (denial) communications and familiarity with the documents; (b) four metrics proposed by Maier *et al.* (2018): (i) *Rank-1*, which counts how many times each topic is the most prevalent in a document; (ii) *intrinsic coherence* of individual topics[10]; (iii) *relevance* (with weighting λ=0.6), which accounts for both per-term-per-topic probabilities ($\phi_{w,k}$) and the marginal probability of each term in the corpus (p_w)[11]; and (iv) *concentration* (Hirschman-Herfindahl Index), which measures the extent to which topics are spread across documents[8]; and (c) LL ratio, which, as previously introduced, quantifies the distinctiveness of topics in one sub-corpus versus the other. Accordingly, three "junk" topics were excluded owing to semantically incoherent word lists, and/or low *Rank-1*, and/or low *coherence*, and/or low LL ratio, and/or high *concentration*.

Remaining topics were validated by intra-topic and inter-topic semantic validity. To evaluate the former, for each topic, we read all documents with relatively large per-document (d)-per-topic (k) probabilities $\theta_{d,k} > 0.2$, with particular attention to terms with high *relevance* scores and that are most exclusive to that topic[8,12]. The guiding questions in our readings were: (i) Is the topic semantically coherent – communicating a substantive theme consistent with the qualitative meaning of the texts?; and (ii) What label should be given to the topic to describe the theme most comprehensively? Table 4 in the main text presents these validated, manually labeled topics. (Note that due to the relatively small corpora under investigation, and, accordingly, a relatively small number of topics emergent from our LDA model, semantic validation based on algorithmic clustering of topics into higher-order themes is not applicable here[8,9,13].)

Finally, following Boussalis and Coan (2016), we evaluated inter-topic semantic validity by comparing LDA model topic assignments against those identified by manual content analysis of a random sample of 72 documents (40% of all documents)[9].

In the pilot phase of human coding, two coders – one author and a research assistant – independently coded 10 randomly selected documents. This involved assigning each document a primary topic of either: one of the 13 topics in table 4; or "other" if none of those LDA model-derived topics meaningfully captured the main theme. The coders then compared and discussed their coding choices. The coders then independently coded an additional 10 randomly selected documents and again reviewed their assignments. Finally, the coders independently coded another 36 randomly selected documents (20% of all documents); the results of this sample were used to calculate intercoder reliability in terms of percentage agreement (81%) and Krippendorf's α coefficient (0.79) using ReCal2 online software[14–16]. Through "negotiated agreement" of discrepancies between coders, intercoder agreement was also calculated (89%; $\alpha = 0.88$)[17].

Having achieved satisfactory intercoder reliability and agreement, one of the coders proceeded to code an additional 36 randomly selected documents. These results, combined with those of the previous 36 coded documents, yielded a sample of 72 randomly coded documents (40% of all documents, including: 47% of internal documents; 44% of peer-reviewed publications; and 33% of advertorials). This sample was then compared against our LDA model's assignments. We find the microaveraged precision and recall for primary topic classifications to be 0.59 and 0.60, respectively. Although these values are lower than common cutoffs of 0.7 to 0.8, they are comparable to those reported by Boussalis and Coan (2016) and are considerably better than rolling a 13-sided dice[9,18].

Moreover, as Boussalis and Coan (2016) note, "assessing a topic model using only the primary topic offers a conservative estimate of performance. Several distinct themes often contribute to a document's composition and deciding which is 'primary' is often quite difficult for both human and machine. Indeed, allowing documents to be composed of multiple topics…is one of the major advantages of using the LDA"[9]. When we account for the two most probable topics identified by our LDA model, the proportion of documents correctly recalled rises to 0.74.

Figure S1 displays the relative prevalence of LDA-generated topics over time in (a) advertorials and (b) internal and peer-reviewed publications. Although, as noted in section S1.4.1, these trends fall short of a comprehensive longitudinal frame analysis and as such should be interpreted with caution, the topic proportions in fig. S1a nevertheless suggest some initial insights. We see, for example, that the topics of 'Climate science uncertainty' and 'AGW science/projections' are interwoven throughout both Mobil's advertorials in the 1990s and ExxonMobil Corp's advertorials in the 2000s. We also observe the strong emergence of the 'Climate policy' topic in the run up to and wake of the 1997 UN climate negotiations in Kyoto. Even more apparent is an ever-growing dominance of the 'Energy/emissions challenge' topic throughout the 2000s.

These trends are broadly consistent with (i) our observations during 'frame package' open-coding of shifts in the relative prevalence of ExxonMobil's public framing devices over time; (ii) our past codings of ExxonMobil's public positions on climate change over time (Supran and Oreskes (2017, 2020))[1,2]; and (iii) Schlichting (2013)'s observations of industry actors' shifting climate change "master frames" over time[29]. The trends we observe paint an overall picture of coevolving topics – and, by approximate extension, frames – whose center of mass has gradually shifted away from explicit attacks on science (represented by our Scientific Uncertainty frame) and towards subtler narratives about energy and emissions (represented by our Socioeconomic Threat and Fossil Fuel Savior frames).

S1.3.3 Log-likelihood ratios of topic weights

We compute LL ratios of topic weights by constructing document-topic matrices for each of sub-corpora α and β. In these matrices, we include only those topics whose weights correspond to ≥1% of each sub-corpus's total word count.

S1.4 'Frame package' analysis

As noted above, due to the relatively small corpora under investigation, a relatively small number of interpretable topics emerge from our LDA model. We therefore adopt a qualitative approach to inductive frame analysis rather than, for instance, algorithmically clustering topics into frames.

The units of analysis in our frame package analysis were individual advertorials. The unit of observation was the advertorial corpus.

S1.4.1 Open-coding

We conducted open-coding using *NVivo* digital annotation software, and used corpus linguistic tools to systematize the process in two ways[19].

First, we used FS and LL as statistical methods for extracting central meanings and locating potential frames; and ran concordance searches to automatically collect text extracts for frame analysis[20,21]. Although we analyzed each advertorial in its entirety, this approach helped us identify the loci for frames. Touri and Koteyko (2015) have previously demonstrated the efficacy of combining LL analysis with the frame package approach in this way[22]. Indeed, this was a mutually reinforcing process in that open-coding aided contextual interpretation of how divergent terms identified by FS and LL analysis construct meanings.

Second, and in parallel, we used LDA analysis to extract topics that may generally be regarded as "frame elements [or] a full frame package, or…a combination of the two" (Walter and Ophir (2019))[12]. Just as divergent terms from FS and LL help extract central meanings and locate potential frames, "regularities of [word] co-occurrence" in topic models, write Klebanov *et al.* (2008), "are considered in some linguistic theories as the major building block for characterizing meaning; this idea is well expressed in the famous distributional hypothesis: "Know the word by the company it keeps""[23]. Thus, in order to further help detect frames shaped by lexical composition, we also ran concordance searches based on LDA top words to automatically collect text extracts for frame analysis. As Van Gorp (2010) notes, "[t]he intention of an inductive framing analysis is to reconstruct the frames that are useful to define a certain topic"[24]. We therefore open-coded together documents sharing similar LDA topic weightings, which tend to display recurring linguistic elements or framing/reasoning devices indicative of frame packages[12,24].

We further investigated discursive constructs by performing collocation searches using the logDice statistic applied to corpora tokenized by sentence[25–27].

Our inventory resulting from open-coding comprised manifest framing devices such as catchphrases, lexical choices, visual images, depictions, metaphors, and exemplars; and (often latent) reasoning devices in the form of apparent definitions of the AGW problem, assignments of responsibility for causing it and/or solving it, identifications of solutions, and moral assessments. As Entman, Matthes, and Pellicano (2009) note, a defining feature of a frame is that it "repeatedly invokes the same objects and traits, using identical or synonymous words and symbols…"[28]. The linguistic tools employed in this study are amenable to the detection of such cues, and therefore to the identification and differentiation of frames from other features such as themes, arguments, and assertions.

Digital annotation during open-coding allows us to code the dates of all entries in this inventory. Following Schlichting (2013), this offers insights into how ExxonMobil's public frames have shifted over time[29]. The primary contribution of our inductive frame analysis, however, is its frame matrix, which may serve as the basis for a coding scheme in future quantitative, deductive, and fully longitudinal content analyses[24,30].

S1.4.2 Axial coding

We codify our axial codings with reference to an inventory of discourses that we assembled based on an informal literature review of past studies of AGW communications by fossil fuel interests[24]. A summary of discourses identified by this literature review is provided in section S3.

S2. SUPPLEMENTAL DIVERGENT TERM ANALYSIS RESULTS

S2.1. Mobil versus ExxonMobil Corp advertorials

In section 2.1.1, we note that because both Mobil and ExxonMobil Corp advertorials often promoted doubt about climate science, terms conveying explicit doubt are common to both corpora and so do not appear in table 1. One example of this is the term "debate", which appears $n_{EM} = 9$ times in ExxonMobil Corp advertorials and $n_M = 17$ times in Mobil advertorials. This corresponds to $FS = 0.37$ and $G_2 = -1.69$, indicating statistically insignificant divergence ($p = 0.24$ and 0.19, respectively). Likewise, "uncertain(/ty/ties)" appears $n_{EM} = 13$ and $n_M = 18$ times, equivalent to $FS = 0.44$ ($p = 0.59$) and $G_2 = -0.35$ ($p = 0.55$). Other common terms displaying statistically insignificant divergence include "(un)know(/n/ing/ledge)", "believe", "compl(ex/exity/icated)", "answer(s)", etc.

S2.2. Advertorials versus internal and peer-reviewed documents

In section 2.4, we observe that ExxonMobil's advertorials statistically overuse terms that reduce AGW to a downstream problem caused by consumer energy demand. We here note that advertorials do, in fact, contain divergent terms of "oil and natural gas" (compared to internal and peer-reviewed publications – see tables 2 and 3) and "fossil fuels" (compared to peer-reviewed publications – see table 3). In the majority of cases, however, these terms are employed in discourses such as Energy Poverty/Prosperity ("Abundant and affordable, fossil fuels have contributed to unprecedented prosperity for much of the human race. In decades to come, the benefits of modern fossil fuel energy will extend even further" [152]); Policy Apocalypse ("World economic health will suffer as nations are forced to switch from fossil fuels…" [181]); and Greenwashing/Symbolic Corporate Environmentalism ("ExxonMobil is also leading the way in increasing safety and reducing marine spills in the oil and natural gas industry."[137,138]). Such examples do not speak to the cause of – or accountability for – AGW or greenhouse gas emissions. If anything, they generally reinforce the narrative that fossil fuels passively satisfy demand; for example: "[F]ossil fuels…[f]or at least several decades, they will continue to be the major source of the world's energy needs"[128]. The number of cases concerning responsibility for AGW or greenhouse gases is statistically insignificant even at $p \leq 0.05$ levels ("oil and natural gas": LL ~ 0.01, FS ~ 0.53; "fossil fuels": LL ~ 2.79, FS ~ 0.63). Virtually all such cases appear in advertorials that simultaneously promote doubt about whether AGW is real and human-caused and/or serious and/or solvable.

S3. LITERATURE REVIEW OF FOSSIL FUEL INDUSTRY AGW DISCOURSES

As noted in section S1.3.2, frame package analysis was guided by an informal literature review of existing studies of AGW communications by fossil fuel interests. Table S1 summarizes the results of this meta-analysis of contemporary (~1990–present) discourses. The scope of this review was limited to publications concerning AGW communications by fossil fuel producers. 15 such studies were investigated. For studies regarding discourses of climate denial and delay by a broader range of actors, such as conservative news media, columnists, think tanks, and other industries, see for example refs. [9,13,31–36]. For a review of AGW framing and discourse literature as a whole, see for example ref. [37]. For detailed taxonomies of Doubt Mongering discourse, as labeled in table S1, see ref. [1] and several of the foregoing references.

S4. FRAME PACKAGE ANALYSIS RESULTS

The following are frame matrices summarizing framing and reasoning devices of each identified frame package.

S4.1 Scientific Uncertainty Frame

Table S2. Frame matrix of Scientific Uncertainty frame package.

Scientific Uncertainty Frame Package		
Reasoning Devices	Description	
Problem	Global warming is unproven	
Cause	Global climate system is complex, science is unsettled	
Moral evaluation	We don't know enough	
Solutions	Wait for better climate science research	
Framing Devices	Discourse	Example/Description
Catchphrases & lexical choices	Climate Risk	"Risk(s) of climate change" "Longterm"
	Doubt Mongering	"Debate" "Gap(s)"
	Scientific/Technological Optimism	"Invest(ing/ment(s))" "Promise"
Visual images	Doubt Mongering	Graphs and charts
	Scientific/Technological Optimism	Graphs and charts
Exemplars	Doubt Mongering	Quotations of contrarian scientists (e.g. Heidelberg Appeal; S Fred Singer)
Depictions	Climate Risk	Amorphous "risk(s)" of AGW
	Scientific/Technological Optimism	Dynamic "breakthrough" university research collaborations
Metaphors	Doubt Mongering	"Weather and climate"; "Climate change: a degree of uncertainty"
Example discourse quotations		
Climate Risk	"[C]limate changes may pose long-term risks. Natural variability and human activity may lead to climate change that could be significant and perhaps both positive and negative."[51]	
Doubt Mongering	"Weather and climate. In the debate over climate change, there is an understandable tendency to use recent weather events to draw conclusions about global warming."[52]	
Scientific/Technological Optimism	"To address the scientific uncertainty, governments, universities and industry should form global research partnerships to fill in the knowledge gap, with the goal of achieving a consensus view within a defined time frame."[53]	

The Scientific Uncertainty frame presents AGW as unproven and, accordingly, advocates additional climate science research before any policy action is taken.

Central to this frame's problem definition and causal attribution is the discourse of 'Doubt Mongering', which promotes false scientific debate about whether AGW is real and human-caused. One example, a 2004 ExxonMobil Corp advertorial entitled "Weather and climate", argued that "In the debate over climate change, there is an understandable tendency to use recent weather events to draw conclusions about global warming"[52]. At work here are the key framing devices of catchphrases (such as "debate") and metaphors (such as "weather and climate"). The advertorial goes on to insist that "in the face of natural variability and complexity, the consequences of change in any single factor, for example greenhouse gases, cannot readily be isolated and prediction becomes difficult... scientific uncertainties continue to limit our ability to make objective, quantitative determinations regarding the human role in recent climate change or the degree and consequences of future change". Visual images (such as graphs and charts) and exemplars (such as quotations of the minority opinions of contrarian scientists) help falsely legitimize such claims.

Discourses of 'Scientific/Technological Optimism' and 'Climate Risk' help further the impression of scientific debate while simultaneously prescribing the moral evaluation that enough is not yet known to take any policy actions, and the solution of further scientific research. "To address the scientific uncertainty", reasons a 2007 advertorial, "governments, universities and industry should form global research partnerships to fill in the knowledge gap, with the goal of

achieving a consensus view within a defined time frame."[53] Such Scientific/Technological Optimism repeatedly alleges "gap(s)" in scientific knowledge and emphasizes the "promise" of "breakthrough" research collaborations. The "risk" rhetoric that emerges in ExxonMobil Corp advertorials serves similar dual functions of presenting AGW as a risk rather than a reality and of thereby rationalizing research rather than policy action, as discussed in section 3.1. As a 2000 advertorial entitled "Unsettled Science" puts it, "[C]limate changes may pose long-term risks. Natural variability and human activity may lead to climate change that could be significant and perhaps both positive and negative."[51] ExxonMobil Corp accordingly argue that "future scientific research will help understand how human actions and natural climate change may affect the world and will help determine what actions may be desirable to address the long-term".

S4.2 Socioeconomic Threat Frame

Table S3. Frame matrix of Socioeconomic Threat frame package.

Socioeconomic Threat Frame Package		
Reasoning Devices	Description	
Problem	Climate policy threatens prosperity	
Cause	Alarmist policy and politics are outrunning science	
Moral evaluation	Binding climate policies are unwarranted and economically dangerous	
Solutions	Voluntary efforts, especially energy efficiency	
	Technology R&D	
	No policy exemptions for developing countries	
Framing Devices	Discourse	Example/Description
Catchphrases & lexical choices	Climate Risk	"Risk(s) of climate change"
		"Longterm"
	Energy Poverty/Prosperity	"Developing/poorer countries/world/nations"
		"Affordable"
	Free-Market Solutionism	"Voluntary steps"
		"Free market"
	Policy Apocalypse	"Economic impact"
		"Jobs/employment"
	Scientific/Technological Optimism	"Develop"
		"Innovat(e/ion(s))"
	Whataboutism	"Developing/poorer countries/world/nations"
		"All nations"
Exemplars	Policy Apocalypse	Projected hardships on U.S. economy and livelihoods
	Whataboutism	Projected emissions of developing countries
Depictions	Climate Risk	Amorphous "risk(s)" of AGW
	Energy Poverty/Prosperity	Concrete benefits of energy allegedly in jeopardy
		Dire forecasts for developing countries
	Free-Market Solutionism	Voluntary, free-market responses
	Policy Apocalypse	Concrete alleged costs of climate policy
	Scientific/Technological Optimism	Company scientists committed to "decades" of technology R&D
		University research collaborations
Example discourse quotations		
Climate Risk	"Businesses, governments and NGOs are faced with a daunting task: selecting policies that balance economic growth and human development with the risks of climate change."[54,55]	
Energy Poverty/Prosperity	"A global approach [to "addressing the risk of climate change"] is needed that recognizes...the need for developing countries to weigh emissions control against energy-intensive economic development which lowers poverty and improves public health."[56]	
Free-Market Solutionism	"Governments should…harnes[s] free markets and voluntary measures…[and] encourage and promote voluntary actions by industry and citizens that reduce emissions and use energy wisely."[53]	
Policy Apocalypse	"Committing to binding targets and timetables now will alter today's lifestyles and tomorrow's living standards...Carpooling in; sport utility vehicles out. High fuel and electric bills. Factory closures. Job displacement...[T]ax or carbon rationing...".[57]	
Scientific/Technological Optimism	"[W]e believe that technology provides the key avenue to solutions that manage long-term risk and preserve prosperity. [This] will almost certainly require decades…".[58]	
Whataboutism	"At what point will developing nations begin to participate in emission-reduction activities?"[59]	

The Socioeconomic Threat frame argues that binding climate policies (such as the Kyoto Protocol) are alarmist and threaten prosperity, urging voluntary measures instead.

Central to this frame is the discourse of 'Policy Apocalypse', which depicts dramatic socioeconomic decline due to climate policies on what Schlichting (2013) observes to be both national (macro) and individual (micro) economic levels[29].

On the macro level, catchphrases of Policy Apocalypse articulating the "economic impact" that climate policies would bring, for example on "jobs/employment", were given added credence by exemplar figures from economic studies. One 1997 advertorial, for instance, cited a study by Charles River Associates predicting "an annual drop in gross domestic product ranging from $105 billion in the year 2010 to $460 billion in 2030", "depending on the timing and severity of the plan selected" to limit emissions[60]. Another advertorial the following year warned that WEFA, Inc. "estimates the cost of achieving the Kyoto target by 2010 would result in a loss of 2.4 million jobs, a doubling of electricity prices and an annual loss in economic output of $300 billion…"[61]. ExxonMobil also made broader moral appeals, such as a 2000 advertorial calling on

policymakers to "Do No Harm"[62]. A key thrust of their argument was that policies such as the Kyoto Protocol could "entail enormous transfers of wealth [from the United States] to other countries".

On the micro level, advertorials depicted damage to individuals' wealth and wellbeing. **"**Committing to binding targets and timetables now will alter today's lifestyles and tomorrow's living standards...", said a 1997 advertorial[57]. "Carpooling in; sport utility vehicles out. High fuel and electric bills. Factory closures. Job displacement...[T]ax or carbon rationing...".

ExxonMobil's scaremongering is offset by, at best, 'Climate Risk' discourse, and at worse, explicit climate denial (which was commonplace through the mid-2000s). As a result of this imbalanced alleged dichotomy, the frame's moral evaluation is that any ambiguous, uncertain "risk(s)" of AGW are outweighed by severe economic damages threatened by mandatory climate policies. Such policies are therefore unwarranted and economically dangerous.

They are also ineffective, 'Whataboutism' discourse argues. For example, quoting a report by The Business Roundtable, Mobil wrote in a 1998 advertorial that "'Without full participation by developing countries, the Kyoto Protocol will not lead to a net reduction of global…emissions.'…The Protocol uses 'differentiated targets' for countries to meet, which potentially could put the U.S. at a disadvantage."[63] Thus, Whataboutism, which also displays elements of discourses that Lamb *et al.* (2020) term "The 'free rider' excuse" and "Policy perfectionism", effectively extends the economic scaremongering arguments of Policy Apocalypse discourse, but does so by directly questioning the efficacy of proposed policies rather than simply highlighting their alleged societal costs[50]. The issue is further confounded by Energy Poverty/Prosperity discourse, which tends to imply that alternative binding policies including developing countries would not be viable either. "Kyoto failed to include developing countries", said an advertorial in 2000. "Yet poorer countries need more energy if they are to provide economic growth and a better life for their people", implying that developing countries should not be included after all.

The only solutions, then, according to Discourses of 'Science/Technology Optimism' and 'Free Market Solutionism', are "voluntary steps". "[I]t is time to move beyond Kyoto", the 2000 advertorial above concludes. "[W]e believe that technology provides the key avenue to solutions…", said a 2002 advertorial[58]. "Governments should…harnes[s] free markets and voluntary measures…", argued another in 2007[53].

S4.3 Fossil Fuel Savior frame

Table S4. Frame matrix of Fossil Fuel Savior (FFS) frame package.

Fossil Fuel Savior (FFS) Frame Package		
Reasoning Devices	Description	
Problem	Climate change is a (potential long-term) risk	
Cause	Consumer energy demand	
Moral evaluation	Climate risk is an energy technology/efficiency challenge in pursuit of energy prosperity	
Solutions	Continued fossil fuels for decades to come	
	Technology innovation in a free-market	
	Individualized energy efficiency improvements	
Framing Devices	Discourse	Example/Description
Catchphrases & lexical choices	Climate Risk	"Risk(s) of climate change"
		"Longterm)"
	Individualized Responsibility	"(Energy) demand"
		"Energy use"
		"Needs"
		"To meet"
	Energy Poverty/Prosperity	"Prosperity"
		"Poor/poverty/lack"
	Fossil Fuel Solutionism	"Oil and gas/natural gas"
		"For generations/foreseeable future/several decades/decades to come/next 25 years"
	Policy Apocalypse	"Economic growth/impact"
		"Wise(r)/prudent/reasonable/responsible/sound(er)"
	Greenwashing/Corporate	"Steps"
	Symbolic Environmentalism	"Tree(s)"
	Scientific/Technological	"New/advanced technolog(y/ies)"
	Optimism	"Solutions"
	Technological Shell-Game	"Natural gas"
		"Limitations/obstacles/barriers/cannot compete"
Visual images	Scientific/Technological	Graphs and charts
	Optimism	Science iconography
Exemplars	Fossil Fuel Solutionism	Conservative clean energy projections
	Greenwashing/Corporate	Donations to environmental initiatives
	Symbolic Environmentalism	Reports of company energy efficiency efforts
		Corporate social responsibility actions and pledges such as "math and science" "education" initiatives
	Individualized Responsibility	Projected energy demand growth
		Personal energy conservation tips
Depictions	Climate Risk	Amorphous "risk(s)" of AGW
	Energy Poverty/Prosperity	Concrete benefits of energy allegedly in jeopardy
		World's poor reliant on fossil fuels for decades to come
	Fossil Fuel Solutionism	Society reliant mostly on fossil fuels for decades to come
	Technological Shell-Game	Renewable energy supply negligible for decades to come
	Scientific/Technological	Photographs of company scientists as face of technology R&D
	Optimism	Dynamic "breakthrough" university research collaborations
Example discourse quotations		
Climate Risk	"[W]e'll need more energy to power our homes, businesses and industries, and to fuel our transportation needs…while addressing the risks posed by rising greenhouse gas emissions…".[64]	
Energy Poverty/Prosperity	"[G]lobal carbon-dioxide emissions are expected to rise through 2030. This is particularly true in developing countries, which will rely on relatively carbon-intensive fuels like coal to meet their needs."[64]	
Fossil Fuel Solutionism	"Oil and gas will be essential to meeting demand."[65]	
Individualized Responsibility	"[G]rowing demand will boost CO_2 emissions."[64]	
Greenwashing/Corporate Symbolic Environmentalism	"For five years we have partnered with the group American Forests to plant trees…this year the partnership planted its two millionth tree."[66]	
Scientific/Technological Optimism	"[W]e believe that technology provides the key avenue to solutions that manage long-term risk and preserve prosperity. [This] will almost certainly require decades…".[58]	
Technological Shell-Game	"[T]echnological progress in these conventional fuels ["oil and natural gas"] holds immediate potential to help reduce emissions on a significant scale…[T]his clean and abundant resource [of "natural gas"] is helping meet our energy and environmental goals."[67]	

S5. DISCOURSES OF DELAY

Each of the following tables displays a selection of highly divergent terms in advertorials, by Log-Likelihood ratio (G^2) and Frequency Score (FS), identified by frame package analysis as framing devices of each of the discourses displayed in figure 1 of the main text. Definitions of each discourse are provided in the captions of respective tables (see table S1 for supporting literature). P-values: * <0.005; ** <0.05; ***≥0.05; otherwise, <0.001 for all G^2 and FS scores.

Table S5. Rhetoric of Climate Risk. Example quotations illustrate how advertorials use divergent terms to present AGW or greenhouse gases as a "(long-term) risk".

Climate Risk rhetoric

Advertorials often say:

	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
risk(s)	49	7	261	72.48 / 56.56	0.93 / 0.8	"Enough is known about climate change to recognize it may pose a legitimate long-term risk, and that more needs to be learned about it."[62]
climate (change) risk(s)/ risk(s) of climate	26	0	10	57.89 / 119.09	1 / 0.98	"It is our view that better scientific understanding of climate change, human influence on it, and the associated risks and possible consequences are needed. We are heavily involved in such scientific research...But we are also taking other actions to minimize the risks of climate change."[68]
longterm	40	17	282	33.14 / 31.82	0.83 / 0.75	" In releasing this [National Assessment Synthesis] report, the [Clinton] administration seeks to gain support for its own [climate] policies, which could damage the economy and employment while accomplishing little in addressing potential long-term climate risks."[69]

Table S6. Rhetoric of Doubt Mongering. Example quotations illustrate how advertorials use divergent terms to promote doubt about climate science and its implications.

Doubt Mongering rhetoric

Advertorials often say:

	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
dont	24	2	0	40.93 / 148.34	0.96 / 1	"We still don't know what role man-made greenhouse gases might play in warming the planet."[57]
improv(e/es/ed/ing/ements)	73	54	500	32.35 / 60.65	0.73 / 0.75	"...improve our understanding of the science of this complex issue."[68]
doom(sday/sdayers)/apocalypse/ hype/scare	11	0	0	24.49 / 67.99	1/1	"Apocalypse no. For the first half of 1992, America was inundated by the media with dire predictions of global warming catastrophes...".[70]
debate	26	12	30	20.05 / 86.15	0.82 / 0.95	"Weather and climate. In the debate over climate change, there is an understandable tendency to use recent weather events to draw conclusions about global warming...".[52]
answer(s)	22	9	22	18.8 / 77.03	0.83 / 0.95	"Within a decade, science is likely to provide more answers on what factors affect global warming...".[71]
believe	21	9	18	17.28 / 77.64	0.83 / 0.96	Quoting Freeman J Dyson: "[C]limate models...are unreliable...[W]e must continue to warn the politicians and the public don't believe the numbers just because they come out of supercomputer".[69]
(un)know(/n/ing/ledge)	57	66	330	9.63* / 59.52	0.64* / 0.78	"[F]undamental gaps in knowledge leave scientists unable to make reliable predictions about future [climatic] changes."[51]
gap(s)	11	7	39	6.01** / 18.93	0.76** / 0.86	"...better delineating gaps and uncertainties that limit our current ability to know the extent to which humans are affecting climate and to predict future changes caused by both human and natural forces."[72]
better science/understanding	6	NA	10	NA / 16.85	NA / 0.93	"Concern over global climate change is triggering actions...Better science and flexible timing also need to be part of the mix."[73]
agree(ment)/consensus	35	45	338	4.12** / 15.55	0.61** / 0.68	"[T]here is no consensus on what constitutes "dangerous levels" of emissions nor is there agreement on when, where and how best to reduce their impact."[60]
compl(ex/exity/icated)	18	NA	165	NA / 8.96*	NA / 0.7*	"Climate science remains extraordinarily complex."[54,55]
natural causes/phenomen(on/a)/ climate/variability/and manmade	16	NA	159	NA / 6.66**	NA / 0.68**	Research "[p]rograms should concentrate on factors that seriously limit current understanding [of AGW]. These include the effects of clouds, aerosols, sea ice, deep-ocean circulation, hydrology and natural climate variability."[74]

Table S7. Rhetoric of Energy Poverty/Prosperity. Example quotations illustrate how advertorials use divergent terms to present energy – and typically, by extension, fossil fuels – as essential to well-being and social justice.

