Environmental Medicine and Clinical Practice:

The Role of Toxicant and Non-ionising Electromagnetic Field Exposure on Health Outcomes and the Ramifications for Clinical Practice.

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Nicole Bijlsma
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List of Abbreviations

ACNEM	Australasian College of Nutritional and Environmental Medicine
AFOEM	Australasian Faculty of Occupational and Environmental Medicine
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
CFS	Chronic Fatigue Syndrome
DoHAD	Developmental Origins of Health and Disease
EDCs	Endocrine Disrupting Chemicals
EEG	Electroencephalogram
EHS	Electromagnetic Hypersensitivity
ELF-EMFs	Extra Low Frequency Electromagnetic Fields
ELF-MFs	Extra Low Frequency Magnetic Fields
EM	Environmental Medicine
EMFs	Electromagnetic Fields
EMP	Environmental Medical Physician
ICNIRP	International Commission for Non-Ionising Radiation Protection
IEI-EMF	Idiopathic Environmental Intolerance attributed to Electromagnetic Fields
IGNIR	International Guidelines on Non-Ionising Radiation
MCS	Multiple Chemical Sensitivity
MPBS	Mobile Phone Base Station
NIR-EMFs	Non-Ionising Radiation Electromagnetic Fields
NREM	Non-Rapid Eye Movement
PIRS-20	Pittsburgh Insomnia Rating Scale-20
POPs	Persistent Organic Pollutants
REM	Rapid Eye Movement
RF	Radiofrequencies
RF-EMFs	Radiofrequency Electromagnetic Fields
SE	Sleep Efficiency
SES	Socio Economic Status
SOL	Sleep Onset Latency
SWS	Slow Wave Sleep
TST	Total Sleep Time
WASO	Wake After Sleep Onset

Preface

This dissertation explores the relationship between environmental exposures and health outcomes, and the challenges clinicians face incorporating environmental medicine into clinical practice. It includes a narrative review, a randomised controlled trial and a qualitative study. Despite the widespread recognition of the connection between environmental exposures and chronic diseases, environmental assessment is largely overlooked in clinical practice. The motivation for this dissertation was the researchers own experience as a clinician and as the founder of the building biology movement (which involves assessing hazards in the built environment) which included witnessing patients with chronic health conditions related to environmental exposures.

The narrative review focused on toxicants and man-made electromagnetic fields, including the increasing levels of exposure, limitations of current risk assessment and regulation, as well as difficulties in linking environmental exposures to health outcomes. The author contributed to the conception of work, searched and compiled the literature, and wrote the manuscript.

The double-blind, randomised, placebo-controlled, crossover pilot study examined the impact of a Wi-Fi enabled device on sleep, given the prevalence of insomnia among patients with environmental exposures. The author participated in the study design and conducted the ethics application and approval, recruited the trial participants, obtained informed consent, assessed the participant's home for suitability, supervised the study, collected the data including recording ambient Radiofrequency Electromagnetic Fields in participant's bedrooms, analysed and interpreted the data, reviewed the literature, and wrote the manuscript.

The qualitative study provided insight into expert clinicians' recognition and assessment of environmental exposures, the challenges they face in treating patients affected by these exposures, and the barriers to incorporating environmental medicine into clinical practice. The author contributed to the study design, obtained ethics approval, recruited and interviewed the participants and obtained their informed consent, interpreted the data, extracted themes from the transcripts and wrote the manuscript.

Abstract

Human exposure to environmental chemicals (toxicants) and non-ionising radiation electromagnetic fields (NIR-EMFs) has increased exponentially over the past four decades and a growing body of evidence suggests these exposures contribute to many chronic diseases typically seen in clinical practice. There are various complexities involved in investigating these exposures and it is unclear how clinicians recognise and assess these exposures, or the barriers and challenges they face incorporating environmental medicine into clinical practice.

The research approach of this thesis was a combination of two literature reviews, qualitative study, and a randomised controlled trial. The literature review revealed population-wide exposures to toxicants are ubiquitous, and the body burden is increasing with each generation. Toxicant exposures account for a significant portion of cancer mortality worldwide as well as neurodevelopmental, neurodegenerative, reproductive and autoimmune issues, along with respiratory and cardiovascular diseases. These exposures are disproportionately distributed among different social classes and races, and toxicant exposures during critical periods of development have been shown to have lasting effects that span generations. In addition, exposure to man-made NIR-EMFs is widespread, yet difficult to study and have been linked to sleep disturbances, childhood leukaemia and brain tumours. This escalation in environmental exposures has occurred concomitantly with an upsurge in the occurrence of patients presenting with chronic and multimorbid conditions.

A review of the literature revealed sleep disturbances has become a significant public health issue, and this has coincided with the widespread deployment of wireless technologies. In order to further investigate the impact of wireless technologies on sleep, a randomised controlled trial was conducted to investigate the impact of multi-night exposure to a 2.45 GHz device (baby monitor) on subjective and objective sleep parameters under real-world conditions. Compared to sham exposure, RF-EMF exposure resulted in a statistically significant and clinically meaningful reduction in sleep quality as indicated by the PIRS-20 scores ($p<0.05$) and a statistically significant increase in EEG power density in the higher frequencies (beta, gamma and theta bands) during Non-Rapid Eye Movement (NREM) sleep ($p<0.05$). No statistically significant differences were observed in heart rate variability or actigraphy.

Risk assessment, setting of exposure standards and the regulation of toxicants and NIR-EMFs is inadequate. There are challenges in establishing a causal relationship between exposure and outcomes due to factors that include**:** multiple routes of exposure, complex mixtures, non-monotonic dose-responses, transgenerational epigenetic effects and identifying susceptible populations. Additionally, there is a lack of standardised tools to assess the quality

of toxicological studies, hindering the evaluation of health risks associated with chronic, low-level exposure to chemicals over a lifetime. Similarly, in the field of EMF research, despite decades of research, most studies display methodological weaknesses that limit the internal validity of the results. Furthermore heterogeneity between studies makes it difficult to compare or collate results and most systematic reviews are unable to draw firm conclusions. While advancements in science, particularly in the omics fields, have provided valuable insights into the complex interplay between genetics and various risk factors over the course of a person's lifetime, risk assessment could be vastly improved for example, by grouping chemicals into classes to facilitate timely protection and prevent regrettable substitutions. Furthermore the regulation of NIR-EMFs needs to account for non-thermal effects, reflect real-world conditions and be conducted over longer periods of time taking into consideration the totality of exposure using personal monitoring devices and mapped to health effects (Apps). Methodologies could also consider exposure dosimetry, placement of exposure devices that are well-defined, consistent, and consider signal features such as modulation, field strength, resonance, pulsing, polarisation and power flux density.

Health care systems have fallen short in their ability to translate knowledge into practice due to challenges accounting for individual differences; determining the strength of evidence and probability of causation, especially when the evidence is inconclusive; and managing conflicts of interest. The absence of public health policy and clinical guidelines and consequent lack of actionable outcomes, often lead to uncertainty in the diagnosis and treatment of patients impacted by environmental exposures. Consequently, despite the call for regulatory reform and the need for training on environmental medicine from numerous stakeholders, environmental assessment is generally overlooked in clinical practice and is largely ignored.

The field of environmental medicine is without rigorous definition and is not integrated into general medical practice. To further explore the complexities and barriers to assessing environmental exposures in clinical practice, a qualitative study was undertaken involving a series of in-depth, semi-structured interviews with clinicians who were members of professional environmental medical organisations. The interviews were recorded and transcribed, and the data was analysed using NVivo 11.3 software to identify dominant themes across the cohort. Whilst clinicians face numerous challenges in assessing environmental exposures due to limited educational resources, lack of definitive laboratory tests, and inadequate training, they agreed that an environmental exposure history is the most valuable clinical tool. Despite extensive postgraduate education and clinical experience, few practitioners consider themselves experts in this field.

Overall the outcomes of this thesis suggests there is a need to publish environmental health research in clinically-related medical journals with actionable outcomes. It is also proposed that environmental health research be incorporated into undergraduate medical training to equip clinicians with the skills to identify patients impacted by exposures, and that Environmental Medicine be established as a medical speciality that involves postgraduate medical training incorporating a personalised medicine approach. This may involve undertaking comprehensive exposure histories (obstetrics, paediatrics, dietary, dental, occupational, trauma, lifestyle and environmental), utilising nutritional and genetic testing, as well as tests to measure toxic load that incorporate ‘omics’ technologies. It is further proposed that educational resources and targeted campaigns be disseminated by health authorities to the public, advising on potential risks of toxicants and NIR-EMFs so that consumers can make an informed choice. By better understanding the relationship between environmental exposures and health outcomes for current and future generations, clinical environmental risk assessment can pave the way for a new era of personalised medicine that unites healthcare professionals, patients, and civil society in exploring the links between the environment and human health.

Thesis Overview & Motivation

Research Motivation

The motivation for this dissertation is the researcher's clinical experience as a naturopath and acupuncturist, her professional experience in assessing health hazards in the built environment, and personal history of ten miscarriages and sleep disturbance. The researcher observed many intractable health issues in patients that appeared to be triggered by environmental exposures and felt that her training did not provide guidelines on how to diagnose or treat these exposures. The researcher also observed a lack of awareness and knowledge about toxicants and electromagnetic fields in clinical practice.

Aims and Objectives

The aim of the thesis was to explore the role of toxicant and non-ionising electromagnetic field exposure on health outcomes, identify challenges clinicians face to recognise and assess environmental exposures, outline the ramifications for clinical practice and explore future directions for incorporating environmental medicine into clinical practice. To achieve this aim, the objectives were to:

1. Review population-wide exposure to environmental toxicants and NIR-EMFs and their relationship to chronic complex diseases.
2. Investigate whether RF-EMFs impact sleep structure and/or subjective sleep quality.
3. Review risk assessment and regulation of toxicants and NIR-EMFs.
4. Explore environmental medicine and identify the challenges expert clinicians in the field face dealing with patients impacted by environmental exposures.
5. Explore the action various stakeholders are taking to understand and mitigate environmental exposures.
6. Explore emerging technologies that enable clinicians to be able to incorporate environmental medicine into their practice.

Thesis Outline

The thesis consists of eight chapters:

- Chapters 1 & 2 provides a review of the rise in the global population's exposure to toxicants and manmade NIR-EMFs and their impact on human health, and the complexities and challenges involved in correlating environmental exposures to adverse health outcomes.
- Chapter 3 presents a double blind, randomised controlled, crossover pilot study investigating the impact of radiofrequencies on subjective and objective measures on sleep quality.

- Chapters 4 & 5 describes how toxicants and NIR-EMFs are regulated, and exposure standards developed and outlines the challenges associated with risk assessment.
- Chapter 6 explores the growth in environmental health research, describes inconsistencies in how environmental medicine is defined, identifies the concerns and actions taken by various stakeholders regarding environmental exposures, and outlines the complexities translating evidence-based healthcare into clinical practice.
- Chapter 7 explores environmental medical practice to determine the populations and exposures that receive the most attention. Semi-structured qualitative interviews with expert environmental clinicians were conducted to identify how they deal with environmental exposures, the challenges they face, and where they obtain their knowledge.
- Chapter 8 describes the implications of the findings and explores future directions for incorporating environmental medicine into clinical practice.

Research Approaches

The research approach used a combination of a literature review, qualitative study, and randomised controlled trial methods. The research began with a literature review, which aimed to explore the rise of environmental exposures and their impact on human health, identify the complexities and challenges involved in correlating these exposures to health outcomes, and assess the barriers to clinical assessment of environmental chemicals. The literature review also looked at the regulatory frameworks and organisations involved in biomonitoring, chemical assessment, and environmental health. The content of the literature review was augmented and expanded to include a review of the rise of NIR-EMF exposures and their impact on health and regulation. This section included a summary of evidence-based reviews on the impact of manmade electromagnetic fields on sleep disturbances.

A review of the literature revealed sleep disturbances has become a significant public health issue, and this has coincided with the widespread deployment of wireless technologies. In order to further investigate the impact of wireless technologies on sleep, a randomised controlled trial was conducted to investigate the impact of multi-night exposure to a 2.45 GHz device (baby monitor) on subjective and objective sleep parameters under real-world conditions. Compared to sham exposure, RF-EMF exposure resulted in a statistically significant and clinically meaningful reduction in sleep quality as indicated by the PIRS-20 scores ($p<0.05$) and a statistically significant increase in EEG power density in the higher frequencies (gamma, beta and theta bands) during Non-Rapid Eye Movement (NREM) sleep ($p<0.05$). No statistically significant differences were observed in heart rate variability or actigraphy.

To further explore the complexities and barriers to assessing environmental exposures in clinical practice, a qualitative study was undertaken involving a series of in-depth, semi-structured interviews with clinicians who were members of professional environmental medical organisations. The interviews were recorded and transcribed, and the data was analysed using NVivo 11.3 software to identify dominant themes across the cohort.

Scope

To maintain scope, the literature review excluded certain types of environmental exposures, such as occupational and industrial exposures, non-ionising radiation above 6 GHz, asbestos, toxic metals and toxicants arising from the pharmaceutical and food industries. It also excluded a discussion on treatment approaches for patients impacted by environmental exposures.

The randomised controlled trial was restricted to healthy adults and had specific inclusion and exclusion criteria. It did not explore the mechanisms by which RF-EMF may impact sleep, personal exposure dosimetry or signal features emitted from the Wi-Fi enabled devices such as modulation, field strength, resonance, pulsing nature, polarisation and power flux density.

The qualitative study was restricted to interviewing expert environmental clinicians who had an undergraduate medical degree, were practising in Australia and/or New Zealand, and were a member of a professional environmental medical association (Australasian College of Nutritional and Environmental Medicine or the Australasian Faculty of Occupational and Environmental Medicine). The interviews were restricted to determine the nature of environmental medicine practice and identify how expert clinicians deal with environmental exposures, including where they obtained their knowledge, the patient populations and exposures that receive the most attention, and the challenges they face. The study did not focus on specific disease states, or treatment approaches and outcomes.

PART A:
THE RISE IN ENVIRONMENTAL EXPOSURES AND CHRONIC DISEASE BURDEN

Chapter 1:
The Rise of Toxicant Exposures and Chronic Complex Diseases

1.1. Introduction

Human exposure to environmental chemicals has increased exponentially over the past four decades and a growing body of evidence suggests that these exposures contribute to many of the chronic diseases typically seen in clinical practice. The failure of genome-wide association studies to explain the vast majority of chronic diseases together with emerging research exploring aberrations in the epigenome and 'exposome' (the total exposures seen during the organism's life) in the aetiology of chronic disease (Paoloni-Giacobino 2011), has led to a paradigm shift in our understanding of chronic non-communicable disease and reconsideration of the health impact of environmental exposures (Laborde et al. 2015). Ongoing large population biomonitoring studies have revealed widespread chemical exposures with levels in humans and wildlife that are known to cause adverse health effects (Calafat 2012; Fernandez et al. 2007; Magnus et al. 2006; Pérez-Gómez et al. 2013; Schindler et al. 2014; Schoeters et al. 2012; Schulz et al. 2012; World Health Organization 2015a). The downstream impact of these exposures has resulted in clinicians seeing a rise in the prevalence of patients with chronic, multimorbid conditions which has been described as a "pandemic of idiopathic multimorbidity" (Genuis 2014:513). This chapter presents results from a narrative review that outlines the increase in the global population's exposure to toxicants and their links to many of the chronic diseases that have substantially increased in prevalence over the past four decades.

1.2. The rise of environmental chemical exposures and body burden of toxicants

Exposure is the "contact between a target and a pollutant on an exposure boundary" (Duan et al. 1990:38). Human exposure to environmental chemicals has increased exponentially over the past four decades as the global middle class has expanded, increasing demand for a range of goods and products (e.g., construction, agriculture, electronics, cosmetics, mining, and textiles). The global sale of chemicals increased from US$171 billion in 1970 (United Nations Environment Programme 2013) to over US$5 trillion in 2017, and is projected to double by 2030 (United Nations Environment Programme 2019a). The number of chemicals in the world is essentially unknown, yet the world's largest database on chemical information - the American Chemical Society's global Chemical Abstracts Service (CAS) Registry^{SM} established

in 1907, currently contains more than 204 million chemicals (American Chemical Society 2024) with around 200,000 new chemicals added each week (Obodovskiy 2015). While many of these chemicals are produced by natural processes, or are inadvertently produced as by-products of fossil fuel combustion or other industrial processes, the number of industrial chemicals in commerce globally is estimated at 40,000 to 60,000, with 6,000 of these chemicals accounting for more than 99 per cent of the total volume (United Nations Environment Programme 2019b). According to the European Environment Agency, 62 per cent of the total volume of chemicals consumed in the European Union (EU) in 2016 were hazardous to health (European Environment Agency 2019). UNEP's report concluded that hazardous chemicals continue to be released in large quantities, that global supply chains and the trade of chemicals and products are increasingly complex, chemical pollution threatens a range of ecosystems and the action to minimise adverse impacts have been estimated in the high tens of billions (US dollars) annually. In addition, the World Health Organisation's estimate that the burden of disease arising from exposure to selected chemicals to impact over 1.6 million lives is likely to be a gross underestimate (United Nations Environment Programme 2019a).

