Health Sciences Practice

Exponent®

Status of Research on Exposure to Radiofrequency Fields and Health in Relation to Advanced Metering Infrastructure

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Prepared for

British Columbia Utilities Commission

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Limitations

At the request of FortisBC Energy Inc. (FEI), Exponent prepared this summary report on the status of research related to radiofrequency exposure and health. The findings presented herein are made to a reasonable degree of scientific certainty. Exponent reserves the right to supplement this report and to expand or modify opinions based on review of additional material as it becomes available, through any additional work, or review of additional work performed by others.

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Acronyms and Abbreviations

°C	degrees Celsius
8-OHdG	8-hydroxy-2-deoxyguanosine
AGNIR	Advisory Group on Non-Ionising Radiation Protection
AM	amplitude modulated
BCCDC	British Columbia Centre for Disease Control
BLM	bleomycin
CDMA	code-division multiple access
DECT	digital enhanced cordless telecommunications
DNA	deoxyribonucleic acid
EMF	electric and magnetic fields
EHS	electromagnetic hypersensitivity
ENU	ethylnitrosourea
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEI	FortisBC Energy Inc.
FM	frequency modulated
g	gram
GBM	glioblastoma multiforme
GGT	glutathione S-transferase
GHz	gigahertz
GSM	global system for mobile communications
GSR	galvanic skin response
HCN	Health Council of the Netherlands
hsp70	heat shock protein
Hz	hertz
IARC	International Agency for Research on Cancer
ICNIRP	International Commission on Non-Ionizing Radiation Protection
IEI-EMF	idiopathic environmental intolerance attributed to electromagnetic fields
ISED	Innovation, Science, and Economic Development Canada
kHz	kilohertz

LAN	local area network
MDA	malondialdehyde
MHz	megahertz
MN	micronuclei
mW/cm^2	milliwatts per square centimeter
NRC	National Research Council
NSPS	non-specific physical symptoms
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
OR	odds ratio
RCT	randomized control (or clinical) trial
RF	radiofrequency
RR	risk ratio
RSC	Royal Society of Canada
SAR	specific absorption rate
SC6	Safety Code 6
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHEER	Scientific Committee on Health, Environmental, and Emerging Risks
SCSA	Sperm Chromatin Structure Assay
SmartPoint	Sensus FlexNet SmartPoint® modules
Sonix IQ gas meter	Sensus Sonix IQ™ advanced meters
SSB	single-strand break
SSM	Swedish Radiation Safety Authority
TEM	transverse electromagnetic
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling
TETRA	two-way terrestrial trunked radios
UMTS	Universal Mobile Telecommunications System
WHO	World Health Organization
W/kg	watts per kilogram
W/m^2	watts per square meter

Executive Summary

At the request of FortisBC Energy Inc., Exponent prepared this summary report on the status of research related to exposure to radiofrequency (RF) fields and health. This report follows upon Exponent's report *Exposure to Radiofrequency Fields in the Environment and from Advanced Metering Infrastructure* (hereafter RF Exposure Report [Exponent, 2021]), which provides considerable background information and descriptions of the physics of RF energy, RF field exposures from typical sources, and RF field exposure from the advanced metering infrastructure of the FlexNet Metering system, as well as evaluation of required compliance with Health Canada's Safety Code 6 (SC6) that governs public exposure to RF fields. Readers may wish to review the RF Exposure Report before reviewing this report to become familiar with terminology, technology issues, and RF signals used to support communications between the Sensus Sonix IQ™ advanced meters (hereafter Sonix IQ gas meter) and the proposed FlexNet network.

RF energy, also known as radio waves or fields, refers to a range of frequencies in the electromagnetic spectrum that is typically defined as between 3,000 Hertz (Hz) and 300 billion Hz. RF energy includes frequencies used to operate various devices and technologies, including amplitude-modulated and frequency-modulated broadcast radio, television broadcasts, mobile phones, cordless phones, garage door openers, baby monitors, wireless computer networks, security systems, radar, and microwave ovens, among others. It also includes the RF signal technology used by the Sonix IQ gas meters and other components of the FlexNet network, which operate on a dedicated licensed portion of the radio spectrum of approximately 900 Megahertz. A thorough analysis of RF field exposure from the Sonix IQ gas meters and FlexNet network, described in the RF Exposure Report (Exponent, 2021), shows that calculated exposures will be far less than from many other sources of RF fields and that indoor exposure to RF fields from the Sonix IQ gas meters is about 24 million times below the SC6 exposure limit.

Research on RF fields and health has examined whether exposure to RF fields can cause short- or long-term health effects in humans. In recent years, research has focused primarily on RF fields from mobile phones, in part because of the now ubiquitous use of mobile phones in our daily lives and also because of the close proximity of mobile phones to the human body.

Researchers have applied a variety of study designs and techniques to investigate potential effects on many aspects of physiology and diseases, including cancer in children and adults and symptoms of electromagnetic hypersensitivity. This report summarizes the study designs and approaches used by scientists in determining whether or how an exposure can affect human health and describes the generally-accepted scientific method (i.e., a weight-of-evidence review) used to arrive at valid scientific conclusions on potential health effects of environmental exposures.

Because of the amount and complexity of the scientific research in this area, comprehensive evaluations of the available scientific evidence have been regularly and repeatedly performed for health and scientific agencies by panels comprised of independent scientists with expertise in relevant scientific disciplines. In the past decade, several organizations have conducted reviews that evaluated studies on exposure to RF fields and health, including the European Union's Scientific Committee on Emerging and Newly Identified Health Risks, the Swedish Radiation Safety Authority, the Health Council of the Netherlands, the Health Protection Agency of the United Kingdom, the International Agency for Research on Cancer, and Health Canada (AGNIR, 2012; HCN, 2013, 2014, 2016; IARC, 2013; RSC, 2014; SCENIHR, 2015; SSM, 2016, 2018, 2019, 2020). This report summarizes the comprehensive risk assessments and reviews of exposure to RF fields and health conducted by these organizations, which have consistently concluded that the scientific evidence in the large number of published scientific studies does not confirm that RF fields at levels below the scientifically-based exposure limits are a cause or contribute to development of any adverse health effects, including cancer, other chronic diseases, or non-specific adverse symptoms that affect well-being.

This report further provides a summary of relevant epidemiologic and experimental studies published after the most recent comprehensive review was completed (i.e., SCENIHR, 2015). These recent studies did not provide sufficient evidence to alter the overall conclusions of the reviewing health and scientific organizations—that the research does not confirm that RF fields are a cause of cancer or any other disease at the levels we encounter in our everyday environment. Regarding health effects from mobile phone use, the World Health Organization website states "*[a] large number of studies have been performed over the last two decades to assess whether mobile phones pose a potential health risk. To date, no adverse health effects*

have been established as being caused by mobile phone use."[1] It should be emphasized that exposure to RF fields at a distance of 1 meter from any of the FlexNet meters is more than 3,000-fold lower than the levels at which biological and health effects have been evaluated in this report to assess potential public health and safety of exposure to RF fields.

The regulatory standard in Canada to ensure public safety is the responsibility of Innovation, Science and Economic Development Canada, formerly Industry Canada, which implements the human exposure limits developed by Health Canada in SC6 (Health Canada, 2015). Health Canada's SC6, and the standards developed by other organizations, set exposure limits far below the level at which even minor effects of the known adverse health effects (elevated body temperature, tissues heating) caused by exposure to high levels of RF fields might occur.

Note that this Executive Summary provides only an outline of the material discussed in this report. Exponent's technical evaluations, analyses, conclusions, and recommendations are included in the main body of this report, which at all times is the controlling document.

[1] https://www.who.int/news-room/fact-sheets/detail/electromagnetic-fields-and-public-health-mobile-phones Accessed April 2021.

1. Introduction

The Sensus Sonix IQ™ advanced meters (hereafter Sonix IQ gas meter) proposed by FortisBC Energy Inc. (FEI) communicate customers' gas usage by wireless radiofrequency (RF) signals. Before reviewing research on RF exposure and health, it is important to understand the basics of RF energy and the strength of RF signals that are associated with the operation of the Sonix IQ gas meter and other components of the FlexNet communication network that FEI proposes to implement in its service territory.

As indicated in the Executive Summary, background information and explanations about RF energy, RF exposures from typical sources, RF exposures from the advanced metering infrastructure components of the FlexNet system, and required compliance with Health Canada's Safety Code 6 (SC6) that governs public exposure to RF fields, are provided in the Exponent report, "*Exposure to Radiofrequency Fields in the Environment and from Advanced Metering Infrastructure*" (Exponent, 2021).

RF energy, also known as radio waves or fields, refers to a range of frequencies in the electromagnetic spectrum. The electromagnetic spectrum includes fields in a continuum of frequencies measured in cycles per second (referred to as Hertz [Hz]) and a corresponding range of wavelengths and energies. The electromagnetic spectrum ranges from waves with low frequencies, low energies, and long wavelengths (e.g., power-frequency electric and magnetic fields [EMF]), to waves with high frequencies, high energies, and short wavelengths (e.g., visible light, X-rays, gamma-rays). The RF range is at the lower end of the spectrum, lower than infrared rays, visible light, and ultraviolet light.[2] It is typically defined as between 3,000 Hz (3×10^3; i.e., 3 kilohertz [kHz]) and 300 billion Hz (3×10^{11}; i.e., 300 gigahertz [GHz]). RF energy includes frequencies used to operate various devices and technologies, including amplitude-modulated (AM) and frequency-modulated (FM) broadcast radio, television broadcasts, mobile phones, cordless phones, garage door openers, baby monitors, wireless computer networks, security systems, radar, and microwave ovens. The RF fields from these

[2] While in some disciplines, RF and electric and magnetic fields (i.e., EMF) are used synonymously, the common usage of EMF in epidemiologic and biological studies primarily refers to the electric fields and magnetic fields associated with the generation of electricity from power lines and all electric devices at 60 cycles per second (60 Hz).

devices are designed and regulated to be far below permitted exposure limits and so prevent the possibility of over exposure that might cause tissue heating.

RF signals have been used for familiar items like radio broadcasts for more than one hundred years, and even before that, for wireless telegraphy since the late 1890s. More recently, technological advancements have used very weak RF signals to operate cordless phones, baby monitors, wireless networks, and mobile phones. While research on exposure to RF energy has been conducted since the World War II era to support development of health-based exposure limits and standards, the recent proliferation of this technology has sparked additional research on RF fields, particularly in regard to mobile phones. Research on RF fields and health has increased in part because mobile phones are in widespread use, are used regularly, and are held next to the human body. In 2017, there were over 31 million mobile phones in use in Canada alone[3] and about 5 billion throughout the world.

Although the main focus of this research has been on mobile phones, the widespread introduction of other devices that transmit RF signals, such as wireless utility meters, also has raised questions by some members of the public and scientists about potential RF exposure at levels below that known to be harmful to human health. The main questions that have arisen in regard to RF fields are about cancer risk from long-term exposures and non-specific symptoms affecting overall quality of life from short-term exposures. These areas are the focus of the overview of research in this report.

The European Union's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published a comprehensive review of the potential health effects of RF energy, static fields, and extremely-low-frequency fields in 2015. Regarding RF fields, the Committee concluded that exposure to RF fields did not cause increased risks of cancer or other adverse effects on health. The purpose of this report is to assess the weight of evidence added since this review to evaluate whether new research would change this conclusion. This report begins with a discussion of factors that affect exposure to RF fields from wireless communication devices, including the Sonix IQ gas meters and associated infrastructure (Section 2). Section 3 provides a description of the methods scientists use to compile and evaluate research on potential effects

[3] https://crtc.gc.ca/eng/publications/reports/policymonitoring/2018/cmr3d.htm Accessed April 2021.

of an exposure on human health and the use of this research by agencies like SCENIHR. Section 4 discusses the nature of the health effects from high exposures to RF energy and the basis for the standards that have been set, and describes the relevant standards applied to ensure the safe use of any device that uses RF energy. Section 5 discusses the reviews that have been conducted by scientific and health organizations. Section 6 summarizes recent research on RF fields, with a focus on studies of cancer and electromagnetic hypersensitivity, and the potential impact of this new research on the conclusions of recent comprehensive reviews, consistent with methods of a health risk assessment described in Section 3.

2. Exposure Characteristics of RF Wireless Communication Devices and FlexNet Meters

RF fields share common characteristics as to their propagation through the air and their interactions with objects as radio waves. The interaction of these fields with objects, however, is largely determined by the characteristics of the object including its size, shape, and composition. In particular, an object's conductivity and permittivity vary according to the frequency of the RF wave. For humans and other organisms, this variation in conductivity and permittivity therefore determines the amount and depth of energy absorption from a particular RF wave.

While the frequency of the RF field, together with the size, shape, and electrical characteristics of the human body, determine the extent of absorbed energy, the intensity of the RF field is strongly influenced by the distance from the source. Close proximity to a weak source such as a mobile phone or other hand-held or worn device provides higher exposure to RF fields than from more powerful sources such as radio or television broadcast stations that are kilometers away. Very large reductions in signal strength occur even at locations a short distance away from an RF source because the signal diminishes with the square of the distance. As described in SC6, limits on the intensity of RF exposure in close proximity to the body are expressed by specific absorption rates (SAR) in units of watts per kilogram (W/kg). Related limits on the strength of RF signals are calculated or measured in units of power density—watts per square meter (W/m^2) or milliwatts per square centimeter (mW/cm^2).

While distance from the RF source is a key component determining the strength of a wireless signal, the duration of time over which one is exposed to RF fields is another important contributor to exposure. Considering exposure as the product of signal strength times the duration exposed is important in the assessment of potential biological and health effects of exposure. Many devices use wireless signals to communicate information, but there are large differences between various RF devices as to the length of time they are designed to transmit. Some sources like AM/FM broadcast stations, global positioning system signals from satellites, and cellular towers transmit continuously. Other sources like mobile phones, cordless phones, home or office Wi-Fi, and baby monitors may be used for long periods. Still other sources are

turned on and transmit for only very short periods, including garage door openers, wireless printers, and citizen band radios. The wireless signals from the Sonix IQ gas meters and similar Sensus FlexNet SmartPoint® modules (hereafter SmartPoint) attachments to existing advanced gas meters are at the lowest end of this latter category (*see* Exponent, 2021, Figure 5) because the elements of the system transmit infrequently and then only for a fraction of a second.

As described in the RF Exposure Report, the method FEI has proposed for collecting information from customers about their gas usage involves the transmission of usage by a customer's Sonix IQ gas meter by sending an RF signal with a fixed duration of approximately 55 milliseconds at 4-hour intervals (Exponent, 2021).

The calculated exposures at 1 meter in front of the Sonix IQ gas meters and SmartPoints are very small, just 0.000057% and 0.000039%, respectively, of the SC6 reference value for whole-body exposure to RF fields in uncontrolled environments occupied by the general public. The RF fields from other less common components of the FlexNet system—Sensus FlexNet SentryPoints™ and Sensus FlexNet Gateways—at greater representative distances are still lower (Exponent, 2021).

The very low signal strength and ultrashort transmission times of the proposed Sonix IQ gas meters and other components of the FlexNet system are important to keep in mind as we review and evaluate human exposures to RF fields in the current epidemiologic research where most exposures were from mobile phones and hand-held communicators that are held close to the body. Exposures from mobile phones, which are the RF source most commonly emulated in experimental studies of animals, produce far greater exposures, almost two million times greater than Sonix IQ gas meters, but still are within SC6 regulatory limits (Exponent, 2021, Figure 5). The exposures applied in many of the animal experiments reviewed here in Appendix 1, however, were even higher, up to 125 times above the SC6 basic restriction on SAR for whole-body human exposure of the general public. Most of these latter studies applied exposures that also exceeded 4 W/kg, an adverse effect threshold above which unacceptable heating of the whole body may occur. The remainder of the animal studies reviewed applied RF fields at lower SAR exposures, but only six studies examined exposures that were below the SC6 whole-

body exposure limit of 0.08 W/kg and none were as low as the SAR value for a person standing 1 meter from a Sonix IQ gas meter (0.000000046 W/kg).[4]

Overall, the exposure to RF fields at 1 meter from the Sonix IQ gas meters or SmartPoints (indoors) is estimated to be on the order of 1.8 million-fold less than the exposure to RF fields from a mobile phone (~at 0.1 W/kg) in the epidemiologic studies reviewed, and more than 42,000-fold lower than the lowest SAR level (0.00014 W/kg) of any *in vivo* animal study of deoxyribonucleic acid (DNA) and chromosomes reviewed here in Appendix 1. These calculated exposures from Sonix IQ gas meters also can be compared to the regulatory limits in SC6. Indoor exposure from Sonix IQ gas meters is about 24 million times below the SC6 exposure limit.

[4] The exposure a distance of 1 meter in front of the Sonix IQ advanced gas meter is 0.000057% of the SC6 reference level (Exponent, 2021, Table B-2). The SC6 whole body SAR limit is 0.08 W/kg (Exponent, 2021, Table 1), so the SAR level is equivalent to 0.000057% × 0.08 W/kg = 0.000000046 W/kg.

3. Evaluating Scientific Research

Health risk assessment approach

A health risk assessment is the scientific method used by scientists worldwide for determining whether or how an exposure in the environment, such as chemicals in the air, water, or food, or devices such as mobile phones or advanced meters, can affect human health. Health risk assessments include four general steps: hazard identification, dose response assessment, exposure assessment, and specific risk characterization.

In the first step, *hazard identification*, scientists identify and review all of the relevant scientific research studies of effects in humans and laboratory animals to determine the types of health problems that might result from exposure. The next step, *dose-response assessment*, is an evaluation of the data from the hazard identification to determine what intensity and duration of exposure causes adverse effects that were identified. The dose-response assessment is the basis for developing exposure limits and regulatory standards. Next, the *exposure assessment,* evaluates the amount and nature of human exposure from the agent being studied. The final step, *specific risk characterization,* compares the dose-response pattern to the amount of the specific exposure being investigated to determine a level of risk for the exposed population. For some exposures, limits already have been developed from the data as a regulatory standard. In such cases, as for exposure to RF signals from advanced meters, the final step is to compare the specific exposure to the relevant standard.

Hazard identification

In a hazard identification, scientists search out and review all of the relevant scientific research studies to determine the types of health problems that an exposure could cause, regardless of the exposure. This process considers epidemiologic studies of humans in their natural environment, experimental laboratory studies of humans or laboratory animals (*in vivo*), and laboratory studies of cells and tissues (*in vitro*) that may provide evidence for a mechanism—the way in which the exposure interacts with biological tissue. These three types of studies provide different but complementary information to determine how an exposure affects biological organisms.

Dose-response assessment

The second step in the risk assessment process is to determine how responses to the exposure relate to the level of exposure. Almost anything in our environment can produce adverse effects if the exposure is high enough, including water and some vitamins, so the goal is to find the level below which adverse effects do not occur.

In a dose-response assessment, scientists evaluate the scientific research to estimate the amount of exposure (dose) that is likely to result in a particular health effect in humans. This is important because many things that might impact human health only do so after a certain amount of exposure has occurred. A simple summary of the dose-response principle is that for chemicals or physical agents that could affect biological function, more is worse. For this reason, laboratory experiments strive to expose animals at the highest level tolerated, to ensure that potential adverse effects are not missed. Then, exposures at lower levels are used to identify exposure levels that do not produce adverse effects. Studies that demonstrate increased effects with higher doses show a dose-response pattern, which, if consistent across valid studies, can support inferences of causality.

The concept that effects of exposure are closely tied to the intensity of exposure is a familiar part of our daily life. We know, for example, that sunlight can burn unprotected skin, but blocking sunlight by the application of sunscreen lowers an individual's exposure to sunlight, thus reduces the risk of sunburn. Another example is that a 6% solution of sodium hypochlorite, commonly known as bleach, carries a warning label that this substance is hazardous, dangerous, and corrosive. But, a similar, highly-diluted solution is used to disinfect many municipal drinking water supplies; in this case, the concentration of sodium hypochlorite is extremely low, and the dose is far too low to produce a toxic effect.

Exposure assessment

The third step of the process is to determine the way in which people could be exposed in a specific situation, including the amount and duration of exposure. This is important because an individual's exposure is one of the major factors for determining the potential for an impact on health.

Specific health risk characterization

The information developed in the hazard identification, dose-response assessment, and exposure assessment is used to reach a conclusion and characterize the specific health risk, if one exists.

Types of studies considered in a health risk assessment

Research studies can be broadly classified into two groups: 1) epidemiologic studies of people and 2) experimental studies of humans, animals (*in vivo*), and cells and tissues (*in vitro*) conducted in laboratory settings. Taken together, epidemiologic, *in vivo*, and *in vitro* studies provide a more complete picture of a possible disease etiology than any one study type alone, given the unique strengths and weaknesses of each study design. In valid risk assessments of exposure to RF and health, epidemiologic studies are considered alongside experimental studies of laboratory animals, while studies of isolated cells and tissues are generally acknowledged as being supplementary.

Epidemiologic studies

One aspect of epidemiologic research provides descriptive statistics on the population, such as birth rates and mortality rates, to help characterize health and disease in the population. These data are collected by public health agencies such as Health Canada to show trends over time or differences among places. Examples include data that show changes in heart disease deaths over time, variations in infant mortality rates among cities, or cancer occurrence in Canada overall and comparisons among provinces. These data are often evaluated to monitor progress in treating cancer or to evaluate the effects of changes in the rate of cigarette smoking on rates of lung cancer or heart disease over time.

Epidemiologists also study people in their natural environment in relation to individual exposure. These studies are often described as observational rather than experimental, although observational studies can include elements of experimental studies; for example, studies of exposure to RF fields can include interventions, such as turning sources of RF fields on or off at various times during the study. Each of the main types of observational epidemiologic study design—cohort, case-control, cross-sectional, and ecological—have been used to obtain information on exposure to RF fields and health.

In a cohort study, a group of people is observed over a long period to determine whether diseases develop in relation to exposures at various levels. This type of epidemiologic study typically provides the most relevant and reliable information, but cohort studies can be cost-prohibitive and time-consuming because they require following a large number of people over a long period, particularly for conditions that develop over years. Many cohort studies are undertaken in occupational environments because of the large populations, relatively high exposures, and the availability of records on individual workers.

To obtain information more readily, epidemiologists frequently use case-control studies. This type of study compares the exposure of people who have been diagnosed with a particular disease (i.e., cases) to a similar group of people who do not have the disease (i.e., controls). The objective is to assess whether the cases had higher or more frequent exposures than the controls, or *vice versa*. One main challenge of a case-control study is to enroll a control group that is, to the greatest extent possible, similar to the underlying population at risk, from which the cases arose. If this condition is met and a difference is found in the exposure level between the two groups, the investigators can have some confidence that the difference is not being caused by some other factor. Another challenge of case-control studies is that they are retrospective (i.e., the study starts after onset of disease so *past* history of exposure must be evaluated).

Cross-sectional studies examine exposure and health outcomes in the study population simultaneously. These studies generally are used to assess the prevalence (or presence) of the exposure and outcome at a single point in time or a short period (this is sometimes described as providing a "*snapshot*" of disease occurrence within the population). In contrast to cohort studies, cross-sectional studies do not follow the study population over time to observe whether disease develops differently in exposed and unexposed populations. Because exposure and outcome are determined at the same time, a main limitation of cross-sectional studies is that no information is available on whether the exposure preceded the outcome; therefore, this study design cannot be relied upon for causal inference.

In ecological studies, researchers examine the exposure and outcome at the population or community level, often by aggregating individual-level data for a specific geographic region or population. For example, researchers may examine RF field exposures and cancer cases within

a specific city or region. These studies are useful when data at an individual level are limited or when there is an interest in examining population-level effects of exposure on an outcome. Because data are examined on a large scale and cannot account for individual-level differences or risk factors, ecological study results are only applicable at the population level and cannot provide conclusions about any one individual's level of risk. Ecological studies are therefore subject to a type of error known as an "*ecological fallacy*," in which the relationship between exposure and outcome observed at the population level are assumed (sometimes incorrectly) to be true for individuals.

In addition to the observational study designs discussed above, researchers also use an experimental epidemiologic study design known as a randomized control (or clinical) trial (RCT). In an RCT, researchers randomly assign the study participants to either an experimental group (i.e., the group that receives the exposure or treatment under study) or a control group, which does not receive the exposure or treatment. Randomizing participants to the two groups reduces the potential for errors (bias) in the study and allows researchers to better isolate the true effect of the exposure or treatment. Because of this, RCTs are generally considered the "*gold standard*" of epidemiologic study designs and provide the strongest evidence for or against a causal association between an exposure and outcome. However, RCTs are not frequently performed to assess the relationship between community exposures and health outcomes, as they are lengthy and expensive to carry out.

The results of epidemiologic studies are expressed as statistical associations—either summarized as an odds ratio (OR) in case-control studies or a risk ratio (RR) in cohort studies. These ratios are a quantitative measure of how an exposure and disease vary together. The strength of an association addresses the question, does this disease occur more often in people with the exposure of concern compared to people who are unexposed? A positive association (i.e., an OR or RR greater than 1.0) indicates that the answer may be yes, but numbers close to 1.0 indicate a weaker link, and higher numbers indicate a stronger link. A positive association may also be interpreted as a measure of the potential increased risk of developing disease in people who are exposed compared to the risk of developing disease in people who are not exposed. While this information from an epidemiologic study may provide an indication of the factors involved in health and disease, it is not used as the sole basis for drawing inferences

about cause-and-effect relationships. Neither a statistical association nor a correlation between any two events is a direct indication of cause and effect, and a positive statistical association or a reported increased risk of disease by itself does not represent a conclusion regarding causation. An observed association may in fact be due to the effects of one or more other factors, including random chance or systematic errors within the study. Because each epidemiologic study is only a sample of the population, and no single study is perfect, the results from any one study cannot be used to establish a causal relationship between exposure and disease. Instead, epidemiologic support for causality is usually based on high-quality studies that report consistent results across many different populations and study designs and are supported by experimental data collected from *in vivo* and *in vitro* studies.

Scientific guidance for assessing the overall epidemiologic evidence for causality was formally proposed by Sir Austin Bradford Hill (Hill, 1965). Hill put forth nine criteria for use in an evaluation of causality for associations observed in epidemiologic studies. These criteria included strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. Hill cautioned that while none of these criteria are *sine qua non* (i.e., absolutely necessary) of causality, the more the epidemiologic evidence meets these guidelines, the more convincing the evidence is for a potential causal interpretation. The use of these guidelines is recommended after chance has been ruled out with reasonable certainty as a potential explanation for the observed epidemiologic association.

The validity of a study depends upon the quality of the data, which depends upon the methods used to collect and analyze the information from which the results were calculated. To evaluate the results of any type of study, whether an epidemiologic study or laboratory research, it is crucial to assess the way the study was designed and conducted, the number of participants, the accuracy of the exposure assessment, and the statistical methods of analysis. This is particularly necessary in epidemiologic studies to determine whether an association is a result of systematic error (bias) in the selection of participants, misclassification of exposures, secondary effects by other variables such as the presence of other exposures or pre-existing conditions (confounding), or random variation (chance). Even if a statistical association from a single study is deemed valid, further scrutiny is warranted to determine if the statistical association indicates a cause-and-effect relationship.

In epidemiologic research, the results of studies with a smaller number of participants may be difficult to distinguish from normal, random variation. This is also the case for sub-group analyses where few participants are estimated to have high exposure levels. Meta-analysis is an analytic technique that combines the published results from a group of studies into one summary result. A pooled analysis, on the other hand, combines the raw, individual-level data from the original studies and analyzes the data from the studies together. These methods are valuable tools for qualitatively synthesizing the results of a large group of studies because they increase the number of individuals in the analysis, which allows for a more robust and stable estimate of association. The disadvantage of meta- and pooled analyses is that they can convey a false sense of consistency across studies if *only* the combined estimate of effect is considered (Rothman and Greenland, 1998). These analyses typically combine data from studies with different study populations, methods for measuring and defining exposure, and disease definitions. This is particularly true for analyses that combine data from case-control studies, which often use very different methods for the selection of cases and controls and exposure assessment. Therefore, in addition to the synthesis or combining of data, meta- and pooled analyses should be used to understand what factors cause the results of the studies to vary (e.g., publication date, study design, possibility of selection bias), and how these heterogeneous factors affect the associations calculated from the data of all the studies combined (Rothman and Greenland, 1998).

When interpreting the results of epidemiologic studies, epidemiologists and other scientists focus predominantly on the main results of the study (i.e., on analyses that were conducted using the entire study population, or the majority of the study population). In addition to the main analyses, researchers may also conduct sub-analyses of the data, in which subsets, or groups, of the study population are analyzed separately based on one or more shared characteristics (e.g., tumor sub-type, length of exposure duration, gender, age, etc.). The goal of sub-group analyses is to examine if and how the relationship between the exposure and outcome of interest varies across different subsets of the population, and sub-group analyses can sometimes lead to additional research questions that should be explored in future studies. However, sub-group analyses are generally considered secondary to the main analyses and should always be interpreted with caution (Fletcher, 2007; Wang et al., 2007). These analyses are not always planned before the data were collected and instead may represent *post hoc*

attempts by researchers to identify any statistically significant associations in the data when none were observed in the main analyses (therefore increasing the chances of their study being published). In addition, sub-group analyses typically include fewer study participants per group compared to the main analyses; this is an issue because small sample sizes decrease the likelihood that a statistically significant finding reflects the true association between exposure and outcome and increase the likelihood that it is due to error or chance.