Energy Poverty/Prosperity rhetoric

Advertorials often say:

	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
developing/poorer countries/world/nations	53	3	196	97.01 / 88.01	0.97 / 0.85	"Energy demand is expected to be 35 percent higher in the year 2030…driven largely by people in the developing world seeking higher standards of living."[75]
challenge(s)	56	5	100	94.08 / 151.75	0.96 / 0.92	"A key goal of our citizenship strategy is addressing the challenge of sustainability balancing economic growth, social development and environmental performance while continuing to deliver superior shareholder returns so that future generations are not compromised by actions taken today."[76,77]
prosperity	15	0	1	33.4 / 85.32	1 / 1	"[G]lobal energy needs are rising, with increasing prosperity in the developing world the main driver of greater energy demand (and consequently rising CO_2 emissions) over the coming decades."[56]
social	22	6	201	24.67 / 11.03	0.88 / 0.7	"[E]fforts to control emissions have important economic and social consequences."[74]
affordable	11	0	6	24.49 / 46.47	1 / 0.97	"Balacing the long-term risks of climate change against society's need for unsubsidized but affordable energy…".[58]
living standard(s)/ standard(s) of living/ quality of life	10	0	0	22.27 / 61.81	1 / 1	"[S]cientists work to provide more definitive answers on the impact that these [greenhouse] gases and other factors may have on our climate system. Let's wait for more answers before taking on obligations that could jeopardize better living standards for all."[78]
poor/poverty/lack	11	7	0	6.01** / 67.99	0.76** / 1	"A global approach [to "addressing the risk of climate change"] is needed that recognizes...the need for developing countries to weigh emissions control against energy-intensive economic development which lowers poverty and improves public health."[56]

Table S8. Rhetoric of Fossil Fuel Solutionism. Example quotations illustrate how advertorials use divergent terms to present fossil fuels and their industry as an essential and inevitable part of the solution to AGW.

Fossil Fuel Solutionism rhetoric

Advertorials often say:

	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
oil and (natural) gas	28	3	92	45.02 / 51.24	0.95 / 0.86	"As Americans look for ways to access more supplies of reliable, affordable energy while at the same time reducing emissions, answers are emerging from what may seem an unlikely source - the oil and natural gas industry."[67]
clean(er)	14	0	36	31.17 / 30.59	1 / 0.89	"[D]iesel could become a viable player, providing motorists with a clean, efficient option."[79]
through/by/in the year 2030	22	9	113	18.8 / 26.47	0.83 / 0.8	"Wind and solar…meet about 1% of total world demand by 2030. Close to 60% to be met by oil and natural gas."[80–82]
continued/continue to	23	10	123	18.69 / 26.43	0.82 / 0.8	"Oil, natural gas and coal will remain essential…In 2030, these fuels will continue to provide approximately 80 percent of the world's energy…".[64]
for generations/foreseeable future/several decades/decades to come/next 25 years	12	3	28	14.1 / 27.91	0.89 / 0.9	"Battery technology just cannot compete with internal combustion engines today or in the foreseeable future…".[83]
fossil fuels	24	NA	149	NA / 22.89	NA / 0.77	"Fossil fuels must be relied upon to meet society's immediate and near-term needs."[84]
rel(y/ied)	8	NA	39	NA / 10.19*	NA / 0.81*	"Among the more promising approaches to addressing the risks of climate change are those that rely upon economically attractive actions and advanced technology. One good example is the increasing use of cogeneration units."[85]

Table S9. Rhetoric of Free-Market Solutionism. Example quotations illustrate how advertorials use divergent terms to denounce restrictive measures and instead promote voluntary/free-market policies.

Free-Market Solutionism rhetoric

Advertorials often say:

	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
mandat(e/es/ed/ing)	15	1	10	26.72 / 59.99	0.97 / 0.97	"[w]e ask the Kyoto delegates to avoid mandates based on uncertain science…".[53]
voluntarily reduce(d) / voluntary initiative/step/measure/action/ effort/approache/use/usage(s)	12	0	7	26.72 / 49.81	1 / 0.97	"[W]e support voluntary efforts to reduce emissions."[61]
bind(ing)/rigid	11	0	11	24.49 / 38.51	1 / 0.95	"Instead of rigid targets and timetables, governments should consider alternatives, including: adopt consensus objectives: encourage voluntary initiatives and government-industry partnerships…".[86]
market(place/-based)	5	NA	13	NA / 10.84	NA / 0.89*	"[G]overnment policies should support long-term research on alternatives but let the marketplace decide which technical approach will gain commercial and consumer acceptance."[84]
flexible	7	NA	33	NA / 9.24*	NA / 0.82*	"These suggestions...avoid regulatory strait-jackets and invite participation by all nations. Because they are flexible, policies can change as experience and knowledge are gained."[74]

Table S10. Rhetoric of Greenwashing/Symbolic Corporate Environmentalism. Example quotations illustrate how advertorials use divergent terms to communicate symbolic corporate environmentalism, including greenwashing. Bowen (2014) defines symbolic corporate environmentalism as "the shared meanings and representations surrounding" "changes made by managers inside organizations that they describe as primarily for environmental reasons" [87]. Greenwashing is a subset of symbolic corporate environmentalism "in which the changes are both 'merely symbolic' and deliberately so".

Greenwashing/Symbolic Corporate Environmentalism rhetoric

Advertorials often say:

	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
percent	104	9	39	175.94 / 478.85	0.96 / 0.98	"Across our operations, we reduced the number of oil spills by 21 percent from 2005 and by an average of over 10 percent annually since 2000."[88]
energy efficien(cy/t)/us(e/age)	56	5	246	94.08 / 79.39	0.96 / 0.83	"We have developed global energy-management system to identify opportunities to further reduce energy use. Energy efficiency has already improved 35 percent in our refineries and chemical plants since the 1970s."[68]
new/advanced technolog(y/ies)	40	2	42	74.58 / 137.51	0.98 / 0.95	"[T]here men and women [at ExxonMobil] are developing amazing new technologies for finding and delivering energy, as well as innovations that will allow us to use energy more efficiently."[89]
steps	36	1	36	71.76 / 126.05	0.99 / 0.95	[W]e have taken steps to reduce our own emissions and initiate reforestation programs."[90]
cut	19	0	9	42.31 / 83.11	1 / 0.98	"In the last three years, we've cut our carbon emissions by more than one million metric tons...".[91]
invest(ing/ment(s))	27	4	243	39.46 / 13.96	0.93 / 0.7	"[W]e're now making the largest ever investment in independent climate and energy research that is specifically designed to look for new breakthrough technologies."[80–82]
tree(s)	28	5	141	38.26 / 34.44	0.92 / 0.81	"In support of American Forests [charity], Mobil this year will fund the planting of 500,000 trees in watersheds, state and national forests and wildlife refuges...".[92]
gcep	17	0	1	37.85 / 97.44	1 / 1	The "Global Climate and Energy Project (GCEP) based at Stanford University...brings together some of the world's best scientific and engineering minds to address this pressing challenge...ExxonMobil is proud to be its lead developer and sponsor...".[93]
hydrogen/fuel cell(s)	26	5	314	34.48 / 6.29**	0.91 / 0.63**	At the "Global Climate and Energy Project (GCEP), initiated at Stanford University in 2002 with the intention of ExxonMobil...[r]esearchers are investigating the use of genetically engineered bacteria to capture solar energy and produce hydrogen...".[94]
improv(e/es/ed/ing/ements)	73	54	500	32.35 / 60.65	0.73 / 0.75	"Mobil 1 AFE [gasoline] can improve fuel economy by up to 2 percent...if one-third of U.S. motorists reduced their gasoline by 2 percent, almost...8 million tons of CO_2 emissions would be saved every year."[95]
innovat(e/ion(s))	17	1	93	30.93 / 19.02	0.97 / 0.79	"Other innovations are still emerging. One is a new engine technology...The result: up to 30 percent better fuel economy and lower emissions."[96]
fuel economy	13	0	63	28.95 / 16.67	1 / 0.81	"ExxonMobil is taking [steps] to address the risk of climate change. These include[e] working to improve energy efficiency and fuel economy...".[97]
cogeneration	12	0	26	26.72 / 29.19	1 / 0.91	"We now have interest in 4300 megawatts of energy-efficient cogeneration facilities globally - enough to reduce global carbon-dioxide emissions by over 10.5 million metric tons annually...".[88]
education	12	0	28	26.72 / 27.91	1 / 0.9	"Over the long-term, investments such as these could also yield real progress in developing the new technologies needed to address global challenges such as climate change...By investing more in math and science education, we can...solve tomorrow's tough challenges...".[98]
stanford	14	1	0	24.62 / 86.53	0.97 / 1	"With initial funding of $225 million [from ExxonMobil and other companies], the Global Climate and Energy Project (GCEP) will unleash the creativity of faculty and students at Stanford and other universities...". Advertorial signed by "Dr. Lynn Orr, GCEP Project Director, Stanford University."[99]
sav(e/ed/ing)	14	1	51	24.62 / 23.55	0.97 / 0.85	"Saving and preserving forests and trees are long-term endeavours. But we are hopeful, and optimistic, that planting trees now will be planting a better future around the world."[66]
protect(/ion/ing)	26	10	109	23.32 / 38.56	0.84 / 0.83	"Many groups work to protect and to expand forests. ExxonMobil is proud to say that we are one of them."[66]
math and science	10	0	0	22.27 / 61.81	1 / 1	"Sustainability means balancing economic, environmental and social goals...[W]e are a leading supporter of math and science education...".[76,77]
plant(ing)	21	7	NA	20.84 / NA	0.86 / NA	"We intend to sponsor several projects to plant and protect trees in the U.S. and internationally."[78]
partner(/ing/ship)	12	1	13	20.47 / 40.76	0.96 / 0.95	"[O]ur scientists and engineers are...[P]artnering with with the U.S. Environmental Protection Agency and Department of Energy in the "Smartway" partnership to improve fuel economy and reduce emissions associated with the transportation of our products."[100]
initiative(s)	18	5	35	19.98 / 46.59	0.88 / 0.92	"Working with leading environmental groups, Mobil will underwrite international projects to plant and protect trees which absorb significant amounts of CO_2. Initiatives like these, which are good for the environment, can be taken while the debate continues."[101]
operations	11	3	99	12.33 / 5.69**	0.88 / 0.7**	" At ExxonMobil, we are taking action...deploying energy-efficient technologies across our global operations...".[56]
universit(y/ies)	23	16	9	11.15 / 104.97	0.75 / 0.98	"[W]e are supporting climate-related research at major universities, including Stanford and MIT."[72]
sponsor/fund/invest/ underwrite/grant(/ed/ing)	34	41	41	5.04** / 110.65	0.63** / 0.95	"We are funding research into the scientific and economic consequences of climate change."[102]
environment(/al/ally)	84	112	527	8.53* / 79.01	0.61* / 0.77	"We all share the same goal: protecting Earth's environment while raising living standards for all."[101]
effort(s) to	18	11	44	10.34* / 40.65	0.77* / 0.9	"[W]e are a leading supporter of math and science education, including efforts to increase the number of women and minorities studying in these fields."[76,77]

Table S11. Rhetoric of Individualized Responsibility. Example quotations illustrate how advertorials use divergent terms to present: (a) consumer demand for energy as the cause of – and culpable for – fossil fuel use, greenhouse gas emissions, and/or AGW; and (b) individual/demand-side actions as accountable for mitigating AGW. By contrast, divergent terms in (bottom) internal and/or peer-reviewed documents often articulate the causality and culpability of fossil fuel combustion.

Advertorials often say:						
	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
(to) meet	65	2	98	128.34 / 191.64	0.99 / 0.93	"To meet this demand, while addressing the risks posed by rising greenhouse gas emissions, we'll need to call upon broad mix of energy sources."[64]
vehicles	33	0	240	73.48 / 25.02	1 / 0.74	"[T]he cars and trucks we drive aren't just vehicles, they're opportunities to solve the world's energy and environmental challenges."[96]
greenhouse gas emissions	42	7	60	58.9 / 126.97	0.92 / 0.94	"We're supporting research and technology efforts, curtailing our own greenhouse gas emissions and helping customers scale back their emissions of carbon dioxide."[78]
energy efficiency	30	1	152	58.76 / 36.65	0.98 / 0.81	"We have invested $1.5 billion since 2004 in activities to increase energy efficiency and reduce greenhouse gas emissions. We are on track to improve energy efficiency in our worldwide refining and chemical operations…".[76,77]
cars	24	0	59	53.44 / 54	1 / 0.9	"By enabling cars and trucks to travel farther on a gallon of fuel, drivers not only spend less money per mile, they also emit less carbon dioxide (CO_2) per mile."[95]
reduce emissions	23	0	25	51.21 / 78.03	1 / 0.95	"During the fact-finding period, governments should encourage and promote voluntary actions by industry and citizens that reduce emissions and use energy wisely. Governments can do much to raise public awareness of the importance of energy conservation."[53]
consumers	21	0	33	46.76 / 60.7	1 / 0.93	"We also are developing new vehicle technologies that can help consumers use energy more efficiently."[76,77]
world	91	64	338	43.45 / 150.55	0.74 / 0.85	"By 2030, experts predict that the world will require about 60 percent more energy than in 2000…As a result, greenhouse gas emissions are predicted to increase too…".[93]
developing countries	27	3	162	43 / 26.94	0.95 / 0.78	Through 2030, "developing countries...will rely on relatively carbon-intensive fuels like coal to meet their needs."[64]
transportation	23	2	121	38.87 / 26.93	0.96 / 0.8	"Ongoing advances in vehicle and fuel technology will be critical to meeting global demand for transportation fuels. They will also help address the risk posed by rising greenhouse-gas emissions."[96]
energy use	23	4	83	31.75 / 39	0.92 / 0.85	"Central to any future policy should be the understanding that man-made greenhouse gas emissions arise from essential energy use in the everyday activities of people, governments and businesses."[74]
people	30	11	61	27.87 / 75.73	0.85 / 0.91	"Thus, we're pleased to extend our support of…American Forests...whose "Global Releaf 2000" program is mobilizing people around the world to plant and care for trees."[92]
demand	40	21	422	27.24 / 14.35	0.8 / 0.67	"[I]n the electric power sector, growing demand will boost CO_2 emissions…".[65]
needs	36	22	71	20.69 / 92.45	0.77 / 0.91	"…fossil fuels must be relied upon to meet society's immediate and near-term needs."[84]
conservation	15	5	66	14.89 / 21.23	0.86 / 0.83	"Prudent measures such as conservation and investment in energy-efficient technology make sense, but embarking on regulatory [climate/energy] policies that may prove wasteful or counterproductive does not."[103]
energy demand	15	14	59	4.38** / 23.59	0.69** / 0.84	"[I]ncreasing prosperity in the developing world [is] the main driver of greater energy demand (and consequently rising CO_2 emissions) over the coming decades."[56]
Internal and/or peer-reviewed documents often say:						
fossil fuel	9	144	359	-66.26 / -4.48**	0.11 / 0.34***	"Release of this amount of CO_2 to the atmosphere raises concern with respect to its effect on the CO_2 greenhouse problem. Global fossil fuel emissions of CO_2 currently amount to about 1.8 x 10^{10} metric tons per year…".[104]
						"Arrhenius put forth the idea that CO2 from fossil fuel burning could…warm the Earth…fossil fuel greenhouse warming…fossil fuel greenhouse effect...".[105]
natuna	0	67	NA	-53.36 / NA	0 / NA	"This would make Natuna the world's largest point source emitter of CO_2 and raises concern for the possible incremental impact of Natuna on the CO_2 greenhouse problem."[104]
due to	5	89	731	-42.94 / -39.08	0.1 / 0.13	"The CO_2 concentration in the atmosphere has increased...The most widely held theory is that: the increase is due to fossil fuel combustion."[106]
						"About three-quarters of the anthropogenic emissions of CO_2 to the atmosphere during the past 20 years is due to fossil fuel burning."[107]
fossil fuel combustion	1	48	NA	-30.69 / NA	0.04 / NA	"[T]here is the potential for our [climate] research to attract the attention of the popular news media because of the connection between Exxon's major business and the role of fossil fuel combustion in contributing to the increase of atmospheric CO_2."[108]
shale	1	41	NA	-25.43 / NA	0.05 / NA	"The quantity of CO_2 emitted by various fuels in shown in Table 1...They show the high CO_2/energy ratio for coal and shale...["Shale oil"] is not predicted to be a major future energy source due to...rather large amounts of CO_2 emitted per unit energy generated (see Table 1)."[106]
ccs	0	NA	374	NA / -34.82	NA / 0	"CCS includes applying technologies that capture the CO_2 whether generated by combustion of carbon-based fuels or by the separation of CO_2 from natural gas with a high CO_2 concentration."[109]
source	6	39	322	-9.08* / -7.16**	0.24* / 0.28**	"[F]ossil fuel combustion is the only readily identifiable source [of CO_2] which is (1) growing at the same rate, (2) large enough to account for the observed increases...".[110]
						Table 1 presents "coal combustion" and "natural gas combustion" as the "source[s]" of CO_2, CH_4, SO_2.[111]
fossil fuel use	0	13	NA	-10.35* / NA	0** / NA	"[F]or scenarios with higher fossil fuel use (hence, higher carbon dioxide emissions…".[107]
fossil fuel co2	0	NA	64	NA / -5.96**	NA / 0***	"This long tail on the fossil fuel CO_2 forcing of climate may well be more significant to the future glacial/interglacial timescale evolution of Earth's climate…".[112]
fossil fuel emissions	0	NA	54	NA / -5.03**	NA / 0***	"We use our Integrated Science Model to...estimate the time variation fossil fuel emissions of CO_2...required to match the [IPCC] concentration stabilization scenarios."[113]

Table S12. Rhetoric of Policy Apocalypse. Example quotations illustrate how advertorials use divergent terms to allege that climate policies will be socioeconomically damaging.

Policy Apolocalypse rhetoric

Advertorials often say:

	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
econom(y/ic)	148	22	714	216.08 / 190.67	0.93 / 0.81	"We ask the Kyoto delegates to...resist agreements that could inflict great economic pain."[53]
economic growth/impact	29	2	74	51.34 / 63.68	0.97 / 0.89	"The report shows how ill-timed or ill-considered [GHG emissions] abatement measures could stunt world economic growth, unsettle global trading patterns and set the stage for new era of trade protectionism."[60]
cost(/s/ly/liest/lier)	61	32	NA	41.58 / NA	0.8 / NA	"[A]s higher energy costs work their way through the economy, the annual loss in GDP could range from $150 billion to $400 billion."[61]
jobs/employment	15	0	40	33.4 / 31.98	1 / 0.89	"WEFA estimates the cost of achieving the Kyoto target by 2010 would result in loss of 24 million jobs…".[61]
tax(es)	20	2	177	32.72 / 10.7*	0.95 / 0.7	"Most economists tell us that such a step [as the Kyoto Protocol] would damage our economy and almost certainly require large increases in taxes on gas and oil."[62]
livelihood(s)/lifestyle(s)	13	0	42	28.95 / 24.11	1 / 0.87	"How much prosperity are Americans willing to forgo? How many lifestyle changes will they have to make? How much more tax will they pay?"[59]
wise(r)/prudent/reasonable/ responsible/sound(er)	39	21	119	25.87 / 75.54	0.79 / 0.87	A "prudent approach to the climate issue must recognize that there is not enough information to justify harming economies and forcing the world's population to endure unwarranted lifestyle changes by dramatically reducing the use of energy now."[62]
disruptive/dislocations/ distortions/unsettled	11	0	8	24.49 / 42.87	1 / 0.97	"Concern about the impact of human activity on the global climate...is triggering actions that may create major dislocations unnecessarily."[114]
suffer/saddled/havoc/pain(ful)/ grave/fatal/turmoil/	17	3	15	23.33 / 62.23	0.92 / 0.96	"Adopting quick-fix measures [for AGW] at this point could pose grave economic risks for the world."[71]
jeopardize/harm/hit/inflict/ plunge/cripple/wreck(ing)	16	6	9	14.62 / 67.06	0.85 / 0.97	"As gaps in climate science are being filled, these approaches can lead to real changes in emissions trends without harming economies and lifestyles."[115]
impos(e/ing)	8	NA	16	NA / 20.38	NA / 0.91	"[T]he impact that some [AGW mitigation] measures could have on jobs and livelihoods will impose extensive burdens on the global community."[116]
consequences	15	NA	81	NA / 17.04	NA / 0.8	"Because of the potentially serious consequences any such [climate action] plan would have on the U.S. economy and peoples livelihoods…".[117]
drastic/rash/premature	6	NA	22	NA / 10.04*	NA / 0.85*	"[T]he jury's still out on whether drastic steps to curb CO_2 emissions are needed."[70]

Table S13. Rhetoric of Scientific/Technological Optimism. Example quotations illustrate how advertorials use divergent terms to give primacy to scientific or technological breakthroughs as the solutions to understanding and/or mitigating AGW.

Scientific/Technological Optimism rhetoric

Advertorials often say:

	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
new/advanced technolog(y/ies)	40	2	42	74.58 / 137.51	0.98 / 0.95	"[W]e are excited to be working on breakthrough technology that could advance the use of hydrogen fuel cells. This new technology…converts traditional hydrocarbon fuels (such as gasoline or diesel) into hydrogen…".[96]
promise	20	0	12	44.53 / 82.39	1 / 0.97	"The promise of technology. One of the brighter hopes in the climate change debate has to be the benefits to be achieved through technology."[118]
invest(ing/ment(s))	27	4	243	39.46 / 13.96	0.93 / 0.7	"[W]e're now making the largest ever investment in independent climate and energy research that is specifically designed to look for new breakthrough technologies."[80–82]
innovat(e/ion(s))	17	1	93	30.93 / 19.02	0.97 / 0.79	"Support for oil and natural gas innovation can reduce emissions."[67]
solutions	26	7	78	29.36 / 51	0.88 / 0.87	"[W]e believe that technology provides the key avenue to solutions that manage long-term risk and preserve prosperity."[58]
develop	29	32	69	5.64** / 66.62	0.65** / 0.9	"Many respected economists conclude that research to develop new technology offers the most effective near-term means to address the long-term response to climate change."[118]

Table S14. Rhetoric of Technological Shell-Game. Example quotations illustrate how advertorials use divergent terms to communicate what Schneider *et al.* (2016) define as "misdirection that relies on strategic ambiguity about the feasibility, costs, and successful implementation of technologies in order to deflect attention from environmental pollution and health concerns".

Technological Shell-Game rhetoric

Advertorials often say:

	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
natural gas	48	18	334	43.87 / 38.95	0.85 / 0.75	"[T]echnological progress in these conventional fuels ["oil and natural gas"] holds immediate potential to help reduce emissions on a significant scale…[T]his clean and abundant resource [of "natural gas"] is helping meet our energy and environmental goals."[67]
electric vehicles/EVs	16	0	11	35.63 / 63.42	1 / 0.97	"[T]he GAO basically concluded EVs aren't ready. Nor are they likely to become so even in the rosiest of scenarios."[83]
limitations/obstacles/ barriers/cannot compete	14	NA	142	NA / 5.54**	NA / 0.67**	"Renewable forms of energy could play role [in the electric power sector], but they have limitations that make them impractical or expensive for most applications."[65]
solar/photovoltaic(s)	31	NA	393	NA / 6.34**	NA / 0.62**	"Solar power is dependent on sunlight availability and is space-intensive. Here again, its potential must be tempered with realism."[119]

Table S15. Rhetoric of Whataboutism. Example quotations illustrate how advertorials use divergent terms to point to other actors that produce – or may in the future produce – more greenhouse gas emissions. It is thereby argued that those actors bear significant responsibility for taking action, and that without their participation, climate policies will be unjust ('free rider' excuse) or ineffective (policy perfectionism).

Whataboutism rhetoric						
Advertorials often say:						
	Advertorials	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
developing/poorer countries/world/nations	53	3	196	97.01 / 88.01	0.97 / 0.85	"Developing countries are not covered by the [Kyoto] Protocol. [Quoting a new report by The Business Roundtable:] "Without full participation by developing countries, the Kyoto Protocol will not lead to a net reduction of global…emissions."…The Protocol uses "differentiated targets" for countries to meet, which potentially could put the U.S. at a disadvantage."[63]
all nations	11	0	3	24.49 / 53.72	1 / 0.99	"Clearly, curbing greenhouse gases is the responsibility of all nations."[86]

S6. ALGORITHMIC TEXTUAL ANALYSIS OF EXXONMOBIL CORP'S FLAGSHIP REPORTS

Our key findings concerning ExxonMobil's advertorials are replicated in other ExxonMobil Corp public AGW communications.

We analyzed all of the company's known and available flagship reports concerning AGW spanning 2002-19. Specifically, from ExxonMobil Corp's 2020 listing of 'Publications and reports', we identified reports pertaining, in whole or in part, to AGW, AGW mitigation, and/or greenhouse gas emissions[120]. By way of ExxonMobil Corp webpages (only recent years of reports are made available), digital archives of ExxonMobil Corp webpages (via Wayback Machine), and other online and private collections, we obtained and analyzed the following editions of those reports (see table S1):

- *Corporate Citizenship Reports*, 2002-16 (discontinued after 2016, replaced by *Sustainability Report*)
- *Sustainability Report*, 2017 (this is the only edition at the time of analysis)
- *Outlook For Energy*, 2005-19 (except 2008 and 2011, which could not be not located)
- *Energy & Carbon Summary*, 2017-18 (these are the only editions at the time of analysis)
- *Innovating Energy Solutions*, 2019 (this is the only edition at the time of analysis)

In the case of *Corporate Citizenship Reports* and *Outlook For Energy* reports, which are broad in scope, only sections primarily concerned with AGW, AGW mitigation, and/or greenhouse gas emissions were extracted for analysis, as indicated in table S1.

All documents were aggregated into a single corpus, pre-processed (this yielded a flagship report corpus comprising 113,695 words), and algorithmically analyzed according to the same protocols applied to advertorials: corpus comparison to internal and peer-reviewed publications (using frequency score (FS) and Dunning Log-Likelihood (LL) ratio G^2 score); and collocation analysis using the logDice statistic. Notable results of these analyses are summarized in the following sub-sections.

Table S16. Inventory of the five ExxonMobil Corp flagship reports analyzed: *Corporate Citizenship Reports*/*Sustainability Report*, *Outlook For Energy*, *Energy & Carbon Summary*, and *Innovating Energy Solutions*. Shown for each report are the editions (years) retrieved and the sections (chapter titles and corresponding pages) analyzed. "NA" = report not located. "-" = no report published, to our knowledge, at the time of analysis.