Large population biomonitoring studies performed across the world have revealed widespread chemical exposures from the womb to the tomb with levels in humans and wildlife that are known to cause adverse health effects. Such studies include the National Health and Nutrition Examination Survey in the USA (Calafat 2012; National Center for Environmental Health (U.S.). Division of Laboratory Sciences 2019), DEMOCOPHES survey in Europe (Schindler et al. 2014), German Environmental Surveys in Germany (Schulz et al. 2012), Flemish Environment and Health Study in Belgium (Schoeters et al. 2012), Esteban cross sectional survey in France (Fréry et al. 2012), Russian Federation (World Health Organization 2015a) and the BIOAMBIENT ES in Spain (Pérez-Gómez et al. 2013) in addition to national birth cohort studies conducted in Denmark (Danish National Birth Cohort) (Olsen et al. 2001), France (French Longitudinal Study of Children Survey) (Vandentorren et al. 2009), Norway (Norwegian Mother and Child Cohort Study (Magnus et al. 2006), and Spain (The Spanish Environment and Childhood Research Network) (Fernandez et al. 2007). Whilst human toxicity data is lacking for most chemicals in widespread use (National Research Council 2015) the Cross-Mediterranean Environment and Health Network successfully created a framework (CROME-LIFE Project) that combines environmental monitoring data with human biomonitoring to estimate population exposure and the environmental health burden (European Commission 2021).

Disturbingly, many environmental chemicals are found in human breast milk and the placenta where they directly affect the foetus (Colles et al. 2008). A landmark study conducted by the Environmental Working Group identified 287 chemicals in cord blood, raising the profile

of the widespread exposures to everyday chemicals (Environmental Working Group 2005), and a number of ongoing international biomonitoring studies such as the Maternal-Infant Research on Environmental Chemicals (MIREC) Study in Canada has identified multiple chemicals in pregnant women, cord blood and infant meconium (Arbuckle et al. 2013). The Canadian 'pre-polluted study' identified 137 chemicals in cord blood, 132 of which are reported to cause cancer and 133 that cause developmental and reproductive problems in mammals (Environmental Defence 2013). The brain of a foetus and infant is particularly vulnerable as the central nervous system is the dominant repository of foetal fat and many environmental toxicants are lipophilic. Consequently, the health impact of chemical exposures is most evident in paediatric medicine where chronic disease has overtaken infectious diseases as the major burden of paediatric illness (Genuis 2010). The obvious and extensive impact of environmental chemicals on children's health contributed to paediatrics being the first medical discipline to identify chemical exposures as an important health issue. The American Academy of Paediatrics consequently established an environmental health committee in 1958 and published its first edition of Paediatric Environmental Health for clinicians in 1999 (Etzel 2012).

While chemical exposure is ubiquitous in the general population, the Environmental Justice Hypothesis suggests exposures are unevenly distributed. This hypothesis, which emerged in the 1980s following the publication of several studies in the USA (Hird 1993; Mohai and Bryant 1992; United States General Accounting Office 1995; White 1992; Zimmerman 1993), suggests environmental hazards are inequitably distributed across class and race (Brown 1995). Yet, the strict bifurcation of communities into categories of Environmental Justice and Non-Environmental Justice is problematic (Krieg and Faber 2004), because much of the literature is based on comparisons of exposure and risk between different populations, rather than on the toxicological and biological impacts of those exposures (Bryant 1995). Furthermore, while some minority groups and those with lower socioeconomic (SES) status are likely to bear a greater burden of environmental toxicants given their lifestyle, proximity to waste sites, industrial emissions and poorer quality ambient air, biomonitoring studies have identified toxicants in all individuals, the type and amount of which varies depending upon lifestyle factors and geographical variation. For example higher SES individuals have been found to have higher burdens of mercury, arsenic, cesium, thallium, perfluorinated compounds, certain types of phthalates and benzophenone-3 as a result of their lifestyle (fish consumption, dental history, homegrown vegetables, cosmetic and sunscreen use) (Tyrrell et al. 2013). In contrast, lower SES individuals have been found to have higher levels of lead, cadmium, antimony, bisphenol-A and other types of phthalates, potentially attributed to smoking, occupation and dietary factors (Tyrrell et al. 2013).

1.3. Environmental exposures and the origins of chronic and complex diseases

A growing body of evidence suggests that chemicals present in air, water, soil, food, building materials and household products contribute to many of the chronic diseases typically seen in clinical practice. The dramatic rise in the number of commercially produced chemicals has resulted in exposure to industrial chemicals being ubiquitous in both developed and developing nations and led to an increasing disease burden that is not yet fully understood. According to the Global Burden of Disease, environmental risk factors contribute 5.18% of all disability adjusted life years, however this estimate ignores uncertain risks and excludes subclinical conditions (Forouzanfar et al. 2015). The real costs are therefore more likely to exceed 10% of the global domestic product (Grandjean and Bellanger 2017). The World Health Organisation estimates 23% of all deaths worldwide equating to around 4.9 million deaths and 86 million disability adjusted life years were attributed to environmental chemicals in 2011 (United Nations Environment Programme 2013; World Health Organization 2018c) and approximately one-quarter of global deaths and 28% of global deaths among children under five (updated analysis for the year 2016), are due to modifiable environmental factors (World Health Organization 2018c).

A review further estimated that the disease burden in the European Union associated with exposure to Endocrine Disrupting Chemicals (EDCs) alone, cost $209 billion or 1.28% of Europe's GDP (Trasande et al. 2016) which was similar to the estimated disease burden associated with phthalate exposure of 1.07% of China's GDP (Cao et al. 2019). The estimated annual costs of exposure to EDCs in Europe attributed to individual disorders has been calculated as follows: male reproductive disorders and diseases €15 billion (Hauser et al. 2015), neurobehavioural deficits and disease at €150 billion (Bellanger et al. 2015) and, female reproductive disorders at €1.5 billion (Hunt et al. 2016).

The latest National Health Survey concluded that half of Australians had one or more chronic conditions (Australian Bureau of Statistics 2022). Many of the chronic diseases that have substantially increased in prevalence over the past thirty years, appear to be related in part to developmental factors associated with nutritional imbalance and exposures to environmental factors (Barouki et al. 2012). For example, the 'developmental obesogen' hypothesis is used to explain why the prevalence of obesity among school age children between the early 1970s and late 1990s has doubled or trebled (Wang and Lobstein 2006). Whilst obesity prevalence has begun to plateau, a growing number of chemical obesogens such as organochlorine pesticides (Agay-Shay et al. 2015; Konkel 2015; Mendez et al. 2011), bisphenols (Bhandari et al. 2013; Liu et al. 2019), PCBs and phthalates (Tang-Péronard et al. 2011) have been found in-utero and are implicated in the development of obesity later in life (Iughetti et al. 2015; Janesick and Blumberg 2012).

1.4. The rise in idiopathic, multimorbid chronic diseases

Clinicians are seeing a rise in the prevalence of patients with ongoing seemingly unrelated persistent complaints. Over the past decade, multiple chemical sensitivity (MCS) has increased over 300% impacting 12.8% of the US population (Steinemann 2018a). In Australia, medically diagnosed MCS impacts 6.5% of the population and a further 18.9% report chemical sensitivity (Steinemann 2018b). While multimorbidity is associated with chemical and electrical sensitivity, it presents an increasingly common and confusing primary care dilemma often labelled as:

- Chronic Fatigue Syndrome (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine 2015; Fukuda et al. 1994),
- Systemic Exertion Intolerance Disease (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine 2015),
- Sensitivity-Related Illness (Gugliandolo et al. 2016),
- Idiopathic Environmental Intolerances (De Luca et al. 2010),
- Fibromyalgia (McCarthy 2016),
- Mast Cell Activation Syndrome (Valent et al. 2019; Weiler 2020),
- Electromagnetic Hypersensitivity (Austrian Medical Association 2012; Belpomme and Irigaray 2020; Belyaev et al. 2016; Bevington 2013; Stein and Udasin 2020),
- Sick Building Syndrome (Jafari et al. 2015) and
- Multiple Chemical Sensitivity (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine 2015).

The symptoms experienced by sufferers diagnosed with these syndromes have remarkably similar presentations that warrants further investigation. The diagnosis of these multimorbid conditions is based on exclusion of other causes, as they have no clear aetiology, pathogenesis, or recognised genetic or metabolic markers that can be observed with standard laboratory testing. Despite the fact that the degree of hypersensitivity often parallels the intensity of the total body burden of bio-accumulated toxicants (Rea 1997; Stein and Udasin 2020), patients with these conditions are relatively understudied (Fraccaro et al. 2015) and frequently considered to have psychogenic illness. Such patients have complex needs, and frequently present with a multitude of health complaints in different organ systems that require attention from a range of medical specialists (Herr and Eikmann 2011).

1.5. Timing and transgenerational epigenetic effects

Exposures during critical windows of development play an important role and early life exposures are significant contributors to chronic diseases throughout the lifespan and across generations (Diamanti-Kandarakis et al. 2009; United Nations Environment Programme and World Health Organization 2013). Compelling epidemiological, pharmacological, and toxicological evidence shows that there are several vulnerable periods of growth and development and during these periods, environmental interactions with the immune system and genome can increase susceptibility to central nervous system and metabolic diseases later in life (Fox et al. 2012). Despite the fact that transgenerational effects arising from poor nutrition and chemical exposures in utero are widely reported in the scientific literature (Barker et al. 2006; Delisle 2002; Fernandez-Twinn et al. 2015; Rice and Barone Jr 2000), the impact of epigenetic factors early in life remains largely unexplored in chemical risk assessment (Wang et al. 2013). This is made more poignant by emerging evidence that in utero and early-life exposures may lead to disordered immune responses in adulthood and lead to heritable, epigenetic modifications in the immune responses of subsequent generations (Thompson et al. 2015).

The first association of transgenerational inheritance of disease was documented in the Dutch famine of 1944 to 1945 where nutritional deprivation in utero was associated with increased risks for obesity later in life (Ravelli et al. 1976). Epigenetic inheritance involving environmental chemicals is documented in the daughters of mothers who took the drug diethylstilbestrol (DES) to prevent miscarriages and later went on to have a significantly higher risk of vaginal cancer and other health complaints (Herbst et al. 1971). Similarly, emerging evidence of transgenerational effects in animal models links autism spectrum disorders to an array of environmental factors such as stress or endocrine disruptors such as vinclozolin and BPA, and inadequate nutrition (LaSalle 2013).

The concept of early origins of disease was first brought to light in 1934 by Kermack and colleagues who suggested that decreased death rates due to all causes were the result of improved childhood living conditions (Kermack et al. 1934). This was later expanded upon by Neel in 1962 (Neel 1962), Forsdahl in the 1970s (Forsdahl 1977, 1978), and in the late 1980s by David Barker who associated nutritional deficits during fetal development and consequent low birth weight, to increased risks for obesity, diabetes and cardiovascular disease and thereby came to be considered as the father of the ‘Fetal Origins of Adult Disease’ hypothesis (Barker et al. 1995). Whilst the Developmental Origins of Health and Disease (DOHaD) has historically focused on nutrition, understanding of the role of early life experience in chronic disease requires an integrated analysis of all aspects of the environment (nutrition, psychosocial stress, drugs, microbiome and environmental exposures) and how they interact

to cause disease (Heindel et al. 2015). Thus, the DOHaD has far reaching implications in clinical practice, and implies a need for clinicians to take an extensive paediatric, environmental, and occupational exposure history and consider the role of nutrition and environmental exposures during critical windows of development to understand the development of chronic illness in later life.

Recent developments in the field of environmental epigenomics has further established that primordial germ cells are uniquely susceptible to toxicant exposures leading to epigenetic modifications (DNA methylation, retained histone modification, tRNA fragments, and non-coding RNAs) that impact subsequent generations. For example, whilst it is well established that low birth weight is associated with maternal smoking during pregnancy (Pereira et al. 2017), grandmother smoking on the maternal side was associated with autistic traits, asthma, allergies and obesity among the second filial generation (Perera et al. 2020). A groundbreaking study on rodents, demonstrated that the pulmonary effects of nicotine exposure during pregnancy are not only restricted to the offspring of the exposed pregnancy, but are also transmitted to subsequent generations, through germline epigenetic alterations (Rehan et al. 2012). The study of gene-environment interactions, however, poses special challenges for clinicians because it requires the capacity to integrate complex information unique to each patient including genetic profiling, assessment of nutritional status and detoxifications pathways, and environmental exposures.

1.6. Chronic disease and toxicant exposures

The list of diseases that may be caused or exacerbated by environmental chemical exposures is extensive and growing. This is particularly so for persistent organic pollutants (POPs) such as polychlorinated biphenyls (PCBs) and organochlorine pesticides, which are endocrine disrupting chemicals (EDCs) that interfere with or mimic the function of natural hormones. These diseases include diabetes (Chevalier and Fénichel 2015; Turyk et al. 2015), infertility (Louis et al. 2013; Zama and Uzumcu 2010; Zeliger 2011a), testicular dysgenesis syndrome (Nordkap et al. 2012; Skakkebaek et al. 2001) which encompasses hypospadias (Kalfa et al. 2015; Michalakis et al. 2014), cryptorchidism (Virtanen and Adamsson 2012; Voigt et al. 2010), testicular cancer (Meeks et al. 2012), and poor semen quality (Carlsen et al. 1993; Najafi et al. 2015; Vrooman et al. 2015), ovarian dysgenesis syndrome (Fowler et al. 2012), neurodegenerative diseases such as Alzheimer's Disease (Genuis and Kelln 2015), respiratory disorders such as asthma (McGwin Jr et al. 2010) and chronic obstructive airway disease (Miller and Marty 2010), as well as autoimmune diseases (Rosenthal and Germolec 2000), obesity (Grün and Blumberg 2009; Heindel and vom Saal 2009; Newbold et al. 2009) and cardiovascular disease (Hoek et al. 2013; Xu et al. 2009; Zeliger 2013). Whilst there are

thousands of studies linking environmental toxicant exposures to various disease states, Table 1 lists exemplar meta-analysis and systematic reviews that summarise the research associated with persistent organic pollutants (POPs).

Table 1. *Recent meta-analyses of persistent organic pollutants (POPs) impact on human health*

Author (s) & Year	Date range	Number included studies	Intervention	Outcome
Dev et al. (2023)	(2005-2021)	7 studies	POPs	A statistically significant association of PCBs with an increased risk of ischemic stroke and all stroke. The review also suggested that living near a source of POPs contamination constitutes a risk of exposure and an increased risk of stroke
Lan et al. (2023)	(2000-2022)	21 studies	POPs	Exposure to POPs was significantly associated with delayed pubertal timing in girls but not in boys
Stratakis et al. (2022)	(2013-2020)	59 studies	POPs	Prenatal DDE and HCB levels were associated with higher BMI z-score in childhood. No significant associations were found between PCB-153, PFOA, PFOS, or pentaPBDEs with childhood BMI
Han et al. (2019)	Unable to access document	8 studies	Pesticides	Pesticide exposure showed positive, statistically significant associations with thyroid cancer
Park et al. (2016)	(2007-2015)	11 studies	Pesticides and dioxin like chemicals	Dioxin-like PCBs and p,p'-DDE was associated with a significantly increased risk of hypertension
Lim et al. (2015)	(2003-2014)	8 studies	POPs	Total POPs showed positive associations with statistical significance on prostate cancer
Nilsen and Tulve (2020)	(1980-2017)	47 studies	Lead, plasticizers, and cigarette smoke	Lead [Pb], phthalates/plasticizers, persistent organic pollutants, and cigarette smoke exposure is significantly related to ADHD in children
Wu et al. (2013)	(2006-2011)	6 studies	Hexachlorobenzene (HCB) and total PCBs	HCB and total PCBs both were associated with type 2 diabetes
Bonde et al. (2017)	(1966-2016)	28 Studies	p,p'-DDE, phthalates and Bisphenol A	Small increased risk of male reproductive disorders following prenatal and postnatal exposure to some persistent environmental chemicals (esp p,p'-DDE)
Iszatt et al. (2015)	(1990-2007)	7 studies	p,p'-DDE and PCBs	Significant increase in growth associated with p,p'-DDE due to prenatal exposure, and a significant decrease in growth associated with postnatal PCB-153 exposure

Emerging evidence links environmental exposures to a pandemic of neurodevelopmental disorders with devastating consequences on family's and the global economy (Grandjean and Landrigan 2014). Whilst the cause of most neurodevelopmental problems is not yet clear, genetic factors are acknowledged as only playing a minor role (Rosenfeld 2015; Sutcliffe 2008) and several hypotheses point to environmental influences as potential causal agents including aberrations in the gastrointestinal microbiota (Rosenfeld 2015), industrial chemicals (Di Renzo et al. 2015; Grandjean 2013; Ross et al. 2013), malnutrition (Goldschmidt and Song 2015; van De Sande et al. 2014), viruses, drugs (Yap et al. 2008) and electromagnetic fields (Herbert and Sage 2013; Posar and Visconti 2014).