Experimental studies

A wide variety of approaches are available for assessing the possible adverse effects associated with exposures in experimental studies. The two general types of experimental studies are *in vivo* studies of the effects of planned exposures (i.e., studies of human volunteers, which are usually short-term, and of whole animals, which are usually longer-term), and *in vitro* studies (i.e., studies of isolated cells and tissues). Compared to epidemiologic and *in vivo* studies, *in vitro* studies generally provide less value to human health risk assessments because responses of cells and tissues outside the body may not reflect the response of those same cells if maintained in an intact living system; thus, their relevance cannot be assumed (IARC, 1992). In addition, the results of *in vitro* studies cannot be interpreted in terms of potential human health risks unless they are performed in a well-studied and validated test system. For these reasons, agencies such as the International Agency for Research on Cancer (IARC) treat data from *in vitro* studies as supplementary to data obtained from epidemiologic and *in vivo* studies, and *in vitro* data are not used directly to assess risks to human health. Therefore, this report considers recent human and animal studies of exposure to RF fields but does not review *in vitro* research. Only human and animal studies of RF exposure were considered because they provide more direct information on human health than *in vitro* studies.[5]

[5] *For example,* SCENIHR (2012), which states, *"[i]n vivo results are considered to have more relevance than in vitro results in the overall assessment of a genotoxic hazard*"(p. 26). SCENIHR (2012) also states, "*In vitro studies contribute to acute toxicity testing and can provide information relevant regarding carcinogenesis and other physiological or pathological processes but cannot replace in vivo conditions or long term exposure conditions*" (pp. 27-28).

Furthermore, the reviews conducted by health and scientific agencies have not provided any indication that *in vitro* studies have influenced their conclusions.[6]

Specific methods are used to reduce subjectivity and avoid systematic error (i.e., bias), in scientific experiments (NRC, 1997). These include the random assignment of subjects to control or comparison groups, the unbiased collection of information (e.g., researchers are not aware of the exposure, also termed "*blind*" to the exposure); control of the environmental and procedural variables during the experiment and after so if a difference between exposed and control groups is observed, it can be unambiguously linked to the intended exposure—not extraneous factors; and the need for replication of results in different studies, at various different laboratories, and across species, all of which strengthen the evidence. In addition, each study should contain enough participants or animals to overcome random variation. These factors serve as guidance for weighing the evidence from studies to reach a decision about cause and effect. The more firmly these criteria are met by the studies, the more convincing the evidence.

Some human and animal studies aim to identify biological processes that may be associated with disease states or injury by measuring so called biomarkers. Abnormal levels of biomarkers may be associated with health problems even though they only may be an indirect indicator. An example might be a low blood count, which can be caused by many factors, and so, by itself, is not diagnostic of any specific disease or condition. Despite such limitations, biomarker studies are often done because of the ease of obtaining samples and low cost of analyses compared to more invasive or more specific biochemical analyses.

Studies in which laboratory animals receive high exposures in a controlled environment provide an important basis for evaluating the safety of environmental, chemical, and drug exposures. These approaches are used widely by health agencies to assess risks to humans from medicines, chemicals, and physical agents, because studies in laboratory animals such as rats and mice have

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[6] *See* for example, IARC (2013), which states, *"[o]verall, the Working Group concluded that there was weak evidence that RF radiation is genotoxic, and no evidence for the mutagenicity of RF radiation*" (p. 415). Overall, the SCENIHR Working Group concluded that "*In most of the [in vitro] studies, no effects of exposure at non-thermal levels were reported, although in some cases DNA strand breaks and mitotic spindle disturbances were observed*" (SCENIHR, 2015, p. 153).

been found to be reasonable indictors of adverse effects in humans (Health Canada, 1994; WHO, 1994; IARC, 2013 preamble; USEPA, 2002, 2005).

From a public health perspective, long-term (chronic) studies in which animals undergo exposure over most of their lifetime, or during their entire pregnancy, are of high importance in assessing potential risks of cancer and other adverse effects. In these long-term studies, researchers examine a large number of anatomical sites to assess changes and adverse effects in body organs, cells, and tissues.

These data are used in the hazard identification step of the risk assessment process to determine whether an environmental exposure at any level or circumstance can produce cancer or damage organs and tissues. Health Canada mandates that experimental lifetime *in vivo* studies or *in vivo* studies of exposures to animals during critically sensitive periods be conducted to assess potential toxicity to humans (Health Canada, 1994). Furthermore, the position of the United States Environmental Protection Agency (EPA) is that, "*...the absence of tumors in well-conducted, long-term animal studies in at least two species provides reasonable assurance that an agent may not be a carcinogenic concern for humans*" (USEPA, 2005, pp. 2-22).

Weight-of-evidence reviews

The risk assessment process includes evaluating the methods used in conducting each individual study included in the hazard identification, analyzing the results, and weighing the evidence, giving more weight to studies of better, more reliable designs (i.e., a weight-of-evidence review). This process is designed to ensure that all relevant studies are considered regardless of their conclusions or support for any particular hypothesis. During the weight-of-evidence review, scientists look for replication of results by different researchers or other laboratories to form conclusions about causality, because no single study is capable of assessing causality independently. Two steps necessarily precede a weight-of-evidence evaluation: a systematic review to identify the relevant literature and an evaluation of each relevant study to determine its strengths and weaknesses.

Several agencies have described weight-of-evidence evaluation and health risk assessment approaches, including the IARC, which routinely evaluates substances such as drugs, chemicals,

and physical agents for their ability to cause cancer; the World Health Organization (WHO) International Programme for Chemical Safety; the EPA, which sets guidance for public exposures in the United States; the European Commission's Scientific Committee on Health, Environmental, and Emerging Risks (SCHEER);[7] and the United States National Toxicology Program (NTP) (USEPA, 1993, 1996; WHO, 1994; SCENIHR, 2012; NTP, 2019; SCHEER, 2018).

In their 2018 report, *Memorandum of weight of evidence and uncertainties Revision 2018,* SCHEER defined a weight-of-evidence evaluation as *"[a] process of weighted integration of lines of evidence to determine the relative support for hypotheses or answers to a question"*(SCHEER, 2018, p. 9). As part of the weight-of-evidence approach, SCHEER identifies, collects, and selects possible sources of scientific evidence (primarily in the form of peer-reviewed publications) related to the risk assessment question under study and then evaluates each line of evidence on its validity, reliability, and relevance. The results from all relevant individual lines of evidence are then gathered into an overall assessment and any remaining uncertainties are addressed. SCHEER notes that in drawing conclusions from the available evidence, it is important to consider all the information together, and states that,

> *… it is not recommended to simply add together weighting from individual lines of evidence… The severity of the effect/outcome and the likelihood of its occurrence in individuals or in the population at large is another factor to take into account at the integration level. One of the crucial points is the identification of the critical effect both in animal and human studies… The key issues in the evaluation of human evidence are to assess whether the results demonstrate a true causal effect, to identify the affected population and to determine to what extent the adverse effects of the exposure might be avoidable* (SCHEER, 2018, p. 30).

[7] On July 8, 2015, SCENIHR was renamed SCHEER. The organization's review of RF research was published under the name SCENIHR, while the revised weight-of-evidence guidelines document was published under SCHEER, which is reflected in the citations used throughout this report.

4. Exposure Limits and Regulatory Standards

When a health risk assessment process indicates that there might be a potential health hazard from higher exposures to a substance or physical agent, a government agency or technical organization is likely to promulgate a standard. A health standard is developed from the hazard identification and dose response assessment of the risk assessment process described above. A health agency or scientific organization typically evaluates three types of studies (epidemiologic, *in vivo*, and *in vitro*) during the risk assessment. Most organizations identify experts in the many relevant disciplines that perform research on the topic of interest to evaluate the research.

Known adverse health effects can be caused by high exposures to RF fields. The effect that occurs first, given sufficient exposure, is a rise in body or tissue temperature. This is the basis of the applicable public exposure limit. Small changes in whole body temperature are actually not an adverse effect if they represent a change similar to daily changes to which our bodies routinely adapt. National and international health and regulatory agencies have set exposure limits to ensure that the warming of tissues is restricted. The goal of the standard is to limit such warming of tissues, since even modest warming of the body can be distracting and should be limited in a working environment. At higher levels of exposure, more serious adverse effects could occur, including effects similar to hyperthermia and local cell damage. Therefore, the exposure limits in the RF standards are set well below the level at which even minor effects from tissue heating might occur (FCC, 1997; Health Canada, 2015; IEEE, 2019; ICNIRP, 2020a).

Health Canada's Safety Code 6

Similar to the way that agencies have established exposure limits for RF fields in the United States and Europe, the scientists that developed Health Canada's SC6 (*Limits of Human Exposure to Radiofrequency Electromagnetic Energy in the Frequency Range from 3 kHz to 300 GHz*) used the risk assessment approach to evaluate all research related to exposure to RF fields and health (Health Canada, 2015).

The objective of any standard, whether it regulates drinking water, air quality, or food safety, is to keep exposure below the lowest level at which any established potentially adverse effect is known to occur. The approach scientists use to develop health-based standards is to set the exposure many times below the level at which research suggests that an effect could occur. This conservative approach helps to compensate for unrecognized limitations in the research and exposure assessment, and to afford additional protection to all members of the population. SC6, as well as standards in many other countries, recognize a SAR value of 4 W/kg as the lowest exposure to RF fields known to produce an adverse effect (whole body heating and sequelae thereto). The number used to lower the exposure limit below the lowest known adverse effect level is referred to as a safety factor. For controlled environments, as in occupational settings, where exposures have been measured or calculated and persons are informed, SC6 applies a safety factor of 10 to set a basic restriction limit on exposure. For uncontrolled environments where the general public might encounter RF fields, SC6 applies a safety factor of 50 to an adverse effect SAR level of 4 W/kg to set the basic restriction limit at 0.08 W/kg.

As with most environmental exposures, few studies of RF exposure include children and other sensitive persons. Several methods are used to develop protection for these populations. One approach is to incorporate information about the mechanism by which the agent affects the human body and ascertain whether children or the elderly would react differently because of biological characteristics. Another is to conduct experimental studies of animals at varying stages of development to determine potential sensitivities of the young and the old. Finally, scientists recommend exposure limits that are comfortably *below* levels known to produce effects. This incorporates the basic scientific concept of dose response, which refers to the principle that the probability of an effect occurring, or the severity of an effect, increases with the dose, or amount of exposure.

Basis for the SC6 standard for radiofrequency exposure

RF standards are called safety standards because they address issues of human health and safety, and they prescribe exposure limits for a level in the environment presumed harmless. An exposure limit is the amount of exposure to RF fields at a specified frequency or a range of frequencies that should not be exceeded in order to protect human health with an adequate

margin of safety.[8] In Canada, RF safety standards are codified in SC6. The purpose of SC6, originally published by Health Canada in 1991, is to "*establish safety limits for human exposure to radiofrequency (RF) fields in the frequency range from 3 kHz to 300 GHz*" (p. I) to protect workers and the public from RF fields and microwave radiation. SC6 applies to "*all individuals working at, or visiting, federally regulated sites*" and has been adopted by Innovation, Science and Economic Development Canada (ISED) as:

> *… the scientific basis for equipment certification and RF field exposure compliance specifications outlined in Industry Canada's regulatory documents (1–3), that govern the use of wireless devices in Canada, such as cell phones, cell towers (base stations) and broadcast antennas. Safety Code 6 does not apply to the deliberate exposure for treatment of patients by, or under the direction of, medical practitioners* (Health Canada, 2015, p. I).

Since its initial publication, SC6 has been periodically updated as new scientific literature becomes available and has undergone a number of revisions with new versions published in 1999, 2009, and 2015, each time with input from the Royal Society of Canada (RSC). During the revision process prior to finalizing SC6, Health Canada also considered input from the public and scientists for the 9 months before the release of the revised SC6 in 2015.

The scientific basis for SC6 was described as:

> *The exposure limits specified in Safety Code 6 have been established based upon a thorough evaluation of the scientific literature related to the thermal and non-thermal health effects of RF fields … Health Canada scientists consider all peer-reviewed scientific studies, on an ongoing basis, and employ a weight-of-evidence approach when evaluating the possible health risks of exposure to RF fields. This approach takes into account the quantity of studies on a particular endpoint (whether adverse or no effect), but more importantly, the quality of those studies. Poorly conducted studies (e.g. those with*

[8] Standards are also used for specifications for manufacturing products to ensure safe construction, or conformity or compatibility among different companies that make the same item, but in this report we are referring to safety standards.

> *incomplete dosimetry or inadequate control samples) receive relatively little weight, while properly conducted studies (e.g. all controls included, appropriate statistics, complete dosimetry) receive more weight. The exposure limits in Safety Code 6 are based upon the lowest exposure level at which any scientifically established adverse health effect occurs. Safety margins have been incorporated into the exposure limits to ensure that even worst-case exposures remain far below the threshold for harm. The scientific approach used to establish the exposure limits in Safety Code 6 is comparable to that employed by other science-based international standards bodies* (Health Canada, 2015, p. 1).

The limits established in SC6 are based upon limiting short-term biological responses to RF fields and do not contain any restriction for long-term or cumulative exposure, noting that:

> *At present, there is no scientific basis for the occurrence of acute, chronic and/or cumulative adverse health risks from RF field exposure at levels below the limits outlined in Safety Code 6. The hypotheses of other proposed adverse health effects occurring at levels below the exposure limits outlined in Safety Code 6 suffer from a lack of evidence of causality, biological plausibility and reproducibility and do not provide a credible foundation for making science-based recommendations for limiting human exposures to low-intensity RF fields* (Health Canada, 2015, p. 2).[9]

Health Canada's mandate regarding human exposure to RF fields from wireless equipment is to carry out research into possible health effects, monitor the scientific literature related to such effects, and develop exposure guidelines for federal activities. These exposure limits are based on the risk assessment process, those established scientific and technical methods for reviewing biological and health research. These exposure guidelines are adopted by ISED, the federal

[9] It should be noted that SC6 states *"[w]hile the biological basis for the basic restrictions specified in this safety code has not changed since the previous version (2009), the reference levels have been updated to either account for dosimetric refinements in recent years ... or where feasible, to harmonize with those of ICNIRP [International Commission on Non-ionizing Radiation Protection"*(Health Canada, 2015, p. 4).

agency responsible for regulating wireless communications equipment (e.g., mobile phones, cell tower sites, smart meters, Wi-Fi) and exposure of the public to RF fields in Canada.

To assist persons to understand SC6, additional information is available in other documents published by Health Canada including *Understanding Safety Code 6*, an overview of the salient points discussed in SC6, including a high-level summary of the purpose of SC6, an overview of its structure, and summaries of the scientific review process and comparison to international standards; a *Fact Sheet – What is Safety Code 6?* provides a brief overview of SC6 and includes a section entitled *Busting Myths on Safety Code 6*, and a *Technical Guide for Interpretation and Compliance Assessment of Health Canada's Radiofrequency Exposure Guidelines Document*.

The implementation, management, and evaluation of RF field exposures compliant with SC6 at the national level is described by ISED for persons in the far field in uncontrolled environments. ISED's *Radio Standards Specification 102, Radio Frequency (RF) Exposure Compliance of Radiocommunication Apparatus (All Frequency Bands)* sets out the requirements and measurement techniques used to evaluate RF exposure compliance of radiocommunication apparatus designed to be used within the vicinity of the human body in conjunction with *TN-261 — Safety Code 6 (SC6) Radio Frequency Exposure Compliance Evaluation Template (Uncontrolled Environment Exposure Limits)*.

5. Agency Reviews of Radiofrequency Fields and Health

Scientific research on exposure to RF fields and health is reviewed regularly by independent scientific and governmental organizations worldwide. These organizations assemble expert panels to conduct weight-of-evidence reviews. The members of these expert panels have the knowledge and mandate to review relevant research and provide scientifically-grounded public health recommendations.

Within the last decade, several prominent regulatory, scientific, and health organizations have systematically reviewed the research on exposure to RF fields and health. These organizations include the IARC, the International Commission on Non-Ionizing Radiation Protection (ICNIRP), the Health Council of the Netherlands (HCN), the Advisory Group on Non-Ionising Radiation Protection (AGNIR), SCENIHR, the Swedish Radiation Safety Authority (SSM), the United States Food and Drug Administration (FDA), and RSC (AGNIR, 2012; HCN, 2013, 2014, 2016; IARC, 2013; WHO, 2014, RSC, 2014; SCENIHR, 2015; SSM, 2016, 2018, 2019, 2020; ICNIRP, 2020a; FDA, 2020). These organizations have all independently reached the same conclusion regarding exposure to RF fields and human health—that exposure below the current scientifically-based exposure limits (e.g., the ICNIRP guidelines) has not consistently or convincingly been established as causing any type of cancer, other chronic diseases, or non-specific symptoms that adversely affect well-being in humans.

Some studies have reported effects from exposure to RF fields occurring below the level that raises body temperature, often called *non-thermal* effects. These studies have been reviewed by these scientific and regulatory agencies, which have concluded that the observed biological effects attributed to non-thermal levels were not consistent or reproducible, are not supported by any plausible biological explanation as to how they could occur, and in some studies the biological effects reported are not known to be linked to adverse effects on health (SCENIHR, 2009, 2015; AGNIR, 2012; RSC, 2014; HCN, 2016; SSM, 2016, 2018, 2019, 2020; IEEE, 2019; ICNIRP, 2020a).

In addition to the agencies listed above, a number of additional provincial and national agencies with responsibilities for public health routinely provide guidance and communicate health

information to the public regarding exposure to electromagnetic fields at varying frequencies. These organizations include the British Columbia Centre for Disease Control (BCCDC), the French Agency for Food, Environment and Occupational Health and Safety, and the Australian Radiation Protection and Nuclear Safety Agency. In this report, information and guidance provided by the BCCDC is summarized in the relevant sections.

Advisory Group on Non-Ionising Radiation

The independent AGNIR published a systematic review of the scientific literature in 2012 for the Health Protection Agency of Great Britain (now part of the National Institute for Health Protection), the United Kingdom's primary government authority on public health. AGNIR reviewed research related to RF field exposure and health published through 2010 and part of 2011 to update its previous reports on electromagnetic fields published since the agency was formed in 1999 (AGNIR, 2012).

Overall, the Advisory Group concluded, *"although a substantial amount of research has been conducted in this area, there is no convincing evidence that RF field exposure below guidance levels causes health effects in adults or children"* (AGNIR, 2012, p. 4). They further stated, *"[t]here are still limitations to the published research that preclude a definitive judgement, but the evidence considered overall has not demonstrated any adverse health effects of RF field exposure below international accepted guideline levels"* (AGNIR, 2012, p. 4). Specific conclusions related to the health outcomes (e.g., cancer, symptoms of well-being) and types of studies (e.g., epidemiologic studies, experimental studies) reviewed are summarized in the relevant sub-sections of Section 6.

British Columbia Centre for Disease Control

The BCCDC has a long history of providing health information to the public about electromagnetic fields at various frequencies. Regarding RF fields, the BCCDC published a *Radiofrequency Toolkit for Environmental Health Practitioners* in 2013 to assist public health officers to assess and communicate the potential risk to health of the many devices and applications that emit RF waves (BCCDC, 2013). The Toolkit included assessments of RF exposure sources; the results of biological studies of cells and animals; human studies of

therapeutic uses of RF fields in medicine; occupational studies; and mobile phone studies of cancer, reproduction, cognitive effects, and non-specific symptoms affecting well-being.

The BCCDC also published its *2016 Review: Radiofrequency and Health* in which it described and compared RF field exposures from common devices, discussed research on potential health effects from RF field exposure, and discussed ways in which members of the public, if they choose, can reduce personal exposure to RF fields, with priority given to personal mobile phone use, and cordless (digital enhanced cordless telecommunications [DECT]) handsets (BCCDC, 2016).

International Agency for Research on Cancer

As an agency of the WHO, IARC routinely assembles international working groups of experts to critically and systematically review and evaluate human, animal, mechanistic, and exposure-related evidence on the carcinogenicity of various human exposures as the first step (hazard identification) in a carcinogen risk assessment (IARC, 2013). These evaluations are published as IARC Monographs. Monograph 102 reviewed non-ionizing RF energy (IARC, 2013).

IARC uses specific terms to describe the strength of the evidence in support of causality between specific agents and cancer in humans or experimental animals: *sufficient evidence of carcinogenicity, limited evidence of carcinogenicity,* and *inadequate evidence of carcinogenicity.*[10] After reviewing the literature on RF fields, IARC concluded that there was "*limited evidence of carcinogenicity"* in humans as a result of positive associations observed

[10] In their 2013 monograph on RF energy, IARC used the following definitions for each term: ***Sufficient evidence of carcinogenicity*** is assigned to a body of epidemiologic research if *"a causal relationship has been established … That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias, and confounding could be ruled out with reasonable confidence"* (IARC, 2013). ***Limited evidence of carcinogenicity*** describes a body of epidemiologic research where the findings are inconsistent or there are outstanding questions about study design or other methodological issues that preclude making a conclusion, i.e., that a causal relationship *"is considered … to be credible, but chance, bias, or confounding could not be ruled out with reasonable confidence"* (IARC, 2013). ***Inadequate evidence of carcinogenicity*** describes a body of epidemiologic research where it is unclear whether the data are supportive or unsupportive of causation because there is a lack of data or there are major quantitative or qualitative issues, i.e., *"[t]he available studies are of insufficient quality, consistency or statistical power … or no data on cancer in humans is available"* (IARC, 2013). In 2019, IARC released revised, but virtually identical, definitions of these terms. *Limited evidence of carcinogenicity,* for example, continues to describe a body of epidemiologic research in which *"[a] causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence"* (IARC, 2019).

between RF field exposure from wireless phones and glioma and acoustic neuroma[11] in some epidemiologic studies. This conclusion was based almost entirely on studies of RF fields from mobile phone communications—including a series of case-control studies from Sweden (Hardell et al., 1999, 2000, 2001, 2002a, 2002b, 2003, 2006a, 2006b, 2009, 2010, 2011) and the multi-national INTERPHONE study (INTERPHONE Study Group, 2010, 2011)—and was based particularly on studies of RF fields from mobile phones. IARC also rated experimental studies of animals for carcinogenicity of RF field exposure as providing *"limited evidence of carcinogenicity."*

Based on these assessments, IARC classified RF fields overall as "*possibly carcinogenic to humans*" (group 2B), which denotes exposures for which there is limited evidence of carcinogenicity in epidemiologic studies and less than sufficient evidence of carcinogenicity in studies of experimental animals. The other IARC classifications are group 1 ("*carcinogenic to humans*"), group 2A ("*probably carcinogenic to humans*"), and group 3 ("*not classifiable as to its carcinogenicity to humans*").[12] These categories are intentionally meant to err on the side of caution. Since 1971, the IARC has evaluated more than 1,000 agents; currently, 80% of the agents evaluated are classified in group 2B or group 3 (IARC, 2021). Moreover, the IARC statement was based on the review of studies involving exposure to RF fields from mobile phones, which is much greater than RF exposure from advanced meters. The IARC report, however, did not comment on the level of exposure.

Royal Society of Canada

Health Canada is the department of the Canadian government responsible for the nation's public health, including setting limits on exposure. As part of its mission to improve the health of Canadians, Health Canada monitors the scientific research on electromagnetic fields, sets limits on RF field exposure, and commissioned a RSC expert panel to review the current Canadian

[11] An acoustic neuroma is also referred to as a *vestibular schwannoma*, which is considered to be a more medically accurate term (Carlson and Link, 2021). For the purposes of this report, we relied the terminology used in the original source material.

[12] As of 2019, IARC no longer uses a Group 4 (*"probably not carcinogenic to humans"*) classification. The one agent previously assigned to Group 4 (caprolactam) was re-classified to Group 3.

exposure limits and assess whether the limits were *"consistent with the scientific literature in setting limits that would protect the public from adverse health risks"* (RSC, 2014, p. 2).

Based on their review of the available scientific literature, the expert panel stated that they agreed with the conclusion of previously conducted evaluations by health and scientific organizations that exposure to RF fields is "*possibly carcinogenic*" (i.e., IARC's group 2B). Regarding studies published following the previous reviews they evaluated, the panel concluded *"[n]one of the newer studies materially affect the conclusions of the authoritative reviews. However, a weight-of-evidence evaluation shows that the current evidence for a causal association between cancer and exposure to RF energy is weak"* (RSC, 2014, p. 82). The panel noted that it *"was unable to identify any established adverse health effects occurring at levels below the [current Canadian exposure guidelines]"* (RSC, 2014, p. 18). Specific conclusions related to the health outcomes (e.g., cancer, non-specific symptoms affecting well-being) and types of studies (e.g., epidemiologic studies, experimental studies) reviewed are summarized in the relevant sub-sections of Section 6 below.

World Health Organization

In 1996, the WHO established the International EMF Project *"to assess the scientific evidence of possible health effects of EMF in the frequency range from 0 to 300 GHz."*[13]

The WHO is currently undertaking a comprehensive and critical review of relevant scientific literature to assess potential effects of RF field exposure in the 100 kHz to 300 GHz range. A preliminary draft review of RF research on health was released in 2014 for consultation and comment by experts on RF fields. The review focused on all studied health outcomes of relevance to human health, including cancer, neurodegenerative diseases, fertility, reproduction and childhood development conditions, and effects on the immune, neuroendocrine, and cardiovascular systems.

Regarding health effects from mobile phone use, the WHO website currently states *"[a] large number of studies have been performed over the last two decades to assess whether mobile*

[13] https://www.who.int/peh-emf/project/EMF_Project/en/ Accessed April 2021.

phones pose a potential health risk. To date, no adverse health effects have been established as being caused by mobile phone use."[14]

Scientific Committee on Emerging and Newly Identified Health Risks

The most recent weight-of-evidence review of RF fields and health was released in 2015 by SCENIHR. The Committee consists of independent scientific experts assembled to provide advice on public health and risk assessments to the Department of Health and Consumer Protection of the European Commission. The Committee addresses questions related to emerging or newly identified health and environmental risks and on broad, complex, or multidisciplinary issues requiring a comprehensive assessment of risks to consumer safety or public health. The 2015 report on the potential health effects of exposure to electromagnetic fields serves as an update to their previous review from 2009 (SCENIHR, 2009). In performing its assessment of the literature, the Committee followed the scientific guidelines it had developed for the assessment of the quality of the evidence of human health risks (SCENIHR, 2012). Specific conclusions of this Committee related to the health outcomes (e.g., cancer, non-specific symptoms affecting well-being) and types of studies (e.g., epidemiologic studies, experimental studies) reviewed are summarized in the relevant sub-sections of Section 6 below.

Health Council of the Netherlands

The HCN is an independent scientific advisory body designed to *"advise … on the current level of knowledge with respect to public health issues and health (services) research"* (HCN, 2016, p. 8). The Electromagnetic Fields Committee of the HCN conducted systematic reviews of the epidemiologic data (HCN, 2013) and experimental animal data (HCN, 2014) on the relationship between RF field exposure and cancer, with the epidemiologic data focusing specifically on the association between mobile phones and tumors of the head. The findings from the two reports were integrated into a third report presenting the Council's overall conclusions after jointly considering both epidemiologic and experimental data (HCN, 2016). Overall, HCN concluded

[14] https://www.who.int/en/news-room/fact-sheets/detail/electromagnetic-fields-and-public-health-mobile-phones Accessed April 2021.

that it *"considers it unlikely that exposure to radiofrequency fields, which is associated with the use of mobile telephones, causes cancer"* (HCN, 2016, pp. 16-17). Specific conclusions related to epidemiologic and experimental studies of cancer are summarized in the relevant sub-sections of Section 6 below.

International Commission on Non-Ionizing Radiation Protection

ICNIRP is an independent, non-governmental scientific organization recognized by the WHO that sets internationally recognized, science-based guidelines on limits of exposure to non-ionizing radiation; provides science-based guidance and recommendations on protection from exposure to non-ionizing radiation; and establishes principles of non-ionizing radiation protection for the formulation of international and national radiation protection programs (ICNIRP, 2009).

In 2020, ICNIRP published the results of their comprehensive review of RF research that they conducted to update their 1998 exposure limits (ICNIRP, 1998, 2020a). The main objective of the report, *Guidelines for limiting exposure to electromagnetic fields (100 kHz to 300 GHz)* was to *"establish guidelines for limiting exposure to EMFs that will provide a high level of protection for all people against substantiated adverse health effects from exposures to both short- and long-term, continuous and discontinuous radiofrequency EMFs"* (ICNIRP, 2020a, p. 483). To set their guidelines, ICNIRP reviewed the scientific evidence for health effects of RF exposure, including reviews conducted by other health and scientific organizations (e.g., WHO, SCENIHR, SSM) and the published literature. Based on their review, ICNIRP concluded:

> *The only substantiated adverse health effects caused by exposure to radiofrequency EMFs are nerve stimulation, changes in the permeability of cell membranes, and effects due to temperature elevation. There is no evidence of adverse health effects at exposure levels below the restriction levels in the ICNIRP (1998) guidelines and no evidence of an interaction mechanism that would predict that adverse health effects could occur due to radiofrequency EMF exposure below those restriction levels* (ICNIRP, 2020a, p. 523).