Year	*Corporate Citizenship Reports/ Sustainability Report*	*Outlook For Energy*	*Energy & Carbon Summary*	*Innovating Energy Solutions*
2002	"Addressing climate-change risk"; "Energy research"; "Environmental performance" (p.9-14)	-	-	-
2003	"Greenhouse gas emissions"; "Advanced fuels and vehicle systems research"; "Fuel cell research"; "Global Climate and Energy Project (GCEP)" (p.10-12)	-	-	-
2004	"Climate change" indexed pages (p.3, 22, 24, 25, 29)	-	-	-
2005	"Environmental performance" (p.20-35)	"CO_2 growth"; "Technology critical to efficiency improvements" (p.18-19)	-	-
2006	"Environmental performance" (p.14-23)	"Global CO_2 emissions"; "Technology options for reducing CO_2"; "CO_2 mitigation options"; "Meeting the world's energy needs" (p.22-25)	-	-
2007	"Environmental performance" (p.14-21)	"World energy and CO_2 emissions"; "Global CO_2 emissions" (p.22-23)	-	-
2008	"Managing climate change risks" (p.30-33)	NA	-	-
2009	"Managing climate change risks" (p.30-35)	"Managing emissions" (p.22-33)	-	-
2010	"Managing climate change risks" (p.32-37)	"Greenhouse gas emissions" (p.32-37)	-	-
2011	"Managing climate change risks" (p.22-25)	NA	-	-
2012	"Managing climate change risks" (p.28-33)	"Emissions" (p.32-35)	-	-
2013	"Managing climate change risks" (p.52-59)	"Emissions" (p.32-35)	-	-
2014	"Managing climate change risks" (p.33-39)	"Emissions" (p.32-33)	-	-
2015	"Managing climate change risks" (p.29-41)	"A shift in the power generation sector"; "Emissions" (p.36-41)	-	-
2016	"Managing climate change risks" (p.16-24)	"Lowering emissions" (p.48-51)	-	-
2017	"Managing climate change risks" (p.16-19)	"Emissions" (p.30-33)	-	-
2018	-	"Emissions"; "Pursuing a 2 °C pathway" (p.29-31, 44-53)	Full report	-
2019	-	"Dual challenge"; "Emissions" (p.3, 37-46)	Full report	Full report

S6.1. "Risk" rhetoric in ExxonMobil Corp's flagship reports

FS and LL analyses identify "risk(s)", "climate change risks", "risks of climate change", etc., to be among the most statistically overused terms in ExxonMobil Corp's flagship reports, compared to both their internal and peer-reviewed publications (table S17). Collocation analysis reveals that across these flagship reports, by far the highest scoring collocate of "climate change" and "global warming" is "risk(s)" (table S18). (Note that, for clarity, we here present the results of FS, LL, and collocation analyses in which all flagship reports were aggregated into a single corpus. Substantively the same results are obtained by treating each type of report as a separate corpus.)

Table S17. "Risk" rhetoric: highly divergent terms invoking "risk" in ExxonMobil Corp flagship reports, versus internal and peer-reviewed publications, by Log-Likelihood ratio (G^2) and Frequency Score (FS). P-values <0.001 for all G^2 and FS scores.

ExxonMobil Corp's flagship reports often say:						
	Flagship	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
risk(s)	396	7	261	322.03 / 768.61	0.97 / 0.91	"A global approach to the risk posed by rising greenhouse gas emissions is needed that recognizes energy's importance to the world's economies."[121]
climate (change) risk(s)/ risk(s) of climate	213	0	10	203.92 / 768.25	1 / 0.99	"Recognizing the risk of climate change, we are taking actions to improve efficiency and reduce greenhouse gas emissions in our operations."[122]
managing climate change risks	52	0	0	49.78 / 206.76	1 / 1	"Managing climate change risks. Climate change risk management strategy. Society continues to face the dual challenge of meeting the world's growing energy demand, while simultaneously addressing the risks of climate change."[123]
longterm	100	17	282	31.61 / 41.46	0.78 / 0.69	"ExxonMobil is engaged in the public discussion to create national and international policies to address climate change risks. Recognizing the long-term nature of these risks…".[124]
address the risks of climate	19	0	0	18.19 / 75.55	1 / 1	"Many uncertainties exist concerning the future of energy demand and supply, including potential actions that societies may take to address the risks of climate change."[125]

Table S18. Three strongest collocates of "climate change" and "global warming" in Mobil advertorials, ExxonMobil Corp advertorials, and ExxonMobil Corp flagship reports, by logDice score.

Mobil advertorials		ExxonMobil Corp advertorials		Flagship reports	
Collocate	logDice	Collocate	logDice	Collocate	logDice
science	11.46	risk(s)	13.01	risk(s)	13.79
gases	11.31	address	11.86	managing	12.78
debate	11.24	human	11.57	policy	12.72

S6.2. Discourse of personal responsibility in ExxonMobil Corp's flagship reports

Table S19 (top half) collates terms in ExxonMobil Corp's flagship reports that (a) based on our frame package analysis of advertorials, are characteristic of a Personal Responsibility frame; and (b) are highly divergent between flagship reports and internal and/or peer-reviewed documents according to LL and FS analyses. As with advertorials, we observe that ExxonMobil Corp's flagship reports disproportionately employ terms that present consumer demand for energy as the cause of fossil fuel production, greenhouse gas emissions, and/or AGW; and disproportionately introduce terms conveying individual and/or demand-side actions as accountable for mitigating AGW. By contrast, Exxon and ExxonMobil Corp's internal and/or academic communications disproportionately recognize AGW and/or greenhouse gases as also an upstream problem caused by fossil fuel supply and burning.

Table S19. Rhetoric of Personal Responsibility: Highly divergent terms in (top) ExxonMobil Corp flagship reports, by Log-Likelihood ratio (G^2) and Frequency Score (FS), characteristic of a Personal Responsibility frame. Example quotations illustrate how flagship reports use these terms to disproportionately present: (a) consumer demand for energy as the cause of – and culpable for – fossil fuel use, greenhouse gas emissions, and/or AGW; and (b) individual/demand-side actions as accountable for mitigating AGW. By contrast, divergent terms in (bottom) internal and/or peer-reviewed documents often articulate the causality and culpability of fossil fuel combustion. P-values: * <0.005; ** <0.05; ***≥0.05; otherwise, <0.001 for all G^2 and FS scores.

ExxonMobil Corp's flagship reports often say:						
	Flagship	Internal	Peer-reviewed	G^2 (Int./P.r.)	*FS* (Int./P.r.)	Example
efficien(t/cy/tly)	570	14	809	440.63 / 634.69	0.96 / 0.82	"ExxonMobil is delivering solutions that enable our customers to reduce their emissions and improve their energy efficiency…".[123]
demand	455	21	422	304.06 / 718.96	0.93 / 0.87	"Globally, rising energy demand will result in higher energy-related CO_2 emissions through 2030…".[126]
(to) meet	224	2	98	195.42 / 523.8	0.99 / 0.94	"As we seek to produce oil and natural gas to meet growing global energy demand…".[127]
challenge(s)	140	5	100	100.2 / 260.12	0.95 / 0.9	"This is society's dual challenge. Billions of people need reliable, affordable energy every day, but their use of energy is contributing to CO_2 emissions."[125]
vehicles	83	0	240	79.46 / 32.6	1 / 0.69	"As the number of vehicles in the world continues to rise, energy efficiency in the transportation sector will become increasingly important. According to the International Energy Agency, approximately 90 percent of petroleum-related GHG emissions are generated when customers use our products...".[124]
consumers	69	0	33	66.06 / 155.66	1 / 0.93	"...the combustion of fuels by consumers generates the majority of GHG emissions…".[121]
energy demand	135	14	59	63.45 / 315.82	0.86 / 0.94	"Increasingly, the world's CO_2 emissions will be driven by developing nations. Overall, non-OECD emissions are likely to rise about 50 percent, as energy demand rises by about two-thirds."[128]
reduce emissions	61	0	25	58.4 / 146.24	1 / 0.94	"[P]rice stability...provides a clear incentive for all consumers to increase efficiency and reduce emissions."[129]
the world	149	26	132	45.83 / 242.82	0.78 / 0.88	"...rising greenhouse gas emissions resulting from the world's enormous requirements for fossil fuels…".[130]
customers	42	0	3	40.21 / 145.84	1 / 0.99	"ExxonMobil develops and produces a range of petroleum-based products that help our customers reduce their greenhouse gas emissions and improve efficiency."[131]
demand growth	31	0	5	29.68 / 95.72	1 / 0.98	"Renewables and nuclear energy see strong growth...to meet demand growth through 2040. Natural gas grows the most of any energy type, reaching a quarter of all demand."[132]
global demand	28	0	4	26.81 / 88.4	1 / 0.98	"The benefits of natural gas. Global demand for cleaner-burning natural gas is expected to increase by more than 50 percent by 2030, making it the fastest-growing major energy source for power generation."[124]
living standards	25	0	1	23.93 / 91.22	1 / 0.99	"Close to 85 percent of the increase in CO_2 emissions[through 2030] will come from developing countries where economic growth and improved living standards are creating huge increases in energy demand."[133]
natural gas demand	23	0	1	22.02 / 83.43	1 / 0.99	"Natural gas will meet a growing share of our energy needs through 2030...Total natural gas demand in the United States and Europe will follow a similar pattern…".[129]
footprint	20	0	3	19.15 / 62.6	1 / 0.98	"[T]he core sustainability challenge for the energy industry is how to provide the energy that enables economic development while reducing the environmental footprint associated with energy use."[124]
needs	89	22	71	17.2 / 155.02	0.71 / 0.89	"Fossil fuels – oil, natural gas and coal – will continue to meet most of the world's needs [through 2030]."[129]
energy needs	29	4	6	11.12 / 85.01	0.82* / 0.97	ExxonMobil is "taking action to position ourselves to help meet future global energy needs. For example, we are: Expanding supply of cleaner-burning natural gas...".[127]
Internal and/or peer-reviewed documents often say:						
fossil fuel(s)	15	198	508	-288.59 / -73.18	0.04 / 0.16	"[T]here is general scientific agreement that the most likely manner in which mankind is influencing the global climate is through carbon dioxide release from the burning of fossil fuels."[110] "[T]he burning of fossil fuels is linked to both climate change and air pollution…".[134]
natuna	2	67	NA	-113.33 / NA	0.02 / NA	"This would make Natuna the world's largest point source emitter of CO_2 and raises concern for the possible incremental impact of Natuna on the CO_2 greenhouse problem."[104]
fossil fuel combustion	0	48	NA	-92.79 / NA	0 / NA	"[T]here is the potential for our [climate] research to attract the attention of the popular news media because of the connection between Exxon's major business and the role of fossil fuel combustion in contributing to the increase of atmospheric CO_2."[108]
due to	44	89	731	-45.32 / -52.39	0.23 / 0.28	"The CO_2 concentration in the atmosphere has increased...The most widely held theory is that: the increase is due to fossil fuel combustion."[106] "About three-quarters of the anthropogenic emissions of CO_2 to the atmosphere during the past 20 years is due to fossil fuel burning."[107]
shale	8	41	NA	-43.3 / NA	0.11 / NA	"The quantity of CO_2 emitted by various fuels in shown in Table 1...They show the high CO_2/energy ratio for coal and shale...["Shale oil"] is not predicted to be a major future energy source due to...rather large amounts of CO_2 emitted per unit energy generated (see Table 1)."[106]
fossil fuel use	0	13	22	-25.13 / -6.48**	0 / 0***	"[F]or scenarios with higher fossil fuel use (hence, higher carbon dioxide emissions…".[107]
fossil fuel consumption	0	10	NA	-19.33 / NA	0 / NA	"The most widely held theory is that…[t]he present trend of fossil fuel consumption will cause dramatic environmental effects before the year 2050."[106]
fossil fuel emissions	0	NA	54	NA / -15.91	NA / 0	"We use our Integrated Science Model to...estimate the time variation fossil fuel emissions of CO_2...required to match the [IPCC] concentration stabilization scenarios."[113]
fossil fuel co2	1	NA	64	NA / -12.5	NA / 0.09*	"This long tail on the fossil fuel CO_2 forcing of climate may well be more significant to the future glacial/interglacial timescale evolution of Earth's climate…".[112]
fossil fuel burning	0	NA	40	NA / -11.78	NA / 0*	"CO_2 emissions from fossil fuel burning are virtually certain to be the dominant factor determining CO_2 concentrations during the 21st century."[135]

S7. CATALOG OF ANALYZED DOCUMENTS

Raw data (original PDF internal documents, peer-reviewed publications, and advertorials) for this study cannot be reproduced due to copyright restrictions. However, tables S20-22 present catalogs of all 180 analyzed documents, which can be obtained at the following public archives:

- All analyzed advertorials can be downloaded from the ProQuest Historical Newspaper Database[136]. Many can also be downloaded from PolluterWatch[137].
- All analyzed internal documents can be downloaded from (one or more of) ExxonMobil Corp[138], *InsideClimate News*[139], and Climate Investigations Center[140].
- All analyzed peer-reviewed documents can be obtained from corresponding journals and conference proceedings.

A catalog of analyzed flagship reports is presented in table S16 above.

Table S20. Catalog of analyzed advertorials.

Date	Authors	Title
21 December 1972	Mobil Oil	A trio glows in Brooklyn
05 April 1973	Mobil Oil	The profits of doom
16 August 1984	Mobil Oil	Lies they tell our children
03 November 1988	Mobil Oil	musings of a fossil fuel person...
06 July 1989	Mobil Oil	People Who Live in Greenhouses...
09 April 1992	Mobil Oil	Boy, we wish we'd said that!
25 February 1993	Mobil Oil	Apocalypse no
11 May 1995	Mobil Oil	Electric vehicles: a promise too far
28 September 1995	Mobil Oil	The sky is not falling
18 July 1996	Mobil Oil	Less heat, more light on climate change
25 July 1996	Mobil Oil	With Climate Change, What We Don't Know Can't Hurt Us
01 August 1996	Mobil Oil	Climate Change: We're all in this together
12 December 1996	Mobil Oil	A policy agenda for tomorrow
06 March 1997	Mobil Oil	Stop, look and listen before we leap
23 June 1997	Mobil Oil	Climate change: Let's get it right
31 July 1997	Mobil Oil	The Senate speaks
14 August 1997	Mobil Oil	When the facts don't square with the theory, throw out the facts
23 October 1997	Mobil Oil	Global climate change
30 October 1997	Mobil Oil	Reset the alarm
06 November 1997	Mobil Oil	Science: what we know and don't know
13 November 1997	Mobil Oil	Climate change: a prudent approach
20 November 1997	Mobil Oil	Climate change: where we come out
04 December 1997	Mobil Oil	Climate change: a degree of uncertainty
11 December 1997	Mobil Oil	Let's not forget the will of the senate
18 December 1997	Mobil Oil	The Kyoto Conference
29 January 1998	Mobil Oil	Post Kyoto, what's next?
02 April 1998	Mobil Oil	Voluntary 'can do'
10 September 1998	Mobil Oil	The Kyoto Protocol: too many gaps
05 November 1998	Mobil Oil	The Kyoto Protocol: a painful response
15 April 1999	Mobil Oil	Helping Earth breathe easier
10 June 1999	Mobil Oil	King of the road?
29 July 1999	Mobil Oil	Where we are and where we may be heading
05 August 1999	Mobil Oil	Some ways to make a difference
12 August 1999	Mobil Oil	Scenarios for stabilization
19 August 1999	Mobil Oil	Lessons learned
16 March 2000	ExxonMobil Corp	Do no harm
23 March 2000	ExxonMobil Corp	Unsettled Science
30 March 2000	ExxonMobil Corp	The Promise of Technology
06 April 2000	ExxonMobil Corp	The Path Forward on Climate Change
10 August 2000	ExxonMobil Corp	Political cart before a scientific horse
24 August 2000	ExxonMobil Corp	Facts and fundamentals
14 December 2000	ExxonMobil Corp	Fleet changes, but slowly
21 December 2000	ExxonMobil Corp	Planting the future
10 April 2001	ExxonMobil Corp	Moving past Kyoto...
17 April 2001	ExxonMobil Corp	...to a sounder climate policy

03 May 2001	ExxonMobil Corp	Renewable energy: today's basics
10 May 2001	ExxonMobil Corp	Renewable energy: tomorrow's promise
19 July 2001	ExxonMobil Corp	Action, not talk: cogeneration and climate
03 October 2002	ExxonMobil Corp	Managing greenhouse gas emissions
22 November 2002	ExxonMobil Corp	A responsible path forward on climate
06 February 2003	ExxonMobil Corp	The global climate and energy challenge
08 January 2004	ExxonMobil Corp	A century of deep-water research
22 January 2004	ExxonMobil Corp	Weather and climate
05 February 2004	ExxonMobil Corp	Directions for climate research
11 May 2005	ExxonMobil Corp	More Energy and Lower Emissions?
14 June 2005	ExxonMobil Corp	More Energy and Lower Emissions?
07 July 2005	ExxonMobil Corp	More Energy and Lower Emissions?
04 August 2005	ExxonMobil Corp	Research Into Climate Solutions
03 August 2006	ExxonMobil Corp	Changing the Game
19 December 2006	ExxonMobil Corp	Multiplier Effects
25 January 2007	ExxonMobil Corp	Taking action to reduce greenhouse gas emissions
09 February 2007	ExxonMobil Corp	Saving Energy and Reducing Greenhouse Gas Emissions
14 February 2007	ExxonMobil Corp	Let's Talk About Climate Change
15 February 2007	ExxonMobil Corp	Addressing the Risks of Climate Change
16 February 2007	ExxonMobil Corp	Let's Talk About Climate Change
24 May 2007	ExxonMobil Corp	Values at Work
18 October 2007	ExxonMobil Corp	answering energy questions
13 March 2008	ExxonMobil Corp	The Fuels of the Future
03 April 2008	ExxonMobil Corp	Energy Efficiency--Once Quart at a Time
03 June 2008	ExxonMobil Corp	More Energy. Fewer Emissions. With Technology, We Can Do Both
24 June 2008	ExxonMobil Corp	Vehicles of Change
20 January 2009	ExxonMobil Corp	Provide Energy. Protect the Environment. A dual challenge for all of us.
14 April 2009	ExxonMobil Corp	Many Parts Working Together
22 May 2009	ExxonMobil Corp	Citizenship for the Long Term
29 June 2009	ExxonMobil Corp	Citizenship For the Long Term
15 October 2009	ExxonMobil Corp	Tackling Climate Risks With Technology

Table S21. Catalog of analyzed internal documents.

Date	Authors	Title
31 October 1977	Shaw, H. to Harrison, J. W.	Environmental Effects of Carbon Dioxide
06 June 1978	Black, J. to Turpin, F. G. (cc: Alpert, N. et al.)	The Greenhouse Effect
07 December 1978	Shaw, H. to David Jr., E. E.	Untitled (request for a credible scientific team)
07 March 1978	Weinberg, H. N. to Gornowski, E. J.	CO2
26 March 1979	Garvey, E. A., Shaw, H., Broecker, W. S., Takahashi, T. presentation to Machta, L.	Proposed Exxon Research Program to Help Assess the Greenhouse Effect
16 October 1979	Mastracchio, R. L. to Hirsch, R. L. (cc: Black, J. F. et al.)	Controlling Atmospheric CO2
19 November 1979	Shaw, H. to Weinberg, H. N. (cc: Werthamer, N. R.)	Research in Atmospheric Science
29 January 1980	Eckelmann, W. R. to O'Loughlin, M. E. J. (cc: David, E. E. et al.)	Exxon's View and Position on "Greenhouse Effect"
09 June 1980	Weinberg, H. N. to Shaw, H. and Werthamer, N. R.	Greenhouse Program
08 July 1980	Werthamer, N. R. to Weinberg, H. N.	CO2 Greenhouse Communications Plan
18 December 1980	Shaw, H. to Kett, R. K. (cc: McCall, P. P. et al.)	Exxon Research and Engineering Company's Technological Forecast CO2 Greenhouse Effect
03 February 1981	Gervasi, G. R. to Northington, G. A. (cc: Preston, R. L. et al.)	CO2 Emissions Natuna Gas Project
05 February 1981	Long, G. H. to Lucceshi, P. J. et al. (cc: Barnum, R. E. et al.)	Atmospheric CO2 Scoping Study
15 May 1981	Shaw, H. to David Jr., E. E. (cc: Barnum, R. E. et al.)	CO2 Position Statement
18 August 1981	Cohen, R. W. to Glass, W. (cc: Weinberg, H. N. et al.)	Untitled (catastrophic effects letter)
18 June 1982	Natkin, A. M. to Weinberg, H. N. (cc: Forshee, M. E. et al.)	CRL/CO2 Greenhouse Program
14 July 1982	Cohen, R. W. to Kimon, P. (cc: Berner, R. et al.)	Untitled (Esso project terminated letter)
21 July 1982	Weinberg, H. N., Cohen, R. W., Callegari, A. J., Flannery, B., et al.	CO2-Greenhouse Effect; Corporate Research Climate Modeling
02 September 1982	Cohen, R. W., Levine, D. G. to Natkin, A. M. (cc: Callegari, A. J. et al.)	Untitled (consensus on CO2 letter)

12 November 1982	Glaser, M. B. to Cohen, R. W. et al.	CO2 "Greenhouse" Effect
17 October 1983	Natkin, A. M. to Preston, R. L. (Esso Eastern) (cc: Gervasi, G. R. et al.)	Untitled (ocean storage environmental concerns letter)
27 October 1983	Gervasi, G. R. to Downing, R. G. et al. (cc: Gates, D. F. et al.)	Background Paper Environmental Issues Natuna Gas Project
1984	Flannery, B., Callegari, A. J., Nair, B., Roberge, W. G.	The Fate of CO2 from the Natuna Gas Project if Disposed of by Subsea Sparging
02 February 1984	Callegari, A. J.	Corporate Research Program in Climate/CO2-Greenhouse
28 March 1984	Shaw, H.	CO2 Greenhouse and Climate Issues (EUSA/ER&E Environmental Conference, Florham Park, New Jersey)
07 May 1985	Shaw, H., Henrikson, F. W. to Lab Directors/Program Managers (cc: Cohen, R. W. et al.)	CR Interactions (handout for June 12th meeting with Lee Raymond)
04 October 1985	Flannery, B. P.	CO2 Greenhouse Update 1985
08 March 1988	Carlson, J. M. to Levine, D. G.	The Greenhouse Effect
02 February 1989	Levine, D. G.	Potential Enhanced Greenhouse Effects, Status and Outlook (Presentation to the Board of Directors of Exxon Corp)
Fall 1989	Flannery, B. P.	Greenhouse Science (CONNECTIONS ExxonMobil publication - "Proprietary information for company use only")
21 December 1994	Bernstein, L. S. to Members of Global Climate Coalition	Primer on Climate Change Science
18 March 2002	Flannery, B. P. to Cooney, P. and Marburger, J. (cc: Randol, A. G.)	Activities

Table S22. Catalog of analyzed peer-reviewed publications.

Year	Authors	Title	Publication
1982	Garvey, E. A., Prahl, F., Nazimek, K., Shaw, H.	Exxon global CO2 measurement system	IEEE Transactions on Instrumentation and Measurement
1983	Hoffert, M.I., Flannery, B. P., Callegari, A. J., Hseih, C. T., Wiscombe, W.	Evaporation-limited tropical temperatures as a constraint on climate sensitivity	Journals of the Atmospheric Sciences
1984	Flannery, B. P.	Energy balance models incorporating transport of thermal and latent energy	Journals of the Atmospheric Sciences
1984	Flannery, B. P., Callegari, A. J., Hoffert M. I.	Energy balance models incorporating evaporative buffering of equatorial thermal response	Geophysical Monograph Series: Climate Processes and Climate Sensitivity
1985	Flannery, B. P., Callegari, A. J., Hoffert, M. I., Hseih, C. T., Wainger, M. D.	CO2 driven equator-to-pole paleotemperatures: predictions of an energy balance model with and without a tropical evaporation buffer	The Carbon Cycle and Atmospheric CO2: Natural Variations Archean to Present, Geophysical Monograph 32
1985	Hoffert, M. I., Flannery, B. P. (eds. MacCracken, M. C., Luther, F. M.)	Model Projections of the Time-Dependent Response to Increasing Carbon Dioxide	Projecting the Climatic Effects of Increasing Carbon Dioxide, United States Department of Energy
1988	Thomas, E. R., Denton, R. D.	Conceptual studies for CO2/natural gas separation using the controlled freeze zone (CFZ) process	Gas Separation and Purification
1991	Kheshgi, H. S., Hoffert, M. I., Flannery, B. P.	Marine biota effects on the compositional structure of the world oceans	J. Geophys. Res.
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Whole-body exposures to radiofrequency-electromagnetic energy can cause DNA damage in mouse spermatozoa via an oxidative mechanism

Brendan J. Houston[1,2], Brett Nixon[1,4], Kristen E. McEwan[1], Jacinta H. Martin[1,4], Bruce V. King[3], R. John Aitken[1,4] & Geoffry N. De Iuliis[1,4*]

Artificially generated radiofrequency-electromagnetic energy (RF-EME) is now ubiquitous in our environment owing to the utilization of mobile phone and Wi-Fi based communication devices. While several studies have revealed that RF-EME is capable of eliciting biological stress, particularly in the context of the male reproductive system, the mechanistic basis of this biophysical interaction remains largely unresolved. To extend these studies, here we exposed unrestrained male mice to RF-EME generated via a dedicated waveguide (905 MHz, 2.2 W/kg) for 12 h per day for a period of 1, 3 or 5 weeks. The testes of exposed mice exhibited no evidence of gross histological change or elevated stress, irrespective of the RF-EME exposure regimen. By contrast, 5 weeks of RF-EME exposure adversely impacted the vitality and motility profiles of mature epididymal spermatozoa. These spermatozoa also experienced increased mitochondrial generation of reactive oxygen species after 1 week of exposure, with elevated DNA oxidation and fragmentation across all exposure periods. Notwithstanding these lesions, RF-EME exposure did not impair the fertilization competence of spermatozoa nor their ability to support early embryonic development. This study supports the utility of male germ cells as sensitive tools with which to assess the biological impacts of whole-body RF-EME exposure.

With rapid advances in technology and increasing demand for electronic communication, mobile phone usage has become virtually ubiquitous in the developed world[1]. Mobile phone devices receive and emit radiofrequency-electromagnetic energy (RF-EME) to transfer information, and accordingly our exposure to this form of energy is now unprecedented. Thus there is a clear imperative to establish public safety guidelines around the use of these mobile devices. It is, however, difficult to meet this demand due to a current lack of understanding concerning how RF-EME interacts with biology. While to date, no overwhelming clinical effects have been associated with RF-EME exposure[2–6], multiple studies suggest that this form of energy can elicit subtle detrimental effects on biological systems[7–10]. Accordingly, the International Agency for Research on Cancer have yet to dismiss the risks of RF-EME, instead classifying this form of energy as a potential carcinogen. While we continue to debate the biological effects of chronic RF-EME exposure, a growing body of evidence now proposes that acute *in vitro* RF-EME exposure can elicit oxidative stress in a range of model cell lines[7,9,11–13]. A leading hypothesis to account for the mechanistic basis of this response is that RF-EME targets the mitochondria, leading to perturbation of proton flux across the inner mitochondrial membrane and promoting electron leakage from the electron transport chain. The resultant formation of superoxide anion serves as a progenitor for additional reactive oxygen species generation (ROS), eventually creating a ROS imbalance and a state of oxidative stress[1,12].

[1]Priority Research Centre for Reproductive Science, School of Environmental and Life Sciences, Discipline of Biological Sciences, University of Newcastle, Callaghan, NSW, 2308, Australia. [2]School of Biological Sciences, Faculty of Science, Monash University, Clayton, VIC, 3800, Australia. [3]School of Mathematical and Physical Sciences, University of Newcastle, Callaghan, NSW, 2308, Australia. [4]Hunter Medical Research Institute, Cancer Research Program, New Lambton Heights, NSW, 2305, Australia. *email: geoffry.deiuliis@newcastle.edu.au

The potential for this mechanism of biophysical interaction provides the impetus for well-designed studies to ascertain the effect of RF-EME following whole-body irradiation regimens that more accurately mimic human exposure. In this context, a focus on the male reproductive system is justified owing to the common practice of storing mobile phone devices in the pant pocket, placing them in close proximity to the reproductive tract. Further emphasizing the relevance of the male reproductive system is mounting evidence that male germ cells are particularly susceptible to RF-EME[14] and the associated production of oxidative stress[7,12]. Indeed, it has been shown that spermatozoa provide a sensitive model to study the specific physical and chemical responses to RF-EME[15]. The situation arises because of the unique architecture and metabolism of spermatozoa, which places these cells at heightened vulnerability to damage by free radicals[16]. Moreover, spermatozoa provide a readily assessable means of monitoring adverse biological effects, through functional parameters such as motility, or more detailed analysis that can pinpoint biochemical disruption and more subtle endpoints such as the accumulation of DNA damage. Besides serving as a sensitive model, these cells are also clinically important, since the induction of DNA damage in the male germ line contributes to infertility[16] and has the potential to propagate in the embryo, altering developmental trajectory and the health of the offspring[16,17].