Environmental exposure to toxicants is related to a significant portion of cancer mortality worldwide (Abel and DiGiovanni 2015). There is a growing body of evidence associating various toxicants with cancer including: air pollutants like asbestos, radon, hexavalent chromium, tobacco smoke and benzo(a)pyrene with lung cancer (Cao et al. 2011; Halasova et al. 2009; Kim et al. 2013; Yang et al. 2016); endocrine disrupting chemicals such as pesticides, dioxins, furans and PCBs with an increased risk for breast cancer (Teitelbaum et al. 2015), endometrial, testicular and prostate cancer (Darbre and Williams 2022; Kim and Lee 2011; Le Moal et al. 2016; United Nations Environment Programme and World Health Organization 2013); arsenic and disinfection by-products with bladder cancer (Bhattacharjee et al. 2013; Villanueva et al. 2003); vinyl chloride with liver cancer (Dogliotti 2006), benzene with leukaemia (Andreoli et al. 2015); and pesticides with childhood leukaemia (Chen et al. 2015; Van Maele-Fabry et al. 2011; Wigle et al. 2009). Even though the incidence of cancer attributable to environmental chemical exposures has not been definitively established (Christiani 2011; McGuinn et al. 2012), the World Health Organisation and the International Agency for Research on Cancer (IARC) suggest that between 7% and 19% of all cancers are attributable to toxic environmental exposures (Straif 2008; World Health Organization 2009). According to cancer biologists, this estimate is likely to be a gross underestimation, as many supposedly non-carcinogenic chemicals that are ubiquitous in the environment have been shown to exert low-dose effects that may contribute to carcinogenesis (Goodson III et al. 2015; Reuben 2010). This is of particular concern as the cancer burden is rising and it is now the leading cause of premature death in most of the countries with high Human Development Index including Australia (International Agency for Research on Cancer 2020).

1.7. Summary

Population-wide exposures to toxicants are ubiquitous, and the body burden is increasing with each generation. Toxicant exposures account for a significant portion of cancer mortality worldwide as well as neurodevelopmental, metabolic, neurodegenerative, reproductive,

autoimmune, respiratory, and cardiovascular disorders. Exposures are inequitably distributed across class and race, and are contributing to a growing number of deaths globally and disability adjusted life years (United Nations Environment Programme 2013; World Health Organization 2018c), resulting in significant economic costs exceeding 10% of the global domestic product (Grandjean and Bellanger 2017). Exposures during critical windows of development play an important role, and early life exposures are significant contributors to chronic diseases throughout the lifespan and across generations. The escalation in toxicant exposure has concomitantly led to an upsurge in the occurrence of patients presenting with chronic and multimorbid conditions. This poses a noteworthy challenge for health policy advisors and clinicians, leaving uncertainty in the diagnosis and treatment of patients impacted by environmental toxicant exposures.

Chapter 2:
Manmade Electromagnetic Field Exposures and Disease

2.1. Introduction

All living things have evolved in the presence of the natural background radiation, such as the Schumann Resonances which plays a vital role in attuning the brain's electrical activity in all animals (Panagopoulos et al. 2023). In contrast, manmade EMFs were only introduced in the past 120 years with electrification, and more intensely in the past 25 years with the rollout of mobile telephony, personal area networks and wireless technologies. There are significant challenges associating non-ionising radiation electromagnetic fields (NIR-EMFs) with health effects, and intense debates have been ongoing for more than two decades. Subsequently, very little of the published research is being translated into clinical practice or health policy. This chapter outlines the increase in the global population's exposure to non-ionising radiation electromagnetic fields (NIR-EMFs), the challenges associating exposure with health effects, and the growing number of studies linking non-thermal exposures with sleep disturbances and chronic diseases.

2.2. Electromagnetic radiation

Electromagnetic radiation is a type of energy in the form of waves of coupled electric and magnetic fields that travel at the speed of light. Electromagnetic radiation is expressed in terms of its frequency (number of wave cycles per second), wavelength and energy. It consists of an electric field and magnetic field component, whose waves oscillate perpendicular to and in phase with one another. Electric fields are associated with the presence of an electric charge (voltage) and are measured in unit of volts per metre (V/m), and magnetic fields result from the movement of electric charge (electric current) and are expressed in terms of magnetic flux density measured in units of microtesla (μT), or as magnetic field strength expressed in amperes per metre (A/m) (International Commission on Non-Ionizing Radiation Protection 2010).

The electromagnetic spectrum is the range of frequencies over which electromagnetic radiation extends, and is divided into two sections: non-ionising radiation and ionising radiation. Non-ionising radiation (NIR) has longer wavelengths and sufficient energy to enable molecules and atoms to vibrate faster (Australian Radiation Protection and Nuclear Safety Agency 2023b). This includes the extremely low frequency electromagnetic field (ELF-EMF) range, radiofrequency, microwave and the visible portion of the spectrum into the ultraviolet

range. In contrast, ionising radiation is a process in which an electron is given enough energy to break away from an atom, resulting in the formation of charged particles (ions) (Australian Radiation Protection and Nuclear Safety Agency 2023c). This includes the x-ray, gamma ray and the cosmic radiation portion of the electromagnetic spectrum.

Extremely Low Frequency (ELF) electric and magnetic fields (EMFs) are produced by both natural and manmade sources and comprise the lower portion of the electromagnetic spectrum in the frequency range 0 to 100 kHz (Australian Radiation Protection and Nuclear Safety Agency 2023a). Natural sources include ionospheric currents, thunderstorms and lightning, and manmade sources exist wherever electricity is generated, transmitted or distributed or used in electrical appliances (World Health Organization 2007b). Radiofrequency electromagnetic fields (RF-EMFs) cover 100 kHz to 300 GHz and includes natural sources such as the sun, the earth and the ionosphere, while manmade sources are mainly used for telecommunication purposes (Australian Radiation Protection and Nuclear Safety Agency 2023b). This includes radio and television broadcasting, radar, satellite, mobile phone base stations, mobile phones, cordless phones, Wi-Fi enabled devices as well as microwave ovens and various medical applications (Australian Radiation Protection and Nuclear Safety Agency 2023b). Both ELF-EMFs and RF-EMFs are forms of non-ionising radiation that will form the discussion of this thesis.

2.3. Natural electromagnetic fields and terrestrial radiation

Life evolved on the planet within a narrow range of radiation parameters within the earth's atmosphere. This includes the natural electromagnetic background arising from the sun, the earth's static magnetic field (geomagnetic field), radioactivity (within the earth's crust, and from the cosmic radiation and x-rays from outer space), gravity, and the Schumann Resonances (the extremely low electromagnetic radiation that propagates between the ionosphere and the earth created by lightning charges). Animals like bees, ants, termites, fruit flies, birds, fish, cows and deer use the geomagnetic field for both migration and homing (Belova and Acosta-Avalos 2015). For humans, the terrestrial radiation provides remarkably low intensity, yet critical frequencies that play an important role in our circadian rhythm, sleep and wake cycles, brainwave activity, neural synchrony, immune function, behaviour, onset of puberty as well as gene expression, cell communication and metabolism (Sage 2015). Interestingly, the Schumann Resonance frequencies (7-8 Hz, 13-14 Hz and 19-20 Hz) closely overlap with the alpha and beta human brain waves (McCraty et al. 2017; Schumann 1952).

Aberrations in natural electromagnetic field exposure may lead to far ranging biological effects. In fact, a significant body of research has demonstrated that fluctuations in geomagnetic activity is associated with elevations in the rates of epileptic seizures, suicides,

aggressive behaviour, sleep disturbances and sudden unexpected death from cardiac pathologies (Fournier 2019). Furthermore, diurnal geomagnetic variation has been found to influence melatonin, cryptochrome, and CG8198 in living organisms resulting in a secondary zeitgeber for biological circadian rhythms (Krylov 2017).

2.4. Manmade versus natural electromagnetic fields

Manmade EMFs are different to the natural EMF background. The electric charges in nature oscillate in all possible directions, are static, never totally polarised, and maintain relatively constant average intensities which allow living organisms to adapt to them over time. In contrast, manmade EMFs are generally polarised and coherent with well-defined frequencies and phases (Panagopoulos 2023b). Wireless communication devices emit microwave carrier waves that are modulated and pulsed by low frequency (ELF) signals and:

> *. . . vary greatly and unpredictably at all times displaying, apart from the ELF pulsing and modulation . . . significant random variability, mainly in the Ultra Low Frequency (ULF) (0-3Hz) band, with intensity variations usually exceeding by more than 30% (and even by more than 100% in many instances) the average values because of the varying information they transmit . . .* (Panagopoulos 2023b:3-4).

Panagopoulos suggests it is these characteristics that induce biological effects and that "…RF/microwave carrier signals alone, without modulation, pulsing, and variability, do not usually induce biological effects other than heating at adequately high intensities and frequencies" (Panagopoulos 2023b:4).

2.5. The rise of manmade electromagnetic field exposures

Considering the course of human evolution, manmade electromagnetic fields have been introduced on the planet relatively recently. Population-wide exposure to ELF-EMFs began early in the 20th Century following the rollout of the electrical grid. Electricity supply in Australia began in the later part of the 19th Century, and "…in 1906 it was reported that throughout Australia there were 46 electric light and power supply stations" (Brady 1996:3). Tasmania and Victoria were the first states to use transmitted supply in 1916 and 1924 respectively, and subsequently led to the development of high voltage transmission. The electrical grid was rolled out across Australia over several decades, with delays during wartime and post war years causing serious power supply shortages, followed by rapid expansion in the late 1950s (Brady 1996). Electric and magnetic fields exist wherever electricity is generated, transmitted and distributed such as high voltage transmission lines, distribution (power) lines, domestic

mains power supply, and electrical appliances (Australia uses 50 Hz). “Since the use of electricity is an integral part of our modern lifestyle, these fields are ubiquitous in our environment” (World Health Organization 2007b:1).

In the past two decades, exposure of the global population to radiofrequencies (RF) has increased by 18 orders of magnitude (Bandara and Carpenter 2018) as a result of the deployment of millions of Wi-Fi enabled devices in homes, workplaces and schools and the rollout of the cell wireless communications network and its associated infrastructure. Wi-Fi has dramatically changed the landscape of how we work, study and interact with each other, and the majority of parents with children under the age of 12 are concerned their child is spending too much time in front of screens (McClain 2022). In the past ten years, the average annual growth rate of mobile broadband subscriptions in the Organisation for Economic Co-operation and Development (OECD) countries alone has more than doubled (Organisation for Economic Co-operation and Development 2023) with an estimated 8.6 billion mobile device subscriptions reported in 2021 globally (Statistica 2023). Ninety three per cent of the global population has access to a cell-broadband network and 98% of young adults in developed countries use the internet (International Telecommunication Union 2020).

The rapid uptake of technology has given rise to a plethora of new terms like Google, Facebook, Twitter, Snapchat, nomophobia (fear of being without a mobile phone), ‘digital dementia’ and ‘digital addiction’. In 2013, the American Psychiatric Association (APA) included ‘internet game disorder’ (IGD) in section III of the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) as a condition warranting more clinical research (American Psychiatric Association 2013) and the World Health Organisation (WHO) included Game Disorder (GD) as a diagnosis code in the 11th final revision of the International Classification of Diseases (ICD-11) (World Health Organization 2018a).

2.6. The rollout of the mobile telecommunications network

Whilst exposures to radiofrequency electromagnetic fields (RF-EMFs) were initially documented in military personnel on radar bases during World War II, and later to AM and FM radio, widespread public exposure did not occur until the mid-1980s with the introduction of the 1G analogue system i.e. the Nordic Cell Telephone (NMT) which used 450/900 MHz modulated frequency with a continuous signal (Wallace and Selmaoui 2019). The second-generation (2G) cell network i.e. Global System for Cell Communication (GSM) was rolled out in 1991 and initially used a 900 MHz frequency pulse-modulated signal band (later 450 MHz and 1800 MHz frequency bands), and introduced digital cell voice and short message service (SMS), requiring a significant increase in the number of Mobile Phone Base Stations (MPBS) installed across the country (Commonwealth of Australia 2017; Wallace and Selmaoui 2019).

The third generation (3G) digital system i.e. Universal Cell Telecommunications System (UMTS) network was launched in 2001 in Japan (Frene and Hurel 2002) and introduced data services in addition to voice and SMS (Commonwealth of Australia 2017). It operates at 2100 MHz range in downlink (MPBS to user) and at 1950 MHz range in uplink (mobile phone to MPBS) (Wallace and Selmaoui 2019). For simultaneous multiple access, the Wideband Code-Division Multiple-Access (CDMA) technology is the most widely used 3G interface which allows high data transmission and provides improved coverage due to spreading of the baseband signals onto a wider bandwidth with coherent uplink detection (Milstein 2000). In addition, CDMA provides improved coverage and system capacity for multiuser detection, as well as supporting efficient packet-access protocol (Korde and Rathkanthiwar 2011). The fourth generation (4G) i.e. Long Term Evolution was launched in 2009 and improved the 3G network by supporting higher data rates through wider channel bandwidths operating primarily at 2600 MHz. This allowed integrated carrier aggregation, Multiple Input Multiple Output (MIMO) architecture, smaller cells and multiple frequencies which increased data access, capacity and improved latency which was much faster and enabled consumers to stream videos on their phone and use Apps.

In 2020, the fifth generation (5G/New Radio) provided enhanced connectivity, ultra-low latency, much faster data rates and greater bandwidth to support the Internet of Things (millions of Wi-Fi enabled devices), autonomous vehicles and virtual reality (Commonwealth of Australia 2017). Compared to existing telecommunication networks, 5G requires a high density infrastructure (Imam-Fulani et al. 2023; Russell 2018) and uses millimetre waves with extremely high frequency from 30-300 GHz (Mezzavilla et al. 2018). Due to limited reach, it requires a large number of low powered cell base stations as ‘small cell antennas’ fitted to existing infrastructure such as streetlights and buildings (Commonwealth of Australia 2017). In addition to small cell antennas, the infrastructure also requires the potential deployment of nearly 20,000 satellites in the earth’s magnetosphere (Seker and Simsek 2022). The mega satellite constellation network referred to as the non-terrestrial satellite network (NTSN) provides highly reliable global coverage with low latency communication particularly through low earth orbit (LEO) mega-constellation platform (Imam-Fulani et al. 2023). These unique capabilities can be integrated as part of the 5G connectivity infrastructure support to facilitate expansion of 5G reach and address coverage challenges by deployment of a 5G satellite-based network (5G Americas 2022). In contrast to the existing mobile phone base stations that transmit available power over a larger area, the small cells used in the 5G network transmit data up to only 300 metres via direct focused beams of energy (beamforming) to a specific area using the MIMO technology consisting of multiple antennas working together to shoot a beam to the nearest cell tower (Imam-Fulani et al. 2023; Nadeem and Biswas 2021; Russell 2018).

2.7. Personal area networks, Bluetooth, and wireless technologies

In addition to the rollout of the infrastructure required to support the telecommunications network, Bluetooth - a personal area network was launched in 1989 and provided data exchange between fixed and cell devices over short distances using radio waves. This was followed in 1996 by Wireless Fidelity (Wi-Fi) a local area network developed by CSIRO to provide data exchange without the use of wires. The combination of Bluetooth and Wi-Fi enabled devices accounts for much of the 'electrosmog' present in homes and public buildings and is now widely adopted by businesses and schools to the extent that hardwired cabled options are becoming obsolete and increasingly difficult to come by. In addition, many cities have adopted WiMAX which is a Metropolitan Area Network (MAN) with a signal radius of up to 50 km (Sharma and Singh 2012), thereby making it difficult for those who live-in built-up areas or apartment buildings to avoid ambient exposures. The rapid development of the infrastructure required to support the network and development of Wi-Fi enabled devices, significantly increased the global populations exposure to manmade RF-EMFs.

2.8. Chronic disease and NIR-EMFs

There has been a significant volume of research published over the past 3 decades investigating the impact of NIR-EMFs with various chronic diseases from childhood leukemia, breast cancer, brain tumours, sleep disturbances and Electromagnetic Hypersensitivity.

2.8.1. Childhood leukaemia and ELF-MFs

The weight of evidence linking manmade electromagnetic fields to various cancers has grown considerably in the past two decades. The first case-control epidemiological study that reported an association between exposure to ELF-MFs and cancer was in 1979, when Wertheimer and Leeper reported that magnetic fields above 0.4 μT (microteslas) from power lines were associated with a doubling in the incidence of childhood leukaemia (Wertheimer and Leeper 1979). Over thirty studies in over nine countries have since been conducted with the majority confirming these findings (Ahlbom et al. 2000; Greenland et al. 2000; Sermage-Faure et al. 2013; Wertheimer and Leeper 1979). In 2002, as a result of the weight of evidence, the International Agency for Research on Cancer (IARC) classified 50Hz magnetic fields as a possible human carcinogen (International Agency for Research on Cancer 2002) based on pooled analyses of epidemiological studies demonstrating a consistent pattern of a two-fold increase in childhood leukaemia associated with average exposure to residential power-frequency magnetic field above 0.3 to 0.4 μT (World Health Organization 2007a). Further epidemiological studies have strengthened the association between manmade

electromagnetic fields and childhood leukaemia as documented in Table 2. The prevalence of exposure to NIR-ELF MF greater than 0.3 μT varies widely between countries. Readings above 0.3 μT impact 11.3% of the population in Mexico (Núñez-Enríquez et al. 2020), but estimated to be <2% of the population in western countries (Salvan et al. 2015). An estimated 1.5% and 2% of all incident cases of childhood leukaemia occurring annually in the European Union is attributable to ELF-MF exposure (Grellier et al. 2014).