Swedish Radiation Safety Authority

The SSM's Scientific Council on Electromagnetic Fields monitors current research on potential health risks in relation to exposure to electromagnetic fields and provides advice on assessing possible health risks (SSM, 2020). In a series of annual scientific reviews, the Scientific Council assesses relevant new data and puts these in the context of available information and present knowledge; the result is a gradually developing health risk assessment of exposure to electromagnetic fields.

The Scientific Council's most recent review on electromagnetic fields was published in 2020 and covered studies published from April 2018 up to and including December 2019. The report covered static, low-frequency, intermediate, and RF fields, and reviewed epidemiologic, human, and biological studies. The Scientific Council's overall conclusion was that *"[n]o new established causal relationships between [electromagnetic fields] exposure and health risks have been identified"* (p. 3) and that the results of the research reviewed *"give no reason to change any reference levels or recommendations in the field"* (p. 4). Specific conclusions related to the health outcomes (e.g., cancer, non-specific symptoms affecting well-being) and types of studies (e.g., epidemiologic studies, experimental studies) reviewed are summarized in the relevant sub-sections of Section 6 below.

U.S. Food and Drug Administration

The FDA, as part of their mission to protect and promote public health, *"monitors new scientific evidence that might impact our understanding of the safety profile of medical devices and radiation-emitting electronic products"* (FDA, 2020, p. 4). In 2020, the FDA released a technical report that summarized the agency's comprehensive review of the available scientific literature related to RF field exposure and human health published between January 2008 and August 2019. The agency's review focused on assessing *"any possible causal relationship between [RF] exposure and the formation of tumors"* (FDA, 2020, p. 4).

Overall, the agency concluded that *"[b]ased on the studies that are described in detail in this report, there is insufficient evidence to support a causal association between [radiofrequency radiation] exposure and tumorigenesis. There is a lack of clear dose response relationship, a*

lack of consistent findings or specificity, and a lack of biological mechanistic plausibility" (FDA, 2020, p. 6). Specific conclusions related to epidemiologic and experimental studies of cancer are summarized in the relevant sub-sections of Section 6 below.

6. Recent Research on Radiofrequency Fields

This section provides a summary of primary, peer-reviewed epidemiologic and experimental research (i.e., published articles that present the authors' original research and findings) published after the most recent comprehensive review—SCENIHR (2015)—was completed through March 2021.[15] The purpose of this update is to assess the impact of these recent studies on the conclusions about adverse effects of relatively low levels of RF energy on such outcomes as cancer and non-specific symptoms, in comparison to the conclusions expressed by the recent weight-of-evidence comprehensive reviews. It focuses on recent epidemiologic and *in vivo* studies of higher quality, regardless of direction of the results, and in general, notes the limitations of weaker studies, such as studies that are too small in size (i.e., too few people or laboratory animals), have not provided adequate controls, or use proxies or less reliable measures of individual exposure assessment. Studies that were identified in the scientific literature as being potentially relevant to the topics under review, but upon examination were of the poorest scientific quality and were not summarized, are listed at the end of the References in Section 8.

The studies summarized in this section examine both near-field exposures (i.e., those close to the body, such as mobile phones and other handsets) and far-field exposures (i.e., from sources located farther from the body such as radio and television transmitters, base stations, and wireless local area network [LAN] access points).[16] Exposures from advanced meters under typical use are in the far field (e.g., ISED, 2015).

[15] SCENIHR (2015) reviewed studies published between 2009 and June 2014, so some studies were included in this report that were published in 2014 after SCENIHR's cut-off date.

[16] Near field and far field are not defined solely by physical distance, but by the physical dimensions of the antenna and distance relative to the wavelength and the signal transmission. The distance to far field is typically close to the size of the wavelength.

Epidemiologic studies of cancer

Summary of prior reviews

Below are statements taken directly from the prior agency reviews discussed in Section 5 that capture the conclusions of national and international health, scientific, and government agencies regarding epidemiologic studies of RF field exposure and cancer.

Advisory Group on Non-Ionising Radiation

> Regarding cancer, AGNIR concluded, "*[t]he overall results of epidemiological studies to date do not demonstrate that the use of mobile phones causes brain tumours or any other type of malignancy, nor do they suggest causation is likely*" (AGNIR, 2012, p. 323). The agency also noted that there is "*very limited information on risks of childhood tumors*" (AGNIR, 2012, p. 323).

British Columbia Centre for Disease Control

> Regarding epidemiologic studies of cancer, the Toolkit published by the BCCDC noted that *"[m]ost of the original studies cited in the reviews did not find an increased risk of head and neck tumours associated with long-term use of [mobile] phones. Because of study design issues and positive findings that have not been replicated by other researchers, doubts remain about whether exposure to RF increases the risk of brain and other cancers of the head and neck"* (BCCDC, 2013, p. 4).
>
> In 2016 the Centre also published its *2016 Review: Radiofrequency and Health*, in which it described and compared RF field exposures from common devices, discussed research on potential health effects from RF field exposure, and ways in which members of the public, if they choose, can reduce their personal exposure, with priority given to personal mobile phone use, and cordless DECT handsets (BCCDC, 2016).
>
> *A major concern about the possible effects of exposure to RF is the development of cancer. Some epidemiologic studies have shown an association between long-term and frequent use of cell phones and specific types of brain tumours, especially ipsilateral tumours (located on the same side of the head as the phone*

> *was used) .... However, despite some positive findings, there has been a lack of consistency in epidemiological studies and meta-analyses as to whether long term and intensive cell phone use is a risk factor for the occurrence of brain tumours….The 'possibly carcinogenic to humans' designation by IARC was based solely on cell phone exposure and not from RF fields from other sources. Studies of cancers, other than brain tumours, and their association with cell phone use have mostly been negative.* (p. 9)

> *… the syndrome of electrohypersensitivity (EHS) has been attributed to exposures from wireless (cell) phone base stations and other RF-emitting devices. People having EHS suffer from symptoms affecting multiple body systems … In such [experimental] studies, subjects who suffer from EHS and healthy controls are assigned at random to either a 'treatment' group receiving a known exposure to RF signals (from cell phone base station antennae for example) or to a sham exposure group (non-exposure condition). A systematic review of the health effects of exposure to RF from mobile phone base stations concluded that most of the randomized laboratory studies had not detected associations between exposure and the appearance of acute symptoms during or shortly after exposure* (p. 12).

International Agency for Research on Cancer

As discussed in Section 4, the IARC expert working group classified RF fields as *"possibly carcinogenic to humans"* (group 2B). This conclusion was based on *"limited evidence of carcinogenicity"* for glioma and acoustic neuroma among mobile phone users, as reported in some epidemiologic studies, as well as "*limited evidence of carcinogenicity*" in experimental animals.

Royal Society of Canada

With respect to epidemiologic studies, the expert panel concluded:

> *[t]he epidemiological evidence is largely limited to a weak association of prolonged mobile phone use with increased incidence of glioma and acoustic*

neuroma. The epidemiological associations are not strong and the various studies are inconsistent with each other (RSC, 2014, p. 82).

Scientific Committee on Emerging and Newly Identified Health Risks

With respect to epidemiologic studies of cancer, SCENIHR concluded:

[o]verall, the epidemiological studies on mobile phone RF EMF exposure do not show an increased risk of brain tumours. Furthermore, they do not indicate an increased risk for other cancers of the head and neck region. Some studies raised questions regarding an increased risk of glioma and acoustic neuroma in heavy users of mobile phones. The results of cohort and incidence time trend studies do not support an increased risk for glioma while the possibility of an association with acoustic neuroma remains open. Epidemiological studies do not indicate increased risk for other malignant diseases, including childhood cancer (SCENIHR, 2015, p. 5).

SCENIHR further concluded:

[t]he totality of evidence of epidemiological studies weighs against cancer risks from base stations and broadcast antennas. In particular, large [epidemiologic] studies modelling RF exposure and investigating the risks of childhood cancers have not shown any association (SCENIHR, 2015, p. 84).

Health Council of the Netherlands

Overall, HCN concluded that it *"considers it unlikely that exposure to radiofrequency fields, which is associated with the use of mobile telephones, causes cancer"* (HCN, 2016, pp. 16-17). The Electromagnetic Fields Committee of the HCN that prepared the review stated, *"data from several epidemiological studies provide some indications for an association between long-term and/or intensive use of a mobile phone and an increased incidence of tumours in the brain and head and neck region,"* but noted, *"the evidence is weak and inconsistent,"* and that incidence data of the relevant cancers *"do not provide any support for such association"* (HCN, 2016, p. 53). The Committee

further noted that while it is *"possible that the exposure to RF EMF resulting from the use of mobile phones plays a role in an association,"* the Committee *"considers it unlikely that such exposure actually induces tumours"* (HCN, 2016, p. 53). The Committee distinguished its conclusions from IARC's findings that a causal interpretation of the relationship between RF field exposure and some cancers is credible, demonstrated by IARC's classification of "*limited evidence*" of carcinogenicity of RF radiation; the Committee stated that it "*considers a causal interpretation unlikely and feels that the combination of bias, confounding and chance might be an explanation for the observations*" (HCN, 2016, p. 53). The Committee acknowledged that the available epidemiologic data suffer from limitations in how the exposure assessments were conducted and noted that, with respect to mobile phone use, "*[t]here is still very limited information on really long-term effects in humans*" (HCN, 2016, p. 17).

International Commission on Non-Ionizing Radiation Protection

Based on their review of the literature, ICNIRP concluded:

> *[t]aken together, the epidemiological studies do not provide evidence of a carcinogenic effect of radiofrequency EMF exposure at levels encountered in the general population. In summary, no effects of radiofrequency EMFs on the induction or development of cancer have been substantiated* (ICNIRP, 2020a, p. 523).

Swedish Radiation Safety Authority

Regarding cancer from mobile phone use, the 2018 SSM report concluded, "*[t]he results were not entirely consistent but mainly point towards a lack of association*" (SSM, 2018, p. 9). The Council's conclusions in the 2019 and 2020 reports remained consistent with this assessment. The 2019 report concluded that studies on brain tumors "*do not give support to any causal relationship with radio wave exposure from mobile phone use*" and the 2020 report concluded, "*[o]verall, the age standardized incidence of brain tumours does not give support to any causal relationship with radio wave exposure from mobile phone use. If there is an impact, it appears to be so weak that it cannot be*

detected in incidence trend studies" (SSM, 2019, p. 3; SSM, 2020, p. 3). The 2020 report further concluded, "*[t]he results of the research review give no reason to change any reference levels or recommendations in the field*" (SSM, 2020, p. 4).

U.S. Food and Drug Administration

The FDA review concluded that the epidemiologic data reviewed *"continue to support the FDA's findings that there is no quantifiable causal link between [radiofrequency radiation] exposure and tumor formation"* (FDA, 2020, p. 87). The report also concluded:

> *… existing epidemiologic evidence is insufficient to suggest that use of cell phones can be considered as an independent etiological factor capable of influencing the incidence of intracranial and some other tumors in the general population. Existing epidemiological evidence indicates that if any risk does exist, it is extremely low compared to both the natural incidence of the disease and known controllable risk factors. As further research is conducted, we will continue to monitor the available information* (FDA, 2020, p. 87).

Studies of personal, partial-body exposure from mobile phones and hand-held radios

Epidemiologic studies on cancer and RF energy have been conducted since the 1970s on a variety of environmental and occupational sources; however, as the number of mobile phones in use has increased over time, research has focused primarily on users of mobile phones and on mobile phone base stations. Mobile phones transmit and receive RF signals and are tested before marketing to verify that they operate in compliance with national RF standards, which limit energy absorption for partial body exposure to the head and neck area where the phone is held.

Near-field exposure from a mobile phone is nevertheless higher that other environmental sources, even if a hands-free device is used, because of the close proximity of a mobile phone to the human body when the phone is on, even if not transmitting during a phone call. In particular, for brain tissues, the mobile phone used at the ear remains the main source of

exposure from commercial devices. Given the dose-response nature of effects on human health, mobile phone exposures represent the highest source of exposure for people in the general population, and therefore, the greatest potential for detecting an adverse response to RF field exposure. Exposures higher than field levels produced by mobile phones are possible in studies of laboratory animals, as described in the sub-section on laboratory studies below. It is important to note that most epidemiologic studies published to date cover the use of mobile phones before the use of texting, data services, and headphones became widespread circa 2011. Phone calls remain more important from an exposure perspective because calls typically result in higher exposure than texting or data services since these modes of operation generally have lower power output, potentially a lower duty cycle, and use the device at greater distance from the head and trunk than phone calls.

Additional epidemiologic studies of mobile phone use and hand-held, two-way personal radios and cancer have been published since the release of the 2015 SCENIHR report. Research on this topic still continues not because epidemiologic and experimental studies have found a problem with RF fields from mobile phones, but because the size of the population using mobile phones is so large, perhaps greater than 5 billion, research will continue to test hypotheses to make sure that even the smallest risk has not been overlooked.

The recent epidemiologic studies of mobile phones and cancer since the SCENIHR report are summarized below, and are grouped by study design (e.g., case-control/cohort studies, cancer incidence rate studies, survival studies, and meta-analyses).

Case-control and cohort studies

Recent studies of mobile phone use and cancer risk include several case-control studies. As discussed in Section 3, case-control studies assess whether cases (those diagnosed with a particular disease) had higher or more frequent exposure compared to the control population (a similar group of people, but without the disease). Case-control studies are well-suited for the analysis of diseases that are rare or have a long-latency period between exposure and disease development (such as many cancers); however, they have several limitations, including the potential for selection and recall bias. For example, the value of using interview or questionnaire responses to assess mobile phone use is constrained by the ability of the

participants to accurately remember and report past exposures and behaviors. In addition, one cohort study was conducted during this time period and is included in this section.

The following case-control and cohort studies have been published since the release of the 2015 SCENIHR report:

- **Moon et al. (2014)** investigated the relationship between vestibular schwannomas and mobile phone use in South Korea using two analyses. First, the authors conducted a case-control study, which included 199 cases, diagnosed between 1991 and 2010, and 238 controls, matched for age, gender, and general health conditions. Exposure was assessed using a telephone-administered questionnaire, which included questions on mobile phone use history, average call duration, and use of hands-free devices, among others. No associations were observed between vestibular schwannomas and duration (in years), time (in minutes per day), or cumulative hours of mobile phone use; the authors noted that the control group had, on average, slightly longer and more frequent mobile phone use compared to the cases. Second, the authors conducted a case-case analysis, in which only the case population was examined to assess potential differences in tumor growth or characteristics. Differences in average tumor volume were observed between regular and non-regular phone users and between heavy and light phone users. No significant differences were observed between long-term and short-term users. Based on this analysis, the authors concluded that *"there is a possibility that mobile phone use may affect existing tumors growth"* (p. 586). Limitations of the study include the exclusion of factors in the analyses that may confound the observed relationship between tumor size and mobile phone use, including the participants' age, and the use of self-reported questionnaire data on mobile phone use, the weaknesses of which are discussed above.

- **Shrestha et al. (2015)** conducted a case-control study to investigate the relationship between mobile phone use and pituitary tumor risk in Finland. The study included 80 cases, diagnosed between 2000 and 2002, who ranged in age from 20 to 69, and 240 controls, matched by age, sex, region of residence, and date of interview. Exposure was ascertained through an interview that captured participants' history of mobile phone use.

The authors reported that participants diagnosed with pituitary tumors were less likely to be regular mobile phone users compared to the controls (suggesting a lower risk of tumor development among regular versus never/non-regular phone users), although the association was not statistically significant. No associations between other aspects of mobile phone use and tumors were observed, including total duration of use and cumulative hours of use. The authors concluded that their study found *"no excess risk associated with self-reported short- or medium-term use of mobile phones,"* which they noted *"is consistent with most of the published studies"* (p. 1159). The authors cited the small number of participants who had used mobile phones for longer than 10 years (two cases, nine controls) as a cause for uncertainty regarding the risk associated with longer-term use. The small size of the overall population is a limitation of this study, as is the use of self-reported data on mobile phone use. The observed reduced risk associated with regular use of mobile phones indicates a potential for methodological or study design issues.

- **Carlberg and Hardell (2015) and Hardell and Carlberg (2015)** are two pooled analyses[17] that investigated the use of mobile and cordless phones and either meningioma (Carlberg and Hardell, 2015) or glioma (Hardell and Carlberg, 2015). Both studies pooled data from Swedish case-control studies previously published by the same authors (Hardell et al., 2006a, 2006b; Carlberg et al., 2013; Hardell et al., 2013). In Carlberg and Hardell (2015), no overall association was observed between meningioma risk and use of mobile or cordless phones, while increases were observed for some sub-group analyses. In Hardell and Carlberg (2015), statistically significant overall associations were observed between both mobile phone and cordless phone use and glioma. Neither publication, however, included data from any other published studies, and therefore do not represent a summary of the available studies in this area; thus, their value as pooled analyses is limited.

- **Yoon et al. (2015)** investigated the association between mobile phone use and glioma development in a case-control study in South Korea. The study included 285 cases,

[17] As noted previously, in a pooled analysis, the raw, individual-level data from the original studies is combined and analyzed together.

diagnosed between 2002 and 2007, who ranged in age from 15 to 69, and 285 controls. Mobile phone use was assessed using a self-administered questionnaire; information was obtained from family or friends, when necessary, if the study participants were too ill or had died. No statistically significant associations were observed between glioma risk and any of the exposure variables assessed (e.g., use of mobile phone [yes versus no], type of phone used, lifetime years of use before diagnosis, cumulative hours of use) in analyses adjusted for other potential risk factors, including age, hair dye use, and alcohol consumption. In a sub-analysis of ipsilateral users,[18] statistically non-significant associations were observed between some of the exposure variables and risk of glioma; however, a dose-response relationship generally was not observed. The authors concluded that their results *"do not support the hypothesis that the use of mobile phone increases the risk of glioma"* (p. 1). In addition to the previously discussed limitations of case-control studies, significant differences were reported between cases and controls in this study for several factors, including that the information from questionnaires from cases was obtained more often from family or friends (proxy respondents) than controls. The larger proportion of cases using a proxy respondent compared to controls created a greater potential for exposure misclassification within the case population.

- **Gao et al. (2019)** examined the association between use of hand-held, two-way terrestrial trunked radios (TETRA) that operate in the 380 to 400 Megahertz (MHz) frequency range and risk of cancer among police officers and staff in Great Britain. The study included 48,518 participants of the Airwave Health Monitoring Study, an occupational cohort study. Exposure was defined as the average monthly personal radio call duration during the year prior to study enrollment (median value=30.5 minutes). No association was observed between personal radio use and either risk of all cancers or risk of head and neck cancers. The doubling of monthly call duration among users was not associated with risk of all cancer and was associated with a weak statistically non-significant increase of head and neck cancers. Similar results were observed when all analyses were restricted to police officers only. The authors reported *"no evidence of*

[18] *Ipsilateral users* refer to subjects who predominantly use their mobile phone on the same side of the head as the tumor location; alternatively, *contralateral users* are subjects who predominantly use their mobile phone on the opposite side of the head as the tumor location.

association of personal radio use with cancer risk" (p. 1). Limitations of the study include the small number of cancers, particularly of the head and neck (45 total), and the lack of consideration of post-enrollment exposure, as participants' habits may change over time.

- **Vila et al. (2018)** examined the relationship between occupational RF fields and intermediate frequency exposure and brain tumors within the INTEROCC multinational case-control study. The study included 2,054 glioma cases and 1,924 meningioma cases, diagnosed between 2000 and 2004, and 5,601 controls. Participants' lifetime occupational history information was collected using a questionnaire. Average exposure levels were then assigned for each RF source reported by the participants (involving work with or nearby radars, transmitters, telecommunication antennas, equipment for medical diagnosis and treatment, among others) using a source-exposure matrix approach developed by the authors in which exposure values were assigned based on existing measurement data (*see* Vila et al., 2017); exposures from different-frequency RF sources were combined by weighing the calculated square ratios of RF electric fields and magnetic fields by the corresponding ICNIRP reference levels. Cumulative exposure levels were then calculated by incorporating frequency and duration of exposure. The authors found that approximately 10% of the study participants were occupationally exposed to RF fields. No statistically significant associations were observed between RF magnetic fields or electric fields and glioma or meningioma, regardless of the exposure time window investigated (1 to 4 years versus 5 to 9 years). The authors concluded that their findings "*do not support a positive association between occupational exposure to high-frequency EMF and either glioma or meningioma risk*" (p. 362). Limitations of the study include the small number of exposed and highly-exposed participants (i.e., >90th percentile of exposures), who comprised ~10% and <1% of the total population, respectively, and the absence of information on the specific frequency ranges of the equipment used. In addition, although the source-exposure matrix represents an improved exposure assessment approach, in that exposures can be assigned on an individual level, it is still preferable to collect personal exposure measurement data.

- **Luo et al. (2019)** conducted a case-control study to investigate the association between mobile phone use and thyroid cancer in Connecticut. The study included 462 cancer cases, diagnosed between 2010 and 2011, who ranged in age from 21 to 84, and 498 controls, matched by age. Mobile phone use was assessed through a questionnaire, completed during an in-person interview; questions inquired about frequency and duration of mobile phone use, and use of hands-free devices. No association was observed between mobile phone use (yes versus no) and risk of thyroid cancer. In sub-analyses, statistically non-significant associations were reported between thyroid microcarcinoma (tumor size ≤ 10 millimeters) and long-term (>15 years) and frequent use (>2 hours per day) of mobile phones; however, these associations did not follow a linear dose-response trend and were not observed for larger tumor sizes. The authors concluded that their study *"found no significant association between cell phone use and thyroid cancer"* (p. 2).

- **Luo et al. (2020)** conducted a follow-up of the same study population as in Luo et al. (2019), which examined whether genetic differences in the study participants impacted the relationship between mobile phone use and development of thyroid cancer. The authors reported statistically significant associations between mobile phone use and thyroid cancer for some genetic variations; however, the biological significance of these findings is not clear.

Summary of case-control and cohort studies

Case-control and cohort studies on mobile phone or two-way radio use published since the release of the 2015 SCENIHR report have not provided clear evidence to alter the conclusions of previous reviews by scientific and health agencies. The studies summarized in this section investigated the relationship between exposures to RF fields in both the general public and in the workplace and several cancer types, including glioma (Hardell and Carlberg, 2015; Vila et al., 2018; Yoon et al., 2015), meningioma (Carlberg and Hardell, 2015; Vila et al., 2018), thyroid cancer (Luo et al., 2019), pituitary tumors (Shrestha et al., 2015), and vestibular schwannomas (Moon et al., 2014), as well as general cancers of the head and neck region (Gao et al., 2019). None of the studies reporting original data identified statistically significant associations in the main analysis. Further, no consistent associations were observed in sub-

analyses performed across the studies, including those examining mobile phone use and tumor size, tumor volume, exposure duration, or exposure frequency. The only study to report an overall statistically significant association with exposure to RF fields from mobile phone use was the Hardell and Carlberg (2015) pooled study of glioma. The results of these recent studies are therefore consistent with the SSM's 2018 report, which concluded that findings from studies of mobile phone use and cancer "*were not entirely consistent but mainly point towards a lack of association*" (SSM, 2018, p. 9).

Cancer incidence rates over time

Since mobile phone use has become widespread and research has expanded to provide increased information, epidemiologists have examined time trends in rates of brain cancer and other tumors of the exposure areas in populations in which there is widespread use of mobile phones. If associations between mobile phone use and brain cancer exist (as suggested in previous publications by INTERPHONE 2010, 2011; Hardell et al., 2006a, 2006b; Hardell et al., 2011) and were to be causal, then given the near universal use of mobile phones in the population, we might expect to see some increase in annual rates of brain cancer, particularly 10 or more years after mobile use became widespread. The period of 10 years or more would allow for the development of tumors, and if the relationship were causal, would show increases in brain cancer rates as more people had a longer period of exposure through mobile phone use.

While examining time trends in cancer rates can be informative, this approach does have some limitations. Trends are generally examined on a large scale (i.e., regional or national level) and thus cannot account for individual-level data on confounding factors and conclusions about a given individual's level of risk cannot be estimated. This is related to the previously described concept of an "*ecological fallacy*," in which inferences about the nature of individuals (or risks) are inappropriately deduced from information gathered on the larger group to which those individuals belong. Because of these limitations, examination of cancer incidence trends over time alone is insufficient to assess whether a causal relationship exists between an exposure and disease.

Since the release of the 2015 SCENIHR report, a number of studies have reviewed national trends of brain cancer and some other cancers as the use of mobile phones has become almost

universal since 1982. Despite dramatic increased prevalence and use of mobile phones in all countries, none of these studies show an increase in the incidence in brain tumors that was attributed to mobile phone use.

In Sweden, the national cancer registry reports no increase in brain cancer, but one group of investigators claim that a subgroup of cases of unknown origin is underreported (Hardell and Carlberg, 2015, 2017). This same group reported inconsistent increases in incidence of thyroid tumors, that is, increases in women but not men (Carlberg et al., 2016, 2020). Another analysis of the incidence of brain cancer in Sweden reports that the overall incidence has been stable from 1982 to 2012, with small increases and decreases within some subgroups (Nilsson et al., 2019). Other investigators in New Zealand (Kim et al., 2015), Australia (Chapman et al., 2016; Karipidis et al., 2018), Japan (Sato et al., 2016, 2017), and Israel (Keinan-Boker et al., 2018) analyzed brain tumor incidence, but reported no change in incidence of brain tumors that appeared to be linked to increased mobile phone use. Philips et al. (2018a, 2018b) reported a rise in malignant brain cancer in the United Kingdom and cited possible causes as an improvement in diagnostic techniques, chance, and exposure to diagnostic computed tomography scans of the head. SSM (2019) in its review of Phillips et al. (2018a, 2018b), noted that the trend for malignant brain cancer did not match the more exponential increase in mobile phone use over the period studied. de Vocht (2019) specifically assessed whether temporal trends in malignant brain tumor incidence were associated with mobile phone use in England. No trend in incidence was traced to mobile phone use or the incidence of acoustic neuroma, meningioma, or benign neoplasms. In the United States and Finland the rates of malignant brain tumors were not reported to have changed during the period since mobile phone use became widespread (Li et al., 2018; Natukka et al., 2019). Davis et al. (2020) report that rates of malignant cancer in Canada and the United States are similar and the differences from rates in the United Kingdom *"is most likely due to factors related to improved data collection practices in surveillance systems … [and] the attribution of any environmental factor as an explanation for past incidence rate patterns is premature."* (pp. 302-303).

Survival Studies

The development of tumors is known to be advanced by exposure to certain chemicals described as tumor promoters. Two studies reviewed the survival of glioma patients in relation to their

mobile phone use pattern prior to diagnosis. One study of poor quality suggested a possible difference in outcome in some user groups; the other higher quality international study reported that regular mobile phone use had no effect on survival and other analyses showed statistically significant improvements in survival.

- **Carlberg and Hardell (2014)** analyzed the survival data of Swedish glioma patients included in their previous case-control studies (Hardell et al., 2006b, 2010, 2011, 2013) to assess whether mobile phone use had an impact on survival. The analysis included a total of 1,678 patients enrolled over the study periods of 1997 to 2003 and 2007 to 2009. Exposure was assessed at the time of enrollment using a mailed questionnaire on the use of mobile and cordless desktop phones. A large fraction of the cases originally enrolled, however, were excluded because they were deceased when the analysis of survival was started. Decreased survival was observed between users of mobile phones for more than 20 years and both glioma and astrocytoma grade IV cancers; similar results were observed for long-time users of all phone types combined and for long-time cordless phone use with astrocytoma grade IV only. Statistically significant associations were not observed for these cancers with hours of cumulative phone use, and a decreased risk (i.e., improved survival) was observed for low-grade astrocytoma and mobile phone use. The authors noted that data on wireless phone use after tumor diagnosis were not available, which is a significant limitation of this study.

- **Olsson et al. (2019)** examined whether mobile phone use prior to diagnosis was associated with survival among glioma patients. The study included 806 cases previously enrolled in the INTERPHONE study diagnosed between 2000 and 2002 and ranging in age from 20 to 69 at diagnosis (*see* Lahkola et al., 2007). Mobile phone use was assessed through a computer-assisted personal interview questionnaire. No indication of reduced survival was observed for patients reporting regular use of mobile phones compared to non-users or non-regular users; all observed statistically significant associations were negative, suggesting better survival for mobile phone users. Results were similar across cancer types (glioblastoma, and high- and low-grade gliomas). The authors reported associations between survival and other covariates, including age at diagnosis, tumor grade and location, and treatment.

Recent epidemiologic, cancer incidence, and survival studies of mobile phone use and cancer have not provided reliable evidence to alter the conclusions of the reviews conducted by scientific and health organizations. The overall findings from the studies summarized above are consistent with the conclusions of the 2015 SCENIHR report that *"[o]verall, the epidemiological studies on mobile phone RF EMF exposure do not show an increased risk of brain tumours … Some studies raised questions regarding an increased risk of glioma and acoustic neuroma in heavy users of mobile phones. The results of cohort and incidence time trend studies do not support an increased risk for glioma while the possibility of an association with acoustic neuroma remains open"* (SCENIHR, 2015, p. 5).