To date, a handful of studies have sought to assess the effects of RF-EME on the male germ line. However, the majority of these studies have focused on isolated spermatozoa or immature male germ cells[12,15,18–21]. While this approach is conducive to examination of the intricate biochemical and cellular responses to direct RF-EME exposure, the use of alternate *in vivo* rodent models is likely to present a closer clinical representation of exposure, which can also serve to extend our understanding of EME-perturbed biochemical pathways highlighted from *in vitro* studies. Whole body models afford the added advantage that they enable observation of the holistic effects of RF-EME on all stages of male germ cell development[22], encompassing the differentiation of germ into spermatozoa and their subsequent functional maturation as they transit the epididymis. With a sustained interest in establishing the biophysical mechanism(s) of action for RF-EME on biology, we report the use of a mouse model to probe reproductive stress following whole-body RF-EME exposure regimens. Specifically, a dedicated waveguide machine (Fig. 1), similar to that developed by Puranen and colleagues[23], was constructed to facilitate exposure of unrestrained mice to RF-EME at 905 MHz with a specific absorption rate (SAR) of 2.2 W/kg. Mice were exposed to RF-EME for 12 h per day, over a period of between 1 to 5 weeks and subsequently the testes and epididymides were collected to investigate the effects of RF-EME on spermatogenesis and sperm function.

Results

Whole-body RF-EME exposure does not elicit gross histological changes in the mouse testis. Following exposure of unrestrained mice to whole-body RF-EME exposure, we first examined the effects of our varied regimens on the average growth rate (Fig. 2a) of irradiated animals over the 5 weeks; revealing no changes in rate between the sham and RF-EME exposure groups. Similarly, gross testis morphology of sham and RF-EME exposed mice also remained comparable to that of control mice (Fig. 2b), with all samples exhibiting healthy tubule growth and extensive germ cell proliferation irrespective of the duration of exposure. All mice were 8 weeks of age at the commencement of the 1, 3 and 5 week study, however, some variance in body weight between cohorts was observed on their arrival. Nevertheless, no significant change in average growth rate was recorded between exposures, over the 35-day study (Fig. 2a).

Guided by our previous studies in which we have shown that *in vitro* RF-EME exposure can induce a state of oxidative stress, leading to DNA damage in some male germ cell types[7,12], we next explored the levels of DNA fragmentation and lipid peroxidation present within the testes of RF-EME exposed animals. For the former analysis, testis sections were probed with an anti-γH2AX antibody, a marker of DNA double strand breaks (Fig. 3). This revealed modest levels of DNA damage, which was largely restricted to meiotic germ cells within the seminiferous tubules. Furthermore, this tissue localization and levels of γH2AX staining were consistent across the panel, with no effect observed due to EME exposure ($p = 0.07$) or time. With regard to lipid peroxidation (Fig. 4), we documented a similar response, with no substantive increases in the lipid peroxidation product, 4-hydroxynonenal being detected within the testis sections of any RF-EME treatment group with respect to the untreated or sham controls ($p = 0.22$).

Whole-body RF-EME exposure adversely impacts the vitality and motility profiles of mature spermatozoa. To explore the effect of *in vivo* RF-EME exposure on mature spermatozoa, we next investigated the outcomes of our irradiation regimen on sperm motility and vitality (Fig. 5). It was observed that the total number of live spermatozoa isolated from the cauda epididymis was diminished with RF-EME exposure ($p < 0.05$) (Fig. 5a), an effect that was particularly evident after 5 weeks of exposure ($p < 0.001$); whereas no changes were observed in our sham-exposed populations. In a similar manner, we noted a significant reduction in the percentage of motile spermatozoa isolated from RF-EME exposed mice following a treatment regimen extending over 5 weeks ($p < 0.05$) (Fig. 5b). This reduction in overall sperm motility occurred commensurate with defects in the objective measurements of progressive and rapid sperm motility (Fig. 5c,d) in exposed mice. In this regard, the impact on both parameters was again most notable following 5 weeks of exposure ($p < 0.001$). Conversely, spermatozoa isolated from the sham exposure groups displayed no such changes in their vitality or motility profile; with both parameters remaining indistinguishable from those documented in an unexposed control group of males.

Whole-body RF-EME exposure elevates oxidative stress and DNA damage in mature spermatozoa. To determine whether the functional lesions in motility and vitality documented in the spermatozoa of RF-EME exposed mice were linked to the induction of oxidative stress, we next investigated the levels of cellular and mitochondrial ROS present in these cells (Fig. 6). Specifically, the dihydroethidium (DHE) fluorescent probe was utilized to provide insight into levels of cellular ROS production (Fig. 6a). Approximately 14% and 75% spermatozoa

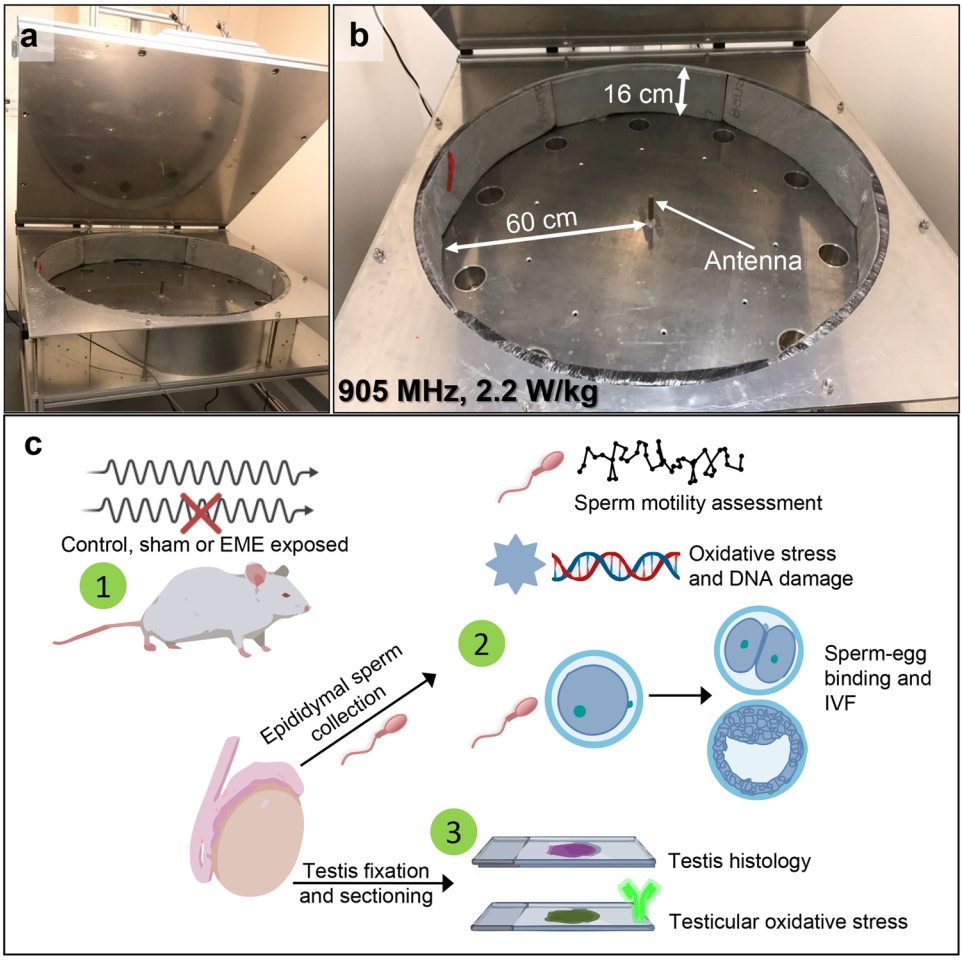

Figure 1. Waveguide instrument used to deliver whole-body RF-EME exposure. Shown are (**a**) the complete waveguide apparatus with lid in open configuration and (**b**) close-up view illustrating the dimensions of the inner chamber. (**c**) A graphical experimental overview. (1) Mice were RF-EME or sham exposed for 1, 3 or 5 weeks and compared to a control population that did not enter the apparatus (untreated). Mice were culled and their spermatozoa were examined using sperm functional assays and a variety of oxidative stress assays (2). The testes of these mice were also examined for gross histological abnormalities and for markers of oxidative stress, via tissue sections (3).

stained positively for DHE in the negative (untreated) and positive (i.e. hydrogen peroxide exposed) control populations, respectively. When the experimental groups were analyzed, neither the sham nor the RF-EME treatment conditions resulted in a significant deviation from basal ROS generation detected by DHE labeling. This was in contrast to mitochondrial ROS production, where the MitoSOX Red (MSR) probe (Fig. 6b) revealed a significant, two-fold elevation in ROS generation within the sperm mitochondria of animals exposed to RF-EME for periods of either 1 or 3 weeks, compared to the control and sham-exposed cell populations ($p < 0.05$). Intriguingly, sperm mitochondrial ROS generation had normalized to basal, control levels following 5 weeks of RF-EME exposure.

DNA damage assays were next employed to gain insight into the consequences of RF-EME induced ROS generation on the DNA integrity of mouse spermatozoa (Fig. 7). The halo assay (Fig. 7a), which evaluates DNA integrity based on the presence or absence of a halo-like stained DNA structure, revealed a modest but significant increase (i.e. ~5–6%) in the percentage of DNA-fragmented spermatozoa following 3 and 5 weeks of RF-EME exposure ($p < 0.05$). Consistent with these findings, the application of an alkaline comet assay (Fig. 7b) confirmed that whole-body RF-EME exposure stimulated sperm DNA fragmentation. After 1 week, sperm DNA fragmentation was elevated by 18%, however, this increase only gained significance after 5 weeks of exposure (23% increase in fragmentation; $p < 0.05$). Given the elevation in mitochondrial ROS, we next demonstrated that this DNA damage was likely oxidative in nature, highlighted by an increase in the percentage of RF-EME exposed sperm displaying positive staining for 8-hydroxy-2-deoxyguanosine (8-OH-dG; Fig. 7c); a biomarker of oxidative DNA damage. Indeed, across each of the three exposure times assessed, RF-EME induced a significant ($p < 0.05$) increase in 8-OH-dG labelling relative to control and sham exposed populations. As anticipated, 8-OH-dG labelling was localized to the nuclear compartment of the sperm head and was consistently more intense in RF-EME treated spermatozoa (Fig. 7d).

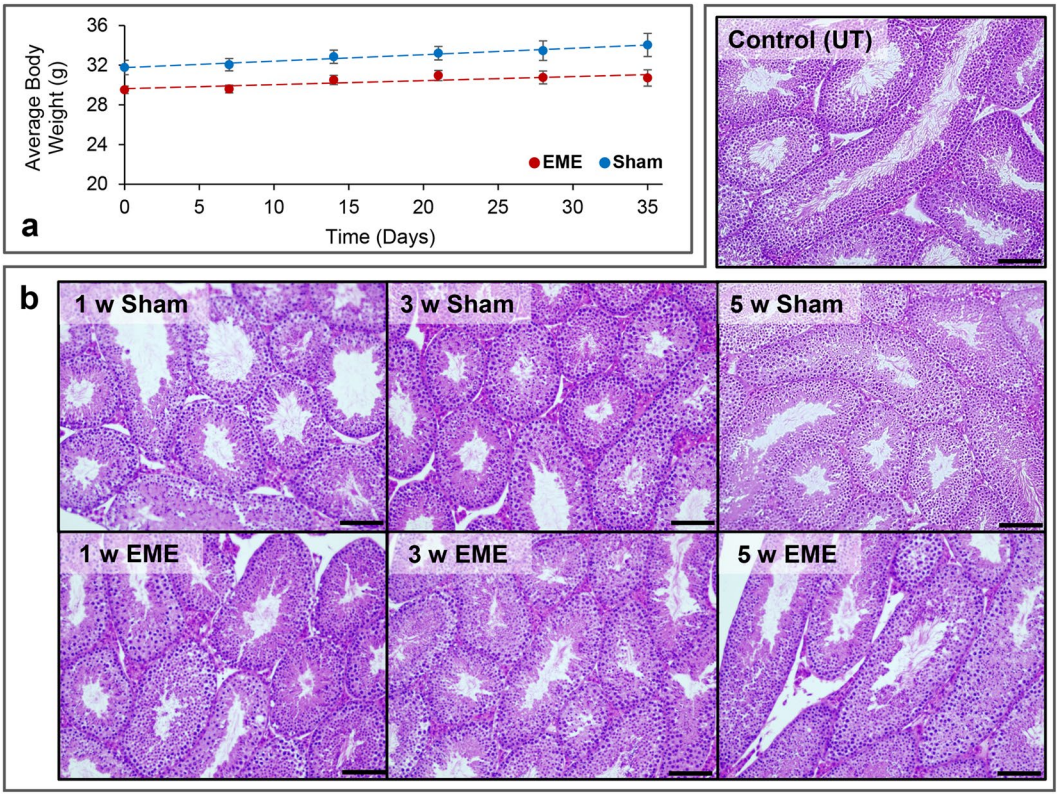

Figure 2. The effect of RF-EME on the growth and testis morphology of C57BL/6 mice. (**a**) Mice were weighed at weekly intervals to investigate the effects of RF-EME on body mass against sham exposed males (n = 8–20 mice measured/treatment group). Red circles represent the mean weight of EME treated mice, whereas blue circles represent the sham exposed group (**b**) Haematoxylin and eosin staining of testis sections was conducted to facilitate comparison of gross seminiferous tubule morphology (n = 3 mice/treatment group). Scale bar represents 400 µm.

Whole-body RF-EME exposure does not impair the fertilization competence of spermatozoa. In order to determine if RF-EME mediated induction of sperm DNA damage was sufficient to compromise the fertilization competence of these cells, we undertook an assessment of selected markers of sperm capacitation and *in vitro* fertilization success utilizing the spermatozoa from 5 week RF-EME exposed mice (Fig. 8). Of the capacitation markers assessed, neither the number of sperm displaying complete flagellum phosphotyrosine labelling (Fig. 8a) or the ability to undergo a calcium ionophore induced acrosome reaction (Fig. 8a) differed significantly between the control and RF-EME treatment groups. Similarly, the average number of spermatozoa bound to the zona pellucida of fixed oocytes was also unchanged across our control (25), sham (25) and RF-EME exposed (19) populations (Fig. 8c,d; $p = 0.99$). As an extension of this assessment of sperm function, the ability of spermatozoa from all three treatment groups to achieve fertilization and progression to the blastocyst stage of development was then investigated. Exposure to RF-EME under our regime, did not exert any observable effect on fertilization rate (Fig. 8d), with all treatment groups resulting in the fertilization of between 83–87% of inseminated oocytes. Furthermore, when these zygotes were cultured through to the blastocyst stage of development (Fig. 8e), a modest increase was observed in the development rate of the RF-EME group, although this did not prove to be significantly different from the sham exposed or untreated sperm groups.

Discussion

Several lines of evidence now propose RF-EME to be capable of inducing a state of oxidative stress in a variety of cell types[24–27], including the male germline[7,12]. It is also well established that spermatozoa are particularly sensitive to oxidative insults, a phenomenon that may be traced to their surplus of oxidizable substrates and restricted antioxidant capacity[16,28]. What remains less certain is how RF-EME is capable of inducing such cellular responses in the absence of a thermal induction mechanism. In seeking to resolve this question, here we have utilized an *in vivo* exposure model that not only approximates the complexities of environmental RF-EME exposures, but also enables the dissection of RF-EME effects on key stages of male germ line development. Specifically, our exposure regimen enabled determination of the interaction of RF-EME with spermatozoa held exclusively within the luminal environment of the epididymis (1 week exposure), as well as those exposed during their progression through a spermatogenic cycle and transit of the epididymal tract (5 week exposure). Consistent with our previous *in vitro* investigations[7,12], we here contribute data to support the dysregulation of sperm mitochondria as a pivotal target for driving RF-EME associated stresses in the male reproductive system.

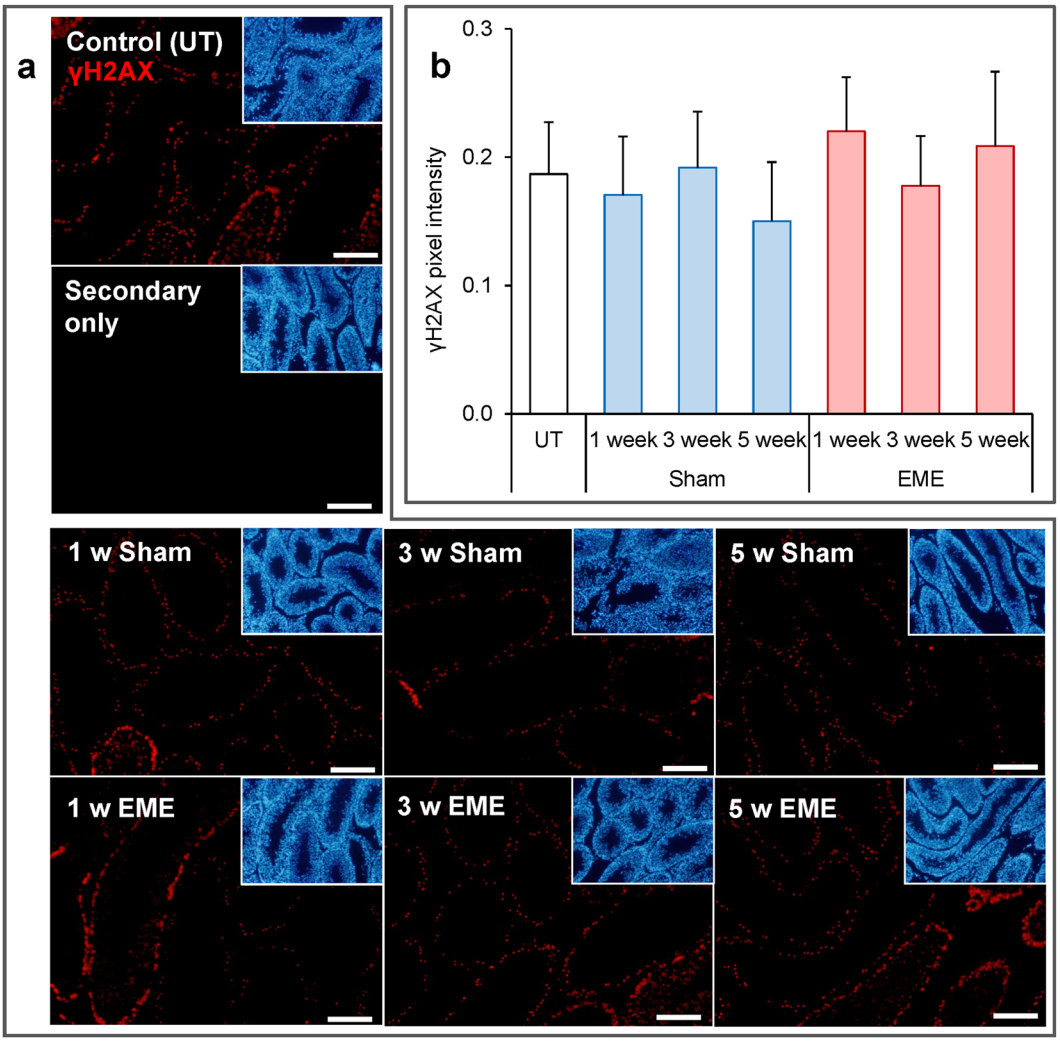

Figure 3. RF-EME exposure does not induce γH2AX expression in the testis. Testis sections from untreated control animals (UT), as well as those of the sham and RF-EME exposure groups, were probed with anti-phospho-γH2AX antibodies (red) to detect DNA double strand breaks. (**a**) Representative images are depicted, with scale bar equating to 400 µm. A secondary antibody only control is also included. Corresponding DAPI (blue) stained images, illustrating tubule morphology are included as insets included in the upper right corner of each panel. (**b**) Analysis of pixel intensity was performed on the germ cell population within the seminiferous tubules in order to quantify γH2AX expression levels across treatments. Graphical data are presented as mean + SEM (n = 3 mice/treatment group, with 8–25 tubules being analyzed for each testis).

In contrast to previous reports of disorganized testicular architecture and spermatogenesis arising from whole-body RF-EME exposure[29,30], the supraphysiological treatment regimen implemented here did not support these findings, with no changes to gross testicular histology observed. Similarly, both the somatic and germline tissue within the seminiferous tubules also proved recalcitrant to RF-EME induction of DNA damage or lipid peroxidation. Such findings are not entirely unexpected given the lack of robust evidence to support the ability of environmental RF-EME exposure conditions to elicit such obvious overt tissue damage[1]. Rather, on the basis of prevailing evidence we consider that any biophysical RF-EME interactions would likely result in more subtle phenotypic changes[1], thus justifying our primary focus on the male germ line as a sensitive model cell type[16] to explore mechanisms of RF-EME mediated stress. Accordingly, we observed a clear attenuation of sperm motility, occurring in concert with increased mitochondrial ROS generation, after 1 and 3 weeks of whole-body RF-EME exposure. In the absence of commensurate increase in cytosolic ROS production, these data provide correlative evidence that sperm mitochondria are indeed prone to RF-EME dysregulation and that the ensuing production of ROS was sufficient to compromise the most vulnerable aspects of sperm cell function. Additional support for this model rests with a growing body of literature implicating RF-EME in the generation of a state of oxidative stress in a variety of cell types other than the male germ line[11,13,31–34].

An interesting observation to arise from our study was that the induction of mitochondrial ROS generation after 1 and 3 weeks of RF-EME exposure was followed by an apparent normalization of mitochondrial ROS after an additional 2 weeks of exposure. At present, we remain uncertain what mechanism(s) could account for the

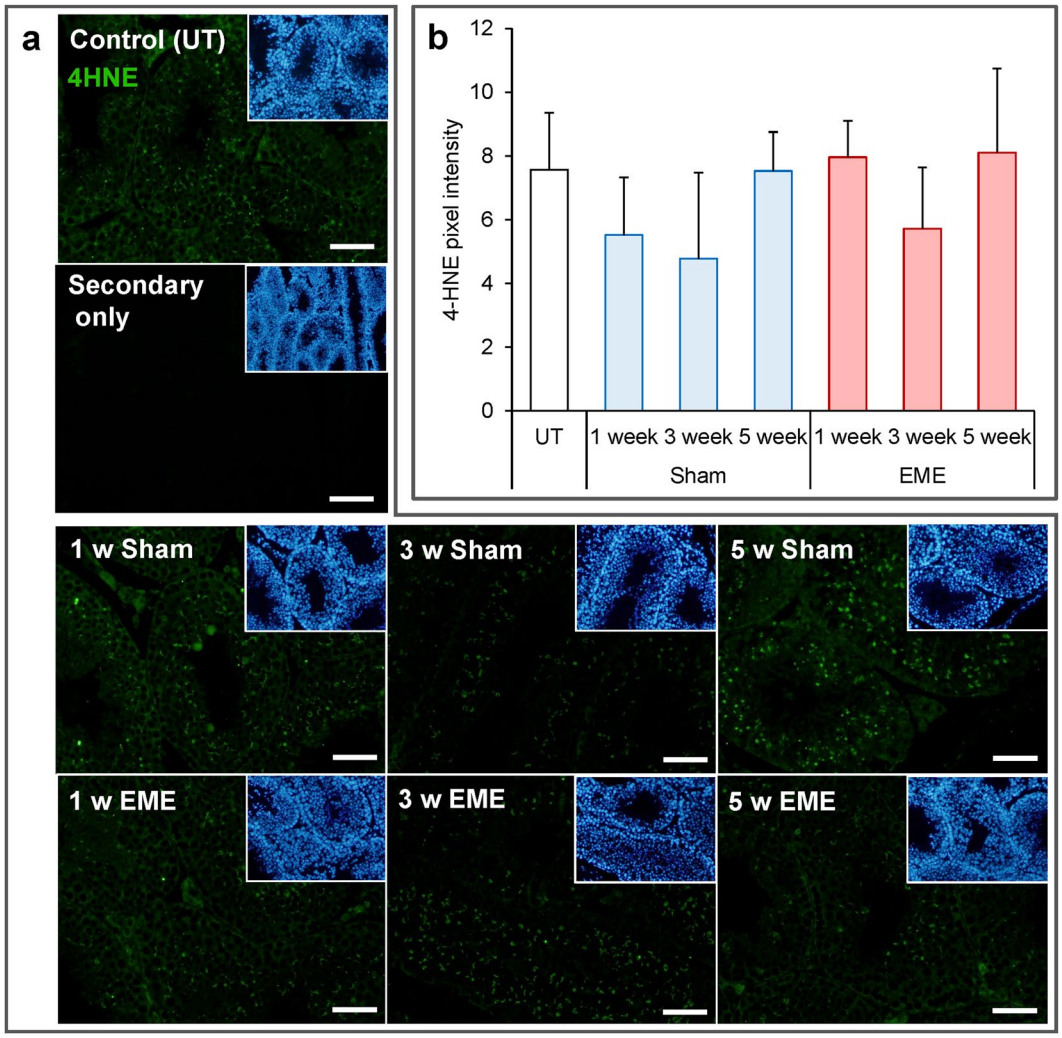

Figure 4. RF-EME exposure does not induce elevated 4-hydroxynonenal formation in the testis. Testis sections from untreated control animals (UT), as well as those of the sham and RF-EME exposure groups, were probed with anti-4-hydroxynonenal antibodies (green) to detect by-products of lipid peroxidation. (**a**) Representative images are depicted, with the scale bar equating to 200 µm. A secondary antibody only control is also included. Corresponding DAPI stained images illustrating tubule morphology are included as insets included in the upper right corner of each panel. (**b**) Analysis of pixel intensity was performed on the germ cell population within the seminiferous tubules in order to quantify 4-hydroxynonenal expression levels across treatments. Graphical data are presented as mean + SEM (n = 3 mice/treatment group, with 10–20 tubules being analyzed for each testis).

mitigation of this response, but speculate they may be associated with reduced mitochondrial function in germ cells subjected to prolonged RF-EME exposure, or that these cells are capable of responding to this challenge through an elevation of intrinsic antioxidant defenses. As an extension of this hypothesis, it is possible that the male reproductive tract also mounts a protective response to chronic RF-EME via an upregulation of exogenous antioxidant production. In keeping with this notion, it has been shown that the concentrations of both vitamin A and E increase in the testis of RF-EME exposed rats[35]. Alternatively, this phenomenon could be linked to morphological changes in the mitochondrion during spermatogenesis[36]; such as the extensive vacuolization these organelles undergo during the maturation of spermatogonia to spermatocytes[37]. Accompanying such changes, mitochondrial activity is also elevated in spermatocyte and spermatid populations, whereas mature mouse spermatozoa are known to limit their investment into oxidative phosphorylation and instead utilize glycolysis to meet their energy demands[38]. Finally, there is also evidence that the mitochondria of caput epididymal spermatozoa are silenced[39], which may afford some protection against perturbed mitochondrial ROS production while also identifying a dynamic sensitivity of spermatozoa. The cauda epididymal spermatozoa sampled after enduring 5 weeks of EME exposure, will comprise a mixture of cells exposed during various stages of germ cell development and maturation, however the majority of the cells will likely have encountered EME as morphologically mature spermatozoa, which may house less vulnerable mitochondria. Irrespective of the mechanism(s) responsible for suppression of ROS production, the downstream detrimental legacy of RF-EME exposure persisted in mature spermatozoa

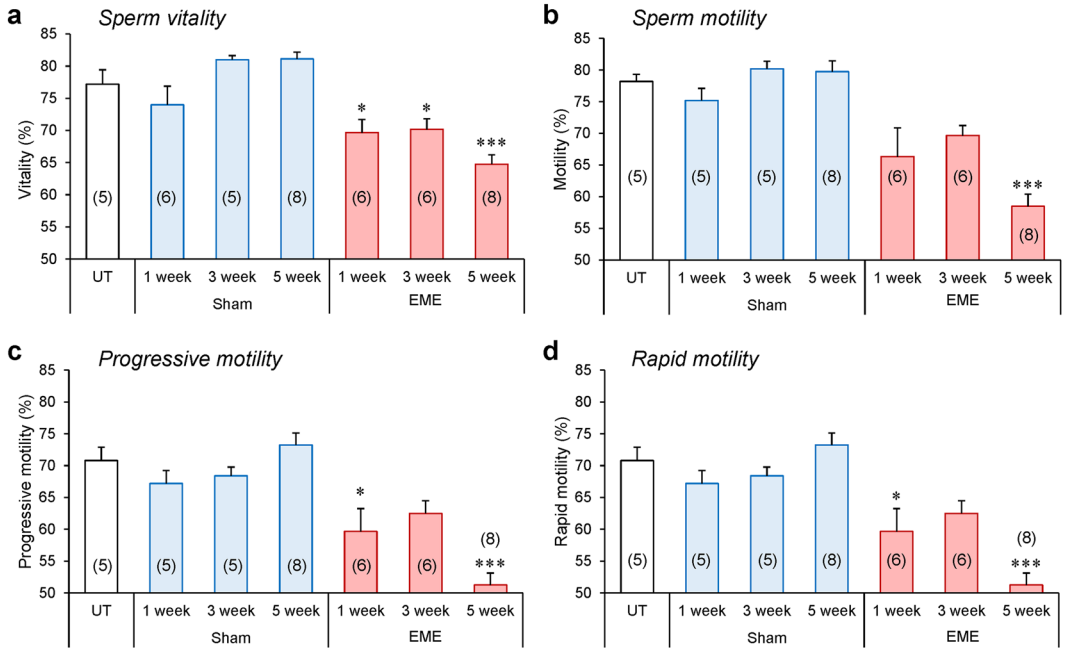

Figure 5. Sperm vitality and motility declines in response to RF-EME exposure. Spermatozoa were collected from the cauda epididymis of untreated control animals (UT), as well as those of the sham and RF-EME exposure groups. (**a**) Sperm vitality was assessed via the eosin-exclusion method. Next, the percentage of sperm displaying (**b**) any form of motility, (**c**) progressive motility, and (**d**) rapid motility was determined using computer assisted semen analysis. Data are presented as mean + SEM (n = 5–8 mice/treatment group), with a minimum of 100 spermatozoa being analyzed from each animal). The number of biological replicates used is denoted in each bar. $*P < 0.05$, $***P < 0.001$.

after 5 weeks of treatment as evidenced by the demonstration that these cells suffered the highest losses of vitality and motility. Thus, although the production of mitochondrial ROS was ameliorated in spermatozoa after 5 weeks of RF-EME exposure, these cells were unable to repair the oxidative damage they sustained during prior exposure.