Table 2. *Examples of Evidence-Based Reviews (EBRs) reporting the impact of manmade electromagnetic field associated with childhood leukaemia*

First Author [year]	EBR design	No of studies (date range)	Focus of review	Intervention(s) Exposure level	Findings (Exposure category)	Conclusions
Ahlbom et al. (2001)	MA	18 CCS (1979 to 1999)	Childhood leukaemia and brain tumours	Exposure to non-ionising (NI) radiation (ELF AC MF EMR)	RR: 2.0 (95% CI: 1.27-3.13) (≥0.4 μT)	Two-fold increase of childhood leukaemia with residential EMF exposures ≥0.4 μT
Amoon et al. (2018)	SR	11 CCS (1993-2016)	Childhood acute lymphoblastic leukaemia	Exposure to NIR ELF AC MF and distance to power lines	OR: 1.39 (95% CI: 0.92-2.10). for children living < 50 m from a 200 + kV power line. OR: 1.65; (95% CI: 1.02–2.67) for children diagnosed before age 5 years	Small increased risk of leukaemia among children who lived in homes < 50 m from higher voltage (200 + kV) power lines
Amoon et al. (2022)	MA	4 CCS (2015 to 2017)	Magnetic fields and childhood leukaemia	Exposure to NIR ELF AC MF and distance to power lines	OR = 1.01, for exposure ≥0.4 μT compared with exposures <0.1 μT	No increased risk of childhood leukemia exposed to ≥ 0.4 μT
Brabant et al. (2022)	SR & MA	38 CCS (1979 to 2021)	Childhood leukaemia and magnetic fields	Exposure to NIR ELF AC MF generated by power lines and electric appliances	OR=1.37 (95% CI 1.05–1.80) for AC MF > 0.4 μT 1.44 (95% CI 0.72–2.88) for children living within 50 m of power lines OR=2.75 (95% CI 1.71–4.42) increased risk arising from exposure to electric blankets	ELF-MF >0.4 μT increased risk of childhood leukemia
Calvente et al. (2010)	SR	15 studies (1979 to 2008):	Childhood leukaemia	Exposure to non-ionising radiation (RF, LF-EMR or ELF-EMR)	Most studies found an association between exposure to EMR & risk of childhood leukaemia	Epidemiological evidence suggests high incidence of leukaemia in children exposed to low EMR of ≥0.3 μT
Carpenter (2019)	SR	12 studies (2001-2015)	Childhood leukaemia	Exposure to non-ionising radiation (ELF Magnetic Fields EMR)	Most studies found an association between exposure to EMR and risk of childhood leukaemia	Significant associations between exposure and risk of leukaemia

First Author [year]	EBR design	No of studies (date range)	Focus of review	Intervention(s) Exposure level	Findings (Exposure category)	Conclusions
Greenland et al. (2000)	MA	15 CCS (1979 to 2000)	Childhood leukaemia	Exposure to non-ionising radiation (ELF AC Magnetic Fields, wire codes)	OR: 1.65 (95% CI: 1.15-2.36) (>0.3 μT)	Epidemiological evidence suggests an association between childhood leukaemia and exposures exceeding 0.3 μT
Kheifets et al. (2010)	MA	7 CCS/ES (1962-2009)	Childhood leukaemia	Exposure to non-ionising radiation (ELF AC Magnetic Fields EMR)	OR: 1.44 (95% CI:0.88–2.36) (⩾0.3 μT)	This study provides further support that MF are potentially carcinogenic and associated with childhood leukaemia
Pelissari et al. (2009)	SR	10 CCS studies (1960 to 2004)	Childhood leukaemia	Exposure to non-ionising radiation (ELF AC Magnetic Fields EMR)	>0.3 μT	Epidemiological evidence suggests the existence of an association between exposure to low frequency magnetic fields and acute lymphoblastic leukaemia in children, but the association is weak
Seomun et al. (2021)	MA	33 CCS studies (1988-2019)	Childhood leukaemia	Exposure to non-ionising radiation (ELF AC Magnetic Fields EMR)	1.72 (95% CI 1.25–2.35 (⩾0.4 μT)	Significant associations were observed between exposure to ELF-MFs and childhood leukaemia
Zhao L et al. (2014)	MA	9CCS (1997-2013)	Childhood leukaemia	Exposure to non-ionising radiation (ELF AC Magnetic Fields EMR)	Total Leukaemia: OR = 1.57, (95% CI = 1.03–2.40); Acute Lymphocytic Leukaemia: OR = 2.43, (95% CI = 1.30–4.55) (⩾0.4 μT)	Magnetic field exposure level may be associated with childhood leukaemia

Abbreviations: CCS: Case-control studies; ECS: Ecologic studies; ELF-EMR: Extremely low-frequency; EMF: Electromagnetic field; ES: Epidemiological studies. LF-EMR: Low-frequency electromagnetic radiation; MF: Magnetic fields; MPBS: Mobile phone base station radiation; NIR ELF-MF: Non-ionising radiation, extra low frequency magnetic fields; RF: Radiofrequencies; RCT: Randomised controlled trial, SR: Systematic review; MA: Meta-analysis

2.8.2. Brain tumours and RF-EMFs

The global burden of central nervous system cancers (the most common being glioma) increased by 17·3% between 1990 and 2016 with the highest rates occurring in Europe and North America and the lowest rates occurring in Africa and parts of Asia independent of sociodemographic index (Patel et al. 2019). High grade gliomas are the most common type of malignant brain tumour, and despite their rarity, cause significant morbidity and mortality (Chien et al. 2015). The overall incidence of brain tumours is rising in the general population (Grech et al. 2020; Poon et al. 2021). In the United Kingdom, between 1995-2015, the annual incidence rate per 100,000 person-years for glioblastoma multiforme more than doubled from 2.4 to 5.0 (Philips et al. 2018); in Malta between 2008 to 2017, the incidence of glioblastoma multiforme rose six fold from 0.73 to 4.49 per 100,000 (Grech et al. 2020); in the Netherlands between 1989-2010 the incidence of gliomas in adults increased from 4.9 to 5.9 per 100,000 (Ho et al. 2014); in Finland between 2000 and 2013, the mean incidence of glioblastoma multiforme rose marginally by 1.6% at 2.9 per 100,000 person, however it increased sharply among 65 to 79 year olds (Korja et al. 2019); in Australia the incidence rates for people aged over 80, more than tripled between 1982 and 2021 (7.5 cases per 100,000 persons to an estimated 24 cases per 100,000 persons) (Australian Institute of Health and Welfare 2023). Furthermore, brain and other central nervous system cancers are the leading cause of paediatric cancer mortality, and between 1998 and 2013, the incidence of glioma increased by 0.77% per year (Withrow et al. 2019) with a predominance in non-Hispanic whites (Muskens et al. 2020).

Environmental risk factors such as ionising radiation, smoking and toxicants like vinyl chloride, nitrosamines, pesticides, petroleum refining and rubber manufacturing are suspected to play a role in the aetiology of glioblastoma multiforme (Vienne-Jumeau et al. 2019; Wrensch et al. 2002). The past decade has also seen a growing number of studies correlating brain tumour incidence with RF-EMF exposure arising from mobile phone use (Coureau et al. 2014; Dobes et al. 2011; Hardell and Carlberg 2015; Hardell et al. 2013a; INTERPHONE Study Group 2010; Wyde et al. 2016). There has also been a number of reports documented on the subject: Barnett Report (Commonwealth Scientific and Industrial Research Organisation 1994); Stewart Report (Independent Expert Group on Mobile Phones 2000); BioInitiative Report (Sage and Carpenter 2012). The most influential mobile phone studies were the INTERPHONE (European), CERENAT (French) and Hardell's (Swedish) study, which identified an increased risk of gliomas (namely Grade IV glioblastoma multiforme) and acoustic neuromas in people who used their phone for at least 30 minutes per day, on one side of the head for a minimum of ten years. The largest study, INTERPHONE involving over 5000 people, identified a 40% increased risk of glioma with cumulative mobile phone use beyond

1,640 hours despite significant methodological flaws (INTERPHONE Study Group 2010), whilst the CERENAT study calculated a 100% increased glioma risk (Coureau et al. 2014) and Hardell's research team identified a 170% increased glioma risk (Hardell et al. 2013a) in addition to increases in other brain tumours (acoustic neuroma and meningioma) especially if mobile phone use began before the age of twenty (Hardell and Carlberg 2015; Hardell et al. 2011; Hardell et al. 2013a; Hardell et al. 2013b; Khurana et al. 2009).

As a result of human epidemiological studies providing evidence of increased risk for glioma and acoustic neuroma, in May 2011, the International Agency for Research on Cancer classified radiofrequency electromagnetic fields (RF-EMF) as a Group 2B possible human carcinogen (International Agency for Research on Cancer 2011b). Since then, there have been significant animal, epidemiological and mechanistic studies that have further strengthened this association (Hardell 2017).

"Biological and animal laboratory studies [have] brought additional evidence for plausibility and analogy" (Vienne-Jumeau et al. 2019:672). The long-term animal study conducted by the United States National Toxicology Program identified an increase in malignant gliomas in the brain and schwannomas in the heart of male rats (Wyde et al. 2016). This was further supported by results from the Ramazzini Institute (Italy) which identified a significant increase in the incidence of heart schwannomas in male rats (Falcioni et al. 2018). The evidence for carcinogenicity of RF radiation exposure is further supported by more recent findings from genetic toxicity experimental studies reporting exposure-induced alterations to key regulators of gene expression (epigenetic modulation) in the hippocampus region of the brain (Kumar et al. 2021) and increased DNA damage (Smith-Roe et al. 2020) in animal models. Furthermore, several meta-analyses showed a significantly increased risk of brain tumours associated with long-term use of mobile phones (Bortkiewicz et al. 2017; Hardell et al. 2013a; Wang et al. 2018; Yang et al. 2017). A recent meta-analysis involving 46 case-control studies found that while regular mobile phone use was not associated with tumour risk, subgroup analysis revealed that cumulative call time greater than 1,000 hours increased the risk of brain tumours significantly (60%) especially in studies with high quality methodology design (Choi et al. 2020). A summary of recent (2021-2024) evidence-based reviews reporting the impact of RF-EMFs on brain and head tumours is documented in Table 3. The outcome of these findings suggest RF-EMF from mobile phone use is associated with ipsilateral brain tumours and the risk is greatest the earlier the age of first phone use, the longer the cumulative exposure (>1,000 hours), and the longer the latency period (beyond ten years). As a result, leading researchers have concluded that the criteria for strength, consistency, specificity, temporality and biologic gradient were fulfilled for evidence of increased risk for glioblastoma multiforme and acoustic neuroma associated with RF-EMF exposure and thereby satisfy the Bradford Hill criteria for causality (Carlberg and Hardell 2017).

Mobile phone subscription rates are positively and statistically significantly associated with death rates from brain cancer 15–20 years from the time of first use relative to deaths from other causes (Mialon and Nesson 2020). The ‘peak’ incidence of brain tumours like glioma and acoustic neuroma with latencies in excess of 20 years (Nadler and Zurbenko 2014), would not be expected in the global population until the latter half of the 2020s as cell phones were not ubiquitous amongst the global population until well after the introduction of wide-band microwave signals (3G onwards) in the early 2000s. According to the International Telecommunication Union, the number of worldwide mobile cellular subscribers was 12.2 per 100 inhabitants in 2000, 33.7/100 in 2005, 76/100 in 2015 and grew to 109.4/100 by 2019 (International Telecommunication Union 2021). Furthermore, mobile phone use amongst the general population and especially the young has been increasing with proliferation of the cellular network. Data extrapolated from the CEFALO study conducted between 2004 and 2008 amongst 7 to 19 year olds identified that the top quartile of controls had a cumulative lifetime use of 2638 calls and 144 h spent on voice calls (Aydin et al. 2011). In contrast, the Mobi-Expo study conducted between 2012 and 2014 amongst 10 to 24 year olds had a higher level of phone use such that it would take the participants less than three years to reach the lifetime use of the highest quartile of CEFALO controls (Langer et al. 2017). In the Mobi-Expo study the participants averaged 30.6 calls per week and spent 60.8 minutes making or receiving calls, and 20–24 year olds made over twice as many phone calls and spent almost four and a half times as long on the phone compared to the youngest group (10 to 14 year olds) (Langer et al. 2017). An Israeli survey of 1600 students showed that at least 95% of adolescents use mobile phones on a regular basis; 16% of them started using mobile phones before the age of 8 years; 11% talk more than 2 hours a day and 37% send more than 30 text messages every day (Israel Ministry of Health 2015).

Table 3. *Examples of recent (2017-2024) Evidence-Based Reviews (EBRs) reporting the impact of RF-EMFs on brain and head tumours*

First Author [year]	EBR design	No of studies (date range)	Focus of review	Intervention(s) Exposure level	Findings (Exposure category)	Conclusions
Vijayan and Eslick (2023)	MA	7 CCS (2002-2022)	Salivary gland tumours and mobile phone use	Exposure to NIR (RF-EMFs)	OR = 1.06 (0.86-1.32)	No significant association between mobile phone usage and risk for developing salivary gland tumours
Pareja-Peña et al. (2022)	SR	3 ES (2009-2019)	Impact of exposure to RF-EMF on brain tumours	Exposure to NIR (RF-EMFs)	Glioma OR = 1.1 to 5.3 Acoustic neuroma OR = <1 to 3.74 Meningioma OR = <1-4.8	Strong causality of brain tumours with RF-EMF exposure Greater risk with longer cumulative exposure and longer latency (>10 years)
Bortkiewicz et al. (2017)	MA	24 CCs (1999-2013)	Intracranial and salivary tumours and mobile phone use	Exposure to non-ionising (NI) radiation (RF-EMFs)	OR = 1.324 (1.028-1.704)	Long-term (≥10 years) use of mobile phone increases risk of intracranial tumours, especially in the case of ipsilateral exposure
Chen et al. (2021)	MA	6 CCs 2 Cohort (1999-2018)	Meningioma and mobile phone use	Exposure to non-ionising (NI) radiation (RF-EMFs)	OR = 0.90 (0.83-0.99)	Mobile phone use led to a borderline decreased adult meningioma risk
Choi et al. (2020)	MA	46 CCS (1979 to 1999)	Brain tumours and mobile phones	Exposure to non-ionising (NI) radiation (RF-EMFs)	OR = 1.60 (1.12-2.30) (>1,000 hours of mobile phone use)	Cumulative call times > 1000 h, cellular phone use increased the risk of brain tumours by 60%

First Author [year]	EBR design	No of studies (date range)	Focus of review	Intervention(s) Exposure level	Findings (Exposure category)	Conclusions
Mialon and Nesson (2020)		Brain cancer death rates for 88 countries (1990 to 2015)	Brain tumour and mobile phone subscriptions	Exposure to non-ionising (NI) radiation (RF-EMFs)	Every additional mobile phone subscription per 100 people is associated with a 2% increase in brain cancer mortality 20 years later.	Mobile phone subscription rates are positively and statistically significantly associated with death rates from brain cancer 15–20 years later.
Miller et al. (2018)	MA	13 CCS (2011-2017)	Brain tumour and phone use	Exposure to non-ionising (NI) radiation (RF-EMFs)	Glioma: OR = 2.91 (1.09-7.76) (>2,638 number of calls) OR = 2.3 (1.7-3.1) (2G, GSM) Meningioma: OR = 2.57 (1.02-6.44) (≥896 hours) Acoustic neuroma OR =4.5 (2.1-9.5) (>20 years)	Increased glioma associated with mobile phone use EMF-RF should be a Group 1 human carcinogen
Röösli et al. (2019)	SR	4 CCS 3 Cohort (2004-2017)	Brain and salivary gland tumours and cell phones	Exposure to non-ionising (NI) radiation (RF-EMFs)	Glioma: RR = 1.11, (0.85–1.46) Acoustic neuroma: OR=1.19 (0.8-1.79)	Epidemiological studies do not suggest increased brain or salivary gland tumor risk with mobile phone use although uncertainty remains regarding long latency periods (>15 yrs) and use during childhood
Vienne-Jumeau et al. (2019)	UR	9 MA (2006-2017)	All brain tumours and mobile phone use	Exposure to NIR (RF-EMFs)	Ipsilateral >10 years	Inconsistent evidence for RF and CNS tumours.