Meta-analyses of mobile phone use

In recent years, several meta-analyses have been conducted that examined the relationship between mobile phone use by individuals and brain cancer. As described in Section 3, meta-analyses, in which the results of multiple studies are aggregated into a larger virtual study, are a valuable analytical tool that increases the number of individuals in the analysis, allowing for a more robust and stable estimate of association. These analyses, however, typically combine data from studies with different study populations, exposure assessment methods, and disease definitions, so they can convey a false sense of consistency across studies if *only* the combined estimate of effect is considered. Rather, the factors that contribute to any heterogeneity between the studies should also be examined. Any differences between studies, including the populations studied, quality of the studies, measures of exposure and responses, modifying or confounding factors, and likelihood of publication of no-effect studies, can undermine confidence in a meta-analysis. In addition, meta-analyses are subject to the limitations of the study designs used in the primary analyses; the value of the meta-analyses results will be contingent on the quality of the underlying studies.

The following meta-analyses have been published since the release of the 2015 SCENIHR report.

- **Lagorio and Röösli (2014)** conducted a meta-analysis of 29 studies, all published by 2012, that examined intracranial tumors and mobile phone use. The studies were classified into five groups, based on geographical region or study population. For all

groups, negative associations were observed between meningioma and regular use of mobile phone, and statistically non-significant marginal associations were observed with long-term mobile phone use (≥ 10 years). Larger, but statistically non-significant, positive associations were observed between long-term phone use and both glioma and acoustic neuroma. The authors reported high heterogeneity between studies and noted that the primary differences appeared to be methodological (e.g., study design, case definition, exposure assessment approach). The authors noted that *"[s]ummary risk estimates based on heterogeneous findings should not be over-interpreted"* and that "*[o]verall, the results of our study detract from the hypothesis that mobile phone use affects the occurrence of intracranial tumors*" (pp. 79, 88).

- **Wang and Guo (2016)** conducted a meta-analysis of 11 epidemiologic studies, published between 2001 and 2008, to evaluate the association between mobile phone use and glioma risk. The analysis included 5,460 cases and 12,603 controls. No overall association was observed between mobile phone use and glioma risk. In a sub-analysis, a statistically significant association was observed between mobile phone use of more than 5 years and glioma risk. The authors, however, noted significant heterogeneity between studies for both the main and sub-analyses and described the observed association with longer-term phone use as "*weak*" (p. 3).

- **Bortkiewsicz et al. (2017)** conducted a meta-analysis of 24 case-control studies that investigated the association between mobile phone use and brain cancer. The analysis included 26,846 cases and 50,013 controls. No associations were reported between overall mobile phone use and any tumor types, including intracranial tumors, brain cancer, glioma, meningioma, and acoustic neuroma. In sub-analyses, statistically-significant associations were observed between intracranial tumor (all types) and both long-term mobile phone use (> 10 years) and ipsilateral mobile phone use. For nearly all analyses, the authors observed heterogeneity between studies.

- **de Siqueira et al. (2017)** conducted a meta-analysis of three case-control studies of mobile phone use and parotid gland tumor development. The analysis included 768 cases and 4,319 controls. A statistically-significant association was observed between

mobile phone use and presence of salivary gland tumors. A significant limitation of this analysis is the small number of studies included, which prevented exploration of sensitivity or sub-group analyses. In addition, as noted by the authors, the studies in the meta-analysis included both benign and malignant tumors and did not make a distinction between them, even though the clinical behavior and genetic profiles of the tumors differ. Because of the limitations, the authors warned that their findings "*need to be read and interpreted with caution*" (p. 2).

- **Prasad et al. (2017)** conducted a meta-analysis on case-control studies published between 1966 and 2016 to investigate whether differences in study quality and funding source explained the variation in results across studies. In total, 22 studies were identified; however, 8 of the studies were part of the same large project (the INTERPHONE study) and thus were not included in the meta-analysis. In an analysis of the remaining 14 studies, no overall association was observed between brain tumor development and mobile phone use; a statistically significant association was observed in a sub-analysis of 7 of the 14 studies that included data on long-term (>10 years) mobile phone use. The authors also examined the results of each of the 14 individual studies and reported that statistically significant associations were more likely to be observed in studies of higher quality. This conclusion is not well-supported by the data however, as studies of higher quality did not consistently report statistically significant associations (only two of the six studies of higher quality reported significant associations) and three of the six studies reported no association at all. The authors also reported that government-funded studies generally received a higher study quality score compared to industry- or mixed-funded studies.

- **Yang et al. (2017)** performed a meta-analysis of 11 studies investigating the potential association between mobile phone use and glioma of the brain. The analysis included 6,028 cases and 11,488 controls. The authors looked at three factors: mobile phone duration (short-term versus long-term), partial laterality (preferred head side use location), and tumor grade. No association was observed between overall mobile phone use and glioma risk. In sub-analyses, statistically significant associations were observed between glioma and long-term (≥10 years) phone use and long-term ipsilateral use. A

statistically significant association was also observed between long-term use and low-grade gliomas; no associations were observed for all other combinations of use duration and head side/tumor grade. The authors concluded that their results suggest that long-term mobile phone use may be associated with an increased risk of glioma but noted that "*current evidence is of poor quality and limited quantity*" and that "*substantial*" heterogeneity was observed between studies (pp. 2, 6).

- **Wang et al. (2018)** conducted a meta-analysis of 10 epidemiologic studies to examine the relationship between wireless phone use and risk of adult glioma. No association was observed between adult gliomas and ever use of wireless phones or in subgroup analyses of tumor location or head side use. A statistically significant association was observed with long-term users (≥10 years). High heterogeneity was observed between studies and the authors noted "*inconsistencies among the studies*" (p. e634). The authors concluded that ever use of wireless phones "*was not significantly associated with risk of adult glioma, but there could be increased risk in long-term users*" (p. e629).

- **Röösli et al. (2019)** performed a meta-analysis of 45 epidemiologic studies investigating the relationship between mobile phone use and tumors of the brain, head, and neck. No statistically significant overall associations were observed between ever users or long-term users (>10 years) of mobile phones and glioma, meningioma, acoustic neuroma, pituitary tumors, or salivary tumors. The results were consistent across several sensitivity analyses conducted to determine the potential impact of any one study on the overall associations. The authors reported "*considerable*" heterogeneity across studies of glioma and acoustic neuroma and noted differences in the strength of the associations by research group (p. 231).

- **Chen et al. (2020)** conducted a meta-analysis of eight epidemiologic studies published up to June 2018 to investigate the relationship between users of wireless phones and meningioma in adults. A negative association was observed between adult meningioma and both ever users of wireless phones and short-term (<5 years) users. No association was observed between adult meningioma risk and mid-term (5 to 10 years) or long-term

(>10 years) users or with ipsilateral or contralateral use. The authors reported no heterogeneity across the studies that would affect this analysis.

- **Choi et al. (2020)** performed a meta-analysis of 46 case-control studies published up to July 2018 to examine whether cellular phone use was associated with tumor development. The majority of the studies (75%) examined brain tumor outcomes; other tumors investigated included tumors of the head and neck and hematologic malignancies. No association was reported between regular cellphone use and tumor development, compared to never or rarely having used a cellular phone. In subgroup analyses, a statistically significant association was reported between cellular phone use and tumor development in studies of high methodological quality, as adjudged by the authors using two published quality assessment tools, and in studies that used blinding at interviews to ascertain exposure (e.g., researchers were not aware of whether participants were cases or controls when interviewing them); an association was also observed between cellular phone use with cumulative call time of greater than 1,000 hours and tumor development. The authors also reported differences in the associations with tumors in subgroup analyses by research group.

- **Shih et al. (2021a)** conducted a meta-analysis of eight epidemiologic studies published up to May 2020 to investigate the association between exposure to RF fields and breast cancer. The authors reported a statistically signification overall association between RF field exposure and breast cancer development; subgroup analyses also reported a significant association among participants age 50 or older. A statistically signification association was observed between the use of mobile phones and breast cancer development; however, the analysis was based on only two studies. No association was reported for occupational exposure to RF fields. A significant limitation of this analysis is the authors' selection of several inappropriate studies for use in the meta-analysis. Two of the eight studies focused on 50-Hz magnetic-field exposure, which is not relevant to RF exposure, and one study focused on male breast cancer, while all the others investigated female breast cancer risk. As a result of this severe limitation, the journal issued a retraction notice in March 2021 "*on account of the number of uncertainties*" with the authors' methodology and study selection (Shih et al., 2021b)

Summary of meta-analyses

Meta-analyses of cancer and mobile phone use published since the release of the 2015 SCENIHR report have not provided clear evidence to alter the conclusions of previous reviews by scientific and health agencies. No overall associations were reported between mobile phone use and several types of brain cancer, including glioma (Wang and Guo, 2016; Bortkiewsicz et al., 2017; Yang et al., 2017; Wang et al., 2018), meningioma (Lagorio and Röösli, 2014; Bortkiewsicz et al., 2017), and acoustic neuroma (Bortkiewsicz et al., 2017). Chen et al. (2020) reported an overall negative association with meningioma. In sub-analyses performed in some of the studies, statistically significant associations were reported between long-term (≥5 or 10 years) mobile phone use and brain cancer. As noted previously, sub-group analyses should be interpreted with extra caution, as the typically smaller sample sizes may decrease the likelihood that a statistically significant finding reflects the true association between exposure and outcome rather than due to error or chance. In their 2016 report, the HCN states "*[s]ome epidemiological studies provide indications for an association between long-term or intensive use of a mobile telephone and an increased risk of tumours in the brain or head and neck region. However, the studies are not consistent and of varying quality... The final conclusion is, that overall the evidence for an association is weak*" (pp. 33-34). The HCN went on to conclude the following:

> *[t]he Committee feels that it is not possible to state that there is a proven association between long-term and frequent use of a mobile telephone and an increase in the risk of tumours in the brain and head and neck region in humans. Based on the strength of the evidence it can only be concluded that such an association cannot be excluded. The Committee considers it unlikely that exposure to radiofrequency fields, which is associated with the use of mobile telephones, causes cancer* (pp. 16-17).

Exposure from distant radiofrequency sources

Epidemiologic studies also examined RF sources other than mobile phones, including mobile phone base stations, AM and FM radio transmitters, television broadcast transmitters, and Wi-Fi. These sources are typically weaker contributors to individual exposure compared to mobile phone use. Radar, AM/FM radio transmitters, and television broadcast transmitters are far more

powerful than mobile phone base stations, but like all types of electromagnetic fields, the strength of the RF signal diminishes rapidly with distance from the source. The proposed FEI network base stations are similar to mobile phone base stations in that they also are low-exposure sources in communities due to generally being located high above ground. Occupational studies focus on occupations with the potential for higher exposure to RF energy, like radar operators and workers at a mobile phone manufacturing facility.

These environmental exposure sources pose difficulties for individual exposure in epidemiological studies because people generally do not spend all their time in one location (i.e., at home), so a valid measurement of average exposure is difficult to determine.

The following epidemiologic studies on exposures from sources other than personal mobile phone use have been published since the release of the 2015 SCENIHR report.

- **Dabouis et al. (2016)** conducted a cohort study on occupational radar exposure in the French Navy. The study included 39,850 military personnel who served on Navy ships during the period from 1975 to 1995; exclusion criteria included female military personnel, personnel of the flotilla, and those who had spent fewer than 200 days on board. Exposure was assessed by electric-field measurements taken in locations where radar exposure levels were expected to be high based on numerical calculations; the mean and peak values were used to represent temporal measurements. The study population was divided into two groups: the "*radar group*" of employees whose occupations took place above the main deck, and the "*control group*" of employees whose occupations were situated under the main deck and who were considered unexposed. Compared to the unexposed group, the all-cause and cancer mortality rates among the radar group were not significantly different, irrespective of time; no effect of age on risk of cancer death was observed. A statistically significant lower mortality rate from respiratory system disease was observed for the radar group compared to the unexposed group. The authors concluded that the results *"did not suggest an increased health risk for military personnel exposed to higher levels of EMF, in particular microwaves emitted by radars and HF [high frequency] communication emitters"* (p. 8). Limitations of the study include the significant portion of missing causes of death (43%);

a lack of smoking data, which is a potential confounding factor; and the use of broad exposure groups that do not account for variability in exposure across or within jobs and tasks. As noted in the study, the use of personal dosimeters would greatly improve the exposure assessment approach.

- **Satta et al. (2018)** conducted a case-control study to examine the relationship between environmental RF field exposure and risk of lymphoma in Italy. The study included 322 cases, diagnosed between 1998 and 2004 and ranging in age from 25 to 74 years, and 444 controls. Exposure was assessed using several methods. First, the study participants responded to a questionnaire on the self-reported perceived distance of the participants' three longest-held residences from fixed radio-television transmitters and mobile phone base stations. Second, the authors obtained spatial data on the location of mobile phone base stations in relation to the participants' geocoded addresses and estimated the RF intensity for all addresses within a 500-meter radius (spatial coordinates for transmitters were not available). Third, the authors collected RF measurements at the door of the longest-held addresses within a 250-meter radius of the base stations. Statistically significant associations were observed between self-reported residential distances within 50 meters to fixed radio-television transmitters and lymphoma, both overall and by one of three sub-types. No associations were observed between mobile phone base stations and self-reported distance, geocoded distance, or estimated RF intensity levels. RF measurement levels were similar between cases and controls. The authors concluded that their results *"do not support the hypothesis of an association between environmental exposure to RF-EMF emissions from mobile phone base stations and risk of developing lymphomas"* (p. 6). The small sample sizes, particularly in subtype analyses and in the highest exposure category, is a limitation of the study. In addition, the exposure assessment approaches used in the study have associated weaknesses. The self-reported distance data are subject to bias; in fact, cases were demonstrated to overestimate their residential distance from mobile phone base stations more often compared to the control population. Geocoding of residential distances can be greatly impacted by potential confounding variables; in this study, the authors adjusted only for vehicle traffic intensity and education. Finally, the RF spot

measurements taken at the residences do not necessarily reflect past exposures or changes in exposure over time.

- **González-Rubio et al. (2017)** conducted an ecological study analyzing the relationship between environmental exposure to RF fields and incidence of lymphomas and brain tumors inside the city of Albacete, Spain, in 2015. The authors divided the geographical areas of the city into 110 micro-environments; exposure to 14 frequency bands of RF fields (ranging from 88 MHz to 6 GHz) were then measured within each area using a personal monitoring device transported around in a bicycle. Within each micro-environment, the average RF field exposure levels and the incidence of various cancers (meningioma, glioma, lymphoma, all brain tumors, and total tumors) were then assessed. The authors concluded that the cancer cases *"have a random spatial distribution"* inside the city and that RF field exposure *"shows little correlation with the incidence of the studied tumors"* (pp. 834, 842). They also noted that *"[n]one of the administrative regions exceeded the legal limit established for the urban zone"* (p. 839). This study has several limitations. The measurements collected around the city do not accurately represent the residents' individual exposure levels inside their homes and other buildings; a small number of cancer cases were included (95 total cases identified); residents may have migrated in and out of the city during the study period; and with any ecological study, it is not possible to assess the potential correlation between the exposure and disease of interest.

Regarding distant RF sources, SCENIHR in 2015 reported that:

> *The totality of evidence of epidemiological studies weighs against cancer risks from base stations and broadcast antennas. In particular, large case-control studies modelling RF exposure and investigating the risks of childhood cancers have not shown any association* (2015, p. 84).

A similar conclusion applies to the studies of radar, mobile base stations, and other fixed transmitters evaluated above that did not report associations of these environmental sources with cancer. The BCCDC confirms that the exposures from such sources are quite low:

> *In British Columbia, a series of power density measurements were conducted in 2004 by a BCCDC team at 20 different sites across the province using a dedicated RF survey unit mounted on a vehicle. The power density readings collected in the survey showed that the base stations were largely compliant with Safety Code 6 (SC6) guidelines with exposures 3000 to 1,000,000 times lower than SC6 limits for uncontrolled (public non-workplace) environments* (BCCDC, 2016, p. 5).

Summary of epidemiologic studies of cancer

In recent years, research has focused predominantly on exposure from mobile phones due to the close proximity of the phone to the human body when in use and the increasing number of mobile phones in use worldwide. Recent epidemiologic studies of RF field exposure from mobile phones provide little new evidence in support of an association between exposure and cancer development. As noted previously, these studies have not provided reliable evidence to alter the conclusion of the 2015 SCENIHR report, which states,

> *Overall, the epidemiological studies on mobile phone RF EMF exposure do not show an increased risk of brain tumours. Furthermore, they do not indicate an increased risk for other cancers of the head and neck region. Some studies raised questions regarding an increased risk of glioma and acoustic neuroma in heavy users of mobile phones. The results of cohort and incidence time trend studies do not support an increased risk for glioma while the possibility of an association with acoustic neuroma remains open. Epidemiological studies do not indicate increased risk for other malignant diseases, including childhood cancer"* (SCENIHR, 2015, p. 5).

When evaluated against established scientific criteria for assessing causality (i.e., the Bradford-Hill criteria), the reviewed studies did not provide consistent evidence in support of a causal relationship between RF field exposure and any of the examined cancer outcomes, including brain tumors. Most of the recently-published case-control studies related to exposure from mobile phones reported no statistically significant positive associations between mobile phone use and cancer. Similarly, statistically significant associations were not reported in the main

analyses of meta-analyses of mobile phone use and several types of brain cancer. As noted in the National Research Council's (NRC) *Reference Manual on Scientific Evidence*, *"[a]lthough lower [associations] can reflect causality, the epidemiologist will scrutinize such associations more closely because there is a greater chance that they are the result of uncontrolled confounding or biases"* (NRC, 2011, p. 602). Further, the reviewed studies demonstrated an absence of a consistent dose-response relationship (i.e., greater exposure leads to an increased likelihood of disease occurrence) between mobile phone use and cancer development. For most human health assessments, the presence of a dose-response relationship is considered *"strong ... evidence that the relationship between an agent and disease is causal"* (NRC, 2011, p. 603). An additional criterion for evidence of causality is the existence of a plausible biological mechanism that is consistent with existing biological and medical knowledge; as noted by the NRC, "*[w]hen biological plausibility exists, it lends credence to an inference of causality*" (NRC, 2011, p. 604). The lack of biological plausibility between mobile phone use and cancer will be discussed in the following section on *in vivo* studies relevant to cancer. As noted in Section 3, while none of the criteria alone are absolutely necessary to establish causality, the more the epidemiologic evidence meets these guidelines, the more convincing the evidence is for a potential causal interpretation. Indeed, the reverse also holds true—the less the epidemiologic evidence meets these guidelines, the less convincing the evidence for a causal relationship.

Several recent studies examining exposure from far-field RF sources also have been conducted. While considerably fewer studies have been published on these sources compared to studies of mobile phone use (which is consistent with mobile phones being considered the predominant source of exposure for most of the population), none of the recently published studies concluded that exposure from distant sources of RF fields is associated with cancer. This includes a cohort study on occupational exposure of military personnel to radar, which reported no significant differences in all-cause or cancer mortality rates between the exposed and unexposed workers, and a case-control study of environmental RF field exposure, which reported no associations between lymphoma and exposure from mobile phone base stations using multiple exposure metrics (e.g., self-reported distance, estimated intensity levels). The findings of these studies are consistent with the SCENIHR's conclusion that "*[t]he totality of evidence of epidemiological studies weighs against cancer risks from base stations and broadcast antennas.*

In particular, large [epidemiologic] studies modelling RF exposure and investigating the risks of childhood cancers have not shown any association" (SCENIHR, 2015, p. 84).

In addition, studies examining cancer incidence rates over time did not observe correlations between cancer rates and trends in mobile phone use over the same period. This is consistent with the trends observed in Canada, and in British Columbia specifically. The Canadian Cancer Society's 2019 *Canadian Cancer Statistics* publication reported an annual average decrease of 0.6% in the overall brain and central nervous system cancer incidence rate for the period of 1984 to 2015; a larger decrease (2.9%) was observed when focusing on recent years only (2011 to 2015).[19] During this same period, beginning in the early 2000s, the use of mobile phones in Canada grew significantly; in 2017, there were over 31 million mobile phone subscribers, a 3.1% increase from the previous year.[20] Further, the 2016 report by the BCCDC states that from 1990 to 2009, the age-adjusted brain cancer incidence rates in British Columbia were "*fairly flat*" among females and "*slightly decreasing*" among males (BCCDC, 2016, p. 9). Research investigating associations between estimates of exposure to distant RF sources and cancer also reported no consistent positive associations and provided no evidence for a causal relationship between RF exposure and cancer. It is important to note that RF exposures from the FEI base stations and mobile phone antennas would be far lower than exposure from mobile phones and hand-held communicators that are held close to the body during use.

In summary, the results of recent epidemiologic studies do not change the classification of the epidemiologic data as *limited*, as determined by IARC, and are consistent with the conclusions of recent agency reviews (e.g., SCENIHR, 2015; SSM, 2018, 2019, 2020) that the evidence does not confirm that RF fields below scientifically-based exposure guidelines cause or contribute to the development of cancer.

In vivo studies relevant to cancer

Human health risk assessments are not based exclusively on epidemiologic studies; experimental studies in animals and humans (i.e., *in vivo*) also play a key role (Health Canada, 2000; WHO, 2010; USEPA, 2002, 2005). *In vivo* experimental studies are particularly

[19] cancer.ca/Canadian-Cancer-Statistics-2019-EN Accessed April 2021.
[20] https://crtc.gc.ca/eng/publications/reports/policymonitoring/2018/cmr3d.htm Accessed April 2021.

important to assess the potential role of magnetic fields in carcinogenic processes (IARC, 1992, 2002). Research on animals has burgeoned over the past few decades as researchers have sought to determine if the results of *in vivo* studies provide some biological plausibility for statistical associations reported in some epidemiologic studies between RF field exposure from mobile phones and cancer of the head and neck.

There are two types of *in vivo* studies. The first type, often described as cancer bioassay studies, focuses on the identification of an adverse effect (i.e., the existence of a hazard) by exposing animals to the highest tolerated doses of RF energy over most of their lifetime. The second type focuses on biological measures that serve as potential indicators of carcinogenic processes, which most often focus on changes that might be revealed during short-term exposures. Since genetic mutations to chromosomes and DNA are known to play a role in the development of cancers in humans and animals, research on the potential genotoxic effects of magnetic fields has been of interest for decades.

Since the most recent comprehensive assessment of RF health research was conducted by SCENIHR in 2015, more recent *in vivo* studies that evaluated the incidence of cancer in exposed and control animals and studies of genetic biomarkers in humans and animals were included in this review.

This update first summarizes the conclusions of the SCENIHR review and prior assessments, and then summarizes the results of recent studies of long-term RF exposure of animals on the development of tumors. Then multiple observational, cross-sectional studies of the distribution of measures of chromosomal or DNA damage in human subjects are reviewed, followed by an assessment of experimental studies in which DNA and chromosome damage markers were measured in animals exposed to RF field or sham-exposure control conditions.

Summary of prior reviews

Below are quotes taken directly from prior reviews that capture the conclusions of national and international health, scientific and government agencies regarding experimental studies of RF field exposure and cancer. In aggregate, these reviews concluded that evidence from experimental studies does not support an effect of RF field exposure on carcinogenic processes.

Advisory Group on Non-Ionising Radiation

Regarding experimental studies, AGNIR concluded that *"[r]ecent animal studies have produced no consistent evidence that RF fields cause or increase the risk of cancer"* and that the studies *"have produced no compelling evidence that RF fields are genotoxic or cause robust carcinogenic effects with exposures below guideline values"* (AGNIR, 2012, p. 172).

British Columbia Centre for Disease Control

Long-term bioassays, designed to determine whether RF exposure either alone or in conjunction with known mutagens can initiate or promote development of cancer in animals, have been uniformly negative. Studies of RF fields and toxicological effects such as DNA damage, micronucleus formation, apoptosis, reactive oxygen species, and gene expression changes have been inconsistent and the results have been contradictory. Positive studies have proven difficult to replicate. There is no consistent evidence that exposure to RF produces biological effects in animal central nervous systems. Recent investigations have been unable to confirm that RF exposure alters blood-brain barrier permeability; however, other aspects of brain physiology are less well studied. Behavioural investigations of the role of RF exposure on animal learning and cognitive function are mixed. Immune function studies have been mostly negative, although most of the studies to date have been conducted in adult animals. Effects of RF exposure on endocrine function, particularly on melatonin levels, have been negative, as have been studies on reproductive function in female animals. Overall, the research studies to date have not provided convincing evidence that RF-field exposure produces adverse biological effects in animals (BCCDC, 2013, p. 2).[21]

[21] BCCDC did not review animal studies in their 2016 report.

International Agency for Research on Cancer

A review of experimental studies of RF field exposures in rats and mice between 1982 and 2011 was reported by the IARC in 2013. The conclusion was that, in aggregate, the studies provided "*limited evidence in experimental animals for the carcinogenicity of radiofrequency radiation*" (IARC, 2013).

Royal Society of Canada

As in earlier studies, the post-2009 studies contain a mix of reports indicating possible genotoxic and epigenetic activity and others showing no evidence of either. There is a wide mix of endpoints (many of which are indirect) and exposure conditions (e.g., different frequencies, modulation schemes, power, exposure duration). There are also methodological weaknesses in many studies (e.g., lack of dosimetry, lack of sham-exposed controls, non-standard assays) ... (RSC, 2014, p. 80).

Animal studies of RF energy and cancer have provided no consistent evidence that exposure to RF energy below SC6 (2013) limits causes or promotes cancer (RSC, 2014, p. 82).

Scientific Committee on Emerging and Newly Identified Health Risks

An updated review of these and some newer studies and analyses prompted SCENIHR (2015) to conclude "*[o]verall, because a considerable number of well-performed studies using a wide variety of animal models have been mostly negative in outcome, the animal studies are considered to provide strong evidence for the absence of an effect [i.e., carcinogenic or other adverse effect]*" (SCENIHR, 2015, p. 86).

Health Council of the Netherlands

... the Committee ... conclude[d] that, on the basis of the results of the animal studies presented in this systematic review, it is highly unlikely that long-term continuous or repeated exposure to RF EMF may have initiating or promoting effects on the development of cancer (HCN, 2014, p. 20).

Overall, the studies discussed in this report show that no effects of long-term exposure to RF EMF on the development or growth of tumours in general, or on specific types of tumours, have been demonstrated in rodents. The findings of the few studies that did indicate effects have either not been observed in repetition studies, or might be explained by thermal effects. It is also possible that they were chance findings. This can also only be the conclusion for the few observed protective effects of RF exposure (HCN, 2014, p. 50).

International Commission on Non-Ionizing Radiation Protection

A few animal studies on the effect of radiofrequency EMF exposure on carcinogenesis have reported positive effects, but, in general, these studies either have shortcomings in methodology or dosimetry, or the results have not been verified in independent studies. Indeed, the great majority of studies have reported a lack of carcinogenic effects in a variety of animal models (ICNIRP, 2020a, p. 522).

U.S. Food and Drug Administration

The in vivo studies conducted between January 1, 2008 and August 1, 2018 and [reviewed by the FDA] have contributed to our collective understanding of the potential effects of [radiofrequency radiation] on mammals. Overall, based on certain limitations, these studies have not produced any clear evidence that [radiofrequency] exposure has any tumorigenic effect. In some cases, the authors of these studies suggested the need for more research based on the reported results. Other authors stated that [radiofrequency] exposure does not result in tumor-initiating or -promoting effects (FDA, 2020, p. 33).

... due to the critical limitations of in vivo studies in assessing the effects of [radiofrequency radiation] exposure to humans (e.g., whole-body [radiofrequency] exposure), we cannot draw conclusions about the impact of such exposure to humans based on these in vivo animal studies. The results

from such studies should not be applied to human cell phone usage as further research is needed (FDA, 2020, p. 34).

Human biomarker studies

Human biomarker studies are mini-epidemiology studies in which biological measurements are made on small groups of persons to determine if they differ on some particular measurement that plausibly may be related to the topic of interest. In the studies reviewed here, such measurements were made of DNA and chromosomes extracted from human cells. If not repaired, damage to DNA might result in a mutation that under specific conditions might develop into cancer, which explains the potential relevance of these studies to cancer processes.

The DNA of every cell of the human body is damaged 10,000 times per day by ongoing cellular processes; in rats and mice this rate is 5 to 10 times higher (Ames et al., 1993). In most cases, multiple other cell processes work to effectively repair this damage, or if severe, remove the damaged cell by programmed cell death. If not repaired properly, a mutation may result that, dependent upon other conditions, could lead to cancer. Hence, in the evaluation of biological processes that might lead to cancer, scientists have used a variety of tests to quantify levels of damage to DNA and chromosomes that contain DNA.