The identification of sperm motility as being vulnerable to RF-EME exposure is consistent, independent evidence that this functional attribute is among of the first to succumb to elevated levels of ROS[40,41]. ROS mediated lipid peroxidation is known to drive the production of reactive aldehydes, such as 4-hydroxynonenal, which causes irreversible protein modifications and alkylation of the sperm axoneme[42]. Where oxidative stress levels may spike at an earlier window in sperm development, limiting the amount of detectable ROS in the sperm collected at 5 weeks, these cells can retain hallmarks of this pathology, in the form of oxidized DNA lesions. Consistent with this notion, we detected an increase in the oxidative stress biomarker, 8-OH-dG, in the nuclei of sperm across all exposure regimens; indicating abundant guanosine oxidation and supporting RF-EME as a mediator of oxidative stress. A similar finding has been reported by Liu *et al.*[19], who documented a significant elevation in 8-OH-dG formation in spermatocytes exposed to RF-EME. Accompanying oxidative DNA damage, we observed elevated sperm DNA fragmentation in the form of single strand breakage following whole-body RF-EME exposure. These data accord with the enhanced levels of DNA fragmentation documented in spermatozoa[7,21,43] and spermatocytes[19] exposed to RF-EME; a phenomenon that may describe a continuum of DNA damage, originating from oxidative DNA insults[44]. While further studies are required to pinpoint variations in the sensitivity of different germ cell populations to RF-EME *in vivo*, our data suggests that a window of vulnerability may extend across both testicular and post-testicular (i.e. epididymal) phases of development.

Not with standing an elevation in oxidative stress mediated DNA damage and an attendant reduction of motility, the spermatozoa recovered from mice exposed to 5 weeks of whole-body RF-EME did not display any associated lesions in their fertilization potential. Thus, these cells retained their ability to capacitate, acrosome react, and bind zona pellucidae at rates that were statistically indistinguishable from those of untreated and sham exposed mice. Moreover, these spermatozoa were capable of supporting normal rates of *in vitro* fertilization and early embryo development. In seeking to reconcile these data, a key limitation is that the *in vitro* fertilization strategy adopted in this study, introduced selection bias for the higher quality, motile spermatozoa which potentially harbour only basal levels of DNA damage. Even in the lowest motility group, after 5 weeks of EME exposure, 60% of the recovered cells remain motile. This notion is consistent with studies of human IVF patients, which have revealed that *in vitro* assays of sperm-zona pellucida binding are highly selective for spermatozoa with intact DNA and normal motility profiles[45]. Alternatively, it is possible that the burden of DNA damage harbored by the fertilizing spermatozoon was sufficiently resolved by the oocyte. In any case, this clearly illustrates, reassuringly, that even at the supraphysiological regimens of whole-body RF-EME exposure used in this study, no overt impairment to fertilization potential and early embryo development was observed. This is perhaps in alignment to the lack of overt morphological changes observed in the reproductive tissue of exposed mice, confirming

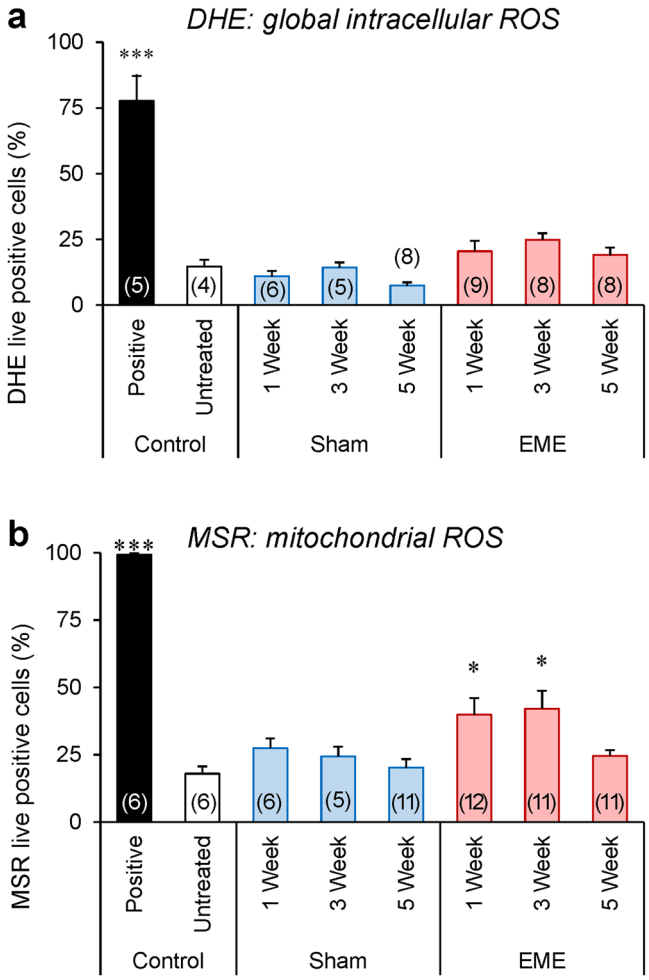

Figure 6. Exposure to RF-EME stimulates the generation of mitochondrial reactive oxygen species. Spermatozoa were isolated from the cauda epididymis of untreated control animals, as well as those of the sham and RF-EME exposure groups. These cells were pre-loaded with fluorescent probes and then analyzed using flow cytometry to assess their generation of reactive oxygen species (ROS). (**a**) Global levels of ROS generated in the sperm cell was assessed with the dihydroethidium (DHE) probe. (**b**) Alternatively, mitochondrial ROS generation was investigated with the MitoSOX Red (MSR) probe. In both instances, a minimum of 10,000 spermatozoa were assessed from 5–12 of animals and data are presented as mean + SEM. The number of biological replicates used is denoted in each bar. $^{*}P < 0.05$.

observations that environmental RF-EME does not contribute to gross biological damages. In this context, and given the evidence of cellular oxidative impacts, we cannot yet discount the possibility of transmission of subtle phenotypic or epigenetic changes in the offspring. Thus, future studies focused on trans- and multi-generational outcomes will likely play a key role in resolving any potential for cumulative changes caused by RF-EME. While more targeted investigations into this aspect of exposure is warranted, it is perhaps comforting that whole-body chronic exposure (life-long, 24 h/day) to electromagnetic fields has been reported to elicit no harmful effects on the fertility or development of mice over four successive generations[46].

In summary, our evidence supports the hypothesis that sustained whole-body RF-EME is capable of inducing a state of oxidative stress in the male germ line, a cell vulnerable to the effects of ROS. Furthermore, our data further implicate the mitochondria as the target for RF-EME biophysical interaction, with a consequential elevation of mitochondrial ROS generation being linked to reduced motility and elevated oxidative DNA damage and DNA fragmentation in the spermatozoa of exposed males. Whilst these lesions were not sufficient to compromise fertilization competence or early embryo development, it will nonetheless be of interest to investigate the trans-generational influence of whole-body RF-EME in future studies.

Methods

Chemical reagents. The reagents used in this study were purchased from Sigma-Aldrich (St. Louis, MO, USA) unless stated otherwise. Fluorescent probes were purchased from Thermo Fisher Scientific (Waltham, MA, USA), unless otherwise stated. All fluorescence imaging was performed using a Zeiss Axioplan 2 fluorescence microscope (Carl Zeiss MicroImaging GmbH, Jena, Germany).

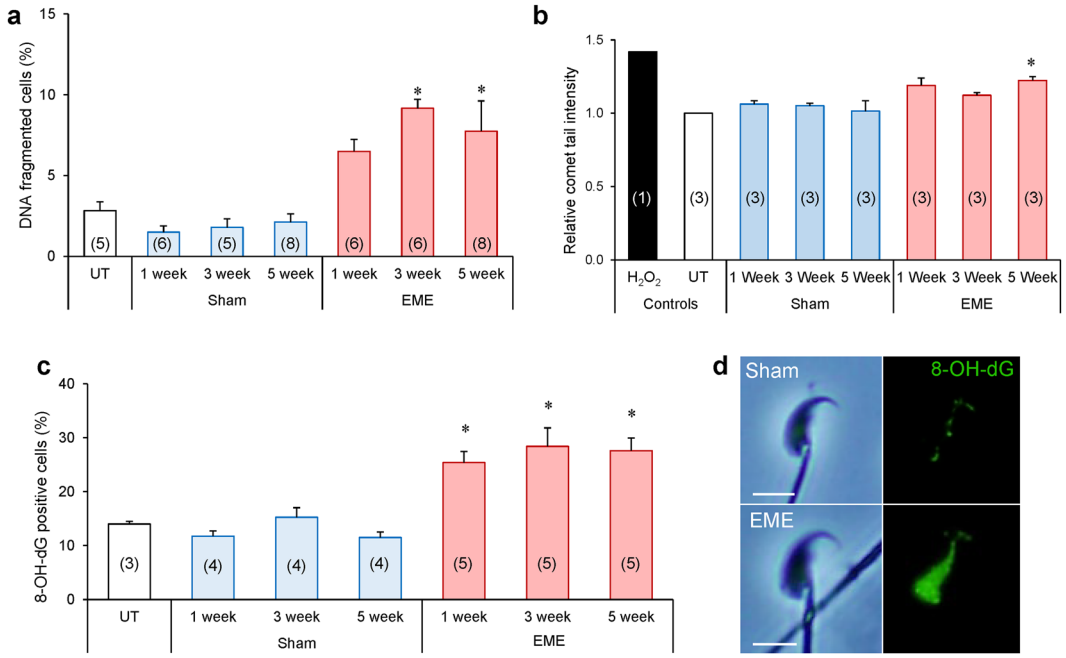

Figure 7. RF-EME exposure induces oxidative DNA damage in spermatozoa. Spermatozoa were isolated from the cauda epididymis of untreated control animals (UT), as well as those of the sham and RF-EME exposure groups. These cells were assessed for DNA fragmentation using (**a**) the halo assay showing the percentage of cells fragmented (n = 5–8 mice/treatment group, each with 100 sperm assessed for each replicate) and then (**b**) quantified by the alkaline comet assay, expressed as percentage tail intensity and normalized to control data for each run (n = 3 mice/treatment, each with 50–70 sperm cells assessed). (**c**) To extend this DNA integrity analysis, sperm were evaluated for oxidative DNA adducts via labelling with anti-8-hydroxy-2-deoxyguanosine (8-OH-dG) antibodies (n = 3–5 mice/treatment). (**d**) Representative images of spermatozoa stained with the 8-OH-dG antibody from the 5 week sham and RF-EME exposed populations are included. The number of biological replicates used is denoted in each bar. Data are presented as mean + SEM. $^{*}P < 0.05$, $^{**}P < 0.01$.

Waveguide design and whole-body RF-EME exposure regimens. Adult (>8 weeks) male C57BL/6 mice were irradiated with 2 W/kg and 905 MHz RF-EME in a waveguide (Fig. 1) for 12 h daily, during a night (7 pm–7 am) cycle while the waveguide lid was closed. This waveguide was constructed by the Physics Department at the UON and comprises a cylindrical aluminium chamber (radius of 60 cm and depth of 16 cm) and mechanically operated lid. The chamber sides were insulated with carbon impregnated foam (RFI Industries, VIC, Australia) to prevent RF-EME reflection. Small fans were implemented for external air circulation into the chamber through the base. RF-EME was generated by a Rohde and Schwarz SMC100A signal generator (Macquarie Park, NSW, Australia), connected to a signal amplifier. Chamber lid operation was controlled by a timed motor in order to raise or lower the lid every 12 h. Mice were housed in plastic cages with Perspex lids and plastic water bottles to ensure there was no metal, which interferes with RF-EME distribution. Cages were arranged radially around a central RF-EME emitting antenna, and oriented so that the water bottle furthest from the radiation source to minimize liquid interference. When mice were removed they were replaced with 'phantoms' composed of a 50 ml Falcon tube filled with 142 mM NaCl in deionized water to mimic blood. Sham exposed males were placed in the waveguide under identical conditions, however, the signal generator was turned off, thus receiving no exposure to RF-EME. All treatment groups were sacrificed at three time points; 1, 3 and 5 weeks of exposure and compared to an untreated control population of mice that were not placed inside the chamber. Mice were weighed weekly throughout the treatment regime (EME or sham exposed) during the time the waveguide lid was open. The weights were recorded after mice were individually placed in a tared container on top of the weigh tray of an electronic balance.

The SAR delivered to the mice was calibrated using a NARDA NBM 520 electric field meter with an EF1891 probe to measure electric fields in the empty irradiation system. Radial electric field measurements were made as a function of distance from the vertical aerial mounted in the center of the system after the antenna length was adjusted to maximize power supplied to the system at a frequency of 905 MHz. For 1 W input to the aerial a maximum electric field of 94 V/m was measured 16 cm from the center, whereas in their slightly larger setup, Puranen *et al.*[23] measured a maximum electric field of 80 V/m at 15 cm from the center. The variation of E field with radial distance and the maximum electric fields in the two setups were found to be similar for the same power input.

The SAR (W kg-1) is related to the electric field, E, in a sample of conductivity σ (S m-1), and density ρ (kg m-3) by

$$\mathrm{SAR} = \sigma|\mathrm{E}|\,2/\rho\ \ (\mathrm{Wkg}-1) \tag{1}$$

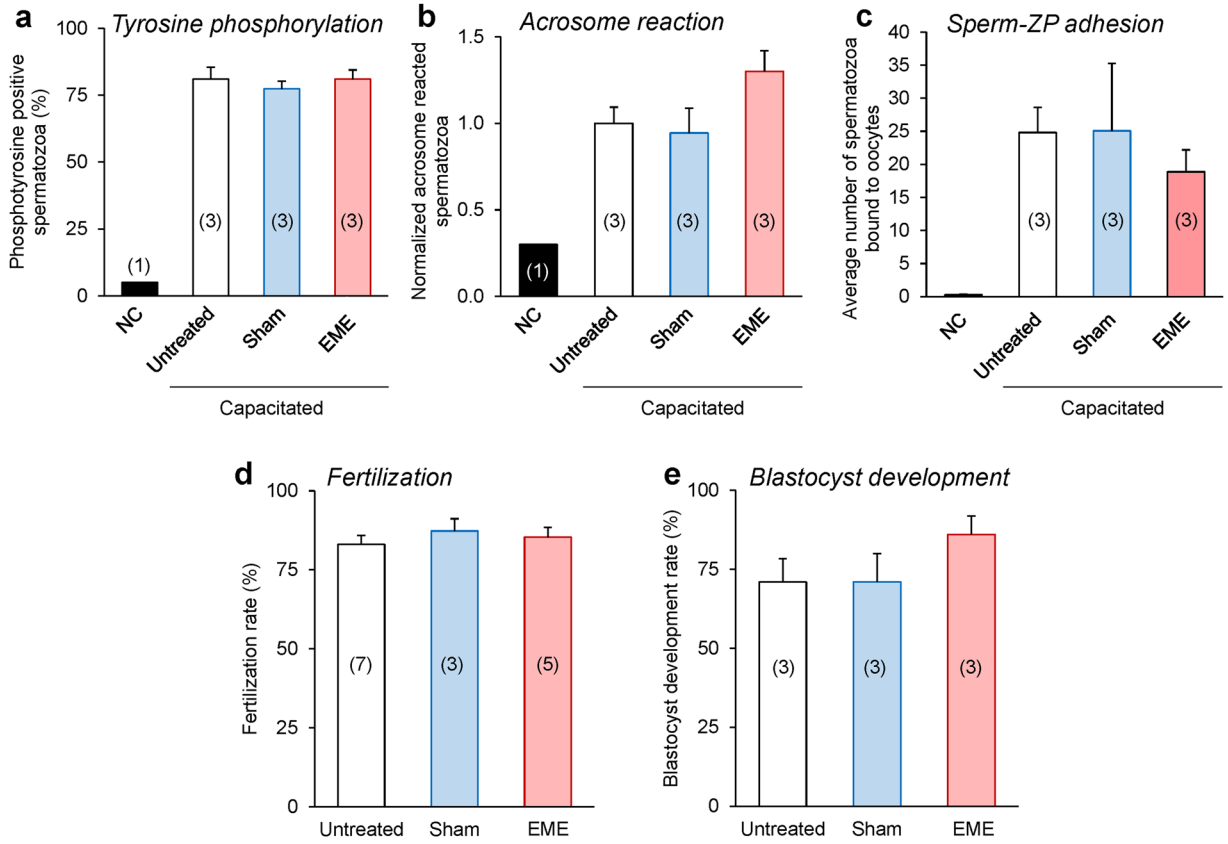

Figure 8. RF-EME exposure did not compromise the fertilization competence of spermatozoa. Spermatozoa were isolated from the cauda epididymis of untreated control animals, as well as those of the 5-week sham and RF-EME exposure groups. These cells were driven to capacitate and then assessed for (**a**) anti-phosphotyrosine labeling of the sperm flagellum, and (**b**) their ability to undergo a calcium ionophore induced acrosome reaction [assessed via peanut agglutinin (PNA) labeling of the sperm outer acrosomal membrane with values being normalized to the untreated control], and (**c**) binding to the zona-pellucida (ZP) of homologous oocytes (the average number of spermatozoa bound to ZP intact oocytes is shown). In each instance a non-capacitated (NC) population of spermatozoa from untreated animals was included as a negative control. Alternatively, spermatozoa were examined for their ability to (**d**) fertilize oocytes *in vitro* and subsequently (**e**) support early embryo development through to the blastocyst stage. In all instances, assessed spermatozoa were isolated from each of three animals and data are presented as mean + SEM, except for (**d**), where 3–7 mice were used. The number of biological replicates is shown in each bar. (**a, b**) A minimum of 100 spermatozoa from each animal were assessed for phosphotyrosine labelling of the sperm flagellum, and PNA labelling of the acrosome. (**c**, **d**) 8–10 oocytes per replicate were assessed for sperm-ZP binding and 11–30 for fertilization, and (**e**) 11–30 embryos were assessed for blastocyst development.

where E is the root-mean-square local electric field strength in V m-1. Puranen *et al.* (2009) measured a SAR of 0.11 W/m for the above 1 W input to the aerial. During our irradiations the input RF power was 20 W, corresponding to an average SAR of 2.2 W/kg since the geometry of our irradiation system is very similar to that of Puranen *et al.*[23].

Assessment of testis sections. Upon dissection, testes were fixed in Bouin's solution, sectioned, dewaxed and rehydrated using standard protocols[47]. One section from each testis was stained with hematoxylin and eosin to investigate testis morphology, while the remainder were prepared for immunohistochemistry as previously described[48]. Antigen retrieval was performed by microwaving slides in 50 mM Tris (pH 10.5) for 9 min. Tissue sections were blocked (3% bovine serum albumin (BSA)-PBST, 10% goat serum) for 1 h at room temperature, washed in PBS for 5 min and labeled with appropriate pairs of primary (either anti-phospho-γH2AX (2 µg/ml) or anti-4-hydroxynonenal (1/300) antibodies in 1% BSA-PBST overnight at 4 °C) and AlexaFluor-conjugated secondary antibodies (1 h at 37 °C). After washing in PBS, sections were counterstained with DAPI (0.5 µg/ml), and viewed using fluorescence microscopy. Mean pixel intensity analysis was conducted on images using ImageJ version 1.48 V (NIH, USA). Pixel intensity determination was performed only on the seminiferous tubules, with surrounding interstitial tissue isolated from this analysis. For γH2AX, meiotic germ cells were excluded from the analysis due naturally occurring high levels of double strand breaks in these cells[50].

Assay/measurement	Untreated control	1 week		3 weeks		5 weeks	
		Sham	EME	Sham	EME	Sham	EME
Body weight	NA	20	20	14	14	8	8
Testis histology	3	3	3	3	3	3	3
Testis staining: γH2AX	3	3	3	3	3	3	3
Testis staining: 4-hydroxynonenal	3	3	3	3	3	3	3
Sperm vitality	5	6	6	5	6	8	8
Sperm motility, progressive and rapid	5	5	6	5	6	8	8
Dihydroethidium staining	4	6	9	5	8	8	8
MitoSOX red staining	6	6	12	5	11	11	11
DNA fragmentation	5	6	6	5	6	8	8
Comet tail intensity	3	3	3	3	3	3	3
8OHdG	3	4	4	4	5	5	5
Tyrosine phosphorylation	3	NA	NA	NA	NA	3	3
Acrosome reaction	3	NA	NA	NA	NA	3	3
Sperm-zona pellucida adhesion	3	NA	NA	NA	NA	3	3
Fertilization	7	NA	NA	NA	NA	3	5
Blastocyst development	3	NA	NA	NA	NA	3	3

Table 1. Number of replicates used for each assay.

Preparation of spermatozoa. Epididymides were dissected immediately after euthanasia and mature spermatozoa were collected from the caudal segment by retrograde perfusion before being resuspended in 1 ml of modified Biggers, Whiting, Whittingham media (BWW)[49]. Objective sperm motility was assessed by computer assisted sperm analysis (IVOS, Hamilton Thorne, Danvers, MA, USA) as previously described[50], and sperm vitality was determined via eosin exclusion.

Determination of ROS production in spermatozoa. Spermatozoa were assessed for ROS generation via flow cytometry with the mitochondrial superoxide probe MitoSOX Red (MSR) or cytosolic superoxide probe dihydroethidium (DHE) in conjunction with Sytox Green (SYG) vitality stain as previously described[51].

Sperm chromatin dispersion (Halo) assay. Spermatozoa were snap frozen in liquid nitrogen and stored at −80 °C prior to analysis. Spermatozoa were defrosted and mixed with 1% low melting point agarose at 37 °C and applied to Superfrost slides (Thermo Fisher Scientific) pre-coated with 0.65% agarose. The slides were sealed with a coverslip and placed at 4 °C to solidify for 5 min. After removing the coverslips, the slides were treated with 0.08 N HCl for 7 min in foil, followed by Halo solution 1 (pH 7.5; 0.4 M Tris, 1% SDS, 50 mM EDTA, 0.8 M DTT) for 10 min and Halo solution 2 (pH 7.5; 0.4 M Tris, 1% SDS, 2 M NaCl) for 5 min at room temperature to lyse the cells, relax and neutralize the DNA. Next, slides were exposed to Tris-boric acid-EDTA buffer (pH 7.5; 0.1 M tris, 0.09 M boric acid, 0.002 M EDTA) for 2 min, then washed in ethanol (70%, 90% then 100%) for 2 min each to dehydrate the slides. After air drying, slides were counterstained with DAPI (0.5 µg/ml) for 10 min at room temperature, rinsed in PBS and mounted.

Alkaline comet assay. The alkaline comet assay was performed as described previously[52]. DNA damage was analysed using Comet Assay IV software (Perceptive Instruments, Suffolk, UK). Hydrogen peroxide treatment (500 µM, 5 min at room temperature) was utilized as a positive control. To compare sperm DNA damage between treatments, percentage tail DNA values of each cell in the treated samples were normalized to that of the average percentage tail DNA of the respective untreated control for each time point. The control itself taking on the value of 1. The normalized data for each sample then contributed to a biological replicate. The average of these replicates are then graphed. The normalization process is required to minimize the noise generated by the small fluctuations in tail intensity between independent runs and days.

Oxidative DNA damage assay. Oxidative DNA damage was assessed by suspending 2×10^6 spermatozoa in Oxidative DNA/RNA damage antibody (Thermo Fisher Scientific) diluted 1/40 in PBST overnight at 4 °C. Cells were then centrifuged for 5 min at 450 × g and washed in PBS before incubation in AlexaFluor-488 goat α rabbit secondary (Abcam, Massachusetts, US) diluted 1/400 in PBST for 1 h at 37 °C. Finally, cells were again washed and resuspended in PBS for counting and imaging via fluorescence microscopy.

Sperm functional assays and *in vitro* fertilization. Cauda epididymal spermatozoa were assessed for their ability to undergo capacitation-associated tyrosine phosphorylation, a calcium ionophore (A23187) induced acrosome reaction and bind zona pellucidae as previously described[53,54]. Alternatively, 2×10^5 capacitated spermatozoa were inseminated into a droplet of oocytes recovered from superovulated female C57BL/6 mice[55]. The gametes were co-incubated for 4 h at 37 °C prior to the oocytes being assessed for fertilization (i.e. extrusion of second polar body and/or pronucleus formation). Zygotes were cultured in HTF medium overnight and transferred into G1 PLUS culture medium (Vitrolife, Stockholm, Sweden) on the morning of day 2 followed by an

additional media change into G2 PLUS medium (Vitrolife) on Day 4[55]. The percentage of fertilized oocytes as well as embryos that had reached blastocyst stage by the morning of day 5 was calculated.