First Author [year]	EBR design	No of studies (date range)	Focus of review	Intervention(s) Exposure level	Findings (Exposure category)	Conclusions
					Glioma: OR=1.9 (1.4-2.4) OR=1.46 (1.12-1.92) Acoustic neuroma: OR=2.4 (1.1-5.3) OR=1.6 (1.1-2.4)	Increased risk for glioma and acoustic neuroma (≥10 years) Evidence for dose-effect dependent on cumulative use
Wang et al. (2018)	MA	10 CCS (1999-2017)	Gliomas and mobile phone use	Exposure to NIR (RF-EMFs)	OR = 1.33 (1.05 - 1.67)	Association with risk of glioma in long-term mobile phone users (≥10 years)
Yang et al. (2017)	MA	11 CCS (2001-2015)	Gliomas and mobile phone use	Exposure to NIR (RF-EMFs)	OR = 2.22 (1.69 – 2.92)	Significant association between long term mobile phone use and glioma especially with ipsilateral use
Zumel-Marne et al. (2019)	MA	2 CCS (2011-2012)	Brain tumours in children and mobile phone and mobile phone base stations (MPBS)	Exposure to NIR (RF-EMFs)	Cell phone OR = 1.36 (0.92 to 2.02) MPBS OR=1.14 (0.83 to 1.55)	No significant association with RF from mobile phone or MPBS and childhood brain tumours

Abbreviations: CCS: Case-control studies; ECS: Ecologic studies; ES: Epidemiological studies; MA: Meta-analysis; OR: Odds ratio; RCT: randomised controlled trial; SR: Systematic review; UR: Umbrella review

2.8.3. Breast cancer and NIR-EMFs

Breast cancer in women under 40 years of age with no family history of the disease, is relatively rare, however a series of case studies documented young women who developed tumours of almost identical histology in the breasts where their phones were placed for up to ten hours per day for several years (West et al. 2013). In addition, two reviews concluded an increased risk of female breast cancer following AC magnetic field exposure (Chen et al. 2013; Zhao J et al. 2014) with exposures above 1.2 µT being significant (Blackman et al. 2001; Harland and Liburdy 1997) especially in premenopausal women (Chen et al. 2013) however there are many studies for which an association were not found (Davis et al. 2002; London et al. 2003; Schoenfeld et al. 2003). Currently the data is inconclusive as to whether there is an increased risk of breast cancer associated with long-term exposure to NIR-EMFs.

2.8.4. Sleep disturbances and RF-EMFs

Digital device use before bed is extremely common amongst children and adolescents (Brushe et al. 2022) and this has been associated with inadequate sleep quantity, poor sleep quality, and excessive daytime sleepiness (Carter et al. 2016). It is suggested that exposure to blue light from LED displays delays the circadian clock and suppresses melatonin (Chang et al. 2015), device-induced arousal decreases the ability to fall asleep, and direct exposure to pulse-modulated RF-EMFs influences EEG architecture (Hamblin and Wood 2002; Lowden et al. 2019; Zhang et al. 2017).

Sleep problems are the most commonly reported complaint attributed to RF-EMF exposure (Austrian Medical Association 2012; Belpomme and Irigaray 2020; Belyaev et al. 2016; Pall 2016), and yet reported relationships between RF-EMF and sleep architecture varies considerably across studies. The majority of studies that investigate pulsed radiofrequencies on sleep quality involve near-head exposure to mobile phones in a sleep laboratory or far field exposures from nearby mobile phone base stations. These studies reveal inconsistent associations, with limited statistical power and short if any, follow-up (Danker-Hopfe et al. 2016; Fritzer et al. 2007; Loughran et al. 2012; Lustenberger et al. 2013; Lustenberger et al. 2015; Schmid et al. 2012; Tettamanti et al. 2020; Vecsei et al. 2018). Two reviews conducted almost a decade ago, concluded there is no evidence for a direct association between mobile phone exposure and severity of non-specific physical symptoms such as sleep problems (Baliatsas et al. 2012; Röösli et al. 2010). However this contradicts a growing number of systematic reviews (see Table 4) that have reported pulse-modulated RF-EMFs related to altered brain physiology indicated by changes in electroencephalogram power in selective bands (alpha, beta, delta or theta) when administered immediately prior to or

during sleep (Hamblin and Wood 2002; Ohayon et al. 2019; Rubin et al. 2011; Zhang et al. 2017).

The heterogeneity between studies appears to depend on the modulation, variability and duration of exposure. For example, the impact of RF-EMF on sleep outcomes are more likely to be seen after longer exposure (>30 min) and with exposure occurring during the entire night (Danker-Hopfe et al. 2016). This is supported by recent laboratory studies in healthy adults that found one-night exposure to a Wi-Fi router resulted in a reduction in global electroencephalogram (EEG) power in the alpha frequency band during Non-Rapid Eye Movement (NREM) sleep (Danker-Hopfe et al. 2020), whereas no measurable effects were seen on spectral power of spontaneous awake EEG with acute Wi-Fi exposure (60 minutes) (Zentai et al. 2015). In light of the widespread deployment of Wi-Fi enabled devices, rising incidence of insomnia and heterogeneity between sleep studies, there is a need to investigate the long-term impact of digital devices on sleep parameters under real world conditions.

Table 4. *Summary of Evidence Based Reviews (EBRs) reporting the impact of manmade electromagnetic fields association with sleep disturbances (2001 to 2021).*

First Author [year]	EBR design	No of studies (date range)	Focus of review	Intervention(s) Exposure level	Findings (Exposure category)	Conclusions
Baliatsas et al. (2012)	SR & MA	4 Studies (2000-2011)	Mobile phone and MPBS	Exposure to NIR (RF-EMFs)	OR= 1.18 (95% CI: 0.8 to 1.74)	Non-significant or contradictory results for sleep problems
Eggert et al. (2020)	EBR	3 RCT (2016-2018)	Mobile phone, TETRA and sleep	Exposure to NIR (RF-EMFs)	Statistically significant result of latency to persistent sleep due to TETRA exposure over one night	One night exposure not statistically significant results for sleep parameters except with exposure to TETRA
Hamblin and Wood (2002)	SR	9 RCT (1995-2000)	Mobile phone and sleep	Exposure to NIR (RF-EMFs) 900 MHz	Increased alpha power in both REM and NREM stages	Enhancement of EEG alpha power with mobile phone exposure using GSM network
Ohayon et al. (2019)	SR	20 Studies (1990-2018)	Mobile phone and 50Hz/60Hz frequencies	Exposure to NIR (ELF-EMFs, RF-EMFs)	Effects of RF-EMF on sleep architecture vary considerably across studies	Pulse modulated RF-EMF effects on EEG power in alpha and beta or delta and theta bands when exposure occurs during sleep
Pall (2016)	SR	26 ES (1974-2014)	Mobile phone or MPBS or TV transmitting station	Exposure to NIR (RF-EMFs)	RF exposure results in a range of neuro-psychiatric effects	Sleep disturbance is the most commonly cited symptom associated with RF exposure
Röösli et al. (2010)	SR	2 RCT 7 Epidem (2005 – 2009)	Mobile phone base station (MPBS) and self-reported sleep measures	Exposure to NIR (RF-EMFs) 900 MHz 1800 MHz UMTS		No association between MPBS and self-reported sleep disturbances

First Author [year]	EBR design	No of studies (date range)	Focus of review	Intervention(s) Exposure level	Findings (Exposure category)	Conclusions
Rubin et al. (2011)	SR	3 CCS studies (2004-2008)	Impact of mobile phone on sleep EEG and movement	Exposure to NIR (RF-EMFs)	Participants moved away from RF source whilst sleeping and longer latency to deep sleep (stage 3) from sleep onset, and reduced SWS	RF exposure impacts sleep EEG
Zhang et al. (2017)	SR	5 Studies (2011-2015)	Mobile phone and Wi-Fi and sleep	Exposure to NIR (RF-EMFs) 884 MHz 900 MHz 2.4 GHz	Changes in alpha and delta bands in NREM (stage 2) sleep with RF exposure	Changes in spectral power of EEG occur during NREM sleep following RF-EMF exposure
Zhou et al. (2020)	SR & MA	17 RCT (1996-2015)	Insomnia and mobile phones	Exposure to NIR (RF-EMFs)	Papers published pre 2000 increased total sleep time OR= 4.80 (95% CI: 3.70-5.90). Papers published post 2001 decreased total sleep time OR =-2.56 (95% CI: -4.25 -0.87)	Short-term exposure to mobile phone RF radiation had no impacts on people's overall sleep outcomes but did reduce sleep period.

† For full methodology, keywords and search strategy see Appendix A

Abbreviations: CCS: Case-control studies; ECS: Ecologic studies; ES: epidemiological studies; RCT: randomised controlled trial; SR: Systematic review; MA: Meta-Analysis

2.8.5. Electromagnetic Hypersensitivity (EHS)

Electromagnetic Hypersensitivity (EHS) or Idiopathic Environmental Intolerance attributed to Electromagnetic Fields (IEI-EMF) is a clinical syndrome characterised by non-specific multiple organ symptoms following acute or chronic exposure to electromagnetic fields (Stein and Udasin 2020). Whilst there is no generally accepted diagnostic procedure or definition to identify patients with this condition, it is widely reported and estimated to impact between 2 and 13% of the population, with the highest incidence reported in the Taiwan Region (Kaszuba-Zwoińska et al. 2015; Szemerszky et al. 2019). Establishing EHS as a medical condition has been challenging as the majority of studies do not find any link between EMFs and EHS, especially in the absence of clinical criteria and objective biomarkers (Verrender et al. 2018). Consistent with a lack of unified IEI-EMF aetiology, a recent case study used a biophysical approach to explore the aetiology of IEI-EMF in three self-diagnosed participants and found limited associations between EMF exposure and reported symptoms, differences in individual patterns, and highlighted the need to use multimodal approach to IEI-EMF investigation (Dömötör et al. 2022). However there are inherent flaws in provocation studies, including the assumption that the participants have EHS (as they are self-diagnosed), exclusion of volunteers with pre-existing health problems, bias introduced by volunteers who withdraw from the study, and bias introduced by nocebo and placebo effects (Leszczynski 2022). Subsequently, the opinion that there is no link between EHS and EMF should be revised because "…the scientific research data is of insufficient quality to be used as a proof of the lack of causality" (Leszczynski 2022:441).

The quest to identify biomarkers associated with EHS was recently undertaken by a team of French researchers. They identified several inflammatory markers in the majority of EHS patients including oxidative/nitrosative stress-related biomarkers and abnormal urine profile (6-hydroxymelatonin sulfate/creatinine ratio). In 8-40% of cases biomarkers associated with opening of the blood-brain barrier including S100B protein and nitrotyrosine as well as histaminemia (high levels of histamine) and circulating autoantibodies against O-myelin (autoimmune response) potentially as a result of oxidative stress were also detected (Belpomme and Irigaray 2020). An association between RF-EMF exposure and myelin deterioration was supported by *in vivo* and *in vitro* and epidemiological studies (Redmayne and Johansson 2014). These biological test findings together with abnormal neurotransmitter profiles of patients with EHS suggest neuroinflammation involving the limbic system and the thalamus of the brain (Belpomme and Irigaray 2020). These researchers also established that most patients with EHS and MCS are females with an average age of 47 and the identified inflammatory markers increase the risk of chronic neurodegenerative disease. Many of the mechanisms described for Multiple Chemical Sensitivity (MCS) apply with modification to EHS

and biotoxin-related illnesses (mould and Lyme disease) as MCS sufferers often have some level of electrical hypersensitivity and EHS sufferers have impaired detoxification systems (Stein and Udasin 2020).

Whilst the World Health Organisation does not recognise EHS as a medical condition in its own right, Sweden was the first country to acknowledge it as a functional impairment (Johansson 2006). The rise in the prevalence of EHS and patients presenting with idiopathic non-specific multiple organ symptoms following exposure to electromagnetic fields, in conjunction with the absence of clinical guidelines, leaves clinicians in a precarious position. This is especially concerning when you consider that humans are intrinsically electrosensitive and that modulated RFR exposure is likely to affect everyone at a cellular level (Redmayne and Reddel 2021). In order to meet this challenge, several publications have since been published to enable clinicians to diagnose and treat patients impacted by environmental exposures. In 2012, the Austrian Medical Association published guidelines for clinicians to assist in the diagnosis and treatment of EMF-related health problems in response to a "…sharp rise in unspecific, often stress-associated health problems that increasingly present physicians with the challenge of complex differential diagnosis" (Austrian Medical Association 2012:1). This was followed in 2015, by a Declaration (International Scientific Declaration on EHS and MCS) by a panel of physicians calling on international and national institutions responsible for health including the World Health Organisation, to recognise EHS and MCS as a medical condition (Royal Belgium Academy of Medicine 2015). "EHS and MCS should be represented by separate codes under the World Health Organisation International Classification of Diseases in order to increase awareness by the medical community and the general public . . ." (Royal Belgium Academy of Medicine 2015:4). This was also reinforced recently by a global syndicate of expert EMF researchers who published a report stating that EHS is an intriguing nascent neuropathological disorder with worldwide high-risk public health implications that should be included in the WHO International Classification of Diseases (Belpomme et al. 2021). In 2016, the European Academy of Environmental Medicine published a 35 page report titled 'EUROPAEM EMF Guideline for the prevention, diagnosis and treatment of EMF-related health problems and illnesses' (Belyaev et al. 2016).

> *Physicians are increasingly confronted with health problems from unidentified causes. Studies, empirical observations, and patient reports clearly indicate interactions between EMF exposure and health problems. Individual susceptibility and environmental factors are frequently neglected* (Belyaev et al. 2016:363).

Despite these detailed publications, little has been translated into public health policy or general medical practice, and little is known about Australian clinicians' approach or assessment of patients with potential environmental sensitivities.

2.9. Summary

While life on earth has coevolved alongside the natural terrestrial radiation, manmade EMFs have only recently been introduced with the advent of electrification, and more intensely in the past 25 years due to the expansion of the telecommunication and personal networks, and wireless technologies. Exposure to NIR-EMFs electromagnetic fields is widespread, yet difficult to study and is not widely considered by clinicians. Unlike natural EMFs, manmade EMFs are totally polarised, coherent, modulated and pulsed by low frequency (ELF) signals which renders them more biologically active.

A growing body of evidence suggests a correlation between NIR-EMFs and a range of disorders, including sleep disturbances, childhood leukemia, brain tumours and Electromagnetic Hypersensitivity. The heterogeneity between studies however makes it difficult to compare studies due to differences in study design, timing and duration of exposures, the type of frequency used, modulation, power density, field strength, pulsing nature, challenges in controlling extraneous confounding factors, bias, and the laboratory or clinical context involved. Consequently, despite decades of research, most studies display methodological weaknesses that limit the internal validity of the results and systematic reviews are unable to draw conclusions. These delays prevent translating this information into health policy and clinical practice and, in the absence of clinical guidelines, some medical organisations have published reports to assist clinicians who play a vital role in addressing these exposures in their patients.

Chapter 3:
Does Radiofrequency Radiation Impact Sleep? A Double-Blind, Randomised, Placebo-Controlled, Crossover Pilot Study

3.1. Abstract

The most common source of Radiofrequency Electromagnetic Field (RF-EMF) exposures during sleep includes digital devices, yet there are no studies investigating the impact of multi-night exposure to electromagnetic fields emitted from a baby monitor on sleep under real-world conditions in healthy adults. Given the ubiquitous use of Wi-Fi enabled digital devices, and lack of real-world data, we investigated the effect of 2.45 GHz radiofrequency exposure during sleep on subjective sleep quality, and objective sleep measures, heart rate variability and actigraphy in healthy adults. This pilot study was a 4-week randomised, double-blind, crossover trial of 12 healthy adults. After a one-week run-in period, participants were randomised to exposure from either an active or inactive (sham) baby monitor for 7 nights and then crossed over to the alternate intervention after a one-week washout period. Subjective and objective assessments of sleep included the Pittsburgh Insomnia Rating Scale (PIRS-20), electroencephalography (EEG), actigraphy and heart rate variability (HRV) derived from electrocardiogram. Compared to sham exposure, RF-EMF exposure resulted in a statistically significant and clinically meaningful reduction in sleep quality as indicated by the PIRS-20 scores ($p<0.05$) and a statistically significant increase in EEG power density in the higher frequencies (gamma, beta and theta bands) during Non-Rapid Eye Movement (NREM) sleep ($p<0.05$). No statistically significant differences were observed in heart rate variability or actigraphy. Our findings suggest that exposure to a 2.45 GHz radiofrequency device (baby monitor) may lead to a clinically meaningful adverse effect on sleep in healthy adults under real-world conditions. Further large-scale real-world investigations with specified dosimetry are required to confirm these findings.

3.2. Introduction

Sleep is an important biological function and sleep disturbances are a risk factor for mortality and are associated with increasing number of chronic conditions including cardiovascular disease, diabetes and obesity (Itani et al. 2017). Sleep disturbances also adversely affect neurological functioning such as altered memory formation (Walker and Stickgold 2006), mood changes and depression especially in children (Goel et al. 2009; Marino et al. 2021), poor mental health (Baglioni et al. 2016), impaired learning ability and poor academic performance

(Seoane et al. 2020), as well as Alzheimer's disease (Harris et al. 2021) and neurocognitive deficits (Lowe et al. 2017). The prevalence of sleep disturbances has increased dramatically over the past two decades and they now affect four out of every ten Australians with considerable impact on social, financial and health-related costs (Deloitte Access Economics 2017).