Since the SCENIHR review, 12 cross-sectional studies of human subjects have been published on the cellular characteristics and circumstances of populations that differ in terms of their estimated or suspected exposures to mobile phone antennas. As a matter of logic and epidemiological science, because the studies cannot determine whether a measured or reported biological or health outcome occurred before, during, or after RF field exposure (NRC, 2011, pp. 560-561), these studies, like other cross-sectional epidemiologic studies of other exposures or RF fields, cannot establish a cause-and-effect relationship. Although cross-sectional studies cannot establish causation, such studies are initiated to test preliminary hypotheses and can be performed at reasonably low cost.

The focus of these biomarker studies was to determine if one-time samples of human cells analyzed for single strand breaks (SSB) in DNA (as detected by the alkaline comet assay)[22] or the presence of micronuclei (MN) chromosome fragments in blood cells differed between groups of apparently similar persons who varied with respect to their estimated RF field exposure. It is important to understand that even though these test methods are referred to as genetic tests, their ability to detect past events is quite limited. These tests are only capable of detecting effects on cells that may have occurred within about 6 hours before collection of the samples for comet assay analysis or 3 days before the collection of samples for MN analysis (Singh et al., 1988; OECD, 2015).

- **Daroit et al. (2015)** reported a cross-sectional analysis of a convenience sample of 20 men and 40 women between the ages of 19 and 33 years recruited from the School of Dentistry in Alegre, Brazil for their use of mobile phones and other demographic data and obtained samples of oral mucosal epithelial cells by scraping the lower lip, border of the tongue, and floor of the mouth. Potential subjects who reported themselves as smokers, having more than two drinks per week, or who displayed oral lesions upon examination were excluded. The cells from each site were spread on slides (1 slide per site) and 1,000 cells on each slide were examined for cytopathological abnormalities after staining for the DNA of cells (Feulgen reaction). The samples were examined under the microscope by one observer who was blinded and who had a reported inter-rater reliability correlation compared with a more experienced investigator characterized by an interclass correlation coefficient > 0.75. As the sites from the lip and tongue are likely to incur damage from sunlight or other non-specific damage, these data are not reviewed here. The samples obtained from the floor of the mouth are more similar to the cheek samples analyzed in other comparable studies and so those measurements are described below. The primary result was that the mean number of MN in cells from the floor of the mouth was not statistically higher in persons using mobile phones more than 60 minutes per week compared to persons using mobile phones less than 60 minutes

[22] The DNA from single cells are applied to an agarose gel, and when a voltage is applied to the gel, single-strands are distinguished from double-stranded DNA as they migrate away from the undamaged DNA, forming a structure that resembles that of a comet. The double-strand DNA is contained in the head of the comet while the single-strand DNA and fragments (SSBs) are contained in the tail of the comet. The percentage of DNA in the tail is considered to be proportional to the percentage of SSBs that occurred in a particular cell.

each week. When the MN from all sites were analyzed together, the mean MN levels were marginally higher in the group with self-reported mobile phone use more than 60 hours per week (p=0.048), largely because of the inclusion of increased MN observed in samples from the lower lip. The authors reported no significant statistical association between the years of cell phone use and mean value of MN at any of the three oral sites; however, the statistical test used compared median values, not mean values. It also should be noted that the statistical analysis erroneously assumed that the measurements at the three sites were independent of one another, although they cannot be independent because the three samples were obtained from the same person. In addition, it was not demonstrated that the distributions of the MN values were sufficiently similar to conclude that the medians were different or that some other difference had been detected.

- **Gandhi et al. (2015)** carried out a cross-sectional study that describes the results of measurements of DNA damage in persons in the city of Amnistar, India, living in the vicinity of a specific mobile telephone base station (sample group, n=63),[23] and those living in a less densely populated area, presumably in a zone outside the city without a mobile phone tower (control group, n=28), in the period from 2007 to 2009. Finger-prick blood samples were collected and later analyzed for fragmentation of DNA strands in white blood cells as measured by the alkaline comet assay. This assay is used to evaluate transient damage to DNA that may have occurred in the few hours prior to sample collection that had not yet been repaired.

  The authors reported a 4.5-fold increase in the mean tail migration length and a 2.5-fold increase in a calculated "*damage index*" (which was dependent in part on measured migration length between those in the sample and control groups). The DNA damage measurements in the sample group did not vary appreciably with differences in the duration of mobile phone use, the duration of daily calls, or estimates of RF fields in SAR ranges. And, contrary to the authors' interpretation of the study, the percent of cells with tails, damage index, and mean migration length of damaged DNA for mobile

[23] The study noted that 90 base station antennas on towers were operating in the city at the time.

phone users was similar to the values for subjects who did not use mobile phones. Moreover, there was no consistent relationship between distance from the base station across the three measures of DNA damage. The limitations of this study are substantial: the investigators did not describe how particular base stations were selected, did not identify the frequency of the RF signals, did not state how subjects were recruited, and did not provide information about the purpose of the study. Additionally, no information was provided as to the procedures for the handling and analysis of the DNA specimens (blinding) to prevent bias during processing and analysis from knowledge as to the source of the samples. Only 100 cells per sample were analyzed for SSBs, while the Organisation for Economic Co-operation and Development (OECD) calls for 150 cells per sample to be analyzed (OECD, 2015).

- **Banerjee et al. (2016)** canvassed 300 patients from the outpatient department of the Kothiwal Dental College in Moradabad, India, to collect samples of cells from their mouth and analyze them for the presence of MN, which are small extra-nuclear bodies containing chromosomal fragments that may form when chromosomal damage has occurred. Associations between MN frequency and mobile phone use, as reported on a questionnaire, were evaluated. The buccal cells from the mouth were stained with a DNA-specific dye and scored by a single person for the presence of MN. Differences between high- and low-use mobile phone owners, type of mobile phone, and use of wired ear buds were reported. First, the authors claimed that the data showed increases in MN counts with long-term use of mobile phones; however, other possible explanations for the results such as selection bias, geographical variations, subjects that differed with respect to diet, health history, and other factors were not considered. Second, only 1,000 cells per subject were analyzed for MN, but OECD requirements call for 4,000 cells per sample to be analyzed (OECD, 2015). Third, the samples were scored by a single person and the study did not state whether this individual was blinded as to the data submitted on the questionnaires.

- **Shaikh et al. (2016)** conducted a similar cross-sectional study as Banerjee et al. (2016). These investigators in Ahmedabad, India, collected information on mobile phone use and health conditions from an unidentified population and divided 120 male subjects

into age-matched, high-use and low-use groups based on estimates of the number of calls made on mobile phones per day and years of use reported by subjects. Cells for analysis were collected by swabbing the inner cheek with a toothbrush and examined by light microscopy for cell types, including MN. The high-use group also reported use of chewing tobacco, smoking, pan masala (a chew made of betel nuts that sometimes includes spices and tobacco), and alcohol use. The differences between MN counts in high-use and low-use groups were very large, just slightly higher than reported for persons "*addicted*" to the chemical exposures listed above. A secondary analysis suggested that the MN counts were greater in persons reporting typical mobile phone use of 3 to 5 hours per day, and somewhat greater counts for persons using mobile phones for 5 to 7, and 7 to 9 hours per day, as compared to persons using mobile phones <1 hour per day. This study did not report any precautions to prevent bias in the analysis and only 1,000 cells per subject were analyzed for MN; OECD requirements call for 4,000 cells per sample to be analyzed (OECD, 2015).

- **Gulati et al. (2016)** conducted another cross-sectional study in the city of Kurukshetra, India, comparing 116 subjects recruited by unknown means living far from a mobile tower (>800 meters) to 106 subjects living near a mobile phone base station (50 to 400 meters). The subjects completed a questionnaire on their demographic characteristics and provided blood samples for analysis of single-strand DNA breaks using the comet assay; inner cheek swabs were also collected for the MN analysis. Most surprisingly, while the authors investigated an association between RF field exposure and proximity to a mobile phone tower, they did not collect information about use of mobile phones, a closer source of RF field exposure. The subjects also were evaluated for polymorphisms in glutathione S-transferase (GGT), a detoxifying enzyme. No significant differences between the near and far subjects were reported for demographic variables, but differences in self-reported conditions, including blood pressure, depression, memory status, insomnia, and hair loss were seen.

  Measurements of RF power density focused on 1.8 GHz and were reported at varying distances, but the number of measurements, the basis for choosing measurement locations, and any methods to exclude interference from RF signals from personal

mobile phones were not included. The authors reported that the measurements of comet tail moments were 25-fold higher and MN levels were 3-fold higher in the near group than in the far group and appeared to track with distance and power density. In the near group, persons with residence time ≥ 9 years had higher MN frequencies than those in the far group and were outside the range of normal values (Bonassi et al., 2011). Only 50 cells from each sample were analyzed for SSBs, whereas OECD requirements call for 150 cells per sample (OECD, 2015). The subgroup analyses indicated that SSBs and MN were only elevated in women and for subjects over the age of 45. While the reported differences may seem large, the most surprising result is that the data failed to show large differences between groups of persons with exposures known to affect DNA damage and MN, including smoking, alcohol use, and tobacco chewing in either the near or far group. In fact, the oral buccal MN frequency of tobacco chewers was lower in both groups than that of non-tobacco chewers. These deficiencies preclude giving any weight to this study. Other limitations included how distances to the mobile phone antenna were determined, the potential overlap in RF exposure with that from other mobile phone antennas or other types of antennas, whether any notable industrial activities existed in either area, or how subjects were recruited. The study reported that the analysis of MN specimens, but not that of the DNA, was double-blind. The study did not report the numbers of subjects whose samples were analyzed in each group.

- **Radwan et al. (2016)** described the demographic, lifestyle, and stress factors of 286 men between age 22 and 45 who attended an infertility clinic in Lodz, Poland. One of the factors investigated was the use of a cell phone. Sperm DNA fragmentation was measured using the flow cytometric Sperm Chromatin Structure Assay (SCSA), which detects the susceptibility of the DNA to denaturation by acid (due to the chromatin structure being fragmented) by the degree of DNA staining with acridine orange. The advantages of this method over other methods is the larger number of sperm screened, the objectivity of the test, and that the method is one that has "*demonstrated clear clinically useful cut-off levels for calculating male fertility potential*" (Bungum, 2012, p. 3; Wright et al., 2014). Statistically significant correlations between subjectively rated work stress and over the age of 40 with high levels of DNA fragmentation were reported. No statistically significant correlations between years of cell phone use and

low, medium, or high levels of DNA chromatin fragmentation were reported, although the percentage of immature sperms was significantly higher in obese patients and cell phone users. Comparable data on men who did not have cell phones or who were not referred to the infertility clinic were not included in this study.

- **Zothansiama et al. (2017)** conducted a cross-sectional study of persons living near or far from six mobile phone base stations operating at 900 MHz or 1,800 MHz in Aizawl, India, the same city studied by Gulati et al. (2015), but in a later time period (2015 to 2016).[24] The investigators obtained blood samples from residents of Aizawl and measured levels of MN in lymphocytes following stimulation by phytohemagglutinin (a mitogen that promotes cell division) for 72 hours *in vitro*; they also measured biochemical markers of anti-oxidant enzymatic activity and lipid peroxidation. The results were summarized for persons grouped by age, mobile phone use, duration (years), daily use (hours), distance from mobile base stations and measured power density, gender, smoking/alcohol consumption, and diet.

  The frequency of MN was lower in the control group (>300 meters from the mobile base station) than the exposed group (<80 meters from the mobile base station). The MN levels of women were lower than for men. While the percent of mobile phone users, duration of use, and daily mobile phone hours of use did not differ between the exposed and control groups, the MN levels measured in these subgroups were significantly higher in the exposed group than the control group. The authors attribute a 21% difference in mean MN levels in cheek cells between residents living near and far from the mobile base stations to low levels of RF exposure from the mobile base stations. The data also show, however, that the differences in mean MN between users and non-users of mobile phones in both groups were <4% even though RF field exposure to the cheeks of mobile phone users would be far greater than from a distant mobile phone base station. Because of the close proximity of cell phones to the body, especially during use, the exposure to

[24] It is curious that Zothansiama et al. (2017) does not mention the prior study by Gulati et al. (2015) that was conducted in the same city.

an RF field is much greater from a person's mobile phone than from a distant mobile phone base station.

While the authors did obtain some data relevant to other possible explanations including selection bias, geographical variations, diet, smoking, and alcohol use, the analyses performed did not adequately explore the relative contributions of such factors versus mobile phone use to MN and other measures. Only 1,000 cells per subject were analyzed for MN, but OECD requirements call for 4,000 cells per sample to be analyzed (OECD, 2015). The authors did not state how subjects were selected, or whether the analyzes of MN and other data were performed without *a priori* knowledge of the group from which the samples were obtained. Altogether, the results suggest that there are differences in the measures obtained from persons in two different parts of the city, but the data are insufficient to determine the basis for those differences.

- **de Oliveira et al (2017a, 2017b)** used convenience sampling via questionnaire to enroll 86 volunteers, age 18 to 30, in this cross-sectional study. The questionnaire asked about age, sex, place of birth, environmental and dietary exposures and habits, and the use of mobile phones (years of use, minutes per day, preferred side of the face, and headset use). Buccal samples from each side of the mouth were collected and 2,000 cells per subject were evaluated for MN by a single unblinded observer using the Feulgen technique with a DNA-specific stain. About 85% of the subjects reported the right side of the head as the preferred phone placement location during use. No statistically significant differences in the number of MN present were reported between males and females, among three different age groups, or according to other variables identified in the questionnaire including tobacco use, years of phone use, hours of daily exposure, or preferred side of the face for mobile phone use. Subjects reporting occupational exposure to genotoxic substances other than tobacco, however, did have significantly higher levels of MN compared to those who did not ($p=0.000015$). Two of the genotoxic exposures identified were xylene and formaldehyde. Some additional analyses of MN distributions by age and occupational exposure were included in a shorter, summary publication (de Oliveira et al., 2017b).

An independent systemic review of studies of mobile phone use and MN in cells of the mouth and a meta-analysis of the de Oliveira et al. (2017a) study and a prior study (Ros-Lior et al., 2012) did not find statistically significant differences in the frequency of MN in cells obtained from both sides of the mouth, which led to the conclusion that "*mobile phone use is not associated with the occurrence of genotoxic effects in the oral epithelium*" (dos Santos et al., 2020, p. 73).

- **Akdag et al. (2018)**[25] identified volunteers for this cross-sectional study from a survey, but no information was provided as to how the volunteers were recruited. Study participants included those who did not report owning a mobile phone and those who did. For persons using smart phones, the head peak SARs ranged between 0.45 and 0.97 W/kg. Other information was gathered from the subjects by self-report about exposure to chemicals, radiation, smoking, drugs, temperature, as well as age, but only data on age of the groups was described in the paper. Male volunteers between 30 and 60 years were allocated to four groups: control (no mobile phone), use for 0 to 30 minutes per day; 30 to 60 minutes per day; and over 60 minutes per day. Each group included 14 volunteers with the median age of approximately 40 years. Cells attached to the roots of hair were removed from within the ear most often closest to the mobile phone during use. Hair cell DNA was extracted for analysis by the alkaline comet assay. Seven parameters were used to describe the results; many of these were interdependent. Only 100 cells per sample were analyzed for SSBs. The OECD calls for 150 cells per sample to be analyzed (OECD, 2015). While not completely consistent across groups, statistical differences between the control group participants and those who reported using mobile phones more than 60 minutes per day were reported for measures of DNA damage. However, when the differences were compared according to duration of use, duration-dependent changes were not always evident. The study participants were not randomly selected and the investigators who analyzed the data were not blinded as to the group from which the samples were obtained. The investigators also failed to collect samples from both ears so as to test the hypothesis that each ear might differ based upon RF field

[25] This paper was excluded by SSM (2020) for review because it did not include a sham-control, which is a serious limitation for an experimental study but less severe for a cross-sectional epidemiologic study. Therefore it was excluded for this review.

exposure, nor could the investigators determine the contribution of a multitude of other factors that may account for differences between persons and groups. For these reasons, and because of the cross-sectional design of the study, no conclusions can be drawn about the contribution of RF field exposure to the reported results.

- **Vanishree et al. (2018)** researchers at the Navodaya Dental College and Hospital in Raichur, India, selected patients from the Outpatient Department for this cross-sectional study. They assigned 30 men and 30 women into a "*low mobile phone user*" group and the same number of subjects per sex into a "*high mobile phone use*r" group; these assignments were based on the number of years of use and number of hours per day of use. Study subjects were limited to those age 20 to 28 and to those without oral lesions or unspecified "*deleterious habits*." The study did not provide a description as to how information about the demographics or history of subjects was obtained. Cells were scraped from the inside of the right and left cheek for analysis. Counts of MN were reported in 1,000 cells per subject. The average MN count of high mobile phone users was slightly, but significantly, greater than the count in the low-user group but a non-DNA-specific stain was used to identify cell nuclei. Within the high-user group, greater MN counts were generally seen in those mobile phones using code-division multiple access (CDMA) rather than global system for mobile communications (GSM) phones and in non-headphone users compared to headphone users; counts were also higher from the cheek on the side of the head most frequently near the mobile phone. Only 1,000 cells per subject were analyzed for MN; OECD requirements call for 4,000 cells per sample to be analyzed (OECD, 2015). No assessment of confounding exposures or medical history was included, which is significant because all the subjects were patients of the Outpatient Clinic. The analyses were not reported to be blinded as to the history of the patients or the results. In addition, as a cross-sectional study, there can be no assurance that the use of mobile phones preceded the development of MN.

- **Senturk et al. (2019)** reported a cross-sectional study to determine if intense RF energy with a frequency of 2.2 MHz applied to ablate enlarged nasal sinuses during surgery was capable of increasing blood levels of indicators of antioxidant or oxidant activity, or both, including damage to DNA as measured by the alkaline comet assay. Blood

samples were obtained from 27 patients on the day prior to surgery and on post-surgical days 1 and 15. Total oxidant levels increased from the day before surgery to post-surgical day 15. Total antioxidants increased above pre-surgery levels on day 1 and 15 post-surgery. The levels of DNA strand breaks in circulating lymphocytes were slightly but not significantly increased on day 1 after surgery; no difference was seen on post-surgery day 15, but the extent of DNA damage was associated with higher total oxidant status on day 15. The physicians provided no information about the patients, their use of medications, including antibiotics (some of which act by damaging DNA, e.g., González et al. [2002]), or blood levels of other parameters that might indicate the leakage of thermally-damaged tissue into the venous circulation.

- **Khalil et al. (2020)** recruited 100 male and female students from Yarmouk University in Jordan who were between age 18 and 30 to provide demographic information and details regarding their mobile phone use in a detailed questionnaire as part of a cross-sectional study. Subjects who reported smoking, drug therapy, illness, use of dietary supplements, mouthwash, and other activities were excluded. The published SAR levels of the volunteers' mobile phones ranged from 0.244 to 1.552 W/kg, but the frequency of the RF signals was not provided. Samples of mucosal cells from both the right and left sides of the mouth were analyzed for damage to DNA using the comet assay and measurements of apoptosis-induced nuclear damage by the terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. One hundred randomly chosen cells from each sample were analyzed for each. Data from male and female participants were pooled for analysis as no significant differences between the sexes were seen with regard to mobile phone use, age, or ear dominance.

  The primary finding was that the percent of cells with DNA strand breaks or cells showing apoptotic damage from the left or right cheek was no different among those who used mobile phones <30 minutes, 30 to 60 minutes, or over 60 minutes, or for those who used mobile phones <5 years, 5 to 10 years, or >10 years (p-values >0.05). This result is complementary to the authors' previous report that 15- and 30-minute phone calls with an 1,800 MHz mobile phone had no significant effect on levels of 8-hydroxy-2-deoxyguanosine (8-OHdG) or markers of oxidative stress (Khalil et al., 2014).

A subgroup analysis of the seven different measures of DNA damage quantified using the comet assay found that almost all measures from both left and right cheeks were significantly associated with the minutes per day of mobile phone use. In contrast, none of these measures were significantly associated with years of mobile phone use in cells collected from the right cheek and only two measures (comet length and tail length) were associated with years of phone use in cells from the left check. Drawing firm conclusions from subgroup analyses that are contrary to the primary study finding is particularly problematic. Analyses of more rigorous randomized medical trials have concluded that "*[a]uthors often claim subgroup effects in their trial report. However, the credibility of subgroup effects, even when claims are strong, is usually low. Users of the information should treat claims that fail to meet most criteria with skepticism*" (Sun et al., 2012, p. 1).

The participants in Khalil et al. (2020) were reported to have been "*randomly stratified into three groups based on the frequency and intensity of phone us**e***." A more accurate description is that the participants were allocated to categories of daily exposure duration and years of phone use by the investigators. The authors stated that the analyses were conducted on coded samples; however, only 100 cells per sample were analyzed for DNA strand breaks, while the OECD calls for at least 150 cells per sample to be analyzed (OECD, 2015). One interpretation of these data is that self-reported low, medium, and heavy users of mobile phones have different behaviors or risk factors that affect not only the occurrence of DNA damage but its appearance (as identified by the seven inter-related measurements of individual cell comets). Another possibility is that the pattern of sub-group analyses does not fully reflect the data collected from the 100 participants because data were reported for only 83 left cheeks and 85 right cheeks, which appears contrary to the authors' claim that "*[n]obody dropped out of the study.*" The claim that "*all confounding factors that could cause cytogenetic toxicity were excluded (tobacco, alcohol, recent medication, systemic factor, etc*." is simply naïve. Excluding volunteers who admitted to such uses and history does not guarantee that persons who did not admit to these confounding exposures, did not have such exposures. Further, the study does not appear to address possible occupational exposures or other exposures that may have been associated with the participants' education.

Summary of human biomarker studies

The conclusions of IARC (2013) on human genetic studies was that "*that there was weak evidence that RF radiation is genotoxic, and no evidence for the mutagenicity of RF radiation*." (p. 415). A review of seven studies (one cohort and six cross-sectional studies) published between 2009 and 2018 looked for associations between proximity to mobile phones or base stations and markers of genotoxicity in small convenience samples (Revanth et al., 2020). The review concluded that "*the majority of the studies found that the effects of mobile phone radiation … having the potential to cause some buccal cell abnormalities*" (p. 280). That conclusion was based on just four of the seven studies and was too limited to be informative.

The papers rated highest for quality by the Revanth et al. (2020) study did not report genotoxic effects of mobile phone use. Despite the importance that Revanth et al. (2020) placed on the importance of using staining cells with DNA-specific stains to avoid mistakenly interpreting cells as having MN (false positives), they did not note that the seven studies reviewed provided evidence to support that concern. Studies that reported more MN in persons classified as having higher exposures to RF fields used non-specific stains (three of four studies) whereas none of the three studies that used stains specific to DNA reported increases in MN among persons with higher RF exposures. In short, the ratings of the papers were based on unclear and superficial criteria which as applied by the reviewers were inconsistent and do not support their conclusion. The four studies that were reviewed by Revanth et al. (2020) that were published after 2014 were reviewed above (Gandhi et al., 2015; Banerjee et al., 2016; de Oliveira et al., 2017; Vanishree et al., 2018).

The studies reviewed here, published after 2014, included five biomarker studies that assessed damage to DNA by the comet assay, six that assessed damage to DNA by the MN assay, including one that used the comet assay and the MN assay and one that used the 8-OHdG assay. One study used the SCSA assay. The reported differences between the levels of these markers and estimates of RF exposure in nine studies were based solely on self-reported mobile phone use. Three other studies described exposure based upon distance from mobile phone base stations, which also included mobile phone use (two studies) and measurements of RF power density at residences (two studies).

All these methods for categorizing subjects by estimated exposure were crude and likely subject to considerable bias. Furthermore, only 3 of the 12 studies reviewed reported that the analyses of the data were performed in a fully blinded fashion. While all studies attempted to some extent to minimize confounding by other exposures, these measures applied were not consistent across studies and appeared not to have been successful. None of the laboratories that performed the sample analyses appeared to have demonstrated expertise, nor the historical database necessary to carry out these complex tests, and none of the data reported in these studies met the criteria required to confirm a clear positive response (OECD, 2015). Also, these cross-sectional studies provided little opportunity to explore dose-response relationships except for three studies that used distance as a surrogate for exposure, which is correlated with measured exposures. All these limitations, in combination with the cross-sectional design of the studies, means that the results of these studies cannot be interpreted as showing a causal relationship between effects of exposure to RF fields on surrogate biomarkers and cancer development.[26]

Cancer assessment of animals after chronic radiofrequency exposure

U.S. National Toxicology Program

In 2000, the NTP began designing and planning a study of rats and mice to be exposed to RF fields simulating those of mobile phones, with signal modulations characteristic of 2G mobile phones (i.e., GSM) and 3G mobile phones (i.e., CDMA). The results were summarized in draft technical reports published for review in March 2018, with separate reports for rats (NTP, 2018a) and mice (NTP, 2018b).

Pilot studies of exposures for 5 days provided strong evidence confirming that exposure of rats to RF fields at 900 MHz and mice to RF fields at 1,900 MHz increased subcutaneous body temperature above 1 degree Celsius (°C) in both rats and mice at exposure levels above SAR

[26] This is consistent with a consensus comment that *"the use of biomarkers for early effects depends on the existence of knowledge about the significance of the event as a predictor of subsequent risk of cancer for humans. In the absence of this knowledge, it is still uncertain whether measurements, in humans, of some biological event known to presage cancer in an experimental system can be taken to add to the evidence from experimental systems alone"* (IARC, 1992, p. 30).

levels of 4 W/kg and 6 W/kg, respectively. In a second 28-day study, groups of pregnant female rats and groups of adult male and non-pregnant female rats and mice were exposed to GSM or CDMA RF fields. The subcutaneous body temperatures of pregnant female rats were significantly increased at exposure to CDMA RF fields at 6 W/kg, and exposure of male mice to GSM RF fields at 5 W/kg and higher significantly increased body temperature.

The main NTP experiments involved exposure of rats and mice to RF fields for 2 years, almost their entire expected lifetime. In the rat study, the subjects were exposed to GSM or CDMA RF fields (1.5 W/kg, 3 W/kg, or 6 W/kg) beginning prior to birth to the end of life. As in the shorter-term studies, significant reductions in body weight gains of pregnant female rats as well as their male and female pups were dose-related with exposure to GSM RF fields. Significantly increased survival over the 2-year period of male rats exposed to GSM RF fields was reported at all SAR levels in a dose-related fashion; the survival of male rats exposed to CDMA RF fields at 1.5 W/kg and 3 W/kg was also increased. Similarly, survival of female rats increased with exposure to CDMA RF fields at 6 W/kg.

The examination of multiple organs in rats at the end of the study showed a trend of increasing malignant schwannomas of the heart with GSM and CDMA SAR levels in male rats, but the incidence was only elevated above historical controls at 6 W/kg in males exposed to CDMA RF fields. An increase in the incidence of brain glial tumors was not reported at any exposure levels in male rats exposed to either GSM or CDMA RF fields, but a weak trend was noted with exposure to CDMA RF fields. In female rats, the NTP labeled this evidence as "*equivocal*," despite no reported statistically significant increases in the incidence of schwannomas in the heart or tumors in the brain, or a dose-response trend with RF field exposure.

Mice were similarly exposed to GSM or CDMA RF fields (2.5 W/kg, 5 W/kg, or 10 W/kg) for part of their lifetime; these exposures began in adulthood. The survival of male mice exposed to GSM RF fields at 5 W/kg and CDMA RF fields at 2.5 W/kg was higher than that of unexposed control mice. Unlike rats, no increase in the incidence of tumors of the heart or brain was reported in any RF-exposed group of mice. Examination at the end of the study showed a higher incidence of malignant lymphoma in female mice exposed to GSM RF fields at 2.5 W/kg and 5 W/kg and to CDMA RF fields at 2.5 W/kg; however, these incidences were not

considered increased at the highest exposure levels (10 W/kg), leading researchers to classify these findings as equivocal. Changes in the incidence of liver cancer were reported for male mice (a decrease in carcinomas at 2.5 W/kg and an increase of hepatoblastoma at 5 W/kg). All tumor rates in mice were within the range of historical rates of control reported in other NTP studies.

Overall, the results of the NTP studies indicate that RF field exposure to levels that cause heating of the body[27] can have acute adverse effects, and that lifelong exposure at slightly lower levels also may increase survival with increasing SAR exposure. With regard to cancer, increased incidence of malignant tumors in the hearts of GSM- and CDMA-exposed males above those reported in unexposed controls and historical controls provide, as the report states, "*clear evidence of carcinogenic activity*" as a positive finding for male rats. For female rats the evidence was rated "*equivocal.*" The report states that data evaluated for both male and female mice only provided "*equivocal evidence of carcinogenicity*" with GSM and CDMA RF field exposure. The level of evidence rated "*equivocal,*" was categorized as "*uncertain findings*."