Study design. Twenty adult male mice were randomly assigned to three treatment groups (untreated control, sham exposure control, RF-EME exposed), determined by the number of mice that could fit in the waveguide (10 cages, 2 mice per cage). Six mice were randomly selected for the 7 and 21 day intervals, while eight mice were selected for the 35 day interval. After each interval the mice were phenotyped for male fertility. For the purpose of this study, we ran the experiment twice to generate sufficient numbers of biological replicates for certain assays, e.g. MitoSOX, where we used 11 replicates. Each of the two treatment cycles consisted of 6 males treated for 1 week, 6 males treated for 3 weeks and 8 males treated for 5 weeks. The individual number of replicates for each assay can be found within the figures and is also shown in Table 1, below. As 20 mice were utilized for end point assays over the period of 5 weeks, the reduction in the number of replicates for body weight measurements decreases with the use of these individuals at the 1 and 3 week time points accordingly.

Statistical analysis. Samples from each animal were considered as a single biological replicate. Experimental data was analyzed using JMP version 11 software (SAS Institute Inc., Cary, NC). Normality of datasets was assessed with the Shapiro-Wilks test ($\alpha = 0.05$). A one-way ANOVA was used to compare normally distributed treatments, with a post-hoc Tukey's honest significant difference test ($\alpha = 0.05$). For data not normally distributed, the Wilcoxon test was used ($\alpha = 0.05$), with a post-hoc Dunn's test. Error bars represent standard error values around the mean.

Ethics statement. All experimental protocols were approved by the University of Newcastle (UON) Animal Care and Ethics Committee (Ethics Number 2014–447) and were performed in accordance with national and international guidelines, including the NSW Animal Research Act 1998, NSW Animal Research Regulation 2010 and the Australian Code for the Care and Use of Animals for Scientific Purposes 8th Ed.

Data availability

All data generated or analyzed during this study are included in this published article.

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B.J.H., B.N., G.N.D. and R.J.A. designed the experimental regime. B.V.K. constructed and tested the waveguide apparatus. B.J.H. performed all experiments with assistance from K.E.M. and J.H.M. B.J.H. drafted the initial manuscript, which was edited by B.N., R.J.A. and G.N.D.

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to G.N.D.I.

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Radiofrequency EMF irradiation effects on pre-B lymphocytes undergoing somatic recombination

Elena Ioniță[1,2], Aurelian Marcu[3], Mihaela Temelie[1], Diana Savu[1], Mihai Şerbănescu[3] & Mihai Ciubotaru[1,2]✉

Intense electromagnetic fields (EMFs) induce DNA double stranded breaks (DSBs) in exposed lymphocytes.We study developing pre-B lymphocytes following V(D)J recombination at their Immunoglobulin light chain loci (*IgL*). Recombination physiologically induces DNA DSBs, and we tested if low doses of EMF irradiation affect this developmental stage. Recombining pre-B cells, were exposed for 48 h to low intensity EMFs (maximal radiative power density flux S of 9.5 μW/cm^2 and electric field intensity 3 V/m) from waves of frequencies ranging from 720 to 1224 MHz. Irradiated pre-B cells show decreased levels of recombination, reduction which is dependent upon the power dose and most remarkably upon the frequency of the applied EMF. Although 50% recombination reduction cannot be obtained even for an S of 9.5 μW/cm^2 in cells irradiated at 720 MHz, such an effect is reached in cells exposed to only 0.45 μW/cm^2 power with 950 and 1000 MHz waves. A maximal four-fold recombination reduction was measured in cells exposed to 1000 MHz waves with S from 0.2 to 4.5 μW/cm^2 displaying normal levels of γH2AX phosphorylated histone. Our findings show that developing B cells exposure to low intensity EMFs can affect the levels of production and diversity of their antibodies repertoire.

Somatic or V(D)J recombination is the process that assembles in all jawed vertebrates the gene segments encoding the variable regions of the specific antigen immune receptors (T cell and Immunoglobulin IG) of the lymphoid T and B cells[1]. This process occurs in lymphocyte precursors, is mediated by RAG (recombination activating gene proteins) recombinase a heterotetrameric complex made of a dimer of RAG1 and two monomers of RAG2[2,3]. RAG1 a member of the DDE transposase/Integrase family is the key catalytic component of RAG. RAG binds specifically to recombination signal sequences (RSS) flanking germinal coding V, (D), J gene segments in the variable region at the IG and T cell receptor loci and catalyzes their rearrangement[4]. RAG recombination generates two DNA hairpins at the coding ends and two blunt double stranded DNA cuts at the signal ends. RAG maintains the paired cleaved ends in proximity and allows the ubiquitous set of non-homologous end-joining (NHEJ) DNA repair enzymes (Artemis, ATM, DNAPk, XRCC4, DNA Ligase IV) to resolve the hairpins and join the cleaved ends. For B and T lymphocytes recombination occurs at two stages during their differentiation[5]. We will discuss only the B lineage development in the bone marrow. First two rounds, D to J (in pre-pro stage) followed by V to DJ recombination (in late-pro stage) occur in pro-B cells at their Ig Heavy chain locus (*IgH*). Once *IgH* locus is rearranged, expressed Igμ together with a surrogate light chain comprising λ5 Vpre B proteins and two Igα, β signaling subunits assemble the pre-B cell receptor(pre-BCR)[6], which marks the large pre-B cell stage. Stromal bone marrow cells secreted interleukin IL-7 binds to their receptor (IL-7R), a signal which is transduced as pro-survival and proliferative[7]. First, IL-7R signals through Janus Kinase 3-(JAK-3)[8] phosphorylating and recruiting the signal transducer and activator of transcription 5A and B (STAT5A and B)[9,10] which stimulate transcription of *Ccnd3* encoding Cyclin D3[11] and of the B cell lymphoma 2(bcl2) gene[12]. Both Cyclin D3 and the anti-apoptotic BCL2 help pre-B cells through cell cycle G1 checkpoint allowing the replication of their DNA. Secondly, IL-7R signals in large pre-B cells through phosphoinositide 3-kinase (PI3K)[13] and protein Kinase B (AKT) phosphorylating the forkhead box O 1, 3 (FOXO1,3) transcription factors, modification which exports them from nuclei and targets the proteins for degradation[14–16]. FOXO1, 3 activate *e-rag* enhancer and *rag1*, *2* genes transcription[14,17]. In large pre-B cells IL-7R also signals via the nuclear factor kappa light chain

[1]Department of Physics of Life and Environmental Sciences, Horia Hulubei National Institute for R&D in Physics and Nuclear Engineering, 077125 Măgurele, Ilfov, Romania. [2]Department of Immunology, Internal Medicine, Colentina Clinical Hospital, 72202 Bucharest, Romania. [3]Center for Advanced Laser Technologies, National Institute for Laser Plasma and Radiation Physics, 077125 Măgurele, Ilfov, Romania. ✉email: mihai.ciubotaru@nipne.ro

enhancer of activated B cells (NF-kB) stimulated by AKT phosphorylation of IKKα serine 23[18]. NF-kB activates Cyclin D4 kinase which targets FOXO1 for phosphorylation and repression[19]. By inhibiting FOXO1, or phosphorylating STAT-5, IL-7R signals are transiently downregulating RAG proteins in large pre-B cells. After four to five rounds of replication the large pre-B lymphocytes get under the influence of cell surface pre-BCR receptor aggregation and stimulation (in absence of a bonified ligand), a signal which antagonizes that of IL-7R, induces cell cycle arrest and transitions cells towards small pre-B stage[20]. Stimulation of pre-BCR cascades through RAS and extracellular signal- regulated kinase (ERK) upregulating the E2A transcription factor expression. E2A binds both Igk intronic and Igk 3' enhancers making the *Igk* light chain locus accessible for recombination[21]. Another effect of pre-BCR stimulation signals through spleen tyrosine kinase(SYK) and B cell-linker protein(BLNK) which together repress PI3K and AKT but stimulate mitogen activated p38 kinase which activates FOXO1 to express RAG[13,20,22]. Consequently, in small pre-B cells subsequent V to J rearrangements occur at *Ig L k* or *λ* light chain loci. Upon completion of a successful V to J recombined allele, the cell develops into naïve immature B cell, exposing IgM B cell receptors (BCR).

Interference of V(D)J recombination with other concurrent exogenous factors favoring DNA DSBs, like ionizing or EM irradiation can induce DNA damage which may lead to oncogenic translocations such as those described in acute lymphoblastic leukemia (ALL)[23,24]. Exposure of human blood lymphocytes from healthy donors to strong EMFs (2 h irradiation with sinusoidal pulses at 4×10^5 V/m 50 Hz with a carrier wave of 10 Hz[25]) causes DNA DSBs and chromosomal lesions whose severity correlate with the intensity of the applied fields and the duration of exposure. However, less clear results come from studies with irradiated lymphocytes using low intensity, high radiofrequency(RF) EMFs (3 kHz–300 GHz)[26]. Most of these studies have assessed the levels of EMF inflicted DNA single and DSBs on lymphocytes using the microgel electrophoresis technique or 'comet assay', which detects brakes with a sensitivity limit of 50 strand events per diploid cell[27]. RF EM irradiation from cell phones was first studied by Phillips et al. in Molt-4 human lymphoblastoid cells exposed for 2–21 h to fields of 813.5 and 836.5 MHz with specific absorption rate (SAR) (2.4–26 μW/g)[28]. Variable degree of DNA damage is reported, mainly induced by high SAR values waves (increased at 24 or 26 μW/g and decreased at 2.4 or 2.6 μW/g) and longer exposures (21 h versus 2 h). Another study by Mashevich et al.[29] reveals that continuous 72 h exposure of human peripheral blood lymphocytes to EMFs of 830 MHz waves, with SAR ranging from 1.6 to 8.8 W/kg lead to SAR dependent aneuploidy with specific abnormalities on chromosome 17. However, in vitro exposure of human blood lymphocytes for only 2 h to short pulses of 2450 MHz, at an average power of 5 mW/cm^2 [30] showed no significant DNA damage as assessed by alkali comet assays. No signs of genotoxicity were found when total human blood leukocytes were in vitro exposed for 24 h either at a continuous or a pulsed-wave 1.9 GHz EMF with a SAR ranging between 0.1 and 10 W/Kg [31]. Absence of significant DNA damage response in human blood lymphocytes was also reported by a study by Stronati et al.[32] in which blood specimens were continuously exposed for 24 h at a Global System Mobile Communication generated EMF of 935 MHz with a SAR of 1 or 2 W/Kg [32]. Similar negative results with respect to EMF induced DNA damage was reported in a study by Hook et al.[33] with cultured Molt-4 human lymphoblasts exposed for 24 h to four types of frequency mobile network modulations around 815–850 MHz with SAR values ranging from 2.4 to 3.2 W/Kg [33].

In our work we test the effects of in vitro irradiating V(D)J recombining pre-B cells with very low doses of RF EM waves. RAG stimulation is obtained either mimicking a pre-BCR stimulus with AKT inhibition, or with a stress inducible Abelson (Abl) kinase inhibitor response via STAT5 phosphorylation inhibition. For both stimuli, near 950–1000 MHz RF EMF cell irradiation, in the absence of detectable DNA DSBs, causes a four-fold reduction in recombination levels in exposed pre-Bs versus that assessed in non-irradiated cells.

Results

Design and specific experimental conditions used to assess *Ig k* locus rearrangements. Our study tests how gene recombination levels are influenced by exposure to EMFs with distinct emitted frequencies and power levels (dose–response). In vitro grown vAbl transformed murine pre-B cells stimulated to recombine V(D)J are exposed to a broadband (0.8–3 GHz) emission antenna which broadcasts an EMF from a RF generator (Fig. 1A upper region). For all experiments we standardized our cellular growing conditions to control irradiation parameters (see Supplemental Material section S1 and Fig. 1Sa and b). RAG expression and V(D)J recombination can be induced in vAbl transformed pre-B cells(differentiating them in small pre-B cells) upon stimulation either with an Abl tyrosine kinase inhibitor imatinib(mesylate of imatinib)(IMA)[34,35](Supplemental Material Fig. 1Sb growing dish wells 1, 2 and 3), or with an AKT inhibitor GSK-690693(GSK)[19](wells 4, 5 and 6 , Fig. 1Sb). Whereas IMA induces RAG by inhibiting vABL-1 tyrosine kinase via a stress-inducible GADD45α action[17,34,35], GSK acts as AKT inhibitor, reducing NF-kB and FOXO1 inhibitory phosphorylation (by CDK4) thus, mimicking a physiologic pre-BCR stimulation[19] (see Supplemental material section S2). Time course experiments with RAG induction in vAbl pre-B cells using both drugs show maximal RAG1 levels after 36 h of stimulation (see Supplemental material S2 and Fig. 2Sa and b). Using this finding, after 48 h post drug induction (to allow recombination), all synchronized cultured cells were harvested and their genomic DNA extracted. A previously described two-steps nested PCR (polymerase chain reaction) which assesses the recombination extent taking place at *Igk* kappa light chain locus (chromosome 6, locus schematic and primer positions shown in Fig. 1B), is templated with the equivalent genomic DNA extracted from 2×10^6 cells from each tested culture set[36,37]. In the absence of V(D)J recombination (control reactions with no stimulation Fig. 1C lane 2) the variable region V and J segments in germline configuration are too far apart on the chromosome to yield appropriate amplification products. The PCR amplification products obtained only from recombined templates (Fig. 1C lane 3) are separated after electrophoretic migration on 1.5% agarose gels and visualized after fluorescent staining with SYBR green (schematic lower drawing Fig. 1A, and gel scan Fig. 1C). This typical nested PCR reaction reports *k* locus recombination events with two detectable products; the predominant one Vk-Jk2 of 280 bp (95%) and Vk-Jk1 of

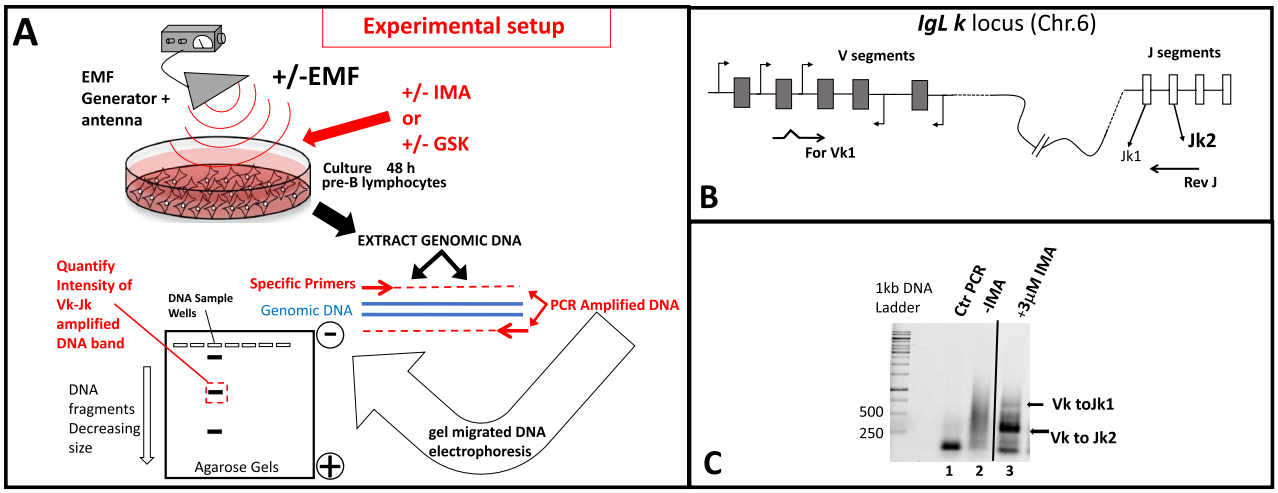

Figure 1. (**A**) Schematic depiction of the flow chart of the experimental design. Murine A-70 vAbl pre-B cells grown with or without exposure to Electromagnetic field influence(EMF), in the absence or presence of RAG stimulation either by Mesylate of Imatinib (IMA) or by GSK-690693(GSK), are harvested and their genomic DNA subjected to a two-steps PCR recombination assay identifying Vk to Jk rearrangements at their *IgL kappa* loci. The electrophoretically separated recombination products (Vk-Jk) are quantified by densitometry to assess the extent of locus rearrangements influenced by EMF. (**B**) Shematic configuration of *IgL k* kappa locus on Mouse chromosome 6, and the positioning of the primers used in the assay. (**C**) PCR reactions electrophoretically separated in agarose gel stained with Sybr green identify the recombined products (arrows show Vk to Jk1 and Vk to Jk2) in lane 3 versus, control reactions lane 1 without genomic DNA, lane 2 templating genomic DNA from uninduced cells (in germline configuration). Such recombination amplified reactions are then used for densitometry quantifications. The entire gel from which (**C**) was cropped displaying amplifications (Vk to Jk response) from cells treated with a wide range of increasing IMA concentrations , is shown in Supplemental Material Fig. 3Sa.

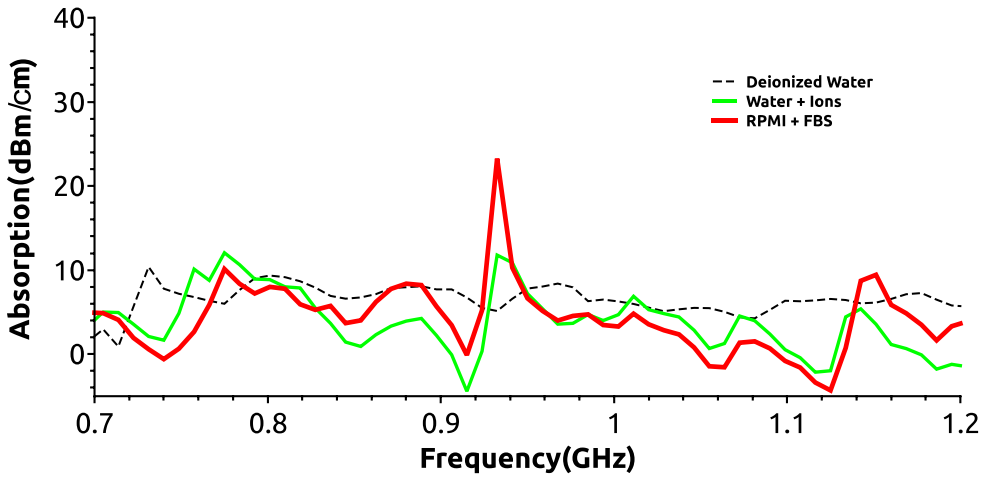

Figure 2. Absorption spectra measurements of filtered deionized water (dashed thin black line), tap water (green thick line Water + Ions) and RPMI cell culture medium with 10% fetal calf serum (FBS)(red thick line RPMI + FBS) All measurements were done using a Keysight-AGILENT-HP N9935A spectrum analyzer as described in "Methods" section.

700 bp (5%)[36] (Fig. 1C lane 3). Densitometric quantifications of the DNA Vk-Jk2 recombination products allow us to assess the EMF influence on recombination (Fig. 1A lower drawing). A dose–response (recombination) effect obtained with increasing IMA concentrations in 48 h stimulated pre-B cells is shown in supplementary Fig. 3Sa, gel and quantified data from three such experiments shown in Fig. 3Sb histograms. The lowest drug concentration (3 µM for IMA and of 10 µM for GSK,) for which maximal recombination effects are obtained, is used for each drug in our irradiation assays. For linear range quantifications of the image scans each reaction uses genomic DNA template at least at three distinct dilutions from the cellular extraction stock solution and the final result may be reported as an average of the three quantified products values corrected by the histone H1 band intensity of the corresponding sample. In Supplemental material in Fig. 3Sc an 3Sd a set of nested PCR

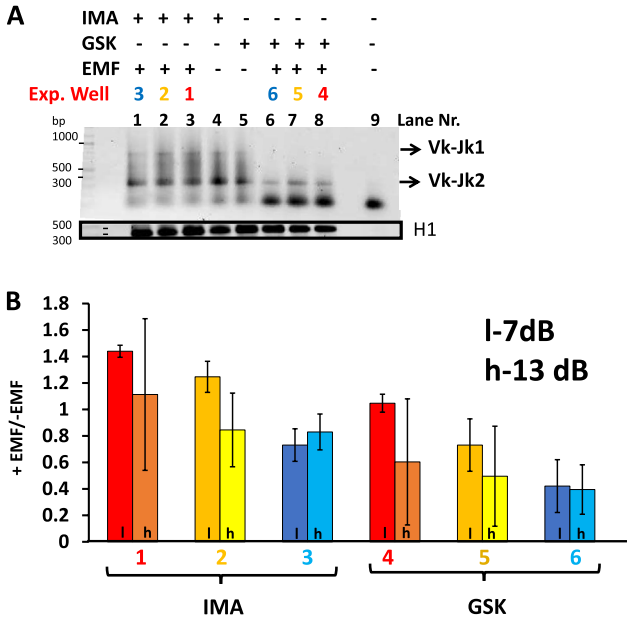

Figure 3. A two steps PCR recombination assay is used to identify Vk to Jk1 or Vk to Jk2 rearrangements from pre-B cells upon RAG induction with Imatinib or GSK. (**A**) A Sybr Green stained 1.5% Agarose TBE gel in which the recombination PCR reactions templated with initial 1:5 dilutions of genomic DNA extracted from each distinct cell treatment lot (2×10^6 cells) are electrophoretically resolved. The cells were either unexposed (gel reaction lanes 4 and 5) or subjected for 48 h to 1 GHz EMF irradiation (lanes 1 to 3 and 6 to 8) with the generator setting at 13 dBm. The color code designating the positions of exposed EMF (exp.Well) wells in the dish is the same with the one used in supplementary Fig. 1Sb. Last lane (9) of the gel, -DNA control reaction. The bottom black box (cropped from a distinct gel) displays Hisone H1 PCR reactions templated with the same amount of genomic DNA as the recombination reactions above(control genomic DNA). (**B**) Identified Vk to Jk2 recombined products were quantified from scanned gels corresponding to PCR reactions from cells +/− Irradiation and the calculated ratios of band intensities expressed + EMF/−EMF(irradiated/nonexposed) for each well (color code consistent with that shown in Fig. 1S). The histograms represent the average values of three independent quantified experiments. EMF-Electromagnetic Field, Recombination pharmacological stimuli (Imatinib, IMA) versus (GSK-690693, GSK). H1, histone H1 control reaction PCR reactions. Darker font histograms correspond to lower 7 dBm (l) and brighter to higher 13 dBm(h) generator power settings.

reactions templated with serial dilutions of input genomic DNA from IMA stimulated cells, followed by quantitation of the signal are shown to illustrate that the assay responds linearly in its amplified Vk-Jk2 band intensity.

EM wave absorption spectrum of the cell culture medium. We measured how the EM waves with frequencies ranging from 700 to 1224 MHz are absorbed by the fetal bovine calf serum supplemented cell culture medium (RPMI + FBS in Fig. 2) in which the pre-B cells are cultured. For comparison only absorption measurements were also performed for deionized water (conductivity < 5 µS/cm), and for ions containing unfiltered tap water samples (see Methods Water + ions, Fig. 2). The measurements were done using a setup in which an emission and a reception horn antenna were spaced 1 m apart with the liquid sample container positioned in the vicinity(1 cm) of the later (see Supplemental material Fig. 4S). The emission antenna was connected to a generator and signals from the receiver antenna were collected and recorded by a standard spectrum analyzer. In Fig. 2 are presented the background corrected absorption spectra per 1 cm width of each liquid sample measured. A well-defined absorption peak is observed at 938 MHz for the RPMI + FBS medium sample which is twice as large as the others measured at this frequency. All samples have similar absorption values for the rest of the tested spectral frequencies. This finding is important since the range of frequencies (720 MHz, 850 MHz, 950 MHz, 1 GHz and 1.2 GHz) to be used for cell irradiation centers our window of exposure between 950 MHz and 1 GHz, proximal to the maximal culture medium absorption peak.

To test how the cell growing medium affects the electric intensity of the exposing fields, EMF electric flux density (D displacement) measurements were made inside the incubator for each mentioned frequency, in the absence or presence of culture medium in the culture plate (Supplemental Material S3 and Fig. 5S). Values greater than one of the $\mathbf{D_m/D_{air\_inc}}$ (1.8–1.95) ratios measured between 750 and 1000 MHz (Supplemental material section S3 and Fig. 5Sc) show in this range, the complete RPMI + FBS cell growing medium selectively potentiates the developed fields.

EMF irradiation effects on V(D)J recombination in v-Abl pre-B cells. Murine vAbl pre-B cells were grown under normal conditions or stimulated either with 3 µM IMA or with 10 µM GSK in the presence/absence of an antenna which emits a generator controlled EMF from waves of 720 MHz, 850 MHz, 950 MHz,

1 GHz, 1.224 GHz each with 7 or 13 dBm output power setting. For all exposures, the antenna was held at 2.4 cm above the composite 6 wells plate as depicted in Supplemental material Fig. 1Sb (lower profile drawing) consistently keeping it in the same location with respect to the incubator walls (Supplemental material S1 and Fig. 1S). Cells were grown +/− EMF constant continuous exposure for 48 h with +/− IMA or +/− GSK. In Fig. 3A is shown a gel with resolved reactions either from nonexposed cells (lanes 4 and 5) or from cells continuously subjected for 48 h to the influence of 1 GHz fields (gel for generator set at 13dBm-h), with both RAG induction treatments (plate Exp. wells IMA 1, 2, 3 and GSK- 4, 5, 6 with color code shown in Supplemental material Fig. 1Sb). Visually one can see, a reduction of Vk to Jk2 recombination products obtained in reactions from irradiated cells versus those from similarly drug induced, non-irradiated cells (see Fig. 3A compare lane 4 non-irradiated to reactions in lanes 1–3 exposed for IMA, and lane 5 unexposed to lanes 6–8 from irradiated GSK stimulated cells). The irradiating effects are most pronounced in the plate wells closest to the actively emitting antenna elements (λ/2 for 1 GHz waves use as main element the 15 cm one located near wells 3 and 6 (Supplemental material Fig. 1Sb) hence, recombination reduction for plate Exp. wells 3, 6 > 2, 5 > 1, 4 or correspondingly gel lanes 1, 6 > 2, 7 > 3, 8). The value of the calculated ratios between recombination Vk-Jk2 PCR band intensities obtained from irradiated/non-irradiated(+ EMF/-EMF) cells for all tissue culture wells are shown as histograms in Fig. 3B. Values less than one show specific Vk-Jk2 recombination reduction associated with EMF irradiation.

Similar experiments were performed with EMF exposures at 720, 850, 950, 1000 and 1224 MHz (each frequency centers on a different antenna element), generator setting either at 7 dBm or 13 dBm. To display a wider palette of EMF dose exposure values we summed up the data from all of the wells in Fig. 4 which displays cell Vk-Jk2 recombination Fractions(+EMF/−EMF -ordinates), against logarithm of measured irradiating power flux density S values (μW/cm^2-abscissas) at each location. Each row of the two panels is for a distinct frequency with panels for each drug located on the same column: Fig. 4A(GSK- left) and B(IMA- right). Consistently all diagrams show power dependent reduction in cellular Vk-Jk2 recombination. S values into the emitting antenna were calculated from antenna recorded voltages, circuit impedance, and antenna constructive elements dimensions and reflect S in the air inside incubator, surrounding the involved culture well. In each panel with dotted black lines we pointed the EMF power dose required to induce a two-fold Vk-Jk2 recombination reduction from that of the non-irradiated lot (+EMF/−EMF 50% reduction shown as 0.5 ratio for Vk-Jk2, Cellular Recombination Fraction). In Fig. 4 when 50% recombination reduction (exposed versus non-irradiated cells) is not reached, the minimal recombination ratios obtained and their inducing S levels are shown in parenthesis. The most remarkable finding of our study is that even for such a small window of frequencies (between 720 and 1224 MHz), the power dose–response effect is dramatically influenced by the frequency of the irradiating EMF. If at 720 MHz one reaches a 0.56/0.70 maximal recombination reduction for 9.49 μW/cm^2 exposure, similar reduction in recombination effects are obtained at 950 MHz and 1 GHz with only 1/15th respectively 1/20th (0.63 or 0.43 μW/cm^2) the power used at 720 MHz. The power dose-cell recombination response curves at 950 MHz and 1 GHz EMFs show by far the most accentuated measured effects (for both drugs). For GSK at 1 GHz irradiation, an almost four-fold decrease in V(D)J recombination (from 0.90 to 0.22) is observed over a moderate increase in S exposure from 0.1 to 4.53 μW/cm^2 (see second from the bottom panel in Fig. 4A GSK 1000 MHz). Both curves in Fig. 4 for 1 GHz display an abrupt recombination decrease at a small increase in S (0.25–1 μW/cm^2) after which the cellular effect plateaus out over a larger window of higher exposure power S values (1–4.5 μW/cm^2). To emphasize the influence of EMF frequency Table 1 shows how recombination fractions (+EMF/−EMF) vary at a relatively constant ≈ 1.5 μW/cm^2 irradiating power flux density S exposure level for all tested EMF frequencies. At this small irradiating power no effect is detectable at 720 MHz, whereas at 950 MHz a two-fold recombination reduction is measured reaching almost three-fold recombination inhibiton at 1 GHz..