The rise in sleep disturbances coincides with the deployment of billions of mobile phones (Taylor 2023) and Wi-Fi enabled devices, and mobile wireless networks that have increased exposure to radiofrequencies by 18 orders of magnitude (Bandara and Carpenter 2018) yet the relationship between RF-EMF exposure and sleep is unclear. Sleep problems are the most commonly reported complaints attributed to RF-EMF exposure (Austrian Medical Association 2012; Belpomme and Irigaray 2020; Pall 2016) and multiple surveys suggest that RF-EMF exposure is closely linked to symptom reporting (Danker-Hopfe et al. 2010; Hutter et al. 2006; Martens et al. 2017). Sleep disturbances are also frequently reported in young adults (Grandner 2017) who also spend the most time using digital devices (Adams et al. 2016), however epidemiological surveys prone to respondent bias, rarely use clinically relevant outcome measures. Furthermore, experimental research on RF-EMF exposure and sleep is complex and far from conclusive (Ohayon et al. 2019). Most experimental studies exploring the effect of pulsed radiofrequencies on sleep quality involve near-head exposure to mobile phones in a highly controlled laboratory environment. Such studies reveal inconsistent associations, with limited statistical power and short or no follow-ups (Danker-Hopfe et al. 2016; Fritzer et al. 2007; Loughran et al. 2012; Lustenberger et al. 2013; Lustenberger et al. 2015; Schmid et al. 2012; Tettamanti et al. 2020; Vecsei et al. 2018). Furthermore, it has been well established that sleep in a sleep laboratory is distorted, especially over a single night (Herbst et al. 2010). It is also suggested that studies focus on real world settings rather than simulated electromagnetic fields as real-life signals are highly variable with unpredictable changes in intensity and waveforms which renders them more biologically active (Panagopoulos 2019b). No study has examined the effect of regular exposure to 2.45 GHz radiation on sleep in real-world situations, despite this type of radiation becoming ubiquitous in modern households.

The uncertainty around the impact of RF-EMFs on sleep is compounded by the uncertainties surrounding the mechanisms of action. A recent review suggests pulsating radiofrequency electromagnetic fields can alter brain physiology, increasing the electroencephalogram power in selective bands when administered immediately prior to or during sleep, however their effect on sleep architecture or clinical sleep outcomes remains unclear (Ohayon et al. 2019). It has been suggested that RF-EMFs may impact sleep through multiple mechanisms including direct exposure to pulse-modulated RF-EMFs influencing EEG architecture (Hamblin and Wood 2002; Lowden et al. 2019; Zhang et al. 2017), suppression

of melatonin from blue light exposure (Höhn et al. 2021; Mortazavi et al. 2018), device-induced arousal decreasing the ability to fall asleep, and/or other factors associated with the use of mobile phones such as media use before bedtime or after lights out (Tettamanti et al. 2020). The proximity and timing of exposure may also be important with a large systematic review and meta-analysis involving 125,198 children concluding that sleep disturbances and daytime sleepiness were significantly more common when a device was in the bedroom, even when the child did not use the device at night (Carter et al. 2016). Further evidence suggests adverse effects of RF-EMF on sleep outcomes are more likely when exposures occur throughout the night (Danker-Hopfe et al. 2016) yet, physiological studies on the effects of Wi-Fi related frequencies on sleep are generally carried out under laboratory conditions rather than real-world settings and report considerable variation on the relationship between RF-EMF and sleep architecture (Sârbu et al. 2020).

We aimed to address the gaps in current knowledge using a robust, double-blind, randomised, placebo-controlled, crossover methodology in a real-world setting, to explore the effects of exposure from a commonly used radiofrequency device used over multiple nights on clinically relevant sleep outcomes in healthy adults. This is a novel approach as the experimental protocol involved participants' own homes and natural sleeping environments with a readily available consumer electronic device, hence obtaining ecologically-valid, empirical evidence.

3.3. Materials and methods

3.3.1. Study design

3.3.1.1. Radiofrequency device, exposure set-up, and power dosimetry

The study involved a 4-week, randomised, double-blind, placebo-controlled, crossover design on healthy adults at their homes in Melbourne, Australia. We compared 7 consecutive all-night exposure to either an active or inactive (sham) pulse-modulated radiofrequency device. The device used was a commercially available Uniden baby monitor (BW 3001 model), consisting of a digital wireless monitor and digital wireless camera with two-way walkie talkie capability. This device has a transmitting power of 15 dBm and employs a frequency range of 2.4 to 2.4835 GHz using a frequency-hopping spread spectrum (FHSS) with Gaussian Frequency Shift Keying (GFSK) modulation to avoid interference. The units were tested prior to randomisation to determine the level of radiation emitted. This was done by placing them two meters apart and using a Gigahertz HF59B Analyser with UBB27 omnidirectional antenna (frequency range between 27 MHz to 3.3 GHz) and a Gigahertz HFW59D Analyser with UBB2410 omnidirectional antenna (frequency range between 2.4 GHz and 10 GHz). The

meters were set at Peak and Peak Hold to establish the minimum and maximum levels over the course of one hour, which were determined to be between 2.2 and 7 mW/m^2. This is well within the International Commission for Non-Ionising Radiation Protection public guidelines of 10 W/m^2 for frequencies above 2 GHz within the far field zone averaged over 30 minutes and the whole body (International Commission on Non-Ionizing Radiation Protection 2020).

Monitor and camera units were placed within two meters of the participant's bedhead depending on their bedroom layout. The baby monitor unit was installed by the researcher within half a meter of the participant's bedhead (bedside table) and the camera unit was installed at the opposite end of the room, 1.8 to 2 metres of the participant's bedhead. All baby units appeared identical, whether they were operational or non-operational, as the digital display, microphones and the operating lights were disconnected from both the active and deactivated units. In addition, only the deactivated baby monitor and camera units had their wireless module removed. The order of exposure was randomised (computer-generated) and fully counterbalanced across participants, with each exposure period separated by a one-week washout period. Double blinding was achieved by having the baby monitors programmed (activated or deactivated) by an independent consultant so no participant or researcher was able to correctly identify the device status. A random code was assigned to each monitor, which were provided sequentially to participants with the codes being changed in the second intervention week to either an active or deactivated (sham) monitor to ensure the opposite condition was met.

3.3.1.2. Electromagnetic field measurements in the bedroom

A visit to the home of potential participants was conducted to explain the study, obtain written permission and to assess electromagnetic field levels in the immediate environment of the bedroom and in particular, on their bed (pillow). The latter was to ensure exposures during sleep would not exceed 0.1 µT for ambient Alternating Current (AC) magnetic fields and were equal to or below 0.02 mW/m^2 radiofrequency fields (27 MHz to 10 GHz). These levels were derived from the Building Biology Evaluation Guidelines for Sleeping Areas (Institut für Baubiologie 2015). AC magnetic fields were measured with the FM10 Fauser (omnidirectional 3-axis digital gauss meter) and radiofrequencies were measured with the Gigahertz HF59B Analyser with UBB27 antenna (frequency range between 27 MHz to 3.3 GHz) and the Gigahertz HFW59D with UBB2410 antenna (frequency range between 2.4 GHz and 10 GHz). Electromagnetic field readings were also taken on the last day of the trial period to confirm Alternating Current (AC) magnetic fields in the bedroom were below 0.1 µT and radiofrequency fields (27 MHz to 10 GHz) were equal to or below 0.02 mW/m^2.

3.3.1.3. Procedure

Participant flow through enrolment, randomisation, follow up and intervention is shown in Figure 1. The four-week study involved baseline (week 1), two intervention weeks (week 2 and 4) and a washout week (week 3). The procedure included eight visits to the participant's home and participants were contacted via text on a regular basis across the study period to ensure compliance and to confirm they understood how to fit and use the devices. An instruction booklet and video were created to enable participants to watch anytime during the study period.

On the first day of the study, the investigator conducted a home visit to measure ambient EMFs in the bedroom and explain how to complete the daily sleep diary and wear the Actiwatch, which was worn across the entire study period (except during bathing). A charger was provided in week 2 or 3 of the study period to ensure the battery life was sufficient.

On day seven of the first week, the investigator conducted a further house visit to demonstrate how to use the PSG monitor (Z-Machine) and heart rate (ECG) monitor and to remind the participants to complete the PIRS-20 survey the following morning (8th day). Use of the PSG monitor involved cleaning the skin behind the earlobes (mastoid: A1, A2) with an alcoholic swab, and the bony protuberance (spine) at the back of the neck (around C7), attaching the EEG electrodes to these locations, and connecting the wires to the PSG monitor. Participants were shown where to place the device (under the pillow) during the night and how to turn the unit off upon waking. During the same visit, the investigator demonstrated how to use the ECG monitor. This involved demonstrating how to clean and attach the three electrodes on the chest (i.e., on the right- and left-hand side of the body under the collarbone (RA / LA) and under the rib cage (LL) and how to attach the leads and turn on the monitor. This procedure was repeated on the seventh night of each week for four consecutive weeks and participants were asked to undertake this approximately the same time of night for each sleep stage (four nights in total over the study period). On day eight, the investigator picked up the monitors and downloaded the data.

On the first day of weeks two and four (intervention weeks), both the monitor and camera units were plugged into a power socket to ensure battery life for the duration of the 7 days. In situations where the socket was not in close proximity to the bedhead and/or the opposite end of the room, an extension lead was used. The monitors were picked up on day 8.

On the last day of the study (day 28), the investigator conducted a final home visit to measure ambient EMFs in the bedroom and blinding was assessed by asking participants which week they thought they received the active intervention (week 2 or 4).

3.3.2. Participants

A power calculation was conducted in order to estimate the preferred sample size for the study. Effect size estimates were based on the findings of Lustenberger et al. (2013) who found a significant decrease in sleep time following Radiofrequency Electromagnetic Field (RF-EMF) Pulses (Mean decrease 9.23 minutes, SD 13.6). Using this result to estimate effect size, a power calculation was conducted estimating a minimum sample of 20 participants with $\alpha = .05$ and power of 80% (G*Power 3.1.9.2) (Faul et al. 2007).

Inclusion criteria were based on age (18 to 56 years), location (lived in a detached home in Melbourne), the absence of existing sleep disturbances or conditions that may affect sleep (pre-existing illness, bed partner, light, noise), being a non-smoker, speaking English and being able to provide informed consent. Participants were excluded from the study if they were taking any medications or supplements or on antibiotic therapy, diagnosed with any chronic condition, recently hospitalised or had surgery, wore a pacemaker, worked nightshifts, had to travel across time zones two weeks before or during the study period, had to use a mobile phone during the night, pregnant or peri or post-menopausal, unable to provide informed consent, smoked or had a BMI over 30 or any other condition that impacted sleep. In addition, participants were excluded if their bed was adjacent to a smart meter, meter panel or inverter, and/or if they had Wi-Fi enabled devices, cordless phones, extenders, or boosters in their bedroom that they were not willing to relocate. Participants were also excluded if the ambient EMF measurement in their bedroom before and after the study, exceeded 0.1 µT or 0.02 mW/m^2. Participants were advised to avoid digital devices for at least one hour before bedtime, go to bed and get up at approximately the same time over the study period and avoid alcohol and caffeine late in the day (after 3pm).

Participants were recruited via an advertisement campaign on social media and assessed for eligibility using the Participant Eligibility Screening Questionnaire to ensure they followed the exclusion and inclusion criteria. Participants deemed eligible were provided with the Participant Information and Consent Form followed with a phone call to address any questions they had and to arrange a time to assess their home.

Between October 2019 and March 2020, twelve adults consisting of 3 men and 9 women participated in the study. The mean age of the females was 41 (SD ±9) and males was 47 (SD ±3) and the mean BMI for females was 22.9 kg/m^2 and males was 24.6 kg/m^2.

3.3.3. Measures

3.3.3.1. Pittsburgh Insomnia Rating Scale (PIRS-20)

Subjective sleep quality was assessed using the Pittsburgh Insomnia Rating Scale survey on the 8th day of each study-week (four times in total over the study period). PIRS-20 provides an index of insomnia severity with a change in score >20 considered to be clinically significant (Sateia and Buysse 2016).

3.3.3.2. Actigraphy

Objective sleep measures were obtained using portable polysomnography and wrist actigraphy combined with a sleep diary. Actigraphy data was collected using a battery-operated wrist actigraphy watch (wGT3X+, Actigraph Pty Ltd) with a solid state piezo-electric accelerometer to generate movement-based voltage and activity counts per epoch. Participants were asked to wear the Actiwatch for 24 hours a day on their non-dominant hand, and data were collected at 30-second epochs. Consistent with recommended standard research guidelines (Buysse et al. 2006), the following objective sleep measures were obtained from this device: sleep onset latency (SOL), sleep efficiency (SE), total sleep time (TST) and wake time after sleep onset (WASO). Actigraphy scoring was done using Cole Kripke algorithm and manually checked against a sleep diary created by the investigator to document when they turned the lights off and went to sleep, the time they woke up, the time they woke up during the night and reasons for this (noise, light, illness, bed partner, kids, temperature etc.), and the amount of time they spent on a digital device (screen time) for the day.

3.3.3.3. Polysomnography (PSG)

Sleep efficiency, sleep latency, sleep time, sleep staging and EEG power spectrum were measured using a portable single-channel polysomnographic monitor (Zmachine® Insight Model: DT-200, General Sleep Corporation) which gathers high quality, objective, epoch-by-epoch, sleep state information and summary sleep statistics (Pedersen et al. 2020). The Z-machine algorithm categorizes the EEG signal on 30-second epoch basis into five different categories 1) Wake, 2) Light sleep (Stage N1 & N2), 3) Deep sleep (Stage N3), 4) Rapid eye movement sleep (REM-sleep) and 5) sensor problem (if the sensor connection fails). The Z-machine algorithm has sensitivity (95.5 %) and specificity (92.5 %) when compared to polysomnographic technology in scoring sleep and wake in adults (Kaplan et al. 2014; Wang Y et al. 2015). Whilst unavoidable interference from radiofrequency and magnetic fields may alter the results from the Zmachine system, interference from RF and magnetic fields is

common to all EEG recordings and not just specific to this EEG system. Following standard procedures with EEG recordings, we engaged in methods to reduce the impact of EMF interference. The device includes patient grounding and 50Hz notch filter to reduce ambient RF interference with the EEG signal. Also, all raw EEG signals were recorded with <5 KOhm impedence and visually inspected for anomalies by an PSG technician with over 20 years experience.

3.3.3.4. Heart Rate Variability (HRV)

The activity of the autonomic nervous system (ANS) was indirectly measured through Heart Rate Variability (HRV), using a battery-operated portable ECG monitor (Contec TLC9803) that had no Bluetooth or Wi-Fi capability. Heart Rate Variability was analysed in 5-minute samples at baseline, washout, and intervention weeks at approximately the same time of night for each sleep stage. The time and frequency domain of HRV was analysed using Kubios (v 3.0.1, Biosignal Analysis and Medical Imaging Group, Finland). Root Mean Square of Successive Differences in R-R intervals (RMSSD) was used as a HRV index. To quantify the degree of sympathovagal balance between sympathetic and parasympathetic activity, we used the mean ratio between the low frequency (0.04–0.15 Hz) and high frequency (0.15–0.4Hz) heart rate variability power (LF/HF) during the sessions (LF/HF ratio). We calculated an index of ANS reactivity to intervention ((increase of HRV or LF/HF ratio from baseline to intervention/baseline HRV or LF/HF ratio)*100).

3.3.4. Statistical analysis

Data analyses were conducted using the Statistical Package for the Social Sciences software (SPSS Inc., Version 28, Armonk, New York, USA). Differences between the Intervention and Placebo EMF Exposure were analysed using paired samples t-test. A p-value <0.05 was regarded as statistically significant.

3.4. Results

Whilst the goal was to recruit 20 participants, due to the strict inclusion criteria and impact of the pandemic, data from only 12 participants were evaluated. Summary statistics for the primary and secondary outcome measures are outlined in Table 1. Sleep quality as indicated by the PIRS-20 was found to be significantly reduced during RF-EMF exposure compared to placebo exposure ($p<0.05$) as illustrated in Figure 2. Three participants (27.3%) scored above the cut off of 20 (out of a total score of 60 for PIRS-20) for risk of clinical insomnia. The raw single-channel EEG signal derived from the Z-machine was converted to EDF format and

analysed using Curry 7 EEG analysis software (Compumedics Pty Ltd). The EEG signal was high/low pass filtered (.3Hz/70Hz) with a 50 Hz notch filter. A statistically significant increase in electroencephalogram (EEG) power density in the higher frequencies (theta, beta and gamma bands) during Non-Rapid Eye Movement (NREM) sleep was observed during RF-EMF exposure compared to sham exposure ($p<0.05$) but not in Rapid Eye Movement (REM) sleep. No differences were observed in Heart Rate Variability or actigraphy. When asked, only 44% correctly identified the week with the active intervention.

There were a few instances where the equipment was not activated correctly and/or non-compliance was an issue. Actigraphy was not collected for four participants across the study period due to equipment failure and/or non-compliance during some of the study period (n=8). PSG was not collected for two participants due to equipment failure (n=10). One participant came down with a flu-like illness in week 4 (intervention OFF) and their PIRS-20 data was not included for that week (n=11).