Although the statistical testing for some measures such as body weight was adjusted for multiple comparisons, these data deserve additional scrutiny because other measures like tumor incidence were not. Given the thousands of pair-wise and trend comparisons made in these reports between exposed and control rats and mice, one must assume that a substantial fraction of the statistically significant differences reported could have been false positive findings (i.e., occurred by chance alone). Further, the SAR level that is considered the threshold above which adverse effects of whole-body exposure to RF fields may be expected is 4 W/kg in rats, non-human primates, and humans (D'Andrea, 1999). This has led federal agencies in Canada, the United States, and Europe to set the standard for whole-body exposure of the general public to be 50-fold lower, at 0.08 W/kg (FCC, 1997; Health Canada, 2015; ICNIRP, 2020a). Most effects reported in the NTP study occurred at levels of RF fields above the accepted threshold

[27] Tissue heating is a well-established effect of RF exposure at sufficiently high levels. Scientifically-established RF exposure limits, however, are set well below levels at which adverse heating of the tissue or body may occur. Thus, the study findings of the NTP study are, in general, not informative with respect to potential effects of low-level RF field exposure from everyday sources, including smart meters.

for thermal effects, which is a strong indication that chronic thermal input is a likely mechanism for effects related to RF exposure.

Following review by an outside *ad hoc* peer-review panel conducted in March 2018, the NTP released its final reports in November 2018 (NTP, 2018c, 2018d). In the final reports, even though the actual study results remained unchanged, some of the conclusions drawn based on these data were revised or upgraded. For example, the final report indicates *"clear evidence"* that exposure to RF fields with GSM and CDMA modulation was associated with development of schwannoma in the hearts of male rats, and *"some evidence"* for tumors in the brain (GSM and CDMA) and adrenal glands of male rats (GSM). The evidence for GSM- and CDMA-modulated carcinogenic effects was rated *"equivocal"* in female rats. Even though the maximum exposures of mice to RF fields were 67% higher than for rats, the evidence for any effects altogether was weaker for mice. In its assessment of the NTP study, ICNIRP (2019, 2020b) expressed concerns about the absence of a blind review of the pathology, and the interpretation of statistical significance given the thousands of statistical comparisons made. The substantially lower survival of the male control rats (28%) compared to all GSM RF-exposed males (50% to 68%) and CDMA RF-exposed males (48% to 62%) in the two highest exposure groups, suggests the "*strong possibility that the decrease in survival resulted in underrepresentation of late-developing tumors in the controls that importantly affected the statistical results*" (p. 530).

An important analysis and review of data in the NTP study was recently published by five scientists at the Federal Office for Radiation Protection in Germany (Kuhne et al., 2020). They show that the temperature increases in heavier male rats imposed by the higher RF field exposure in the NTP study were much greater than it appeared ("*likely exceeded 1.4 °C for more than 300 days*") leading to stress on the heart that would explain cardiomyopathy and malignant tumors of the nerve sheaths in the heart (schwannomas).

Ramazzini Institute

A recent study conducted at the Ramazzini Institute in Italy exposed rats to 1,800 MHz GSM RF fields for 19 hours per day from gestational day 12 (in utero) until the end of life at calculated SAR levels of 0.001 W/kg, 0.03 W/kg, or 0.1 W/kg. A partial summary of the results

was selected by the authors for publication (Falcioni et al., 2018). The exposures were planned to simulate RF field exposures in the environment from a fixed mobile phone base station, not a mobile phone. The rats were exposed in cages with 5 rats per cage, with a minimum of approximately 200 rats per sex per group. Body temperature was not measured.

The investigators did not report that they had randomly assigned the rats to the control and treatment conditions, which is a major flaw in the design of the experiment (Hooijmans et al., 2014). No effects on food or water intake, body weight, or survival in male or female rats were reported. The investigators reported 120 additional statistical calculations to describe the potential differences between groups of rats exposed or not exposed to RF fields on numerous measures. Using a criterion of $p < 0.05$, one would expect about six statistically significant differences to be reported just by chance alone in the two tables of data presented, but from all the calculations, only one single table entry indicated a statistically significant difference. In male rats at the highest exposure of 50 volts per meter (said to correspond to an SAR of 0.1 W/kg), 1.4% were diagnosed with a schwannoma in the heart, whereas no rats were diagnosed with this tumor among the control rats. No other differences in the entire report were statistically significant.

If these calculations had been even partially corrected for multiple comparisons, as had been done in some of the analyses in the NTP study, there would be no statistical differences at all between the groups exposed to RF fields and the control group. Moreover, the claim of the investigators that the large number of rats in each group makes it a better study than that of the NTP study is undercut because the rats were exposed in cages with five rats in each. Therefore, the cage, and not the individual rat, should have been considered the experimental unit for analysis, and the sample size for all the analyses should have been divided by five for the calculations of statistical significance. Still other shortcomings of the statistical analysis have led some to fault the Falcioni et al. (2018) report and call for "*a major revision of their conclusion*" (Sara et al., 2020). The response of the authors to this criticism was that the study nominally complied with OECD (2012) guidelines and addressed the lack of transparency about the statistical analysis by stating that additional data "*will be published in the forthcoming publication*" (Belpoggi et al., 2021). While Belpoggi et al. (2021) responded primarily to issues

of form, their response did not mitigate the potentially more serious statistical limitations to the results of the Falcioni et al. (2018) report.

The EPA has criticized the Ramazzini Institute's assessments of histological data and has "*decided not to rely on RI [Ramazzini Institute] data on lymphomas and leukemias in IRIS [Integrated Risk Information System] assessments*" (USEPA, 2013). Further, they have warned risk assessors about problems with the cancer bioassays conducted by the Ramazzini Institute, including the accuracy of the cancer diagnoses; the categorization of tumors; errors in identifying cellular changes such as leukemia/lymphoma in certain tissues that appear to be due to infections and tissue inflammation; an unexplained significant rise in the incidence of leukemia/lymphomas over time in control groups unrelated to the exposure under study; the lack of complete reporting and documentation of analytical specifications; failure to control or analyze for potential litter effects; and the use of common controls for multiple studies (Gift et al., 2013). These concerns all pose additional reasons to be cautious regarding the Ramazzini Institute study data.

In May 2020, ICNIRP published a brief summary and evaluation of the NTP and Ramazzini Institute studies (ICNIRP, 2020b). Overall, ICNIRP concluded:

> *Although NTP … [2018c] and Falcioni et al. (2018) both reported significantly elevated rates of carcinogenic outcomes in male rats, their results are not consistent with each other, nor with the NTP (2018b) mouse or female rat results, nor with the RF cancer literature generally (SCENIHR 2015; HCN 2016; SSM 2018). The NTP's outlying finding is further complicated by important methodological limitations, including the effect of the greater lifespans of the exposed rats on the statistical analyses, lack of blinding in the pathological analyses, and a failure to account sufficiently for chance in the statistical analyses. Collectively these two studies' limitations preclude drawing conclusions about carcinogenicity in relation to RF EMFs* (pp. 530-531).

A scientist involved in the NTP study before he retired replied to criticisms of the study from ICNIRP (2019, 2020b) and others (Melnick, 2019, 2020). While Melnick argued for his view,

ICNIRP's response to Melnick was factual (ICNIRP, 2020c) and provides justification for current plans for the NTP[28] as well as Japan and Korea, to attempt to replicate and improve upon the NTP study.

In a statement issued in November 2018 on the NTP studies, the Director of the FDA's Center for Devices and Radiological Health opined that the findings of the NTP studies "*should not be applied to human cell phone usage*." The FDA further concluded that "*[b]ased on our ongoing evaluation of this issue, the totality of the available scientific evidence continues to not support adverse health effects in humans caused by exposures at or under the current radiofrequency energy exposure limits. We believe the existing safety limits for cell phones remain acceptable for protecting the public health*" (FDA, 2018).

A third commentary on these studies was offered in a newsletter by a group of scientists assembled by the Swiss Federal Office for the Environment (BERENIS, 2018). The limited commentary reported on selected aspects of these studies and pointed out that "*the results of the NTP study are mostly relevant for the exposure situation when using a mobile phone close to the body. In contrast, the Ramazzini study observed carcinogenicity at levels as high as the environmental exposure limits, with no statistically significant effect at lower doses*" (p. 7).

In their 2019 report, SSM reviewed the NTP studies. The SSM's conclusions were as follows:

> *Two studies on carcinogenesis have a number of positive aspects, including their size and the duration of the exposure and the attempts to provide a comprehensive analysis of the pathology. However, the results are inconsistent between the studies in terms of the exposure levels where increased tumour incidences are observed, and the main endpoint, schwannoma of the heart, is only a very rare tumour in humans and therefore, likely, the public health relevance is not very high. Moreover, it is a tumour that has never been reported in experimental RF cancer studies, so it is peculiar at the least that it now appears in two studies that were published at the same time, and that it shows up only in rats and not in mice. A discussion on the effects of heating at*

[28] https://ntp.niehs.nih.gov/whatwestudy/topics/cellphones/index.html Accessed April 13, 2021.

> *the high exposure level in male rats is missing. Altogether the Council does not feel that these studies can be considered as clear indications for carcinogenicity of RF fields in humans* (p. 56).

Another in-depth review of the NTP studies was performed by the German Federal Office for Radiation Protection (BfS, 2019). The scientists noted several methodological weaknesses and inconsistencies in the NTP study results that "*clearly limit the meaningfulness of the study*," including many of the same limitations that were noted by ICNIRP, FDA, and SSM above. The scientists of the Federal Office for Radiation Protection concluded that the NTP study findings did not support the designation of *clear evidence* or *some evidence for a carcinogenic effect* and that the animals' exposures were much higher than human exposure limits and thus not directly relevant to human exposure to RF fields from mobile phones:

> *… after careful analysis of the various results, [the Federal Office] sees indications but neither a clear nor some evidence for a carcinogenic effect at high whole-body exposures - which were clearly above the limit values …* (BfS, 2019, p. 1)

The evidence for the interpretation that thermoregulatory stress explains the response of male rats in the NTP study (NTP, 2018c) was further buttressed in a study published by five scientists in the Federal Office for Radiation Protection in Germany. Kuhne et al. (2020) provided detailed analyses of temperature measurements reported for male rats in the NTP study. These analyses showed that the rise in the body temperature of male rats was much greater than acknowledged in the NTP report and provided "*evidence that for most of the main 2-year study, the average SC body temperature fluctuation of male rats in the 6 W/kg exposure group was higher than reported in the pilot studies…*" (Kuhne et al., 2020, p. 475). This explains the higher incidence of cardiomyopathy and schwannoma in aged male rats, which have reduced thermoregulatory control because of heavier body weights and a lesser ability to dissipate heat by vasodilation of the tail.

Summary of chronic exposure animal studies

The newest animal studies of chronic exposure to RF fields do not alter the weight of evidence accumulated from previous research reviewed by scientific agencies indicating that RF fields at very low levels are not harmful. The NTP reports suggest potential adverse effects of short- and long-term exposure to RF fields at levels at or above historically-recognized thresholds for causing increases in body temperatures and adverse effects upon which exposure standards are based. Further, the results of the Ramazzini Institute study are consistent with there being no effect of RF fields at exposure levels that are about 100-fold lower than those of the NTP study, a finding consistent with prior research. In a health risk assessment based on a review of the literature that accompanied its latest standard, ICNIRP (2020a) concluded:

> *A few animal studies on the effect of radiofrequency EMF exposure on carcinogenesis have reported positive effects, but, in general, these studies either have shortcomings in methodology or dosimetry, or the results have not been verified in independent studies. Indeed, the great majority of studies have reported a lack of carcinogenic effects in a variety of animal models… Thus, when considered either in isolation (e.g., ICNIRP 2019) or within the context of other animal and human carcinogenicity research (HCN 2014, 2016), their [NTP and Ramazzini] findings do not provide evidence that radiofrequency EMFs are carcinogenic* (p. 152).

Cancer assessment of animals after short-term RF field exposure

Studies of short duration are commonly performed to determine if the development of an already established tumor type is increased following exposure to the agent under study. Two studies of this design were reviewed.

- **Lerchl et al. (2015)** attempted to replicate an earlier study from his laboratory (Tillmann et al., 2010) that reported effects of RF field exposure on the development of tumors initiated by the carcinogen ethylnitrosourea (ENU) because the interpretation of the results in the earlier study were clouded by an infection of *Helicobacter hepaticus* that affected the mice in the study.

From the offspring of the mothers, 4 groups of 96 mice were assembled; sham + ENU; 0.040 W/kg RF + ENU; 0.4 W/kg + ENU; and 2 W/kg + ENU. The mice were exposed for 23.5 hours per day for 72 weeks to 3G mobile phone Universal Mobile Telecommunications System (UMTS) 1,996 MHz RF fields. The characteristics of the signals were not included in the paper but were imputed for the analysis here from the previous study. The investigators performed histopathological analyses of the brain, kidney, spleen, liver, lymph nodes, and lungs that were confirmed in an independent review. Exposure to RF + ENU significantly increased tumors of the lungs (adenomas and carcinomas) and carcinomas in the liver, a result confirmed by Bayesian analysis of SAR exposures at 0.4 W/kg. The survival times were not affected by exposure to RF fields. These findings were similar to their previous study; however, in either study the incidence of tumors was not clearly proportional to exposure, and they were similar for exposures that varied by 50-fold. Although this study was reviewed SSM (2016), SSM did not point out that the mice were not randomly allocated to treatment groups, the sham groups were older than the other treatment groups, and the analysis was not blinded.

- **Ouadah et al. (2018)**, like in a number of previous studies, examined the effects of RF field exposure on the development of glioblastoma multiforme (GBM) tumors initiated in rats by injection into the brain. In this study, 30-day old male Wistar rats were injected with C6 tumor cells whose development into tumors mimics GBM in humans. Seven days after injection, the rats were randomly assigned to cage control or sham control (n=15), and the groups of rats were exposed to 0.25 W/kg (n=18) or 0.5 W/kg (n=39) 5 days per week for 45 minutes until death or sacrificed 30 days after injection. RF field exposure had no effect on tumor size, location, proportion of dividing cells (Ki67 protein marker), or vascularization (CD31 marker). The brains of rats injected with tumor cells and exposed to RF fields, however, had lower semi-quantitative ratings of immune cell invasion and CC3 immunoreactivity indicative of apoptosis (programmed cell death marker CC3). The stress of restraint of the rats in the sham group did not result in different outcomes from the cage control group. The study authors were careful to blind the investigators during each step of the experiment as to the groups to which the samples belonged to avoid any potential bias. While RF field

exposure had no effect on tumor development, the clinical significance of a change in a marker for apoptosis is not known and the authors concluded that "*[f]urther replication studies are needed to confirm these observations*" (p. 539).

Summary of short-term cancer studies

SCENIHR (2015) concluded in its review of long- and short-term *in vivo* animal studies that "*[o]verall, because a considerable number of well-performed studies using a wide variety of animal models have been mostly negative in outcome, the animal studies are considered to provide strong evidence for the absence of an effect.*" (p. 86).

The results of the subsequent studies do not clearly complement any previous work by other investigators or break new ground as to potential effects of RF field exposure on the development of specific tumor types and are consistent with SCENIHR's earlier conclusion.

Studies of DNA and chromosome damage in animals

Although lifetime studies of animals exposed to physical or chemical agents are regarded as the gold standard for the assessment of potential effects of exposure on the development of cancer, health and scientific agencies also look to shorter-term *in vivo* studies of genetic (DNA and chromosome) effects to assess these as potential mechanisms for the initiation of tumors. Such studies are frequently undertaken to confirm indications of genetic or chromosomal damage reported from EMF exposure of isolated cells *in vitro*.

The most widely used and validated tests for the detection of DNA damage and mutation are performed on bacteria and yeast organisms. Overall, the absence of any "*signal*" from these tests is quite clear—RF fields are not mutagenic (IARC, 2013). Other tests with lesser validation have been applied to human and animal cells but many such *in vitro* studies have reported mixed results; the differences between exposed and control groups were often small, and as reported in two large meta-analyses of such studies (Vijayalaxmi and Prihoda, 2008; Vijayalaxmi and Prihoda, 2012), the variations were almost always within historically-reported levels measured in unexposed control cells. Based on this analysis, Vijayalaxmi (2016) laid out minimum criteria for the design and performance of cell, human, and animal studies. Further, in a comprehensive and updated meta-analysis of 225 *in vitro* studies published in 2017, the

previously-reached conclusions were confirmed by Vijayalaxmi and Prihoda (2019). Their analyses demonstrated that 30% to 50% of the studies of RF exposure on indicators of genotoxic effects in mammalian cells failed to control any of four variables affecting overall study quality: blind analyses often were not included, adequate descriptions of exposure dosimetry were not provided, positive controls were not mentioned, and it was often not stated if unexposed cells were treated in exactly the same manner as exposed cells with the exception of RF field exposure. To this list of deficiencies, others have added the misinterpretation of statistics and the pre-specification of analyses (Foster et al., 2019). To overcome issues relating to the quality of the methods used to assess SSBs, Schuermann et al. (2020), in an attempt to replicate key studies from two universities, were unable to repeat effects of GSM 1,950 MHz at a SAR of 2 W/kg on measurements of SSBs in two human cell lines or to identify effects of UMTS, Wi-Fi or RF-identified modulated fields on DNA and DNA repair. Tests for DNA damage that might be expressed as an increase in sister chromatid exchange also were negative following exposure to a 4.9 W/kg UMTS-modulated signal. The authors thus concluded that "*[c]lassical and advanced genotoxicity testing and DNA repair assessment produce no conclusive evidence for a disturbance of DNA integrity or changes in the DNA repair capacity, following wEMF (modulated electromagnetic field) exposure*" (p 14). Despite the high sensitivity of new methods of detecting damage to DNA, there are recognized problems regarding the variability in the results of the comet assay; for example, differences between replicate samples analyzed within and between laboratories, and in the interpretation of comet assays has impeded its acceptance as a reliable tool (Langie et al., 2015; Forchhammer et al., 2012).

To uncover the reasons for the inconsistency in the reported *in vitro* genotoxicity studies of exposure to RF fields, a protocol has been published by European agencies for a systematic review of this research according to guidelines recommended by the NTP Office of Health Assessment and Translation (Romeo et al., 2021).

Despite the absence of convincing evidence for effects of RF fields on the DNA or chromosomes of human and animal cells *in vitro*, other *in vivo* experimental studies of animals exposed to RF fields have looked for alterations in the double-strand DNA structure of single cells as measured by the alkaline comet assay and fragmentation of chromosomes containing DNA by the detection of MN within blood cells. Another assay used in some studies as a

surrogate indicator of DNA damage measures the conversion of deoxyguanosine in DNA to 8-OHdG, which is a major product of oxidative damage. Although measurements of other aspects of cell function often related to oxidant and antioxidant indicators are typically reported in such studies, they were not the focus of this assessment.

- **Furtado-Filo et al. (2014)** reported that 12 pregnant rats were exposed for 0.5 hours per day to 950 MHz RF fields at SAR levels of 0.03 to 0.01 W/kg during gestation. After delivery, the pups were allocated to a sham group and exposure continued for 0.5 hours daily for 0, 6, 15, and 30 days at which time six rats from each exposure group were decapitated and the livers removed for analyses of DNA damage (comet assay), fatty acid content, lipid peroxidation, catalase, and protein oxidation. The SAR exposures were: neonates, 0.88 W/kg; 6-day-old rats, 0.51 W/kg; 15-day-old rats, 0.18 W/kg; and 30-day-old rats, 0.06 W/kg. They reported that damage to DNA in exposed rats, as measured by the alkaline comet assay, was the same as in controls at birth or 6 days later, but was less at 15 days and greater at 30 days of age (both $p < 0.05$). The control rats were sham-exposed and the exposures varied from 0.51 to 0.88 W/kg at 0 and 6 days after birth, respectively, and declined to 0.18 W/kg at 15 days and 0.06 W/kg at 30 days due to the increase in body mass with age. Only 100 cells from each tissue were analyzed, but results were averaged with those of a duplicate slide. The authors regarded these results as "*very peculiar*" and speculated that the results reflected age differences in sensitivity, a decline in repair capacity at 30 days of age or "*artifact of the technique.*" The control rats were sham-exposed, but the authors did not report that the rats were randomly allocated to treatment groups or that precautions were taken to minimize bias (e.g., by coding the samples so that the investigators performing the analysis were blinded as to source or history of the samples).

- **Furtado-Filo et al. (2015)** was similar in design to the previous Furtado-Filo et al. (2014) study, except that the exposure of the six rats in each groups ended at birth or 6 days thereafter and the analysis was limited to the right and left hemispheres of the brain. The SAR exposures were calculated to range from 0.44 W/kg during gestation to 0.35 W/kg on day 6 after birth. The SAR values above that appear in the paper are less than the range described in the paper's abstract (1.14 to 1.32 W/kg). Exposure of the

sham-control rats was reported at far lower levels, ~ 2 x 10^{-5} W/kg. The authors report that they found no statistical difference between the levels of SSBs in the brains of the exposed and sham-control rats as measured by the alkaline comet assay. Only 100 cells from each tissue were analyzed, but results were averaged with those of a duplicate slide.

- **Deshmukh et al. (2015)** exposed male Fischer-344 rats (150 to 200 grams [g]) in groups of six to RF fields at 900, 1800, 2450 MHz, or control conditions for 180 days at the same SAR level of 0.00006 W/kg. The investigators assessed the brain tissue concentration of heat shock protein (hsp70) and amount of DNA damage, as measured using the comet assay. While the methods for exposing the rats to RF fields in a transverse electromagnetic (TEM) cell are well-known, the rats were exposed in groups while restrained, which can result in stress and DNA damage (Consiglio et al., 2010). The body temperature of the rats was measured before and after exposure to RF fields. Behavioral tests also were performed but are not relevant and therefore not discussed further. While the samples from the exposed groups and the sham control group were coded and assessed in a blinded fashion to prevent bias, the animals were not randomly assigned to these treatment groups to prevent systematic bias related to body size or housing history. No change in body temperature was reported (data not shown), but statistically significant increases in hsp70 and DNA damage were reported. The differences between the groups for four computed indices of SSBs (Olive tail moment, tail moment, percent of DNA in head, and tail length) were larger with groups exposed to 1,800 MHz and 2,400 MHz, roughly 25% greater than those reported at 900 MHz.

  The interpretation of these data is clouded because the investigators did not express these measures in units that account for the amount of tissue contained in each sample, such as per gram of tissue or per milligram of protein. Any variation in the size of the brain tissue analyzed between animals would appear as a difference in the concentration in the extract, even if the concentrations of hsp70 or DNA in the living tissue were the same. The differences between hsp70 values across all groups were very small, and the effective size of the groups is n=1 because of group exposures, so the result is null and the statistical differences between the groups is overstated. The differences between the

groups for four indices of DNA damage were larger, with groups exposed to 1,800 MHz and 2,400 MHz roughly 25% greater than reported at 900 MHz. These results are virtually the same as the results these investigators published in other studies in which rats were exposed for 30 days (Deshmukh et al., 2013), 60 days (Megha et al., 2015), and 90 days (Deshmukh et al., 2016). In fact, the results appear to be exactly the same in some respects. For example, the percent tail DNA in the hippocampus for sham exposed, and those exposed to 1,800 MHz and 2,450 MHz in a 180-day experiment (Figure 5A in Deshmukh et al. [2015]) differed by less than 2.7% from the values reported for a 30-day experiment (Figure 2 in Deshmukh et al. [2013]). Similarly, the difference between each of the four groups in the 30-day experiment differed from those in a 60-day experiment by less than 2.2%. Given the small number of animals in each group, the inherent variability of samples over time, and some expected error in measurement of values across the published papers, the close similarity of values from different experiments is not credible. The authors reported "*[i]mages from 100 cells (50 from each replicate slide) were analyzed*" (p. 286).

- **Zong et al. (2015)**, in previous research, reported that exposure of mice to 900 MHz RF fields at SAR levels of 5.48 mW/kg, 54.8 mW/kg, and 548 mW/kg provided protection against subsequent sub-lethal or lethal ionizing gamma radiation (Cao et al., 2010, 2011; Jiang et al., 2012, 2013), an effect replicated by other investigators. In the most recent study (Zong et al., 2015), male ICR mice (25 g) were individually exposed to 900 MHz RF fields at a SAR of 0.0548 W/kg in a TEM cell for 1 hour per day for 7 days. Blood samples from each group of eight mice were analyzed for SSBs using the alkaline comet assay. Mice exposed to RF fields did not produce higher levels of SSBs as measured by tail moment or tail length compared to sham-exposed controls.

  Four hours later, other groups of mice were injected with bleomycin (BLM), a chemical known to damage DNA, some of which were sham-exposed (sham + BLM) or RF-exposed (RF + BLM). Starting 20 minutes after injection, one mouse from each group was removed at 30-minute intervals to see how exposure to RF fields affected DNA repair in white blood cells due to BLM treatment. Following injection of BLM, all mice showed increased SSBs, but the mice previously exposed to RF + BLM showed

significantly lower SSB levels ($p<0.0001$) than mice injected with the BLM alone or sham + BLM, showing that exposure to RF fields prior to chemically-induced DNA damage speeded up repair of damaged DNA.

Measurements of other indices of oxidative damage in the blood, liver, and lungs of control, sham, and RF-exposed groups did not differ. In groups treated with BLM, pre-exposure to RF fields produced significant reductions in the oxidative damage marker malondialdehyde (MDA) in the liver, while the lungs exhibited a significant increase in the concentration of superoxide dismutase, an anti-oxidative enzyme. These data demonstrate that RF fields did not cause DNA damage or increase oxidative stress but accelerated the repair of DNA damage by BLM in the liver and lung. The investigators randomized mice to the treatment groups and conducted all analyses blind. The inclusion of BLM in this study qualifies as a "*positive*" control to demonstrate that the assay was capable of detecting SSBs. The authors reported "*[f]or each animal and for each exposure, 50 comets were analyzed for comet tail length (microns) and tail moment (ratio)*" (p. 272).

- **Sahin et al. (2016)** measured an indicator of DNA damage (8-OHdG) and an indicator of lipid peroxidation (MDA) in the brains of female rats exposed in groups of 9 to 2.1 GHz RF fields at a calculated SAR level of 0.4 W/kg for 6 hours per day (5 days per week) for 10 and 40 days. Identical measurements were made of brain tissue from groups of six female rats placed in the exposure apparatus without exposure to RF fields (sham control) for these same periods. Compared to the sham-exposed groups, the authors reported a statistically significant increase in DNA damage of the exposed rats after 10 days, but a statistically significant reduction in DNA damage after 40 days of exposure. No sense can be made of these data, however, because the amount of DNA damage observed in the control groups was so discrepant: the average DNA damage in the 40-day control group was 150% greater than in the 10-day control group, and similar to the levels observed in the 10-day RF-exposed group. MDA levels were higher in brains of the 40-day control rats than in the brains of RF-exposed rats. No differences in the MDA levels of exposed and control rats were seen in the 10-day exposure groups. The differences between control groups kept under similar conditions indicate that

factors unrelated to RF field exposure confounded the results. In addition, since the rats were exposed in groups, they shared a common experience and thus their data were not independent, as required by the statistical method applied. Although the rats were properly allocated to the treatment by a randomized procedure, the investigators were not reported to be blinded as to the identity of the specimens during the analysis of the results.

- **Akdag et al. (2016)** compared the average level of SSBs (via comet assay) in the brain, kidney, liver, testes, and skin of male albino rats exposed for 12 months to 2.4 GHz RF fields at average SAR (0.0001414 W/kg) and maximum SAR (0.007127 W/kg) levels to a sham-exposed control group. Eight rats were assigned to each group and the rats were exposed in these groups without restriction on their movement. No statistically significant differences between these groups were reported, with the exception of in the testes, where an increase of approximately 20% was reported. The exposure system was better described than in most studies and evaluated by both measurements and calculations. The interpretation of the study is limited, however, because the rats were not randomly assigned to groups, no information regarding the health status and development of the animals was provided, and the analysis of the data was not blinded. In addition, the statistical assumptions of the Mann-Whitney test for differences between groups were not fulfilled because the rats assigned to each group were not randomly allocated and the exposures and housing of the groups violated the assumption that the results obtained from each rat were independent of those obtained from others in each group. Only 50 randomly selected cells from each tissue were selected for DNA analysis.

- **Güler et al. (2016)** examined the brain tissues of male and female rabbits randomly allocated to four groups each containing nine rabbits per sex. Group I served as a sham-control group; the other groups were exposed to simulated 1,800 MHz GSM signals at an estimated SAR of 0.018 W/kg either beginning 1 month after birth (Group II), for a 7-day period in gestation (Group III) or both. However, exactly how exposures were done is unclear. Specifically, it is reported that the rabbits were exposed for 15 minutes per day for 7 days (females) or for 14 days (males); this suggests that the females could not

have been exposed in both periods. Further, the duration of extrauterine exposure after 1 month was not stated. At the end of the exposures, measurements in the brain were made of oxidative DNA damage via the TUNEL method, 8-OHdG (a DNA damage marker), and MDA (a marker of lipid oxidation); visual histological examination of the brain tissue was also done. No differences between males and females were reported for 8-OHdG or MDA. Despite the description of the results provided by the authors to the contrary, the levels of 8-OHdG also were almost identical for all four exposure groups. Semi-quantitative ratings of cellular changes were virtually nil in Groups I and II; more mild and moderate changes, most consistently described as gliosis, were reported in Group III and IV. Staining of cells in TUNEL treatments did not show that apoptotic degenerating cells were present. Although the TUNEL analysis was reported to have been done in a blinded fashion, it was not clear whether the other analyses were performed on coded samples.