To circumvent the cellular growing medium polarization effects (which significantly change polarity at 720 MHz and above 1100 MHz, Supplemental material 3S and Fig. 5Sc) or its enhanced wave absorption at 938 MHz (Fig. 2), we intentionally represented in Fig. 5 the recombination fractions for two constant electric field intensity E exposure values, measured inside the medium; one of 0.4 V/m (Fig. 5A.) and the other of 0.6 V/m (Fig. 5B). The approximative intensity of the emitted electric field was calculated in the cell medium from the measured electric flux density ($\mathbf{D_m}$ displacement) values[38] described in the previous section, and averaged for the central plate well. For both E values and both pharmacological stimuli (IMA-red and GSK-blue) the most accentuated plots concavities (maximal irradiation induced recombination reduction effect), correspond to 950–1000 MHz. At both E values represented in Fig. 5 the recombination ratios are unaffected by EMFs at 720 MHz. In contrast, at 1000 MHz, a two-fold reduction is observed for the 0.4 V/m EMF intensity, and a three (IMA) to four-fold (GSK) decrease is measured at the stronger 0.6 V/m field exposure. The electric fields dose exposures -recombination reduction effects in Fig. 5 and those reported for EMFs power dose exposures in Fig. 4 are qualitatively similar. These data strongly suggest that exposure even to very low irradiation doses from specific 900–1000 MHz radiofrequency waves dramatically affect in irradiated pre-B cells the efficiency of V(D)J recombination at their Ig kappa locus.

Histone H2AX phosphorylation shows no detectable DNA DSB damage cell response in EMF exposed pre-B cells. We asked whether the observed EMF irradiating effects on V(D)J recombination are due to DNA damage and presence of unrepaired DSBs. Impairment of DNA integrity can be assessed by the extent with which irradiation induces H2AX histone phosphorylation (γH2AX), a process associated with DNA DSBs and their intranuclear repair. The nuclear γH2AX repair foci are the fairest indication that the NHEJ DNA repair machinery acts properly in these cells repairing DSBs caused by any DNA lesion-causing agent[39,40]. We grew cells under similar stimulation (+/− IMA, +/− GSK) and +/− EMF irradiation conditions (7 dBm or 13 dBm generator power settings at 950 MHz) with those described above but instead of extracting DNA, the harvested cells were fixed and doubly stained: (a) with Hoechst 33342 dye (for nuclear total DNA staining in

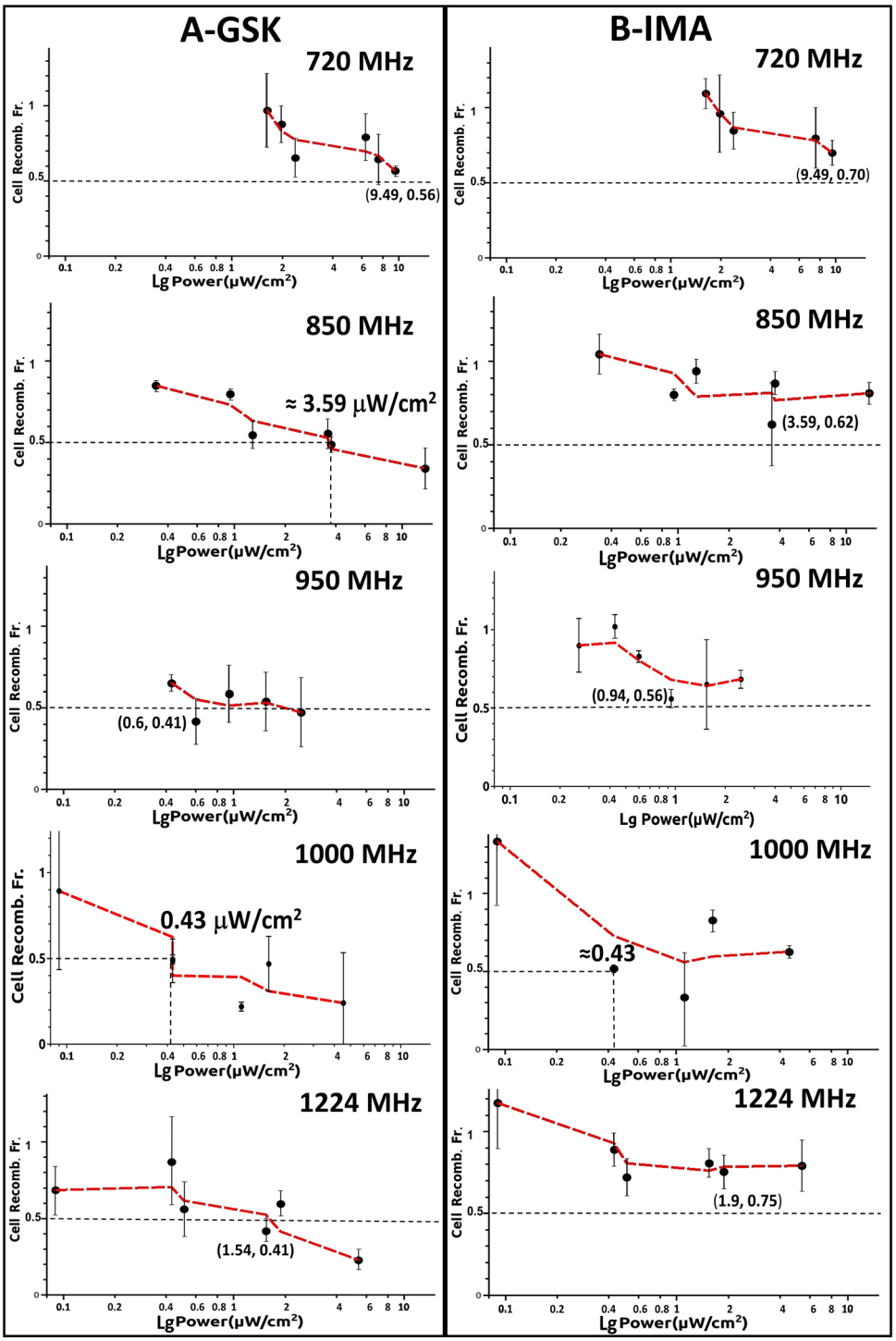

Figure 4. The EMF power dose-cell recombination response curves at 720, 850, 950, 1000 and 1224 MHz for both types of pharmacological agents stimulating RAG expression (**A**) (GSK-690693, GSK), and (**B**) (Imatinib, IMA). Cell Recomb. Fr. expresses the ratio values of measured Vk-Jk2 recombination quantified from cells grown in + EMF/-EMF (irradiated/non-exposed) conditions. Bottom abscissa displays logarithm of S power flux density values (Power μW/cm^2) measured around the emitting antenna inside the CO_2 5 vol%, and 95% water humidity incubator air conditions, expressed as a single range in all panels(logartithmic scale). The black dotted line denote a level of EMF induced two-fold recombination reduction (Cell recomb. Fr. = 0.5), whereas when this level is not reached in the experiment the coordinates of the lowest obtained Cell Recomb. Fr. are given. The red dotted line connecting markers is just a Moving Window Average line which accounts for the average between successive data points displaying the trend of data variation. The error bars represent standard deviation (SD) values from three independent experiments.

Fraction recombination +EMF/−EMF (EMF at S ≈ 1.5 μW/cm²)		
	Response stimulus	
Frequency (MHz)	GSK	IMA
720	0.97 ± 0.2	1.09 ± 0.1
850	0.56 ± 0.1	0.8 ± 0.1
950	0.53 ± 0.2	0.65 ± 0.3
1000	0.38 ± 0.1	0.46 ± 0.3
1224	0.41 ± 0.1	0.8 ± 0.1

Table 1. Lists the measured cell recombination fraction (+EMF/−EMF) at a relative constant power flux density S value of 1.5 μW/cm² for all tested frequencies.

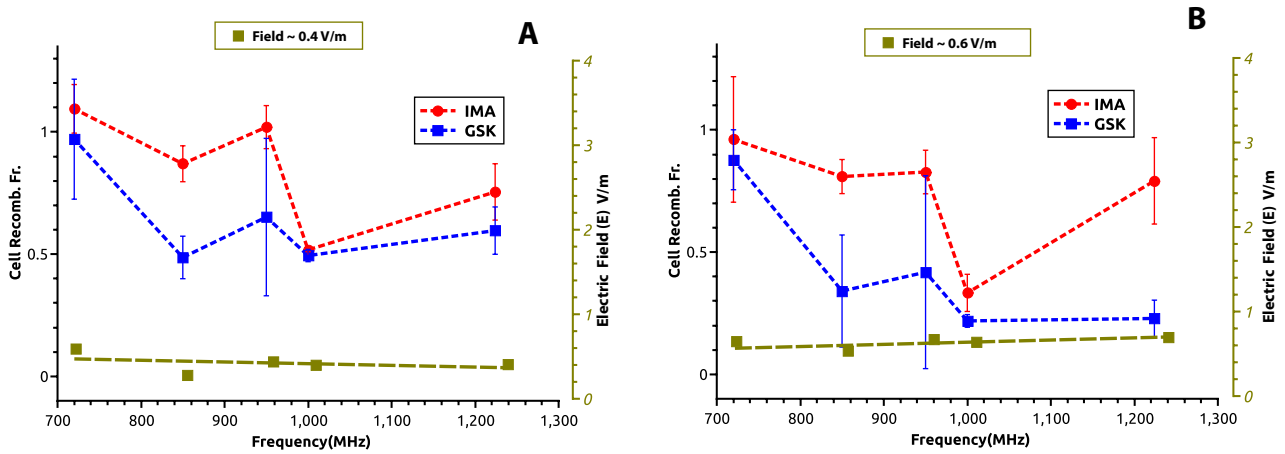

Figure 5. Variation of cell recombination fraction (+EMF/-EMF) with the field irradiation frequency shown in each panel for a constant receiver EMF electric intensity field E calculated in the cell culture medium. (**A**) EMF electric field intensity E 0.4 V/m, (**B**) EMF electric field intensity E 0.6 V/m. The pharmacological agents stimulating RAG expression GSK-690693, GSK-blue, and Imatinib, IMA-red. The pale green dotted line shows the relative constant distribution of measured electric field as a function of frequency. The error bars represent standard deviation (SD) values from three independent experiments.

blue) and (b) immunofluorescently with anti γH2AX antibodies yielding a Cy2 green fluorescence which identifies DNA DSBs repairing γH2AX foci[40](see Methods). As a DNA DSBs control an extra lot of cells were either noninduced o similarly drug treated but instead of EMF they were subjected to a quick 1 Gy, X ray irradiation dose prior to their harvest. Nine immunofluorescent images are shown in Fig. 6 A-I where blue contours show the cell nuclei and the green dots the DNA DSBs repairing γH2AX foci from: cells treated with +/− DMSO solvent control, +/− GSK, +/− IMA, +/− EMF set at 950 MHz, 7dBm exposure and the control lot of cells exposed to 1 Gy X ray. Such foci were also counted and their number reported per cell to a number of total 100 counted cells gathered from more than twenty successive field views for each experimental lot (shown as histograms in Fig. 6J for both 7 dBm and 13 dBm generator power settings). 1 Gy dose X ray irradiated cells are shown in Fig. 6B control with DMSO solvent, E with IMA, H with GSK and in 6 J the corresponding foci/cell counted histograms. All images (Fig. 6B,E,H) and the quantified histograms from X ray irradiated cells show similar and considerable DNA DSB lesions with consequent accumulation of γH2AX repair foci, regardless of the chemical stimulus used. On the contrary, the long 48 h EMF exposure experiments do not show signs of detectable unrepaired DNA DSB damage (Fig. 6C DMSO solvent, F with IMA and I with GSK, and counted foci/cells in Fig. 6J), above the background level of non-irradiated control cultures (Fig. 6A,D,G and ctrol. histograms in Fig. 6J). Exposing for 48 h cells to EMF , regardless of drug treatment, does not seem to inflict significant/ cumulative unrepaired DNA DSB lesions, (unlike those caused even by mild quick irradiation with 1 Gy dose of X rays). Only such DNA injuries could have caused a detectable accumulation of repairing γH2AX foci at the time of their harvest. Indirectly, these results suggest that the significant EMF induced reduction in pre-B cells recombination reported in Figs. 3B, 4, 5 and Table 1 is probably not caused by an enhanced level of accumulated unrepaired DNA DSBs.

Discussion

V(D)J recombination the central process in lymphocyte development physiologically generates DNA DSBs during its course, when cells become susceptible to external sources of DNA damage[5]. Our work tests how pre-B lymphocytes exposure to low dose EMFs of frequencies ranging from 720 MHz to 1.2 GHz, used in utilitarian purpose telecommunication, affects the efficiency of their *Igk* loci rearrangements. First, we established a setup

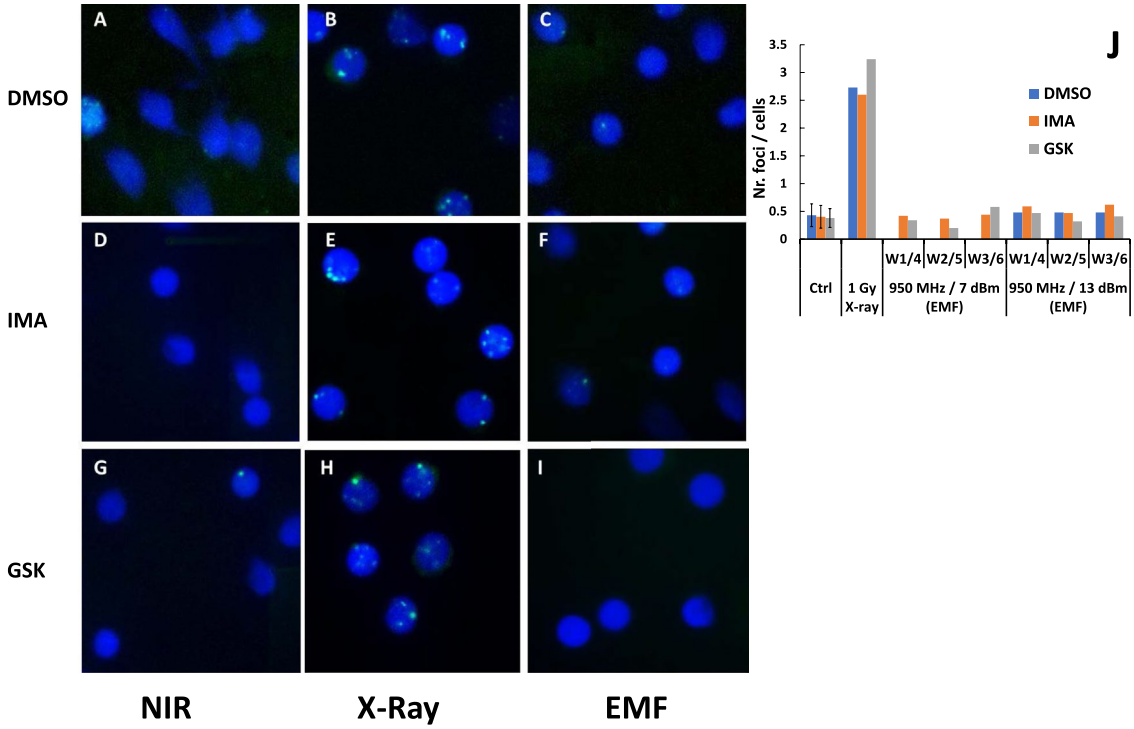

Figure 6. (**A**–**I**) Immuno-fluorescence detection of γH2AX phosphorylated histone foci in pre-B cells exposed to EMF or X ray irradiation. The γ H2AX foci are shown in bright green—γ-H2AX, whereas DNA staining is in blue – nuclei. (**A**) Control solvent (DMSO) treated cells Nonirradiated (NIR); (**B**) Control (DMSO) treated 1 Gy X-ray irradiated cells(X-Ray); (**C**) Control (DMSO)treated EMF exposed (waves at 950 MHz, with emission generator power setting set at 7 dBm-EMF); (**D**) IMA treated NIR; (**E**) IMA, X-ray; (**F**) IMA, EMF; (**G**) GSK, NIR; (**H**) GSK, X-ray; (**I**) GSK, EMF. (**J**) Number of counted foci per /cell represented as histograms. W1/4 refers to growing plate wells 1 and 4, W2/5 wells 2 and 5 and W3/6 wells 3 and 6 equivalent positions with respect to which cells were EMF irradiated, with generator power setting set at 7 dBm and 13 dBm. GSK is cells treatment with 10 μM GSK-690693, IMA their treatment with 3 μM Imatinib. ANDOR camera assisted by IQ Live Cell Imaging software and foci analysis with Imaris for Cell Biologists software (both from OXFORD Instruments).

to control the EMF developed inside the cellular growing medium in a typical cell culture incubator. Cultured pre-B cells synchronously recombining V(D)J were EMF exposed during a 48 h window, which starts with RAG expression and ends with the NHEJ DSBs DNA repair[5]. A nested PCR assay is then used to study the cellular EMF irradiation gene effects.

The measured data in Figs. 3B, 4, 5 and Table 1 consistently show, EMFs cause a dose dependent reduction in V(D)J recombination in the irradiated pre-B cells, with similar effects for both RAG inducing stimuli (IMA or GSK) used. The magnitude of effects is tightly determined by the EMF frequency. A two-fold reduction in Vk-Jk2 recombination at *Igk* locus narrowly can be obtained by an emitted S power value of 9.49 μW/cm^2 at 720 MHz (Cell Recomb. Fr. 0.56 for GSK and 0.7 for IMA), whereas this effect may be achieved by a field developing one twentieth of that S dose at 1000 MHz (0.5 Cell Recomb. Fr. for both drugs at 0.43 μW/cm^2) (Fig. 4). The recombination reduction although observed for all EMFs tested, seems to be maximal for 950 and 1000 MHz waves, a small domain where the serum containing cell culture medium displays maximal EMF absorbance (Fig. 2), and augments by its molecular polarization the EMF electric intensity (supplementary Fig. 5Sc). We measured EMF local antenna emissive S values only in the incubator air surrounding the cell culture plate. Despite this limitation we measured and calculated the average irradiated electric field intensity E, inside the culture medium. The maximal effects were measured at 950 and 1000 MHz, where *Igk* recombination levels for an EMF of E 0.4 V/m are only half (Fig. 5A), or for one of 0.6 V/m E a quarter of those reported for same E values at 720 MHz (Fig. 5B). E dose effects parallel the frequency dependency described for the antenna emitted power dose S. However, the cell medium electric properties mentioned above, (increased absorbance and polarization between 900 and 1000 MHz), cannot account for the frequency results shown in Fig. 5 for irradiations at constant electric field E values. Besides such intrinsic medium properties there must be also a major EMF frequency direct influence on the cellular components linked to recombination.

Various wireless network service providers use for mobile phone communication frequencies ranging between 700 and 2100 MHz. At 1 cm distance, during outgoing calls the measured emitted field E intensities vary with +/– 5–15% from the 41.25 V/m (recommended ICNIRP value) with cell phone models, whereas their maximum output recorded power levels for a GSM1800 net varies between 0.25 and 1 W[41,42].

We assessed if the low dose 48 h EMF irradiations cause DNA DSBs and detectable γH2AX repair foci in exposed cells. From the levels of detected γH2AX repair foci of the EMF irradiated pre-B cells we could not reveal in exposed cells above background DNA DSBs repair activity (Fig. 6 compare panel A with C, G with I, and histograms in Fig. 6J). Using chromatin immunoprecipitation (ChIP) Savic et al.[43] show considerable γH2AX accumulation near Jk5 in IgK locus after 24 h post STI571 (Imatinib) treatment of pre-Bs, but a dramatic more than two-fold decrease in γH2AX detection as cells were kept from 24 to 48 h post STI571 treatment[43]. We could not detect above background γH2AX foci levels in IMA or GSK treated cells after 48 h culture growth. This could be due either to a considerable post RAG DSBs repair recovery, or to a reduced sensitivity of our immunofluorescence assay (less sensitive than ChIP in detecting γH2AX). The onset of DNA DSBs either prior to or during pre-B cells maturation inhibits *rag1*, *2* transcription[44] and reduces the levels of *Igk* locus rearrangement events[45]. These cellular stress effects are caused by ataxia teleangiectasia mutated (ATM) kinase either via NF-kB, FOXO1 signaling[44,46] or via GADD45α inhibition[45], both pathways directly targeting *rag* genes transcription levels. If very few EMF induced DSBs (below those detectable by γH2AX foci assay), or breaks already repaired before our cell harvests could have reduced RAG expression in our experiments(via ATM kinase) this could explain our observed reduced recombination effects. We used in our experiments two RAG induction stimuli, IMA sensitive to ATM kinase via GADD45α inhibition [44–46] and the second GSK690693 AKT-inhibitor insensitive to this signaling pathway[19]. If very few EMF induced DNA DSBs would have reduced RAG expression prior to, or during drug action, one would have expected experiments to show a more accentuated recombination reduction for IMA than that obtained for GSK treatment. Instead, the experimental data in Figs. 3B, 4, 5 and Table 1 show for both drugs very similar EMF induced reduction of *Igk* loci rearrangement levels(if not even slightly more pronounced reduction for GSK). IMA although a more potent RAG inducer than GSK has the disadvantage that post recombination blocks cells in Go phase preventing further their division[36,47–49]. On the contrary, the AKT inhibitor GSK-690693 not only is a weaker RAG induction stimulus (closer to the one physiologically occurring in small pre-B cells)[50,51] but also enables cells to divide prior to and after *Igk* loci rearrangements and protect their progress to the next stage of development[19]. Because our PCR assay intentionally uses the amount of templating genomic DNA from the same number of 2 millions harvested cells, replication would have "diminished the EMF recombination reduction" in GSK treated cells in contrast to those incubated with IMA (the later, on the contrary, "freezes" the EMF effect on BCL2 maintained survivors). As pointed earlier, in treated cells, both drugs show very similar EMF induced reduction of rearrangements in treated cells. Although we cannot fully refute that the observed EMF recombination effects may have been caused in irradiated pre-B cells by undetectable DNA DSBs via ATM, the line of evidence gathered from our experiments in Figs. 4, 5, 6 and the arguments presented above for the comparative IMA/GSK treatments make this mechanism a less likely candidate for their account.

Indirectly our work addresses the longstanding question of how innocuous low dose EMF irradiation from our telecommunication devices may be and whether it may affect the immunity of our organisms. It remains only to our speculation to extend the observed recombination effects induced by small EMFs from an in vitro culture system to the in vivo situation on the ability of irradiated B cells to elicit an unaltered antibody response to antigen challenge.

Methods

Materials. DNA oligonucleotides were purchased from Life Technologies and IDT DNA: Vk degenerate primer 5′ GCTGCAGSTTCAGTGGCAGTGGCAGTGGRTCWGGRAC 3′ where S is G or C, R is A or G, W is T or A, Jk2-1 primer 5′ CAAAACCCTCCCTAGGTAGACAATTATCCCTC 3′ and Jk2-2 primer 5′ GGACAG TTTTCCCTCCTTAACACCTGATCTG 3′. For Histone H1 gene control amplifications the following primers were used: H1fw 5′ GGCTGCTATCCAGGCAGAGAAGAACCG 3′, H1rv: 5′ GCTTTGGAGGCGCCTTCT TGGGCTTG 3′.

Murine pre B cells transformed with Abelson virus (v-Abl preB, A70 line, that harbor a Eμ-Bcl2 transgene) were a kind gift from Barry Sleckman Duke University[47]. The cells were maintained in RPMI 1640 medium, supplemented with 10% FBS (both from GIBCO), 50 μM 2-mercaptoetanol and induced at 0.5×10^6 cells/ml density either with 3 μM Imatinib Mesylate (IMA) (SIGMA-ALDRICH) or with 10 μM GSK-690693(GSK)(GLAXOSMITHKLINE, SELLECK-chem) in solutions with 0.1% DMSO. After 48 h the cells were collected and analyzed using the nested PCR described below.

Pre-B Cells irradiation was performed with a 1 Hz–1.224 GHz, 13 dBm radiofrequency generator (Hameg Instruments 1 Hz–1.2 GHz programmable synthesizer HM8134-3, used throughout our study as emission generator) using a broadband irradiating 800 MHz–3 GHz LTE ATK-LOG ALP logarithmic antenna, in a regular CO_2 incubator (SANYO Electric Co. MCO-17AIC), with CO_2 5 vol. %, and 95% purified water humidity. Cells were grown at 37 °C in 5 ml medium in standard six flat bottom wells (16.8 ml capacity) polystyrene lidded plates (Corning Costar), which were always positioned in the same place with respect to the incubator walls (in the center of the incubator, see Supplemental material Fig. 1Sa) and the emission antenna (antenna central guiding label positioned midway between wells 3 and 6 at 2.4 cm above the mid plane of the plate, see supplementary Fig. 1S). Two parallel sets of experiments were performed with wells 1, 2, 3 containing cells stimulated with 3 μM IMA, whereas wells 4, 5 and 6 cells were stimulated with 10 μM GSK (Fig. 1SB).

Two steps nested PCR reactions for K locus recombination. Template DNA was prepared for PCR using a modified technique developed by Schlissel[37]. Pre-B A-70 v-Abl cells were harvested after 48 h incubation with IMA[36,47], GSK[19] or unstimulated. Cultured cells (2×10^6–2 millions) were pelleted for 15 s in a microfuge, washed once in PBS(phosphate saline buffer pH 7.2), resuspended in 200 μl PCR lysis buffer (10 mM Tris pH 8.4, 2.5 mM $MgCl_2$, 50 mM KCl, 200 μg/ml gelatin, 0.45% NP40, 0.45% Tween-20 (CALBIOCHEM), and 60 μg/ml Proteinase K(Boehringer), and incubated at 56 °C for 3 h followed by 15 min at 95 °C. Dilution of templates

was done with PCR lysis buffer without Proteinase K. Two successive PCR amplifications were done in a final volume of 50 µl containing 2 to 5 µl template DNA, 10 mM Tris–HCl (pH 8.4; at room temperature), 50 mM KCl, 2.5 mM $MgCl_2$, 200 µg/ml gelatin, 0.2 mM of all four dNTPs (all from ThermoFisher scientific), each oligonucleotide primer at 0. 4 µM (20 pmol each primer per reaction), and 1 U TAQ DNA polymerase (GoTaq PROMEGA) in nested reactions. First step PCR reactions for 25 cycles use Vk, and Jk2-1primers. In the second step various dilutions (from 4 µls 1:100 dilution of first PCR to 0.5 µls of the first undiluted PCR) are individually used to template the second PCR reactions to which Vk and Jk2-2 primers are added and an additional round of 30 cycles amplification is performed. Cycling steps were: an initial 1 min denaturation at 94 °C, then repeated cycles each, 30 s at 94 °C, 0.5 min annealing at 50 °C, and 1.5 min polymerization at 72 °C. A final additional 5 min extension step was performed at 72 °C [36,37]. PCR products were resolved on 1.5% agarose gel, stained either with ethidium bromide or Sybr Green (THERMOFISHER scientific) and visualized using the PharosFX system (BIORAD). The bands intensities were quantified using QuantityOne software.