Figure 1. *Reporting of trials flows diagram for crossover study involving a baby monitor (intervention).*

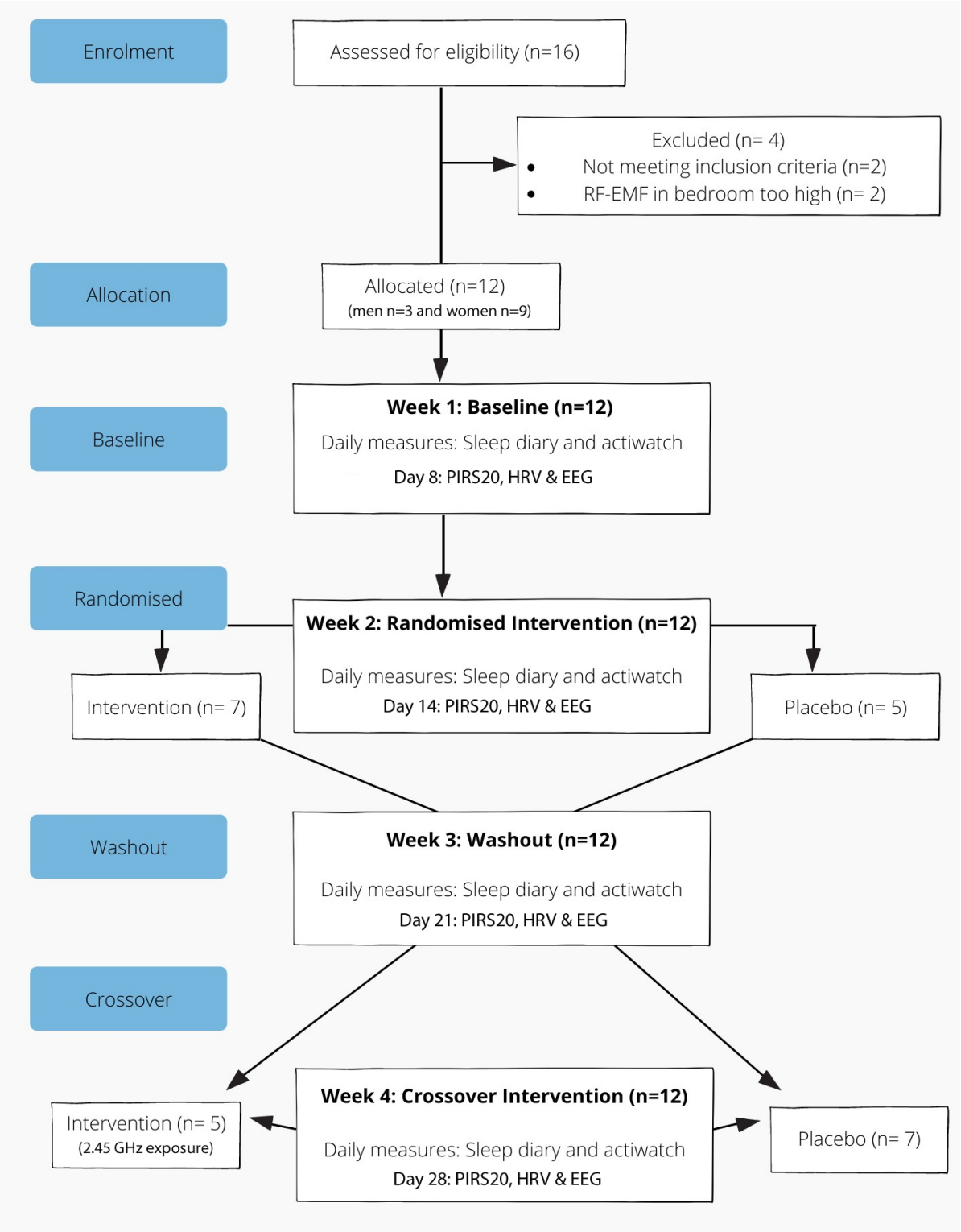


Table 5. Summary Statistics for Primary and Secondary Sleep Outcome Measures.

Results from the primary outcome measure of this study (Pittsburgh Insomnia Rating Scale-20), are shown below. Secondary outcome measures included Actigraphy, Polysomnography, Heart Rate Variability (HRV), and EEG Frequency Analyses from NREM sleep. Heart Rate Variability and EEG analyses were derived from 5-minute samples matched for time of night (within 60 minutes) within sleep stages across conditions.

	Baseline Week 1 ***Mean ± SD***	**Washout Week 3** ***Mean ± SD***	**Intervention On** ***Mean ± SD***	**Intervention Off** ***Mean ± SD***	***n***	***t*-statistic, *p*-value; Bootstrap *95% CI*.**	**Effect Size (Cohen's *d*)**
Primary Outcome							
PIRS-20	8.91 **±** 4.35	8.36 **±** 4.46	14.64 **±** 7.21	9.63 **±** 3.56	11	*t* = 2.48, ***p* =.03***; BCa [1.18, 8.73]	*d* = 0.75
Secondary Outcomes							
Number of Awakenings (NOA)	17.73 ± 3.94	15.60 ±6.32	16.37 ± 3.00	16.10 ± 6.89	11	*t* = 0.11, p =.46; BCa [-2.96, 4.14]	d = 0.04
Actigraphy							
TST	409.37 **±** 42.55	397.35 **±** 56.78	412.99 **±** 27.78	406.38 **±** 74.85	8	*t* = 0.29, *p* =.78; BCa [-63.92, 53.06]	*d* = 0.10
SE	89.38 **±** 4.01	90.25 **±** 3.23	89.57 **±** 3.41	89.66 **±** 6.85	8	*t* = -0.32, *p* =.97; BCa [-5.97, 5.27]	*d* = 0.02
WASO	48.56 **±** 21.24	40.83 **±** 14.30	46.43 **±** 15.26	38.80 **±** 17.91	8	*t* = 0.93, *p* =.47; BCa [-2.90, 19.27]	*d* = 0.33
Polysomnography							
SOL	26.60 **±** 17.28	15.33 **±** 9.16	22.74 **±** 14.79	22.92 **±** 14.99	10	*t* = -0.05, *p* =.96; BCa [-6.00, 6.06]	*d* = 0.02

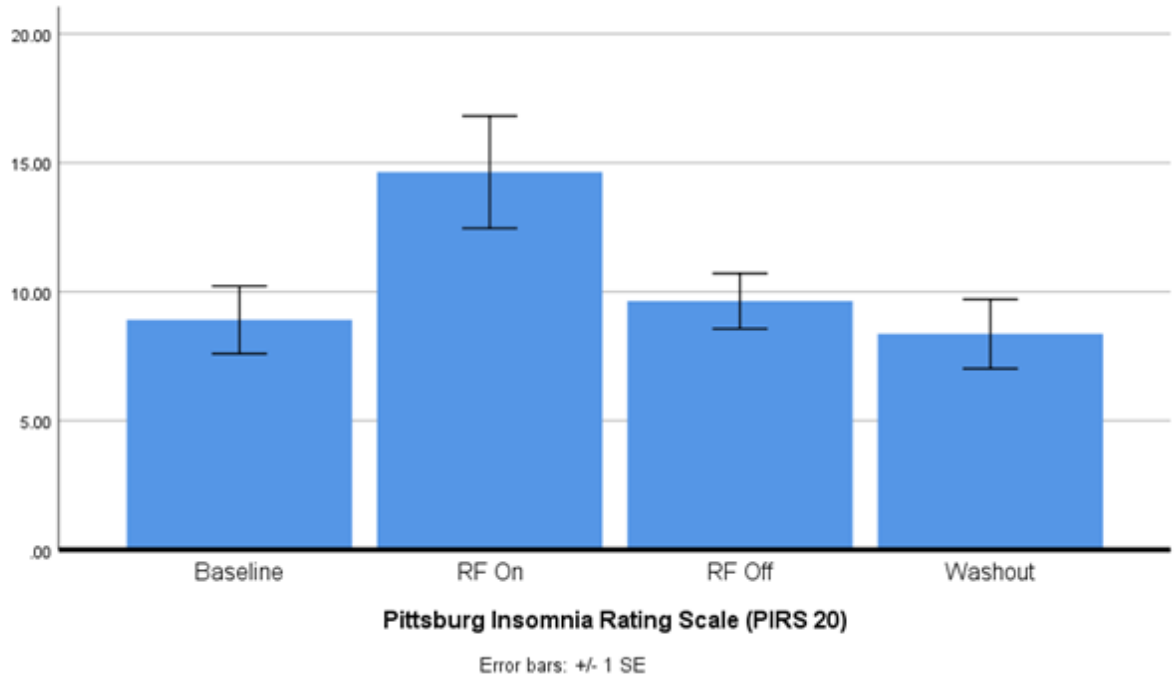
	Baseline Week 1 ***Mean ± SD***	**Washout Week 3** ***Mean ± SD***	**Intervention On** ***Mean ± SD***	**Intervention Off** ***Mean ± SD***	***n***	***t*-statistic, *p*-value; Bootstrap *95% CI*.**	**Effect Size (Cohen's *d*)**
TST	405.94 ± 55.91	405.47 ± 56.74	396.33 ± 43.02	378.42 ± 68.75	10	t = 0.72, p =.49; BCa [-32.28, 60.96]	d = 0.23
SE	83.61 ± 4.54	86.14 ± 5.53	82.77 ± 8.78	84.15 ± 4.83	10	t = -0.60, p=.56; BCa [-6.00, 3.03]	d = 0.19
WASO	44.46 ± 27.50	39.26 ± 34.66	50.64 ± 46.47	40.65 ± 28.25	10	t = 0.94, p =.38; BCa [-5.46, 27.51]	d = 0.30
SWS Time	62.06 ± 38.23	67.00 ± 37.21	80.43 ± 23.74	66.12 ± 27.32	10	t = 1.67, p =.13; BCa [-1.41, 32.16]	d = 0.53
REM Time	99.07 ± 35.00	110.47 ± 40.17	110.52 ± 33.34	99.48 ± 30.61	10	t = 0.81, p =.44; BCa [-14.94, 39.72]	d = 0.26
Heart Rate Variability							
SWS RMSSD	47.28 ± 19.09	42.50 ± 19.84	39.23 ± 20.10	29.00 ± 15.30	8	t = 1.73, p =.13; BCa [-3.31, 18.13]	d = 0.61
SWS LF/HF Ratio	2.19 ± 2.78	1.17 ± 0.63	1.24 ± 1.05	3.62 ± 8.19	8	t = -0.84, p =.43; BCa [-8.19, 0.67]	d = 0.30
NREM RMSSD	31.70 ± 4.98	40.07 ± 16.24	67.34 ± 65.93	36.68 ± 23.78	8	t = 1.27, p =.24; BCa [-0.15, 70.25]	d = 0.45
NREM LF/HF Ratio	2.88 ± 3.56	3.46 ± 3.90	4.53 ± 6.49	1.58 ± 1.24	8	t = 1.21, p =.26; BCa [-1.00, 7.72]	d = 0.50
REM RMSSD	41.47 ± 13.34	36.27 ± 12.89	49.74 ± 16.86	41.76 ± 32.67	8	t = 0.99, p =.36; BCa [-10.00, 23.27]	d = 0.35
REM LF/HF Ratio	1.75 ± 0.89	1.87 ± 1.92	2.11 ± 1.33	1.33 ± 0.65	8	t = 1.42, p =.20; BCa [-1.00, 1.652.11]	d = 0.55

	Baseline Week 1 ***Mean ± SD***	**Washout Week 3** ***Mean ± SD***	**Intervention On** ***Mean ± SD***	**Intervention Off** ***Mean ± SD***	***n***	***t*-statistic, *p*-value; Bootstrap *95% CI*.**	**Effect Size (Cohen's *d*)**
Electronic Device Use (Hours/Week)	24.07 **±** 14.89	24.60 **±** 15.25	20.37 **±** 8.85	21.45 **±** 9.55	9	*t* = 0.46, *p* =.66; BCa [-5.85, 3.57]	*d* = 0.15
NREM EEG Power Density (μV^2)							
Delta (1-3Hz) EEG Power Density	.48 **±**.37	.33 **±**.31	.53 **±**.45	.55 **±**.42	10	*t* = 0.19, *p* =.92; BCa [-0.32, 0.39]	*d* = 0.03
Theta (3-8Hz) EEG Power Density	.05 **±**.08	.07 **±**.19	.36 **±**.36	.08 **±**.15	10	*t* = -2.76, ***p* =.04***; BCa [-0.48, -0.11]	*d* = 0.87
Alpha (8-13Hz) EEG Power Density	.04 **±**.05	.07 **±**.17	.32 **±**.35	.11 **±**.22	10	*t* = -1.97, *p* =.16; BCa [-0.44, -0.04]	*d* = 0.63
Beta (13-30Hz) EEG Power Density	.05 **±**.04	.08 **±**.19	.67 **±**.69	.07 **±**.09	10	*t* = -2.95, ***p* =.03***; BCa [-1.05, -0.22]	*d* = 0.93
Gamma (30-70Hz) EEG Power Density	.08 **±**.07	.21 **±**.53	1.06 **±** 1.04	.24 **±**.40	10	*t* = -3.24, ***p* =.02***; BCa [-1.29, -0.37]	*d* = 1.04

KEY: PIRS-20-Pittsburgh Insomnia Rating Scale-20; TST-Total Sleep Time; SE-Sleep Efficiency; WASO-Wake After Sleep Onset; SOL-Sleep Onset Latency, SWS-Slow Wave Sleep; REM-Rapid Eye Movement; NREM-Non-Rapid Eye Movement; EEG-Electroencephalogram. ***** Indicates $p < 0.05$

Figure 2. *Pittsburgh Insomnia Rating Scale-20 Item Version (PIRS-20)*

Sleep quality as indicated by the Pittsburgh Insomnia Rating Scale-20 Item Version (PIRS-20) after a week of Baseline (No RF-EMF Device), one week of RF-EMF exposure (RF-ON), one week of sham exposure (RF-OFF) and an intervening week of "Washout". Across all participants, average PIRS-20 was found to be significantly reduced during RF-EMF exposure compared to sham exposure ($p<0.05$.)



3.5. Discussion

This study is the first double-blind, randomised, placebo-controlled study on the impact of the exposure to a multi-night radiofrequency device (baby monitor) on clinically relevant sleep outcomes under real-world conditions. The results of the PIRS-20 reveal that 7 consecutive all-night exposure to RF-EMF led to reduced subjective sleep outcomes with three participants (27.3%) scoring above the threshold for risk of clinical insomnia. Poorer subjective sleep outcomes as measured by the Karolinska Sleepiness Scale has been reported following a 3-hour exposure to a mobile phone 884 MHz (Lowden et al. 2011), however studies involving near field exposures to a 900 MHz frequency over six nights using Pittsburgh Sleep Quality Index (Fritzer et al. 2007) or operator-recorded mobile phone use (GSM/UMTS network) at baseline and sleep outcomes both at baseline and at the 4-year follow-up using the Medical Outcome Sleep Questionnaire (Tettamanti et al. 2020) did not report significant effects on sleep.

Despite the small sample size and the study being potentially underpowered for detecting differences in objective measures, the clinically relevant changes in the PIRS-20 coincided with a statistically significant increase in theta, beta, and gamma EEG power density during non-rapid eye movement (NREM) between conditions. These statistically significant findings suggest there are large effect sizes relative to the noise in these measures and are consistent with research on mobile phone exposure, which shows significant modification of the alpha band (Wallace and Selmaoui 2019) and increased power of various frequencies (Loughran et al. 2012; Loughran et al. 2019; Lowden et al. 2011; Schmid et al. 2012; Vecsei et al. 2018). In one review, the EEG power in the alpha frequency range was reported to be increased in ten, decreased in four, and not affected in eight studies (Danker-Hopfe et al. 2019). Another review concluded that the mechanism by which RF-EMFs may impact sleep is likely to be due to an increase in the electroencephalogram power in selective bands when exposure occurs immediately prior to or during sleep (Ohayon et al. 2019). Whilst the EEG power in the alpha frequency range was not statistically significant in this study, the effect size of d = 0.63 (Table 5), power .95 and alpha of .05, suggests a projected sample of 35 using G*Power would be required to observe a significant difference between the exposure and sham exposure conditions. It has been suggested effects of RF-EMF on sleep outcomes are more likely to be seen after longer exposure (>30 min) and with exposure occurring during the entire night (Danker-Hopfe et al. 2016) and this is consistent with our findings, yet it is difficult to draw definitive conclusions as there are many complicating and confounding factors.

Comparing the results of this study with the findings of other studies is a significant challenge because most studies on RF-EMF and sleep have focused on short-term exposure to mobile phone frequencies under simulated conditions in laboratory settings, or

epidemiological surveys prone to respondent bias (Ohayon et al. 2019; Panagopoulos 2023b). Two reviews conducted a decade ago, concluded there is no evidence for a direct association between mobile phone exposure and severity of non-specific physical symptoms such as sleep problems (Baliatsas et al. 2012; Röösli et al. 2010). However, this contradicts a growing number of systematic reviews that have reported pulse-modulated RF-EMFs related to altered brain physiology indicated by changes in electroencephalogram power in selective bands (alpha, beta, delta or theta) when administered immediately prior to or during sleep (Hamblin and Wood 2002; Ohayon et al. 2019; Rubin et al. 2011; Zhang et al. 2017). The heterogeneity between studies appears to be due to multiple factors including differences in study design, timing of exposure relative to sleep, as well as proximity and duration of exposures. In addition, the type of radiofrequency devices employed, the type of frequency used, modulation, power density, field strength, pulsing nature, challenges in controlling extraneous confounding factors, varying criteria for participant inclusion, statistical power and bias, and the laboratory or clinical context involved also vary widely between studies.