- **Jeong et al. (2018)** studied the brains of young and aged C57BL/6 female mice for changes in biochemical indicators of the aging process, including markers of oxidative damage to lipids and proteins, damage to DNA, cell-initiated death (apoptosis), and neuroinflammation. Aged mice (12 per group) were randomly assigned to either sham-exposure or 1,950 MHz RF fields at an SAR of 5 W/kg for 2 hours per day, 5 days per week for 8 weeks (from age 14 to 22 months). The exposures took place in a reverberation chamber specially designed to produce uniform, reproducible exposures (Lee et al., 2012). Another group of unexposed 3-month old mice were included as young controls. The analyses were performed blind. The investigators reported that 16 of the 19 markers of aging were statistically greater in the aged mice than in young control mice, sometimes up to 10 times greater. When the brains of aged rats exposed to RF fields or sham conditions were compared, however, no statistically significant differences between these groups were observed, including quantification of protein expression of 8-OHdG, a marker of DNA damage in histological sections of the brain. The total number of cells examined and the number of cells staining for 8-OHdG were not specified.

- **Jonwal et al. (2018)** divided 16 male Swiss mice into 2 groups—8 mice exposed to 2.45 GHz RF fields with a calculated power density of 0.25 mW/cm^2 and an estimated SAR exposure of 0.09 W/kg; and 8 mice placed in a similar chamber without exposure (sham control). Two mice were placed in each chamber for 2 hours each day for 30 consecutive days. The ratio of polychromatic erythrocytes to normochromatic erythrocytes in the blood was measured at the end of the 30-day period. Although a lowering of this ratio is sometimes considered as a marker for MN, this is an overinterpretation and only can be considered as an indicator of differences in the maturation of red blood cells (Vijayalaxmi and Prihoda, 2019). Other evaluations were conducted of serum testosterone levels and oxidative stress markers in the testes (reactive oxygen species; MDA; and related enzymes glutathione peroxidase, superoxide dismutase, and catalase); testis histopathology was also examined. The exposed group showed more MN than the control group ($p<0.001$), which was suggested to be consistent with markers of histological and oxidative damage indicators in the testes. The authors did not report how the mice were allocated to the treatment groups, whether the mice were exposed in groups, or if blinded procedures were used to prevent bias in the analyses of the data. The number of cells upon which the results reported as ratios obtained by flow cytometry analyses was not specified, but the numbers would be expected to be thousands of cells.

- **Alkis et al. (2019a**) assessed the potential linkage between measures of DNA damage and multiple indicators of oxidation processes. Male Sprague-Dawley rats (n=7 per group) were randomly assigned to sham, 900 MHz, 1,800 MHz, and 2,100 MHz RF exposures at intensities between of 0.638, 0.166, and 0.174 W/kg, respectively; these exposures occurred in a plastic carousel chamber for 2 hours per day for 6 months. The authors reported an increase in SSBs in the brains of the rats exposed to 2,100 MHz RF fields, as measured by comet tail intensity, but no increase in SSBs as measured by tail moment in any other group exposed to different frequencies of RF fields. In contrast, statistically significant increases in the levels of 8-OHdG, another indicator of DNA damage, were reported with exposure to all three RF field levels. The levels of five other indicators of oxidative stress generally increased in a manner similar to that of 8-

OHdG. The authors did not explain the discordance between the measurements of DNA damage using different metrics, and the magnitude of the effects were inversely related to the intensity of exposure as measured by SAR. A number of the experimental procedures were not described, including whether the rats were continuously housed in the exposure chamber or were only maintained in there during the 2 hours of exposure. The analysis of the data was not reported to have been blinded as to the exposure status of the sample. The authors analyzed 100 cells for DNA and 1 test for 8-OHdG from the brain.

- **Alkis et al. (2019b)** performed a study similar in design to the previous study (Alkis et al., 2019a), except in this study, the investigators made measurements on the testes of rats following exposures that were the same as in the previous study: RF fields at frequencies of 900, 1,800 MHz, and 2,100 MHz, and SAR levels of 0.638, 0.166, and 0.174, respectively. The sham and RF field exposures were applied to rats for 2 hours per day for 6 months. Tissue samples were processed and 100 nuclei randomly selected from each tissue sample were analyzed for SSBs by the comet assay and for 8-OHdG for oxidative damage. Measurements of tail intensity were statistically higher in the groups exposed to 1,800 MHz and 2,100 MHz, but not 900 MHz. The exposed groups showed no significant differences from the sham-control group for SSBs measured by tail moment. The levels of 8-OHdG in the exposed groups were significantly greater than that of the control. The levels increased with frequency, but were inversely related to the calculated SAR levels. No measures to prevent bias in the handling and analysis of samples were described.

- **Houston et al. (2019)** reported on multiple aspects of the testis and sperm of male mice exposed to 905 MHz at 2.2 W/kg SAR for 12 hours per day for 1, 3, or 5 weeks. No gross histologic changes were seen in the control or exposed groups; nor did the testis from these groups exhibit cells with damaged double-stranded DNA (as stained by anti-γH2AX antibody).

  In contrast, sperm showed small increases in fragmented DNA (halo assay) that became statistically significant only in the group exposed for 5 weeks. Increases in 8-OH-dG

oxidative damage in weeks 1, 3, and 5, and SSB in the comet assay also were reported. The OECD (2015), however, states that the comet assay for SSBs is "*not considered appropriate to measure DNA strand breaks in mature germ cells (i.e., sperm)*" (p. 16).

Despite the findings above, the investigators reported that assessments of sperm health and *in vitro* fertilization of eggs did not reveal any impairment of the fertilization process.

The authors noted that, in contrast to some previous reports, they observed no structural disorganization within the testis and that an earlier study had reported no harm to fertility with life-long exposure over four generations of mice. The authors appropriately minimized systematic error by randomly assigning mice to the exposure groups and used hydrogen peroxide as a positive control to assure the proper detection of an agent known to damage DNA in the comet assay. However, for some of the results discussed above, the observations were made on as few as three mice and up to five mice, and no sample coding procedures were described to minimize potential bias in the analysis. Additionally, during exposure, two rats were exposed together, so the results should have been aggregated together for the statistical analyses.

- **Lerchl et al. (2020)** followed up on a hypothesis arising from their 2015 study (discussed above) that exposure to RF fields might promote the development of tumors initiated by a chemical carcinogen. In this study, three groups of pregnant female mice were exposed in individual cages to 0 (sham control), 0.04 W/kg, or 0.4 W/kg SAR at 1,960 MHz RF fields for 24 hours per day beginning on day 7 post-conception. On day 14 post-conception, the pregnant mice were injected with the chemical carcinogen ENU, and at 24, 36, and 72 hours later, the fetuses were removed and the tissues stained to reveal DNA damage. The fluorescence of DNA adducts was measured in 10 cells per slide of brain, liver, and lung tissue, and many slides were reviewed so that about 84,000 cells in the entire study were evaluated. The authors concluded that "*RF-EMF exposure does not trigger increased DNA damage in the fetal brain, lung, and liver*" above the damage caused by ENU. Although the overall results show no deviations attributable to RF field exposure (either additive or multiplicative effects), the statistical analysis

should have considered that the number of experimental units is not the number of fetuses, but the number of pregnant mothers (n=3) that contributed fetuses to each experimental group (Lazic, 2010). The statistical error that arises by exposing rats in groups, however, was avoided by exposing each pregnant rat individually.

- **Sharma and Shukla (2020)** cited studies of RF fields on some behavioral and cognitive processes in protozoa and earthworms as the basis to study such processes in rats. In this experiment, groups of rats were exposed to 900 MHz RF fields at SAR intensity of 0.231 W/kg calculated at the brain for 1, 2, or 4 hours each day for 90 days, and their behavior and biochemistry was compared to sham-controls. After completion of the behavioral studies, the brain was assayed for multiple indicators of oxidative stress, glutathione metabolism, and the activity of an enzyme that regulates levels of acetylcholine, a neurotransmitter. A histological examination of the hippocampus of the brain was supplemented by measurement of DNA damage via the comet assay. The length of the comets on 50 cells was measured. Unlike some other studies reviewed, the tail length, tail momement, and percent of cells detected as comets were all extraordinarily similar across the different durations of daily exposure (1 to 4 hours) and increased above that observed in sham controls in a monotonic fashion. Results presented for the other biochemical measurements made in the study showed a similar appearance. Although the rats were randomly allocated to the experimental groups (n=6/group), they were confined together in groups of four during exposure. Additionally, the investigators did not indicate if the rats were restrained in the experimental chambers for 90 days or were returned to home cages after each period of exposure. From the limited description of the experimental procedure, it appeared that the six rats assigned to the sham-control group did not have the same test experience as the rats in the exposed groups. This may have meant that only two sham control rats were matched to six exposed rats at each period of exposure duration. The 50 cells examined is far fewer than the 150 cells the OECD recommends to be analyzed per sample. Finally, the investigators did not describe any procedures to prevent inadvertent bias by coding the animals and tissues to hide their group identity.

- **Smith-Roe et al. (2020)** reported on the results of a secondary study to the NTP mobile phone project described above in which rats were exposed according to the same parameters as in the main studies, but instead of continuing for 2 years, the animals were euthanized at 19 weeks (rats) and 14 weeks (mice). The results were also reported in final technical reports from NTP (NTP, 2018c, 2018d). Samples from three brain regions, the liver, and blood were analyzed for SSB damage; the blood also was analyzed for MN. Each group consisted of five rats or five mice of each sex. The same sham exposure group was used for both GSM and CDMA exposures. The authors stated that "*the only clear positive result [for SSBs] was observed in the hippocampus cells of male rats exposed to the CDMA modulation when evaluated using the 100-cell scoring approach*" (p. 7); however, that result was not confirmed when 150 cells per sample were evaluated. Equivocal results were reported for the frontal cortex of the same rats. No increase in SSB levels was observed in the cerebellum of the brain or in the liver of male rats and no increase in SSBs was seen in any tissue evaluated in female rats exposed to GSM RF fields.

  Statistically significant increases in SSBs were reported to occur in the hippocampus and frontal cortex of male mice in both the GSM and CDMA groups and in the white blood cells of female mice (CDMA only). Effects of CDMA exposure on the liver of female mice did not meet the criteria for statistical significance. No effects of GSM exposures were reported in any tissues of female mice. The results described above were based on analyses of 150 cells per sample. A comparison of the results of analyses of 100- and 150-cell samples revealed variability, but this appeared to be explained by the inclusion of other aspects of DNA damage, not just SSBs. For some tissues, considerable inter-animal variability was observed that "*exceeded 30% in some cases*," but this variability was much less in samples from white blood cells. No clear or large effects of exposure were reported for MN in either rats or mice.[29] An important aspect not discussed in this

[29] *"To maintain the overall significance level at 0.05, the trend as well as the pairwise differences from the sham control group were declared statistically significant if P<0.025. A result was considered positive if the trend test was significant and if at least one exposed group was significantly elevated over the sham control group, or if two or more exposed groups were significantly increased over the corresponding sham control group. A response was considered equivocal if only the trend test was significant or if only a single exposed group was significantly increased over the sham control"* (NTP, 2019c, p. 250; NTP, 2019d, p. 162).

report was that the few increases in SSBs reported in male rats only occurred at the highest SAR level, 6 W/kg CDMA, and in male mice at 5 W/kg and 10 W/kg CDMA and at 10 W/kg GSM.

While the reputation and methodology of the NTP is highly regarded, this study did not fully describe how mice or rats were randomly allocated to treatment or control groups or that the analysis of the samples was conducted in a blinded fashion. Other scientists (Vijayalaxmi et al., 2020) have pointed out that the observed variability in measured SSBs is a likely consequence of a delay between death and removal of the brain, a serious concern. The NTP admitted that "*[t]he possibility that the longer interval from exposure cessation to tissue collection for the female rats may have been a factor in the absence of any detectable exposure-related increases in DNA damage cannot be ruled out due to the increased opportunity for DNA repair during this interval*" (NTP, 2019c, p. 115). Other concerns raised by Vijayalaxmi et al. (2020) were that positive controls were not included as required by standard protocols; that there was an overreliance on statistical p-value analyses without correction for multiple comparisons; that the authors relied on data from a single rat for a significant elevation of SSBs in the hippocampus with CDMA exposure at 6 W/kg; that there was "*an anomalously low value*" of SSBs in males exposed to CDMA accounting for differences at all three exposure levels; and that the occurrence of SSBs is not related to the DNA magnitude of exposure (i.e., the SAR). The concern raised by Vijayalaxmi et al. (2020) about the method and timing of obtaining samples has a general application to all the studies that measured SSBs by the comet assay. In any study that did not rapidly sacrifice the animals by decapitation in a random order unrelated to the treatment group, large differences in SSBs could be expected whether or not any RF field exposure had occurred.

- **Alkis et al. (2021)** This study is similar to that of Alkis et al. (2019a), except that it presented data on the liver of rats exposed to RF fields at two frequencies that also differed in SAR levels: 1800 MHz at 0. 62/W/kg; and 2100 MHz at 0.2 W/kg. The rats were exposed for 2 hours/day for 7 months and compared to sham-control rats. The comet assay was used to measure DNA damage, and 8-OHdG was measured to assess oxidative DNA damage. Other assays evaluated various oxidative stress indicators.

None of the exposures increased DNA damage as indexed by the tail moment, but the tail intensity index was increased by exposure to both frequencies. The levels of 8-OHdG increased significantly with frequency and SAR. The rats were randomly assigned to exposure groups and the tests and analyses were performed in a blind fashion. Only 100 cells per rat were examined in the comet assay.

Summary of DNA and chromosome damage in animals

The BCCDC summarized the status of research in this area in 2013 as:

> *Results of studies of DNA damage, micronucleus formation, apoptosis, production of reactive oxygen species, gene expression changes, and other genotoxic effects carried out using RF exposure of animal models (mice and rats) tend to be contradictory. Positive results found in one species are usually not replicated. Overall, the criteria important in establishing a causal relationship between short-term or long-term RF exposure and changes in gene expression, apoptosis, production of reactive oxygen species and other potential biologic changes in animal physiology are lacking. Such criteria include consistency of results over several studies among similar animals and strong associations between exposure and response with control for potential confounding factors. This lack of consistent evidence reduces the likelihood that significant adverse physiologic effects occur in animal models due to RF exposure* (BCCDC, 2013, p. 149).

SCENIHR (2015) concluded that "*Overall, because a considerable number of well-performed studies using a wide variety of animal models have been mostly negative in outcome, the animal studies are considered to provide strong evidence for the absence of an effect*" (p. 86).

A considerable number of new studies have assessed the potential effects of RF exposure on DNA and chromosomes in rats and mice, although prior studies of isolated cells *in vitro* provide scant *a priori* justification for conducting more *in vivo* experiments. The range of exposures between the lowest and highest SAR was over 70,000-fold and the duration of exposure ranged

from 7 days to as long as 1 year. Few studies were of high quality, as indicated by elementary failures to randomly allocate animals to treatment groups, to conduct analyses of the data in a manner that was blinded as to the history and treatments of individual animals, to include positive controls to demonstrate that the assays were working properly, and to perform statistical analyses that treated group exposures differently from individual animal exposures. An additional limitation is that few studies except those conducted by the NTP collected data at multiple levels of exposure to assess dose-response relationships. Several studies by Alkis et al. (2019a, 2019b, 2021) assessed effects of exposures to RF fields at multiple levels of exposure measured by SAR. Similarly, another group of investigators (Deshmukh et al., 2015, 2016; Megha et al., 2015) assessed effects at multiple levels of SAR. Both groups of investigators, however, varied the SAR levels at the same time they varied the frequency of the RF field. Studies by the Alkis group all reported a lowering of DNA damage levels as SAR levels increased, perhaps a non-intuitive finding. In contrast, the Deshmukh group of investigators, reported an increase in levels of DNA damage over a range of increasing SAR levels. The interpretation of these trends in SAR reported by both groups of investigators are confounded by the potential role of frequency. Although results reported by Smith-Roe (2019) for the NTP study do include tests for dose response in four tissues and blood,[30] and two brain regions for analyses of 100 cells in male rats exposed to CDMA-modulated fields. Since two of these three trends were driven by SAR exposures at 6 W/kg and one at 3 W/kg, there is scant evidence for any effects at lower SAR levels.

Most studies focused on brain tissue because of the IARC's attention to the statistical associations reported in several large epidemiologic studies between high mobile phone use and tumors of the brain. For indicators of possible DNA damage, few dose-response relationships with SAR were evident across these studies reviewed. In the group of studies conducted by NTP, however, some statistically significant dose-response trends were found, but in individual comparisons of exposed and control groups at specific SAR levels, the SSBs measured by the comet assay were only statistically different at SAR levels of 5 W/kg in mice and 6 W/kg in rats, which are well above the permitted whole body exposures of the general public of

[30] "*A result was considered positive if the trend test was significant and at least one dose group was significantly elevated over the control, or if two or more dose groups were significantly increased over the corresponding control*" (Smith-Roe et al., 2019, p. 5).

0.08 W/kg in Canada, the United States, and Europe. One study reported mixed effects in liver tissue where both an increase and a decrease in SSBs were reported, but no such response was reported in the NTP study. A few other studies also reported mixed results for the testis.

Summary of in *vivo studies* of cancer

The cross-sectional observational studies in which characteristics of volunteer subjects were categorized by presumed or measured RF field exposure and measured SSBs or MN were overall of poor quality with regard to exposure assessment, sample size, and methods to minimize potential biases and confounding by other factors, and standards for the detection of these markers of damage to DNA. In addition, by their design such studies are not suitable for assessing causal hypotheses.

The results of two studies that evaluated survival and histopathological analyses of multiple organs reported by the NTP and the Ramazzini Institute provided outlier findings compared to multiple previous studies of long-term exposure that had reported no effect of RF field exposure on the development of tumors. Despite the large number of animals in these studies, limitations in the design and interpretation of them preclude any straight-forward interpretation of the results. Comprehensive reviews to date have not concluded that these studies provide support for the idea that RF field exposure causes cancer. Additional studies are planned to address issues raised by these studies.

Two other studies that evaluated the effects of RF field exposure on the development of tumors initiated by the injection of a chemical carcinogen (Lerchl et al., 2015) or grafted small tumors into the brain of healthy animals reported mixed results (Ouadah et al., 2018). The former suggested a greater effect on tumor development with RF field exposure while the latter suggested no effect. Both studies had significant limitations in the methodology and analysis of the data.

Tests for DNA damage in the comet assay, chromosome damage in the MN assay, measurements of 8-OHdG, and cytotoxic damage were conducted in 16 experimental studies of animals. The results are summarized in Appendix 1. Eight experiments were reported by investigators in the NTP study (Smith-Roe et al., 2020). In the NTP study, the effects on measured SSBs reported at the stated cut-off value of $p<0.025$ were in the brains of male rats

exposed to 900 MHz CDMA signals at 6 W/kg, and in male mice exposed to 1,900 MHz CDMA signals at 5 W/kg and 10 W/kg, or to 1,900 MHz GSM signals at 10 W/kg. No evidence of damage to chromosomes from RF field exposure was evident in measures of MN. No evidence of cytotoxicity (necrosis or apoptosis) to the brain or liver was reported (NTP, 2018c, 2018d).

In the other 15 studies carried out by diverse investigators, the evidence for effects was scattered, with 5 studies reporting no effect, 3 studies reporting increases in an indicator, and 7 studies reporting both increases and decreases depending upon tissue and indicator. Given that the exposure systems, number of animals tested per group, histopathology experience, exposure levels, and procedures to minimize bias of these studies do not match the characteristics of the NTP study, it is unreasonable to ascribe those reported effects to RF field exposure, particularly as the effects were not clearly tied to the level of exposure in a dose-related fashion. The rationale for emphasizing factors other than RF field exposure as the likely explanation for their results also is justified because the exposure levels in the non-NTP studies at which effects on DNA indicators were reported were up to 70,000-fold lower than the highest SAR levels in the NTP study. In the one study that could be considered a partial replication of the NTP mouse study, since it tested exposures at an SAR of 5 W/kg, no increase in SSBs was reported in contrast to the NTP report. It also is important to note that, as with human biomarker studies, none of the experimental animal studies that reported increases in SSBs or MN met the criteria for a positive determination of DNA damage. The one laboratory that had a history of expertise in the measurement of SSBs and met other qualifications required by the OECD to be regarded as a high quality study did not report any effect of RF field exposure on measures of SSBs (Zong et al., 2015).

In addition, the NTP study reported that the lowest specific RF exposure level at which a potential adverse effect on DNA and chromosomes was in male mice at 5 W/kg. This level is higher than the accepted threshold of 4 W/kg for disruption of body homeostasis for temperature in rats and humans, a level above which core body temperature could be expected to be raised by about 1°C (ICES, 2019; ICNIRP, 2020a). In the short-term studies reviewed in this report, only Deshmukh et al. (2015) measured the temperature of the animals, but the SAR level was so low that no temperature elevation was observed (nor expected). In the NTP genetic studies, no

measurements of body temperature were taken. In the NTP pilot studies, the only recordings of body temperature were from sensors implanted under the skin, which could give lower readings than core body temperature. Given the variability of exposure and the size and behavior of animals, it is quite possible that the exposures in the NTP genetic studies and in the main study could very well have raised the body temperature of some animals by 1°C or more. This point is made by SCENIHR, which noted that effects of exposure to RF that are not related to tissue heating are difficult to interpret, except where exposures are very low.

> *... the (macroscopic) biochemical and physiological responses depend on temperature. Most chemical properties, chemical reaction kinetics and cellular processes are temperature dependent. Therefore, any claimed borderline between thermal and non-thermal effects necessarily needs to be defined with regard to specific effects such as triggering the onset of thermoregulatory reactions. Therefore, to generally claim that effects observed below exposure limits would necessarily be non-thermal is misleading and ignores this basic relationship* (SCENIHR, 2015, p. 58).

A prior in-depth review of genetic measures of rats and mice by IARC concluded:

> *Approximately half of the laboratory studies of genetic damage in mammalian systems, generally rats and mice, had limitations related to reporting on the exposure system, small sample sizes and exposures that induced thermal effects, or that were so low as to be no challenge to the animals. Of the remaining studies, many were satisfactory and of comparable quality, but showed contradictory results. [and] concluded that there was weak evidence that RF radiation is genotoxic, and no evidence for the mutagenicity of RF radiation* (IARC, 2011, pp. 414-415).

A review of genotoxic research that included exposures to RF fields provided the caveat that while the literature included reports as described above for SSBs and other parameters, the evidence that these lead to downstream mutations has not been confirmed. Lai et al. (2021) stated, "*available data do not suggest mutagenic effects after RFR (radiofrequency radiation) exposure*" (p. 2).

Non-specific symptoms

The primary focus for this section of the report is on the recent studies of low-level, far-field exposures to RF fields and non-specific symptoms related to well-being. The WHO identifies electromagnetic hypersensitivity (EHS) as applying to "*some individuals [who] report mild symptoms and react by avoiding the fields as best they can, [and] others [who] are so severely affected that they cease work and change their entire lifestyle.*"[31] A WHO Working Group subsequently suggested that the term EHS be replaced by Idiopathic Environmental Intolerance attributed to Electromagnetic Fields (IEI-EMF) because of a lack of evidence for any clear link of effects from electromagnetic field exposure (Hillert et al., 2006).

Epidemiologic studies and human experimental studies have evaluated whether exposure to relatively low levels of RF energy can cause short-term and long-term symptoms. The scientific literature includes studies of exposure from sources that are both near-field (i.e., mobile phones) and far-field (i.e., wireless LANs, base stations, and advanced meters). Some studies include methods to assess whether people can perceive RF field exposure at these low levels.

Summary of prior reviews

Advisory Group on Non-ionising Radiation Protection

AGNIR (2012) provided the following summary regarding symptoms of well-being:

> *Although numerous observational studies have attempted to assess the association between exposure to RF fields and symptoms, many of these have suffered from important methodological deficits. In particular, the common reliance upon self-reported exposure measures or limited spot measurements within a single place in the home, together with the frequent failure to account for potentially important confounders, makes it impossible to draw any firm conclusions from many of the studies* (AGNIR, 2012, p. 252).

[31] https://www.who.int/peh-emf/publications/facts/fs296/en/ (Accessed April 13, 2021).

British Columbia Centre for Disease Control

> *In general, subjects who are self-declared with 'EHS' do not reliably detect RF when blinded to the source, and RF fails to trigger symptoms in self-declared EHS individuals in a reliable, reproducible, and consistent way. However, provocation studies are limited to examining acute (short-term) exposure to RF, and acute symptoms and the effects of cumulative, chronic exposure to RF on persistent human health symptoms have not been studied thoroughly* (BCCDC, 2013, p. 5).

Royal Society of Canada

The panel of scientists convened by the Royal Society of Canada reported that taken together, research in the past ten years does not provide "*firm evidence for the hypotheses that people with IEI-EMF can perceive RF energy at levels below the limits in SC6 or that there is a causal link between exposure to RF energy and their symptoms*" (RSC, 2014, p. 18).

Scientific Committee on Emerging and Newly Identified Health Risks

SCENHIR's conclusion regarding symptoms attributable to IEI-EMF stated:

> *The symptoms that are attributed by people to RF EMF exposure can sometimes cause serious impairments to a person's wellbeing. However, research conducted since the previous Opinion adds weight to the conclusion that RF EMF exposure is not the cause of these symptoms. This applies to the general public, children and adolescents, and to people with IEI-EMF. Recent meta-analyses of observational and provocation data support this conclusion* (SCENIHR, 2015, p. 143).

International Commission on Non-Ionizing Radiation Protection

> *In summary, no reports of adverse effects of radiofrequency EMF exposures on symptoms and wellbeing have been substantiated, except for pain, which is*

related to elevated temperature at high exposure levels (from both direct and indirect radiofrequency EMF exposure) (ICNIRP, 2020a, p. 519).

Swedish Radiation Safety Authority

In their Thirteenth Report on Recent Research on EMF and Health Risk in 2019, SSM concluded:

In terms of symptoms, several studies reported associations with self-reported mobile phone use but not for exposure from transmitters. These studies may indicate that other aspects related to frequent mobile phone use (e.g. distraction or stress) than RF-EMF exposure may have an impact on health-related quality of life (SSM, 2019, p. 49).

In the most recent Fourteenth Report in 2020, the SSM stated the following:

New studies on mobile phone use and media use in relation to health-related quality of life, cognitive function and behaviour of children and adolescents often report associations. Some studies point to other exposures related to media use, but not RF-EMF, as a causal factor since the strongest associations were found with e.g. texting, which causes minimal amounts of exposure. These studies show that it is challenging to separate effects from RF-EMF exposure from other aspects of mobile phone use such as being woken up during night, blue light exposure or addictive behaviour. This is especially the case when dealing with outcomes like health-related quality of life, cognitive functions or behaviour (SSM, 2020, p. 46).

World Health Organization

A number of studies have investigated the effects of radiofrequency fields on brain electrical activity, cognitive function, sleep, heart rate and blood pressure in volunteers. To date, research does not suggest any consistent evidence of adverse health effects from exposure to radiofrequency fields at levels below those that cause tissue heating. Further, research has not been

able to provide support for a causal relationship between exposure to electromagnetic fields and self-reported symptoms, or "electromagnetic hypersensitivity.[32]

Experimental studies

Since the SCENIHR (2015) review, several studies have been published, many of which have been reviewed by SSM (e.g., 2015, 2016, 2018, 2019, 2020). Therefore, those will not be reviewed in detail but will be referenced as appropriate in the context of more recent studies. New studies not reviewed elsewhere are discussed below.

- **Andrianome et al. (2019)** is part of a larger research program by these investigators on the issue of IEI-EMF. Previously, they reported that the levels of alpha amylase, an enzyme in saliva that breaks down starches and has been suggested by some to be an indicator of general stress levels, were higher in IEI-EMF persons than control subjects (Andrianome et al., 2019).

  The purpose of the study was to identify a biomarker for IEI-EMF and responses to environmental stimuli that persons had suggested were the cause of their symptoms. Ten of the subjects from the previous study (eight women and two men), who identified themselves as having IEI-EMF symptoms for the past 2.4 to 21.3 years were included in the study. Each subject reported symptoms (not specified) prior to this study as occurring in response to any one of five specific RF wireless signals. None disclosed having psychiatric conditions or taking medications. They agreed not to drink coffee or alcohol for the 24 hours before testing sessions and not to brush their teeth or exercise within 1 hour of the test session.

  Subjects were tested in two sessions about 1 week apart: a sham-exposure session and an RF-exposure session. In both sessions, saliva samples were collected at the beginning of the session and after each 5-minute period in which they were exposed to 900 MHz

[32] https://www.who.int/en/news-room/fact-sheets/detail/electromagnetic-fields-and-public-health-mobile-phones. Accessed April 13, 2021.