Kappa locus amplification products analysis. Each Vk-Jk2 product band density of the gel scan image is quantified and the ratio between the densitometry value of the PCR product band detected from cells grown in the presence of EMF and the corresponding one without field exposure (EMF+/EMF−, Cell Recomb. Fr., Figs. 3, 4, 5) reports the changes in V(D)J recombination occurred upon each cell treatment (IMA/GSK). To normalize for DNA extraction levels we performed similar PCR amplifications from the same amount of template DNA using a pair of primers H1fw and H1rv to specifically detect the histone H1 gene.

γH2AX foci analysis for irradiation induced DNA damage cellular response. Cells were grown under similar conditions with those described above for recombination assays. Additionally, a DNA DSBs control cell lot either uninduced or one for each RAG stimulus (IMA or GSK) was exposed to a quick 20 min X ray cumulative dose exposure of 1 Gray (X-ray irradiation with a slow rate 50-milligray /min with a Mevatron Primus 2D, 6MV, SIEMENS instrument) prior to their harvest. The samples were irradiated at 100 cm distance from the source axis, the field size being of 30 × 30 cm. The dosimetry was performed using a water phantom (1 cm water depth). Symmetry and homogeneity were checked, the dose proved to be homogenous throughout the sample in the used plates. For all treatments, twenty minutes after harvest, instead of extracting DNA, the cells from each individual culture type were separately spread onto clean designated slide sets using a Cytospin Centrifuge. The cells were then fixed with paraformaldehyde, permeabilized with Triton X and then doubly stained with: (a) Hoechst 33342 dye (THERMO SCIENTIFIC) (for their nuclei-DNA total staining in blue) and (b) immunofluorescently with primary unlabeled anti γH2AX antibodies of mouse antigen specificity complemented with secondary Cy2 labeled anti primary source antibodies (rat anti mouse IgG Cy2 detection antibodies-green)(both from SIGMA ALDRICH); to identify in green the DSB repairing γH2AX foci[40]. The slides were examined with a fluorescence microscope (OLYMPUS BX60) with adequate filter for the fluorophores, and images of the nuclei and γH2AX foci recorded with a camera connected to the microscope. The images were analyzed using specific analysis software to quantify the number of foci per each cell treatment type, and morphologically to indicate their level of dispersion or nuclear positioning (see Fig. 6).

Western blot analysis for endogenous RAG time course induction in pre-B cells (Supplemental material Fig. 2S) following IMA/GSK treatment was performed as previously described in our work using anti RAG1 and anti RAG2 mouse monoclonal antibodies (gift from Dr. David G. Schatz, Yale University), and control sample purified murine core RAG1(384–1040) and coreRAG2 (1–387) fused to Maltose binding protein (MBP-40kD) which were transiently expressed in co-transfected HEK293T cells[52] (source ATCC CRL-3216).

Absorption spectra measurements were made using two identical broadband (0.8–16 GHz) horn antennas facing each-other and placed at 1 m distance. The measurement subjected sample was placed in close proximity (1 cm) of the receiver whereas the emission antenna (supplementary Fig. 4S a and b), was coupled to the generator. The receiver antenna was connected to a commercial Spectrum Analyzer (Keysight-AGILENT-HP N9935A, 0.1- 9 GHz) on which the received signals were recorded and analyzed. The shown absorption spectra in Fig. 2 were obtained after subtraction of the background spectra with no liquid sample placed in the container in front of the receiver antenna. The deionized water used for measurement has the conductivity < 5 µS/cm, whereas the used unfiltered tap water with ions has the following characteristic measured chemical parameters per liter (l) pH 6.5–9.5, Conductivity < 800 µS/cm, ammonia < 0.5 mg/l, free residual Chlorine < 0.5 mg/l, Fe < 200 µg/l, Mn < 50 µg/l, Al < 200 µg/l, nitrites < 0.5 mg/l, nitrates < 50 mg/l, Borate salts 1 mg/l, Chlorides 250 mg/l, Sulphates 250 mg/l, 65 mg/l calcium carbonate, Hardness < 5degrees (dGH).

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Author contributions

E.I. has performed all the cell irradiation experiments, maintained the pre-B cells in culture, performed PCR from genomic DNA and quantified the amplification results. A.M. and M.S. have performed all the experiments to measure the EMF parameters used in irradiation, absorption spectra, power flux density and electric field intensity measurements. M.T. has performed the experiments to detect and quantify the γH2AX foci whereas D.S. helped in interpreting the results of their foci/cell analysis. M.C. has designed the experiments, performed the analysis and interpretation of the cell irradiation experiments, supervised experiments and wrote the manuscript. All authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to M.C.

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Expert Report
Christopher J. Portier, Ph.D.

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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)	Cohort	1999-2009, UK	Middle-aged women	Glioma	<5 years 5-9 years ≥10 years Excluding first 3 years <5 years 5-9 years ≥10 years	89 185 40 66 148 29	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)	ND	Ever used (asked 1999-2005)
Benson et al. (2014)		1999-2011, UK			Follow-up to 2011 <5 years 5-9 years ≥10 years	Not given	0.96 (0.75-1.23) 0.86 (0.72-1.02) 0.77 (0.62-0.96)		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				Avg 1 call per week for 6 mo
					<660	23	1.06 (0.59-1.91)	0.41	
					(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 hrs	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.

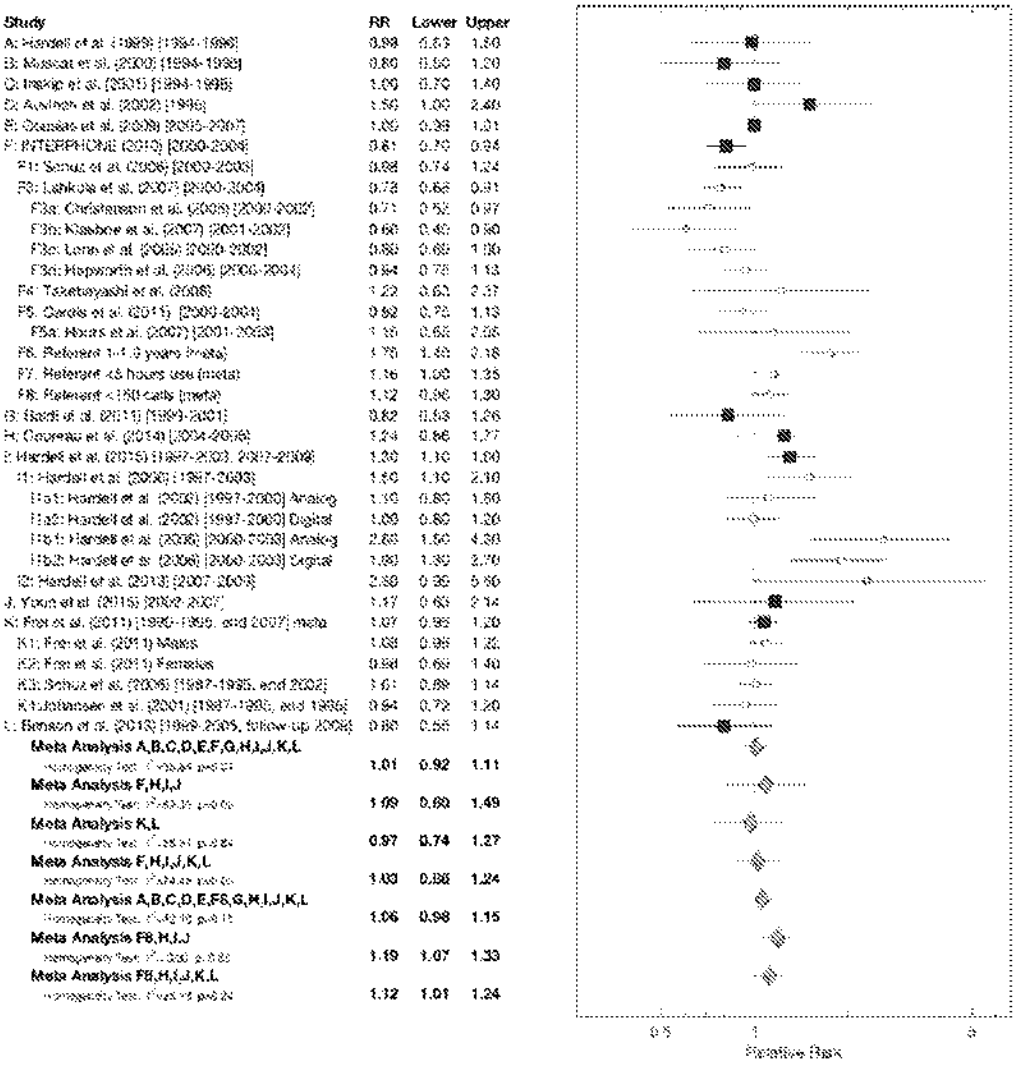


Figure 1: Forest plot and meta-analyses of regular use or ever use of cellular telephones and the risk of glioma [studies with a solid blue square either single studies that stand alone or pooled studies that encompass numerous single studies; open squares are individual studies or smaller pooled studies;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

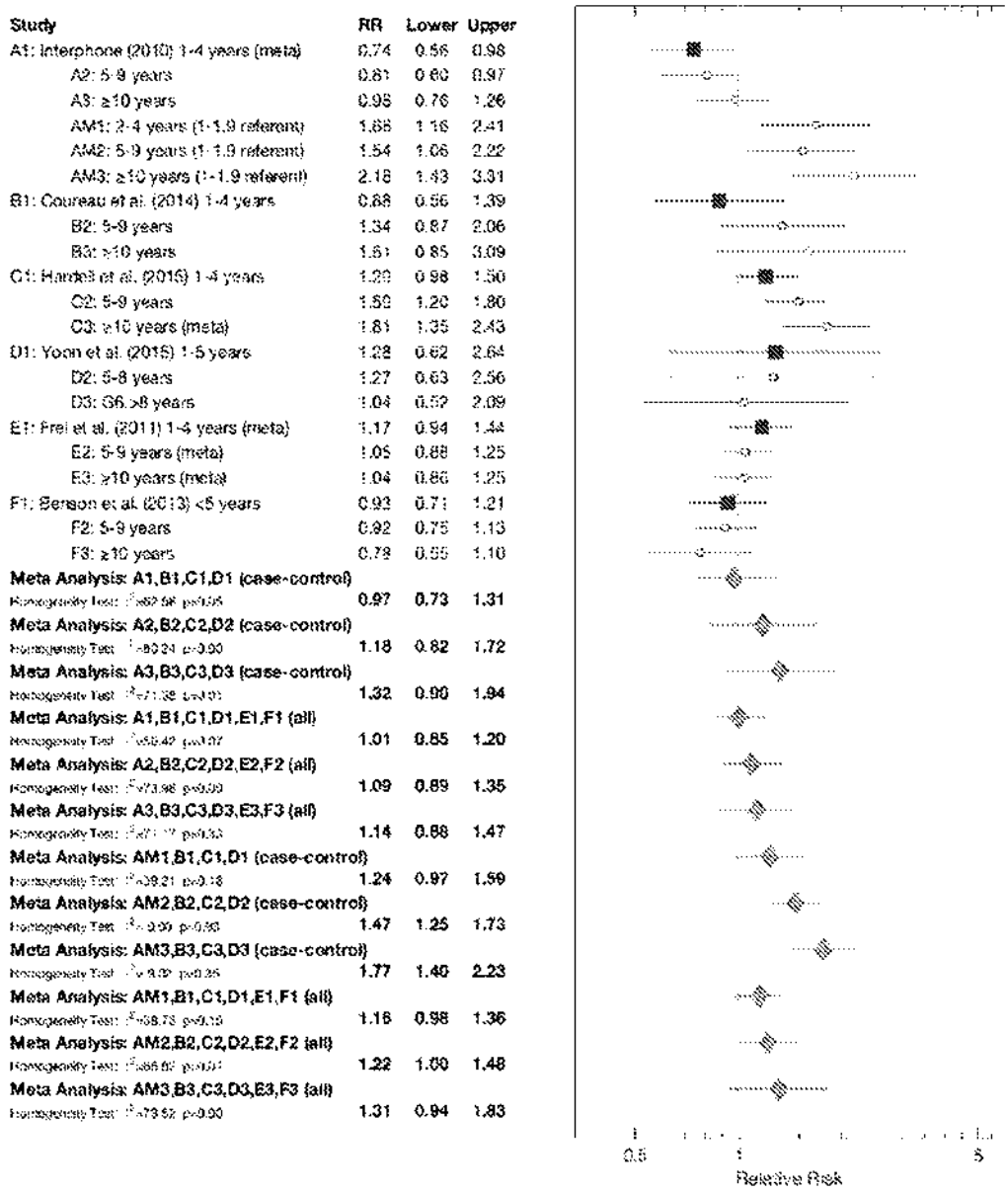


Figure 2: Forest plot and meta-analyses of duration of use of cellular telephones and the risk of glioma [studies with a solid blue square are either single studies that stand alone or pooled studies that encompass numerous single studies; open squares area second analysis from that same paper; red diamonds 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 8. 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			ND	Any use
					1995-1998	7	0.7 (0.3-2.0)		2+ calls/w
					1993-1994	9	1.5 (0.6-3.6)		
					≤1992	6	1.2 (0.4-3.4)		
					<1990	2	1.3 (0.2-6.6)		
INTERPHONE (2010)	CC	2000-2004, 13 countries	30-59, Both	Acoustic neuroma	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	54	0.81 (0.53-1.24)		
					5-114.9 hours	198	0.92 (0.71-1.20)		
					115-359.9 hours	57	0.74 (0.49-1.13)		
					360-1639.9 hours	26	0.55 (0.29-1.03)		
					≥1640 hours	4	0.63 (0.14-2.80)		
					5-9 years before reference date				
					<5 hours	4	0.84 (0.21-3.40)		
					5-114.9 hours	77	0.97 (0.67-1.41)		
					115-359.9 hours	55	0.95 (0.62-1.45)		
					360-1639.9 hours	64	0.74 (0.49-1.12)		
					≥1640 hours	36	1.05 (0.62-1.78)		
					≥10 years before reference date				
					<5 hours	0	-		
					5-114.9 hours	8	0.81 (0.30-2.14)		
					115-359.9 hours	6	0.28 (0.09-0.86)		
					360-1639.9 hours	17	0.39 (0.20-0.74)		
					≥1640 hours	37	1.93 (1.10-3.38)		
Pettersson et al. (2014)	Case-Control	Sweden	20-69, Both	Acoustic Neuroma	Cumulative # calls				Avg 1 call per week for 6 mo (lag 1 yr), weighted hands-free
					<1,100	72	1.21 (0.82-1.78)		
					1,100-4,400	71	1.07 (0.71-1.61)		
					4,400-13,850	79	1.22 (0.83-1.80)		
					≥13,850	75	1.20 (0.79-1.82)		

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	I/I & r/r (97 cases)	1.08 (0.93-1.28)			Avg 1 call per week for 6 mo (lag 1 yr)
					I/I & 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.

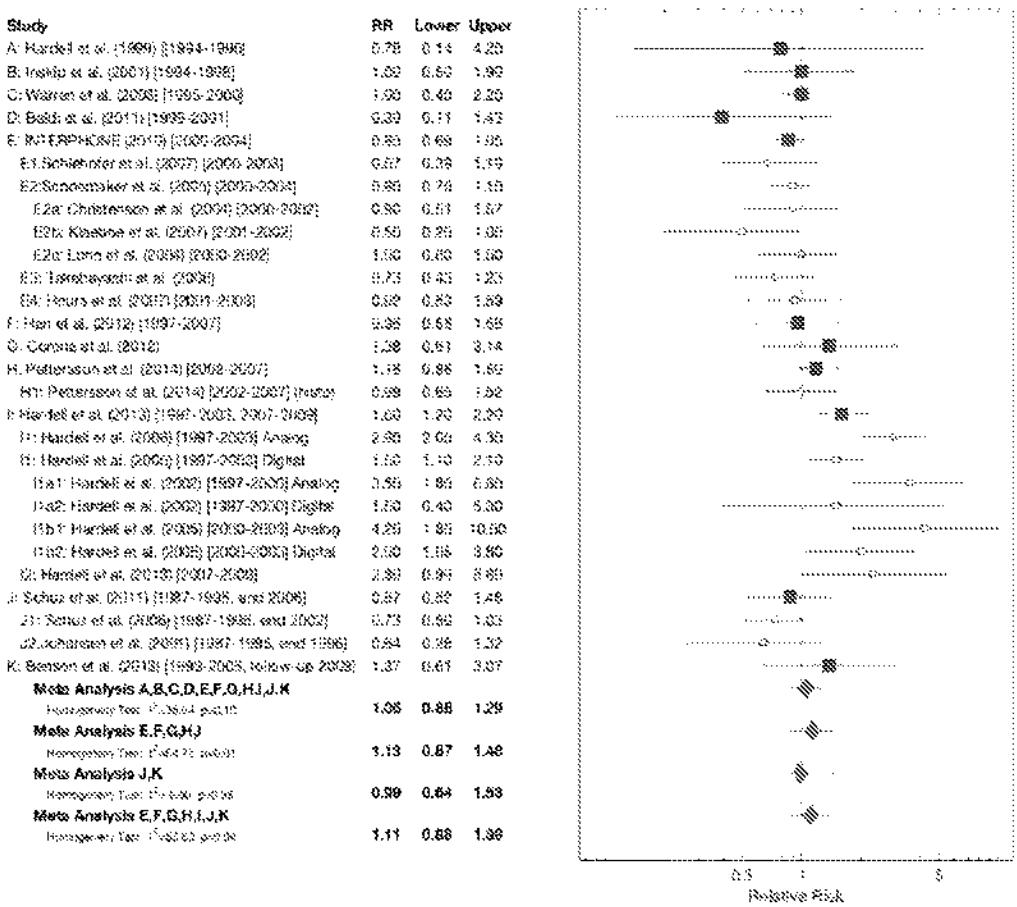


Figure 3: Forest plot and meta-analyses of regular use or ever use of cellular telephones and the risk of acoustic neuroma [studies with a solid blue square either single studies that stand alone or pooled studies that encompass numerous single studies; open squares are individual studies or smaller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

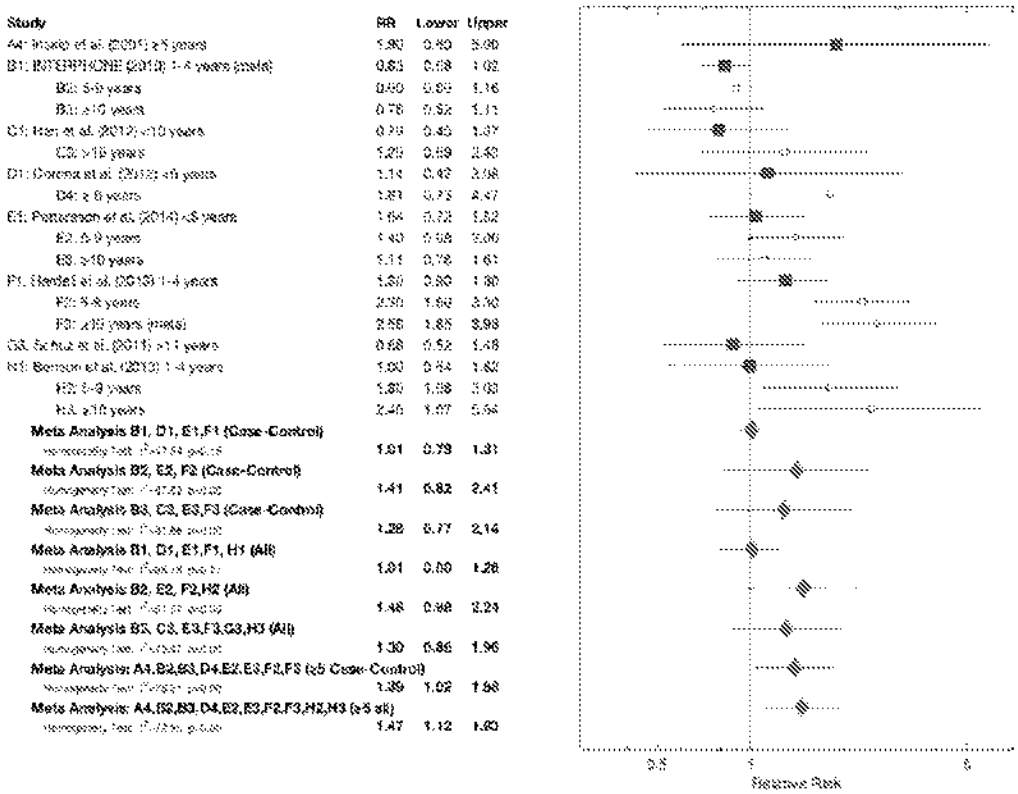


Figure 4: Forest plot and meta-analyses of duration of use of cellular telephones and the risk of acoustic neuroma [studies with a solid blue square are stand alone; red diamonds are meta-analyses, the columns and the figure are as in Figure 1]

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 18 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 18)

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 ↑	Rare tumor, biological call
				Brain glioma ↑	
				Adrenal pheochromocytoma ↑	Lowest 2 exposures, no trend
				Brain meninges ↑	Biological call
				Prostate gland ↑	Rare tumor, biological call
				Pituitary pars distalis ↑	No trend, extensive hyperplasia
				Pancreas islets ↑	Low exposure group, no trend
			F	Heart schwannoma ↑	One exposure only, rare tumor
		CDMA 900 MHz	M	Heart schwannoma ↑	
				Brain glioma ↑	Rare tumor, biological call
				Pituitary pars distalis ↑	One exposure, no trend
				Liver tumors ↑F	Rare tumor, increased but not significant
				Heart schwannoma ↑	Marginal finding
				Brain glioma ↑	Rare tumor, 3 in lowest group, no sig, no trend
				Adrenal pheochromocytoma ↑	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

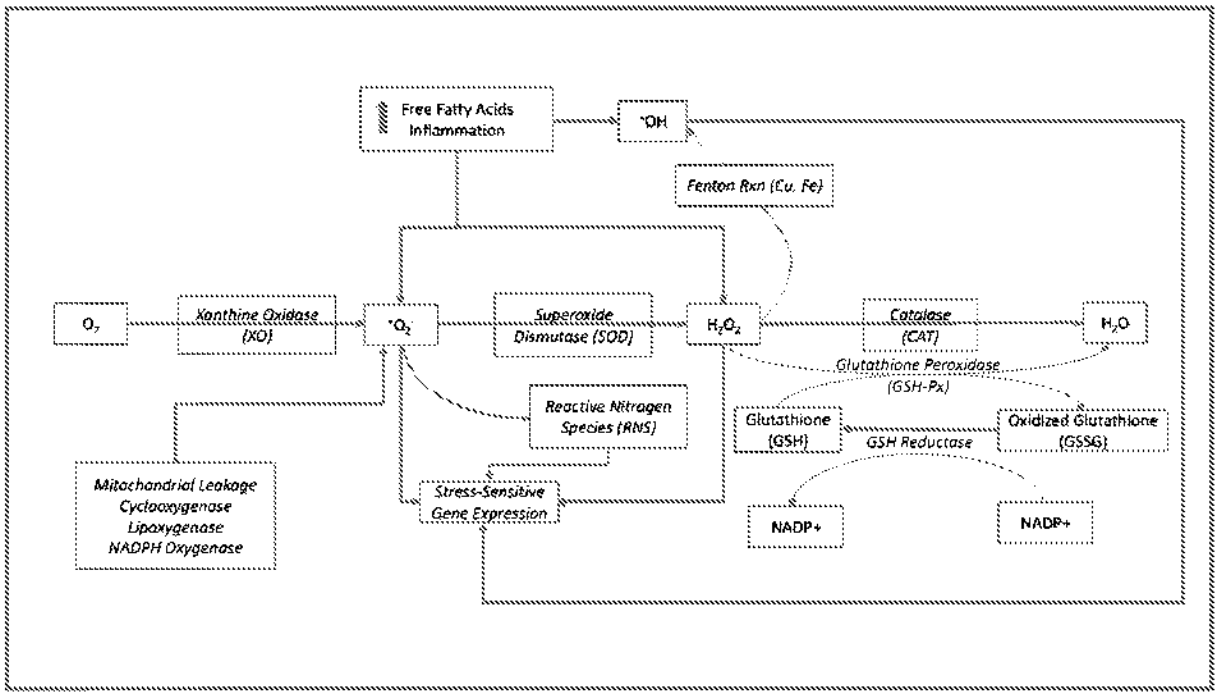
Oxidative stress refers to an imbalance between the production of reactive oxygen species (free radicals) in a cell and the antioxidant defenses the cell has in place to prevent this. Oxidative stress has been linked to both the causes and consequences of several diseases [221-226] including cancer [39, 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.

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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.

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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.
Seattle, WA
United States
Ph: +1-206-395-3308

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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6. Espín-Pérez, A., Portier, C. J., Chadeau-Hyam, M., van Veldhoven, K., Kleinjans, J., de Kok, T., Comparison of statistical methods and the use of quality control samples for batch effect correction in human transcriptome data, PLOS One 13(8), 2018

7. Apte, JS, Messier, KP, Gani, S, Brauer, M, Kirchstetter, TW, Lunden, MM, Marshall, JD, Portier, CJ, Vermeulen, RCH, Hamburg, S., High-Resolution Air Pollution Mapping with Google Streetview Cars: Exploiting Big Data, Environmental Science and Technology 2017, **51** (12) 6999-7008

8. Sand S, Parham F, Portier CJ, Tice RR, Krewski D. Comparison of Points of Departure for Health Risk Assessment Based on High-Throughput Screening Data. *Environ Health Perspect* (2017) **125** (4) 623-633 . doi: 10.1289/EHP408. PubMed PMID: 27384688.

9. Cote I, Andersen ME, Ankley GT, Barone S, Birnbaum LS, Boekelheide K, et al. The Next Generation of Risk Assessment Multi-Year Study-Highlights of Findings, Applications to Risk Assessment, and Future Directions. *Environ Health Perspect* (2016) **124**(11):1671-82. doi: 10.1289/EHP233. PubMed PMID: 27091369; PubMed Central PMCID: PMCPMC5089888.

10. Parham F, Portier CJ, Chang X, Mevissen M. The Use of Signal-Transduction and Metabolic Pathways to Predict Human Disease Targets from Electric and Magnetic Fields Using in vitro Data in Human Cell Lines. *Frontiers in public health* (2016) **4**:193. doi: 10.3389/fpubh.2016.00193. PubMed PMID: 27656641; PubMed Central PMCID: PMCPMC5013261.

11. Portier CJ, Armstrong BK, Baguley BC, Baur X, Belyaev I, Belle R, et al. Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). *Journal of epidemiology and community health* (2016) **70**(8):741-5. doi: 10.1136/jech-2015-207005. PubMed PMID: 26941213; PubMed Central PMCID: PMCPMC4975799.

12. Scinicariello F, Portier C. A simple procedure for estimating pseudo risk ratios from exposure to non-carcinogenic chemical mixtures. *Archives of toxicology* (2016) **90**(3):513-23. doi: 10.1007/s00204-015-1467-z. PubMed PMID: 25667015.

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28. Portier, C. Toxicological decision making on hazards and risks – status quo and the way forward: current concepts and schemes of science-driven decision making – an overview. *Human and Experimental Toxicology* 2009 **28**(2-3), 123-125

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36. Xia, M; Huang, R; Witt, KL; Southall, N; Fostel, J; Cho, MH; Jadhav, A; Smith, CS; Inglese, J; Portier, CJ; Tice, RR; Austin, CP Compound cytotoxicity profiling using quantitative high-throughput screening. *Env. Health Perspectives* 2008 **116** (3): 284-291

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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

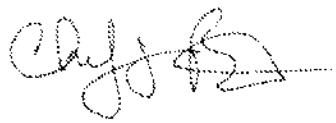
Seitz v. Monsanto, St. Louis City, MO
Kane v. Monsanto, St. Louis City, MO
Bogner v. Monsanto, St. Louis County, MO
Neal v. Monsanto, St. Louis CCity, MO

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