GSM signals, 1,800 MHz GSM signals, 2.45 GHz Wi-Fi signals, DECT signals,[33] or sham exposures. RF signals were presented at an intensity of "*about 1 V/m*" at the head and body. The 10-minute periods between exposures were used for the collection of samples, which were analyzed for levels of alpha amylase, immunoglobulin A (a major component of the immune antibody system that protects against infection), and cortisol. The study was planned so that neither the subjects nor the investigators analyzing the data were aware of the exposure conditions during the study or prior to its conclusion (i.e., a double-blind procedure). Only 3 of the 10 subjects correctly guessed whether RF exposure or no exposure was administered on test days. The investigators found no effect of RF field exposure on levels of alpha amylase, immunoglobulin A, or cortisol in the saliva of the subjects. These results indicate that exposure to RF fields of varying frequency or modulation does not affect these biomarkers or produce generalized stress in IEI-EMF subjects. The strength of the study is that it was designed to be double-blind to prevent awareness of the exposure conditions from affecting the behavior or actions of the subjects or the experimenters. The number of subjects, however, was small, the individual RF field exposures were of short duration and not described in detail, and the study did not include subjects who identified as having no IEI-EMF symptoms.

- **Selmaoui et al. (2018)** sought to determine whether variations in the conductivity of the skin,[34] interpreted as a measure of sympathetic autonomic activity, is affected by RF field exposure. Twenty-eight male and female volunteers were recruited for the study. The mean age of study subjects was 24 ± 3 years, and the subjects did not differ with regard to blood pressure, body mass index, or age. Inclusion criteria included regular sleep habits, absence of medications, being a non-smoker, and no neurological or psychiatric illness. Subjects were requested to avoid alcohol, coffee, or stimulants for 24 hours prior to testing, and to avoid mobile phones for 2 hours prior to testing. The subjects were tested in two sessions, sham exposure or RF field exposure, according to a counterbalanced, randomized design. Neither the study nor the investigators were aware

[33] Frequency was not specified, but likely to be 1,880 MHz to 1,900 MHz.

[34] This is sometimes called the galvanic skin response because it reflects a change in current flow across the skin when a constant voltage is applied that occurs due to changes in conductance related to the activity of sweat glands.

of the exposure conditions (double-blinded) until after data analysis. The exposure consisted of 26 minutes of sham exposure or 26 minutes of RF field exposure using a 900 MHz GSM mobile phone at 0.93 W/kg attached to the left ear. The galvanic skin response (GSR) was recorded as the voltage measured between electrodes attached to two fingers of the left hand. Signal audio tones at an intensity of 60 decibels on the A-weighted scale initiated the recording of GSR for 2.75 minutes at intervals of 6 minutes. Recordings of the subjects taking deep breaths were made to confirm the expected GSR response. Although differences in tonic and phasic GSR responses were measured between sessions, these differences were present both before and after exposures, so could not have been a result of either sham or RF field exposures. The authors did not replicate a reported effect of mobile phone RF fields on the latency of the GSR response of IEI-EMF persons to stimuli (Johansson et al., 2008), but did confirm the absence of an effect of mobile phone RF fields on GSR, as reported in other studies (Wilén et al., 2006, Andrianome et al., 2017; Eltiti et al., 2009; Stevens, 2001).

Summary of experimental studies

Reviews by health and scientific agencies of experimental studies of IEI-EMF up to 2015 have not concluded that exposure to RF signals from mobile phones or other sources can be detected by persons or that such exposures cause symptoms or disturbances to well-being. That conclusion is not changed by the results of more recent studies published since 2015, including those reviewed by scientists in SSM's Scientific Council on Electromagnetic Fields reports or by the results of two more recent experimental studies reviewed above.

Epidemiologic studies

As noted above, many of the experimental and epidemiologic studies published since the SCENIHR (2015) report were reviewed by SSM (2016, 2018, 2019, 2020). Some of the epidemiologic studies on IEI-EMF that were reviewed in recent SSM reports included investigations into the potential association between actual and perceived exposure to EMF/RF fields and non-specific physical symptoms (NSPS) in the Netherlands (Baliatsas et al., 2015, 2016), mobile phone use and non-specific symptoms in South Korea (Cho et al., 2016, 2017), modeled and perceived exposure to RF fields from mobile phone base stations and non-specific

symptoms and sleep disturbances in the Netherlands (Martens et al., 2017, 2018), and the use of wireless communication devices and symptoms in Switzerland (Schoeni et al., 2016, 2017). The SSM Council's review of these and other studies resulted in the Council's most recent conclusions that "*other aspects related to frequent mobile phone use (e.g. distraction or stress) than RF-EMF exposure may have an impact on health-related quality of life*" (SSM 2019, p. 49) and that "*[s]ome studies point to other exposures related to media use, but not RF-EMF, as a causal factor since the strongest associations were found with e.g. texting, which causes minimal amounts of exposure*" (SSM 2020, p. 46).

- **Ikinci Keleş and Uzun Şahin (2021)** conducted a cross-sectional survey in Turkey to investigate cell phone use behaviors and reported changes in health following exposure to RF fields. The authors administered a questionnaire to 1,019 university students, age 18 to 24, that collected self-reported information on the participants' cell phone usage, "*general health problems*," "*sleep problems*," and "*health problems arising after cell phone use in the previous six months*" (Ikinci Keleş and Uzun Şahin, 2021, p. 140). The survey results indicated that students spent an average of 4 to 8 hours per day on their cell phones. Duration of daily cell phone use was significantly associated with the self-reported symptoms of headache, carelessness, fatigue, numbness, and feeling tired on awakening, but was not associated with other symptoms, including dizziness, lack of concentration, and sleep onset latency. The participants were also asked whether they knew their cell phones' SAR value; only 2% of respondents correctly identified this value for their cell phone. Limitations of this study include the inability to establish a temporal relationship between the exposure and outcomes of interest (i.e., failing to demonstrate that the cell phone use occurred prior to the onset of the reported health symptoms), the lack of personal RF exposure measurements, the reliance on self-reported symptoms, and the potential for confounding.

- **Kacprzyk et al. (2021)** conducted a meta-analysis of six epidemiologic studies to investigate the association between mobile phone use and tinnitus. The included studies varied by study design (cohort, case-control, and cross-sectional) and exposure assessment method and were therefore assessed separately. Two cohort studies assessed exposure to mobile phones using network operator data; no significant association was

observed between tinnitus and high exposure to mobile phones (defined using the highest exposure category in each study) compared to low exposure. Similarly, no significant associations were reported in analyses that included studies of self-reported exposure. Limitations include the small number of studies included in the analysis and the variability in study design and exposure assessment methods, as well as the use of self-reported exposure data in the majority of the studies.

- **Lopez et al. (2021)**, in a cross-sectional survey, examined the relationship between select health indicators and electromagnetic radiation measurements in a neighborhood in Spain concerned about the surrounding telephone antennas. The study was conducted "*at the request of a neighborhood association… concerned about the proximity of the [telephone] antennas to their homes*" (Lopez et al., 2020, p. 2). The authors designed a survey to collect information on "*health indicators that may be sensitive to RF electromagnetic radiation*" including headaches, dizziness, and parameters related to sleep and tiredness. The survey also collected information on the amount of time the participant had lived in the home. A total of 268 surveys were conducted, including 174 surveys from participants living in the exposed area and 94 living in a control area (defined based on a cutoff distance to the antennas of approximately 300 meters). In addition, a total of 105 indoor and outdoor measurements were collected at the residences using a spectrum analyzer and isotropic antenna (frequency range: 700 MHz to 6 GHz). For the statistical analyses, the authors categorized the resulting power density measurements into three bins: low exposure (7-1,775 microwatts per square meter [$\mu W/m^2$]), medium exposure (>1,775-3,543 $\mu W/m^2$), and high exposure (>3,543-5,311 $\mu W/m^2$). A statistically significant association was reported between medium or high exposure and headache intensity, frequency of dizziness, number of hours slept per day, and several of the tiredness indicators. The authors also noted that the prevalence of cancer in the study population was 5.6%, which they reported was significantly higher than that of the total Spanish population. Limitations of the study include its cross-sectional study design, the inclusion of a non-random sample of concerned study subjects who are more likely to report having the symptoms of interest (i.e., selection bias), the use of an unvalidated survey to collect health information, and the lack of

personal measurements to capture the participants' true exposure levels. These limitations result in the study being of limited scientific value.

- **Meng et al. (2021)** conducted a cross-sectional survey to investigate mobile phone use characteristics and sleep quality among 4,234 medical students in China. Mobile phone use characteristics and sleep quality data were collected via questionnaire from December 2016 to January 2017; the questionnaire collected mobile phone use information that included purpose of use (e.g., entertainment, work, information), posture during use (e.g., sitting, standing, lying down), distance between the user's eyes and the screen, daily cumulative use time, and use time before bed. The authors reported that 100% of the participants used mobile phones frequently (defined as an accumulated daily use time of greater than 1 hour). Poorer sleep quality was associated with increased daily accumulated use time (>5 hours) and increased use time before bed with the lights off (>30 minutes). Limitations of this study include its cross-sectional design, the lack of information on potential confounders not related to mobile phone use that may impact sleep quality (e.g., physical or mental conditions, environmental exposures) and the use of self-reported exposure data. The cross-sectional design of the study also means that a causal relationship between mobile phone use and sleep quality cannot be established.

- **Caumo et al. (2020)** examined the use of electronic devices among adolescents in Brazil and the potential impact on sleep quality. The study included 177 students, ranging in age from 11 to 18, from six public schools in Porto Alegre. Use of electronic devices (grouped by television/computer monitors; tablets/portable video games; and mobile phones) was assessed using an electronic usage diary. A high prevalence of device use at night-time (after 8:00 PM) was observed; approximately 70% of participants reported night-time mobile phone use. For mobile phones, both higher duration of night-time use and later final-use time were associated with worse sleep quality. Poor sleep quality was also associated with shorter sleep duration on school days and a delayed midpoint of sleep on weekends. Limitations of this study include the lack of personal RF field exposure measurements and the potential for findings to be a result of reverse causality (i.e., that participants who have difficulty sleeping may be more likely to use their

devices when they cannot sleep, rather than the use of device being the cause of sleeping issues). Potential confounding by underlying psychological conditions is another concern in the study.

- **Bolte et al. (2019)** examined whether NSPS reported in persons with self-reported sensitivity to RF fields were associated with measured RF field exposure levels in the Netherlands. The study included 57 participants, ranging in age from 16 to over 65, who were equipped with a personal dosimeter worn for 5 consecutive days and measuring 12 different frequency bands (i.e., FM radio [88-108 MHz], TV3 [174-233 MHz], TETRA [380-400 MHz], TV4 and TV5 [470-830 MHz], GSM uplinks [880-915 MHz], GSM downlinks [925-960 MHz], data collection system [DCS] uplinks [1,710-1,785 MHz], DCS downlinks [1,805-1,880 MHz], DECT [1,880-1,900 MHz], UMTS uplinks [1,920-1,980 MHz], UMTS downlinks [2,110-2,170 MHz], and Wi-Fi [2,400-2,500 MHz]), as well as a global positioning system logger and an electronic diary that collected information on NSPS. The authors analyzed the data using time-weighted average exposures and two different time lags (0-1 hours and 1-4 hours after exposure); associations were assessed on both the group level and individual level. No statistically significant associations were observed at the group level between measured personal exposure and NSPS. In a sub-analysis of 36 participants who attributed their most important health complaint to a measurable RF source, statistically significant associations were observed for only one participant (between Wi-Fi and total NSPS score and severity). Observed significant associations were not always consistent between the two different time lags. Among the 36 participants included in the sub-analysis, Wi-Fi exposure was the self-declared most important source of health complaints; of the 21 participants who were excluded from the sub-analysis, 16 could not name the RF source or frequency band attributed to their health complaints, and 4 attributed their complaints to a source that was actually ELF-EMF. The authors acknowledged that the observed associations at the individual level may be due to residual confounding and thus "*the outcomes have to be regarded very prudently*" (p. 1).

- **Cabré-Riera et al. (2019)** investigated the association between cordless and mobile phone use and sleep quality in adolescents in Spain. The cross-sectional study included

258 participants, age 17 to 18. Information on the use of phone and screen devices (e.g., laptop, tablet, television, or video game consoles) was collected from self-reported questionnaire data; the Mobile Phone Problematic Use Scale was used to assess "*problematic*" (as defined by the Use Scale tool) mobile phone use dependency. Sleep quality was assessed both subjectively (using a sleep quality index) and objectively (using actigraphy data collected for 7 nights). The authors reported that habitual (defined as the 15th to 80th percentile of use) or frequent (>80th percentile) "*problematic*" mobile phone use was associated with lower sleep quality compared to occasional (<15th percentile) use; lower sleep quality was also associated with one or more cordless phone calls per week. No associations were observed between sleep quality and mobile or cordless phone call duration. Both decreased sleep efficiency and increased minutes of wake time after sleep onset were associated with higher tablet use; no associations were observed between other devices and any of the sleep measures assessed. The authors concluded that "*sleep displacement, mental arousal, and exposure to blue light screen emission might play a more important role on sleep than a high RF-EMF exposure to the brain*" (p. 341). Limitations of this study are similar to those noted for Caumo et al. (2020) in that they lacked personal RF exposure measurements for the participants, there was the potential for reverse causality of the findings, and there was potential for confounding.

- **Elliot et al. (2019)** investigated the association between TETRA radio use (380-400 MHz) and absence due to sickness among British police officers in the Airwave Health Monitoring Study. The study included 32,102 participants; personal radio use was estimated using self-reported information combined with a call data record database and was linked to records of absence due to sickness. No significant differences in risk of absence due to sickness were observed between personal radio users versus non-users, including for several sub-analyses, and users had a statistically significant lower rate of absence due to sickness compared to non-users. For most causes of absence due to sickness, the risk of absence was lower among users than non-users. Among users only, slight significant associations were observed between a doubling of radio use and the risk and rate of absence due to sickness. The authors concluded that the results showed "*similar or lower risks of sickness absence in TETRA radio users compared with non-*

users" and that the highest risk of absence due to sickness observed in users with greater radio use "*may reflect working pattern differences among police personnel rather than effects of radiofrequency exposure*" (p. 148).

- **Wdowiak et al. (2019)** assessed the relationship between RF field exposure and emotional disorders in Polish women employed in two specific industries. The study included 200 women, half of whom worked in the health service sector, while the other half worked as shop assistants in shopping centers. Physical activity and symptoms of depression and anxiety were assessed using self-reported questionnaires. RF field exposure was assessed using a dosimeter worn for 10 hours on the participants' left arm, which measured electromagnetic fields in the following ranges: GSM 900 (880-960 MHz), GSM 1800 (1,710-1,880 MHz), UMTS (1,920-2,170 MHz), DECT (1,880-1,900 MHz), and WLAN (2.4-2.43 GHz). The authors used the dosimeter readings to determine if the source of the fields was a base station or mobile phone device. Women working in shopping centers were observed to spend significantly more time per day using a mobile phone compared to women working in the health service. Increased daily mobile phone use time was correlated with decreased feelings of depression and increased anxiety in women working in the health services sector, increased daily Internet use time via the mobile phone was correlated with increased feelings of depression for women working in the shopping centers. No consistent patterns were observed between depression or anxiety symptoms, or with individual ranges of RF field levels. When assessing other risk factors, correlations were observed between anxiety level and level of education in women in the health service industry and between level of depression and physical activity in women working in shopping centers.

Summary of epidemiologic studies

Reviews by health and scientific agencies of epidemiologic studies of IEI-EMF up to 2015 did not conclude that exposure to RF signals from mobile phones or other sources cause symptoms or disturbances to well-being. That conclusion is not changed by the results of more recent studies published since 2015, including those reviewed by scientists in SSM's recent Scientific Council on Electromagnetic Fields reports and those summarized above. Several recent cross-sectional studies were conducted in which information on mobile phone use and various health

symptoms were collected via questionnaire or electronic diary. While some of the studies reported an association between various metrics of mobile phone use and self-reported symptoms, such as headache and fatigue (Ikinci Keleş and Uzun Şahin, 2021) or poor sleep quality (Caumo et al., 2020; Meng et al., 2021), the cross-sectional design of these studies means that a causal relationship between mobile phone use and the health outcomes of interest cannot be established. These studies also had other important limitations, including the lack of personal RF exposure measurements, the reliance on self-reported symptoms rather than clinical evaluations, the potential for confounding, and the potential for reverse causality in the observed relationships. The one recent study that collected RF exposure measurements using personal dosimeters (Bolte et al., 2019) found no statistically significant overall associations between measured personal exposure and non-specific physical symptoms. Taken together, the results of recent epidemiologic studies of IEI-EMF do not change the conclusions of the scientific and health agencies that have previously reviewed the research in this area.

Other health conditions studied

A number of additional health conditions have been investigated in the scientific literature to assess whether RF field exposure could contribute to these conditions. These health outcomes include, but are not limited to, nervous system and neurobehavioral effects (e.g., neurological diseases, effects on cognitive function, impacts on hearing or vision), cardiovascular conditions, reproductive and developmental effects, and various conditions of the head and neck region (including disorders of the eye). While studies investigating these outcomes are not covered in this report, they have been reviewed by the expert panels established by several of the scientific and health organizations previously discussed (ICNIRP, 2009; AGNIR, 2012; SCENIHR, 2015; SSM, 2016, 2018, 2019, 2020). The overall conclusions of these review panels remain consistent, that the scientific evidence does not confirm that exposure to RF fields below scientifically-based exposure guidelines cause or contribute to the development of any adverse health effects, including chronic diseases and other health conditions as listed above.

Specific conclusions of the SCENIHR (2015) report related to these health conditions include the following (p. 6):

Overall, there is a lack of evidence that mobile phone RF EMF affects cognitive functions in humans.

Human studies on neurological diseases and symptoms show no clear effect, but the evidence is limited.

The previous SCENIHR Opinion concluded that there were no adverse effects on reproduction and development from RF fields at non-thermal exposure levels. The inclusion of more recent human and animal data does not change this assessment.

Human studies on child development and behavioural problems have conflicting results and methodological limitations. Therefore, the evidence of an effect is weak.

Studies on male fertility are of poor quality and provide little evidence.

Effects of exposure on foetuses from mother's mobile phone use during pregnancy are not plausible owing to extremely low foetal exposure.

7. Conclusion

In this report, recent scientific research related to RF field exposure and human health has been reviewed to determine whether the findings impact the conclusions reached in comprehensive reviews completed by scientific and health organizations, including the 2015 review by SCENIHR. Many of these agencies, including SCENIHR, use a weight-of-evidence approach to critically evaluate the scientific literature, which aims to ensure that all relevant studies are considered, regardless of their conclusions or support for (or against) any particular hypothesis. Based on their reviews, these organizations have concluded that research does not confirm that RF fields at the levels we encounter in our everyday environment are a cause of cancer, chronic disease, or other adverse health effects.

This report focused primarily on epidemiologic and experimental studies of cancer and symptoms of well-being. Although many studies on RF exposure and health have been published in the last decade, the findings from these studies did not provide sufficient evidence to alter the overall conclusions of health and scientific organizations. When evaluated against established scientific criteria for assessing causality (i.e., the Bradford-Hill criteria), the reviewed studies did not provide evidence in support of a causal relationship between RF field exposure and adverse health effects. Research studies of the poorest quality were identified but not considered in this report, which is consistent with the approach taken in reviews conducted by SCENIHR and SSM.

Several factors contribute to a person's exposure to RF fields, including frequency and intensity of the RF field, duration of exposure, and distance from the source of the field. Most of the epidemiologic studies on RF field exposure and health focus on exposures from mobile phones and hand-held communicators that are held close to the body during use. In contrast, the components of the FlexNet system will be located at considerably farther distances from a person's body. Although fewer recent epidemiologic studies examined exposure from distant sources of RF fields, none concluded that exposure from these sources was associated with cancer. In addition, the wireless signals from the proposed FlexNet system are transmitted infrequently and only for fractions of a second. Overall, the RF field exposure outdoors from any of the FlexNet meters are estimated to be more than 3,000-fold lower than the levels at

which biological and health effects have been evaluated in this report, and when deployed, will produce RF fields at levels far lower than other existing sources.

In summary, neither the reviews conducted by scientific and health organizations nor the recently published research provide a reliable scientific basis to conclude that the operation of FortisBC's proposed FlexNet system will cause or contribute to adverse health effects or physical symptoms in the general population. Exposures to RF fields from the proposed Sonix IQ gas meters are significantly lower than the levels at which biological and health effects have been studied and are substantially lower than the exposure levels produced by other common sources of RF fields.

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As SCENIHR notes, "*In some areas where the literature is particularly scarce, it has been considered important to explain why the results of certain studies do not add useful information to the database*" (SCENIHR, 2015, p. 22). Identified studies that have not been considered in this report because they did not fulfill quality criteria are listed below:

Experimental Studies

Reference	Reason Not Included
Erdem Koç G, Kaplan S, Altun G, Gümüş H, Gülsüm Deniz Ö, Aydin I, Emin Onger M, Altunkaynak Z. Neuroprotective effects of melatonin and omega-3 on hippocampal cells prenatally exposed to 900 MHz electromagnetic fields. Int J Radiat Biol 92(10):590-595, 2016.	Incomplete data analysis; This study was rejected for review by SSM (2018) because of incomplete dosimetry.
Ibitayo AO, Afolabi OB, Akinyemi AJ, Ojiezeh TI, Adekoya KO, Ojewunmi OO. RAPD Profiling, DNA Fragmentation, and Histomorphometric Examination in Brains of Wistar Rats Exposed to Indoor 2.5 Ghz Wi-Fi Devices Radiation. Biomed Res Int 2017:8653286, 2017.	No exposure description, no randomized assignment to treatment, no blinding, no quantitative analyses.
Kivrak EG, Altunkaynak BZ, Alkan I, Yurt KK, Kocaman A, Onger ME. Effects of 900-MHz radiation on the hippocampus and cerebellum of adult rats and attenuation of such effects by folic acid and *Boswellia sacra*. J Microsc Ultrastruct 5(4):216-224, 2017.	No sham control and multiple other problems
Pandey N and Giri S. Melatonin attenuates radiofrequency radiation (900 MHz)-induced oxidative stress, DNA damage and cell cycle arrest in germ cells of male Swiss albino mice. Toxicol Ind Health 34(5):315-327, 2018.	No sham control.
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Epidemiologic Studies

Reference	Reason Not Included
Al-Qahtani K. Mobile Phone Use and the Risk of Parotid Gland Tumors: A Retrospective Case-Control Study. Gulf J Oncolog 1(20):71-78, 2016.	Not a peer-reviewed publication; this study was rejected by SSM (2018).
Carlberg M and Hardell L. Evaluation of Mobile Phone and Cordless Phone Use and Glioma Risk Using the Bradford Hill Viewpoints from 1965 on Association or Causation. Biomed Res Int 2017:9218486, 2017.	This publication was rejected by SSM (2019) for being a narrative review (i.e., secondary research).
Hallberg O. Cancer incidence vs. FM radio transmitter density. Electromag Biol Med 35:343-347, 2016a; Hallberg, O. Cancer versus RM radio polarization types. Eur J Cancer Prev 25:357-360, 2016b.	In their 2017 review, SSM noted that *"[d]ue to unclear methods (unclear selection of areas in Sweden, unclear selection of European countries), undefined source of transmitter data, undefined source and undefined underlying types of cancer data, lack of individual exposure estimates, the study is not informative as to an association of FM radio transmitters and the types of cancer in question"* (p. 72).
Kjellqvist A, Palmquist E, Nordin S. Psychological symptoms and health-related quality of life in idiopathic environmental intolerance attributed to electromagnetic fields. J Psychosom Res 2016;84:8-12.	Did not include any form of RF exposure assessment; this study was rejected by SSM (2018) for not in any way studying the association between RF fields and a health outcome.
Lin JC. Mobile-phone RF/Microwave exposure and memory performance scores in adolescents. Radio Science Bulletin 366:32-35, 2018.	Not a peer-reviewed publication.
Martens AL, Slottje P, Smid T, Kromhout H, Vermeulen RCH, Timmermans DRM. Longitudinal associations between risk appraisal of base stations for mobile phones, radio or television and non-specific symptoms. J Psychosom Res 112:81-89, 2018.	Study of associations between risk appraisal of base stations and non-specific symptoms; this study was rejected by SSM (2020) for not studying non-ionizing electromagnetic fields

Appendix 1

Summary of Animal DNA and Chromosome Studies

Study	Species	Sex (Weight, g)	N/group	Frequency	SAR (W/kg)	Duration	Cytogenetic	Comet Assay (SSB)				Oxidation (8-OHdG)
								Brain	Liver	Blood	Testes/Lung	
Furtado-Filho et al. (2014)	Rat	M+ F (?) M Day 0 (5-6) Day 6 (10-12) Day 15 (22-32) Day 30 (46-78)	6	950 MHz	Prenatal 0.03-0.01 0 days 0.88 6 DAYS 0.51 15 days 0.18 30 days 0.06	0.5 hr x (21 prenatal + 0, 6, 15, 30 days)			NO 0 days 6 days ↓15 days ↑30 days			
Furtado-Filho et al. (2015)	Rat	M+ F (?) M Day 0 (5-6) Day 5 (10-12)	6	950 MHz	Prenatal 0.35-0.55 0 days 1.32 6 days 1.14	0.5 hr x (21 + 0, 6 days)		NO				
Deshmukh et al. (2015)		M (150-200)		900, 1,800, or 2,450 MHz	0.0005953 0.0005835 0.0006672	180		√				
Zong et al. (2015)	Mouse	M (25)	8	900 MHz	0.0548	7			NO	NO		
Sahin et al. (2016)	Rat	F (200–256)	6-9	2.1 GHz	0.4	10, 40		√				↑10 days ↓40 days
Akdag et al. (2016)	Rat	M (313)	8	2. GHz	0.0001414	12 mo		NO	NO		√-Testis/No-Lung	
Güler et al. (2016)	Rabbit	M, F	9	1.800 MHz	0.018	15 min/day 1 mo +		NO- Brain NO-TUNEL				
Jeong et al (2018)	Mouse	F ?	14	1,950 MHz	5	22 mo		NO				NO
Jonwal et al (2018)	Mouse	F ?	12	2.45 GHz	0.09	30						NO
Alkis et al. (2019a)	Rat	M (283)	7	900 MHz, 1,800 MHz, 2,100 MHz	0.638 0.166 0.174	2 hr/day 6 mo		NO NO √				√ √ √
Alkis et al. (2019b)	Rat	M (~282)	7	900 MHz, 1,800 MHz, 2,100 MHz	0.638 0.166 0.174	2 hr/day 6 months					NO-tm, ti/ NO-tm,√-ti/ NO-tm,√-ti/	√ √ Testes √
Houston et al. (2019)	Mouse	M (30-33)	3 ? 3	905 MHz	2.2	12 hr/day 1, 3, 5 wks	Testis – NO Sperm				NO- γH2AX/ NO tail intensity/ √ -Halo/	√ -Sperm
Lerchl et al. (2020)	Mouse	M/F (20)	3-6 (pregnant mice)	Ethylnitrosourea + 1,960 (UMTS)	0.04 0.4	24 hr 36 hr 72 hr	NO NO NO	NO NO NO	NO NO NO		/NO /NO /NO	
Sharma and Shukla (2020)	Rat	M (120-150)	6	900 MHz	0.231	1 hr/day 2 hr/day 4 hr/day 90 days	√ √ √	√ tm, tl, % cells √ tm, tl, % cells √ tm, tl, % cells				
Smith-Roe et al., 2020*	Mouse	F	5C 15E	1,900 MHz (GSM)	2.5-10	14 wk	NO#	NO	NO	NO		
Smith-Roe et al., 2020*	Mouse	F	5C 15E	1,900 MHz (CDMA)	2.5 10	14 wk	NO#	NO	NO	NO		

Study	Species	Sex (Weight, g)	N/group	Frequency	SAR (W/kg)	Duration	Cytogenetic	Comet Assay (SSB)				Oxidation (8-OHdG)
								Brain	Liver	Blood	Testes/Lung	
Smith-Roe et al., 2020*	Mouse	M	5C 15E	1,900 MHz (GSM)	2.5 10	14 wk	NO#	√ (only 10 W/kg)	NO	NO		
Smith-Roe et al., 2020*	Mouse	M	5C 15E	1,900 (CDMA)	2.5-10	14 wk	NO#	√ (only 5, 10 W/kg)	NO	NO		
Smith-Roe et al., 2020*	Rat	M	5C 15E	900 (CDMA)	1.5-6	19 wk	NO#	√ (only 6 W/kg) (only Hippocampus)	NO	NO		
Smith-Roe et al., 2020*	Rat-	M	5C 15E	900 (GSM)	1.5-6	19 wk	NO#	NO	NO	NO		
Smith-Roe et al., 2020*	Rat	F	5C 15E	900 (CDMA)	1.5-6	19	NO#	NO	NO	NO		
Smith-Roe et al., 2020*	Rat	F	5C 15E	900 (GSM)	1.5-6	19	NO#	NO	NO	NO		
Alkis et al., 2021	Rat	M (280)	6	1,800 MHz, 2,100 MHz	0.62 0.2	2 hr/day 7 months			NO-tm, √-ti NO-tm, √-ti			√-Liver

*Results also reported in NTP (2018a, 2018b, 2018c, 2018d); # Cytogenetic analyses not reported in Smith Roe et al. (2020) but in NTP (2018a, 2018b, 2018c, 2018d).

Acronyms and Abbreviations: √-, Yes, reported; ti, comet tail intensity; tm, comet tail intensity; hr, hour; C, control; E, exposed.