The impact of commonly used Blue-Tooth and Wi-Fi enabled devices such as routers, baby monitors and cordless phones on clinically relevant sleep indicators has not been widely studied. To date there have only been two published studies examining the effects of Wi-Fi frequency exposure (using 2.45 GHz frequency band) on sleep with mixed results and these have been done in simulated laboratory settings rather than in a real-world context. A study involving a one off 60-minute Wi-Fi exposure in healthy adults resulted in no changes to the spectral power of spontaneous awake electroencephalographic activity (Zentai et al. 2015), while another study reported that one-night exposure to a Wi-Fi router in a sleep laboratory resulted in a reduction in global EEG power in the alpha frequency band during NREM with no change in subjective sleep parameters (Danker-Hopfe et al. 2020). In the present study, a statistically significant increase in theta, beta, and gamma EEG power density during NREM sleep was observed alongside a significant reduction in subjective sleep quality with multi-night exposure to 2.45 GHz radiation. Although speculative, it is possible that this observed change in NREM EEG is related to poorer subjective sleep quality due to increased cortical arousal in NREM sleep (Force 1992) or other mechanisms that are currently unknown.

3.6. Strengths and limitations

The strengths of this study include the robust randomised, double-blind, placebo-controlled, crossover design and the inclusion of healthy adults in a real-world context. Using a commercially available RF device designed to be placed in the bedroom over seven consecutive all-nights and the use of a clinically relevant measure of sleep as the primary outcome also provides ecological validity. Whilst variability between placements of the camera

and monitor units is likely to impact exposure received by the participants, each participant acted as their own control across the two conditions, and spot measurements conducted on the participant's bed at the beginning and end of the study confirmed exposures did not exceed 0.1 µT and 0.02 mW/m^2.

There are limitations of this study that arise from the real-world conditions, including the inability to control extraneous variables such as the participant's behaviour and the need to account for exposures to multiple devices during the day which could have confounding effects. In addition, even though exposure levels in the bedroom of each participant was assessed before and after the study, continuous monitoring of RF-EMF exposure was not undertaken. Whilst variability between placements of the camera and monitor units is likely to impact exposure received, each participant acted as their own control across the two conditions and spot measurements conducted on the participant's bed at the beginning and end of the study confirmed exposures did not exceed 0.1 µT and 0.02 mW/m^2. The multiplicity of analyses may indicate the finding of a reduction of PIRS-20 with NIR-EMF exposure could be due to chance. It also highlighted, despite only recruiting twelve participants, the effect size for the PIRS-20 could be considered large (d = 0.75), whereas the effect size observed for a range of objective measures varied between 0.02 and 0.61 (small and medium).

Extrapolating the results of this study to exposure from devices that employ different frequencies and/or modulations is a challenge. It has been suggested that modulated or pulsed RF-EMFs are more bioactive than non-modulated or non-pulsing fields of the same carrier frequency and of the same average intensity (Panagopoulos 2022). The devices used in our study used an operating frequency range between 2.400 ~ 2.4835 GHz similar to many Wi-Fi enabled devices, however the modulation used was Gaussian Frequency Shift Keying (GFSK) with a frequency-hopping spread spectrum (FHSS). Given these features, the results of this study may be more applicable to devices that employ GFSK modulation such as GSM, DECT and Personal Area Networks such as Bluetooth and wearables (Liberg et al. 2018).

Another limitation that arose because the study was conducted at home, was that the EEG recording was limited to a single channel portable EEG system, which does not provide the same precision in calculating global EEG spectral power as multi-electrode lab-based studies. Furthermore, the small sample size (n= 8-12) means that the study was underpowered to detect small differences in subjective and objective measures. The finding of statistically significant effects for the PIRS-20 (d=0.75) and increased electroencephalogram (EEG) power suggest large effect sizes. As the sample consisted of healthy adults, it is not known whether the results can be generalised to other age groups or clinical populations. A larger follow-on study would need to consider limiting the number of secondary measures to reduce inflation of type 1 error rate due to multiple comparisons. For

example, actigraphy did not appear to provide the accuracy or fidelity of sleep assessment required (as it is based on movement algorithms), so this measure is not recommended in follow-up studies.

3.7. Conclusion

Our preliminary findings suggest radiofrequency devices may have a clinically relevant and meaningful adverse effect on sleep in healthy adults in real-world scenarios as these effects are associated with statistically significant changes in the EEG during non-rapid eye movement (NREM). In light of the small sample size and limitations of the study, further large-scale investigations are required to confirm these findings. Future studies should include exposure dosimetry, placement of exposure devices that are well-defined, consistent, and consider signal features such as modulation, field strength, resonance, pulsing, polarisation and power flux density. Until further studies verify or provide evidence contrary to these findings, caution should be exercised when using RF-EMF devices in bedrooms.

3.7.1. Trial registration

This trial was registered with the Australian New Zealand Clinical Trials Registry (ID: ACTRN12621000213842) and was conducted in accordance with the Declaration of Helsinki and approved by the RMIT University Human Research Ethics Committee (Approval #21794). Informed consent was obtained from all individuals included in this study.

3.7.2. Data availability statement

The datasets generated and/or analysed during the current study are available from the corresponding author on request.

3.7.3. Author contributions

NB contributed to the conception of work, ethics approval, recruiting the participants, methodology, investigation (home assessments), analysis and interpretation of data, reviewed the literature and drafted the manuscript. MC contributed to the conception of work, ethics approval, methodology and editing. RC contributed to methodology, analysis and interpretation of data, and editing. GK contributed to editing.

3.7.4. Funding

This research received no funding.

3.7.5. Conflict of interest

Author 1 (NB) is the CEO of the Australian College of Environmental Studies, which teaches Building Biology and Electromagnetic Field testing. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

PART B:
RISK ASSESSMENT AND REGULATION OF TOXICANTS AND NON-IONISING RADIATION ELECTROMAGNETIC FIELDS (NIR-EMFs)

Chapter 4:
Risk Assessment and Regulation of Toxicants

4.1. Introduction

Risk assessment and the regulation of toxicants play a crucial role in the establishment of health policies which serve as the basis for clinical practice guidelines. Dose-response relationships form the basis of most contemporary systems for risk assessment, causation analysis, and the setting of exposure standards, however when it comes to toxicants, they are fraught with challenges such as conflicts of interest associated with study outcomes (Wells 2017), and the inability to account for mixture effects and individual risk factors. Furthermore the introduction of untested chemicals into the environment has been made possible through inefficient enforcement, regulatory complexity and fragmented overlapping authorities (Reuben 2010; Sass and Rosenberg 2011). Vast numbers of commercial chemicals in widespread use have not been adequately assessed for neurodevelopmental toxicity, endocrine disruption or other toxic effects (Kassotis et al. 2020; Vandenberg 2019; Vandenberg et al. 2023). This chapter will discuss how toxicants are assessed and regulated, the challenges associated with risk assessment, and the ramifications for clinical practice.

4.2. Dose response and low dose effects of toxicants

In contrast to the vast majority of acute conditions and infectious diseases where cause and effect is easily established, exposure to low levels of thousands of environmental chemicals over a lifespan requires a paradigm shift in the way in which causality is established. While compelling epidemiological, animal and *in vitro* evidence is required to prove harm from a chemical exposure (Reuben 2010), there is a lack of well-accepted tools to objectively, efficiently and systematically assess the quality of published toxicological studies (Segal et al. 2015) making it difficult to assess health risks associated with low level exposure to hundreds of chemicals over a life time. Thus, for almost every conclusion about chemical-related health risks, it is possible to find a dissenting view (Whaley 2013) and the vast majority of scientific reviews conclude that more research is needed.

Dose-response relationships follow the path laid by epidemiologist, Sir Austin Bradford Hill, and form the basis of most contemporary systems for risk assessment and causation analysis (Hill 1965). Such biological gradient assessments involve giving increasing levels of an individual chemical to a group of test animals with the key objective of providing a dose-response assessment that estimates a point of departure (traditionally the no-observed-

adverse-effect (NOAEL) level or the lowest-observed-adverse-effect level), which is then used to extrapolate the quantity of substance above which adverse effects can be expected in humans (Goodson III et al. 2015). In his seminal paper, Hill provided guidance on weighing the evidence for causality and argued that to derive a valid dose-response gradient, quantitative estimates of environmental exposure should consider: strength of evidence, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy (Hill 1965). While Hill pointed out that a plausible dose-response linear relationship "… adds a very great deal to the simpler evidence" and strengthened argument for causality, he acknowledged if confounding factors existed then the cause-and effect interpretation became a "more complex relationship" (Hill 1965:298). Krewski et al. (2022) argues that Hill's concepts were originally designed with only observational (epidemiologic) data and did not consider experimental data and the integration of different sources of evidence. Furthermore, he acknowledges that establishing causality between exposure and outcome requires a careful evaluation of the available evidence, "…particularly in the presence of diverse sources of information, which may report inconsistent findings and which maybe of unequal relevance or reliability" (Krewski et al. 2022:668).

The existing chemical risk assessment framework only involves hazard identification and exposure assessment (Pool and Rusch 2014). Hazard identification assesses the ability of a chemical to cause harm at various dosage levels, and exposure assessment evaluates the dose that might be received at target tissue after contact. Such assessments rely heavily on data extrapolated from human epidemiology, animal testing and cell culture/*in vitro* laboratory studies (Darbre 2022b). This data fails to account for multiple routes of exposure, mixture effects, transgenerational epigenetic effects or individual human risk factors such as age, gender, genetics, nutrition, psychosocial determinants and comorbidities (Amiard and Amiard-Triquet 2015; National Research Council 2007; Pool and Rusch 2014; Zeliger 2011b).

Inadequacies in current chemical risk assessment procedures are highlighted by the wide variation in exposure standards across jurisdictions, along with vast numbers of commercial chemicals in widespread use that have not been adequately assessed for neurodevelopmental toxicity, endocrine disruption or other toxic effects (Kassotis et al. 2020; Vandenberg 2019; Vandenberg et al. 2023). EDCs in particular pose a dilemma for risk assessment as these chemicals exhibit non-monotonic dose-responses whereby the effect of low doses cannot be predicted by the effects observed at high doses (Goodson III et al. 2015; Vandenberg 2015). In addition, a growing number of scientists are questioning the use of linear dose-response models for classifying carcinogens. These models do not account for the complex and permutable pathogenesis of many cancers (Thompson et al. 2015). Such inadequacies were highlighted as early as the 1970s by Bruce Ames who subsequently

developed the AMES test for assessing the mutagenic potential of chemical compounds (Ames 1979).

4.3. Exposure standards and conflicts of interest

A significant volume of data used to establish safety in risk assessment associated with toxicants, is subject to conflict of interest from industry who fund the studies and who may influence how the results are interpreted. The Organisation for Economic Co-operation and Development mandates that industry provides all the data for most pre-market chemical risk assessments to establish safety, despite their conflict of interest (Tweedale 2017). Furthermore the risk assessment process is frequently conducted in consultation with industry, involving scientists employed by various corporations, taking into account what is practicable in the workplace (Castleman and Ziem 1988, 1994), along with a consideration of economic output and future innovations.

As a result of the challenges and inadequacies of the existing risk assessment frameworks, there is a wide variation in exposure standards across jurisdictions depending upon the approach adopted. In the USA, the 'low-dose linear extrapolation' approach is favoured and legislated through the Toxic Substance Control Act (TSCA). This is in contrast to the 'margin of exposure' approach used in Europe which is regulated through REACH (Registration Evaluation, Authorisation and Restriction of Chemicals) (Boobis 2010). While REACH is a preventative approach that places the burden of proof on industry to show safety, TSCA provides authority for the government to regulate and assess chemical safety (Pool and Rusch 2014). Once an industrial chemical has been tested and its point of departure has been established, it is up to government and non-government organisations to develop ambient air and occupational exposure limits. The government organisations include: Environmental Protection Agency, US National Institute for Occupational Safety and Health, Safe Work Australia and the European Commission's Scientific Committee on Occupational Exposure Limit Values. The American Conference of Governmental Industrial Hygienists is a prominent non-governmental organisation with widely adopted guidelines in English speaking countries. Furthermore, non-occupational exposure standards for indoor air quality in residential environments are lacking despite numerous guidelines published by the World Health Organisation (World Health Organization 2015b) and the US Environmental Protection Agency on indoor air quality (United States Environmental Protection Agency 2015b).

Existing chemical risk assessment practices have come under scrutiny from various governmental and non-governmental bodies. These include: US Environmental Protection Agency (United States Environmental Protection Agency 2015a), National Resource Defence Council (Sass and Rosenberg 2011), European Union (who developed REACH), the National

Academy of Sciences and the Institute of Medicine (Pool and Rusch 2014). Also, medical organisations such as the American Medical Association (American Medical Association House of Delegates 2008) and the American Academy of Paediatrics (Paulson and Council on Environmental Health 2011) have raised their concerns.

4.4. Chemical mixtures and 'something from nothing' effects

The prediction of health risks based on NOAEL not only fails to account for non-monotonic dose-responses and real-life exposures which typically involves exposure to multiple chemicals across a lifespan and across generations, it also fails to consider 'something from nothing' effects whereby unpredictable additive, antagonistic or synergistic adverse effects may occur at doses around, or below points of departure (Kortenkamp et al. 2009). Mixture effects can be either synergistic or antagonistic, i.e. with effects stronger or weaker than expected under the additivity null hypothesis (Martin et al. 2021) and synergistic mixtures are defined as those that elicit an observed effect that is at least two-fold greater than the predicted effects (Cedergreen 2014). A recent systematic review involving 1220 'mixture' studies, reported the following outcomes: additivity (28.3%), followed by synergism (24.3%) and antagonism (19.2%) and concluded that very few studies go beyond binary or tertiary mixtures such that the field is over-descriptive, repetitive, and under-theorised and should move on to address real-world challenges (Martin et al. 2021).

Lifetime effects of exposure to chemical combinations are largely unstudied (Reuben 2010), and may only become evident after people have become sick (Zeliger 2011b). For example, carpenters exposed to formaldehyde, terpenes and dust particles below their point of departure are reported to exhibit dyspnea, nose and throat irritation, chest tightness and productive cough (Alexandersson et al. 1982) and complaints of headache, skin, eye, nose and throat irritation are reported in painters despite airborne exposure levels being below the known irritation levels for the single chemicals (Hansen et al. 1987). Similarly, weakly oestrogenic chemicals that are too small to be detected individually can jointly increase the actions of potent, endogenous sex steroids (Rajapakse et al. 2002) and chemical mixtures can act synergistically to exert pro-carcinogenic and anti-carcinogenic effects that contribute to the accumulation of somatic mutations and instigate the hallmarks of cancer (Brisson et al. 2015; Czarnota et al. 2015; Goodson III et al. 2015). Inorganic arsenic is one such example. At high levels in drinking water, arsenic is a well-established human carcinogen associated with bladder, lung and skin cancer (International Agency for Research on Cancer 2012), however at lower doses, its cancer risk may depend upon other variables such as smoking, and on differences in individual susceptibility, either genetically based or via nutritional status or other conditions (Tsuji et al. 2014). This observation parallels the well-established finding

that smokers exposed to asbestos have a significant increase in lung cancer risk compared to non-smokers (Ngamwong et al. 2015). Thus, until a risk assessment paradigm is designed for mixture effects, traditional risk assessment tools need to be used with caution when evaluating chemical mixtures (Fuhrman et al. 2015).

Pesticides are one of the most well researched toxicants when it comes to mixture effects. The triazine herbicides, azole fungicides, pyrethroid insecticides, and cholinesterase inhibitors (organophosphate and carbamates) for example at environmentally relevant doses, are known to interfere with metabolic degradation of other xenobiotics (Cedergreen 2014; Martin et al. 2021). In addition, pesticide formulations such as 'Roundup' have been shown to be significantly more toxic than their active principle (glyphosate), due to the inclusion of adjuvants that increase their potency, yet are not accounted for in safety assessments (Mesnage et al. 2014).

The evaluation of mixture effects is hampered by a lack of knowledge of the molecular pathways involved along with the large numbers of pollutants and their many potential combinations (Delfosse et al. 2015). One theory of how chemical mixtures may elicit unexplained effects, is based on the observation that mixture effects commonly occur when chemical mixtures contain at least one lipophilic and one hydrophilic chemical (Zeliger 2011b). Lipophilic chemicals promote the permeation of hydrophilic chemicals through mucous membranes (Zeliger 2011b). This is important because lipophilic barriers in the body (skin and mucous membranes) serve as the body's primary protection against the absorption of environmental chemicals (Rea 1992). The octanol-water partition coefficient, or K_{ow}, which classifies the lipophilic character of a given chemical, is a useful parameter for environmental risk assessment that is used extensively by authorities in the European Union (European Commission 2003). Most lipophilic toxicants can permeate the body's membranes, and lipophilic chemicals with a K_{ow} greater than 2, are frequently used by the cosmetic industry as chemical penetration enhancers, as adjuvants in pesticides to increase the solubility of the active principle and by the pharmaceutical industry in drug-delivery systems to enhance transdermal drug delivery (Wiedersberg and Guy 2014).

4.5. Individual factors and susceptibility to toxicants

Whilst risk assessment plays a crucial role in understanding and managing potential risks, extrapolating Hill's concepts in patients impacted by environmental exposures is challenging as there are numerous confounding factors that impact individual susceptibility. These include age, gender, ethnicity, genetics, nutritional status (nutrigenomics and nutrigenetics), intestinal microbiota and other lifestyle factors such as diet, smoking, exercise and hobbies, psychosocial determinants and comorbidities (Amiard and Amiard-Triquet 2015; National

Research Council 2007; Pool and Rusch 2014; Zeliger 2011b), the co- or pre-administration of other drugs (Clayton et al. 2006; Zeliger 2011b) and epigenetic states (Latham et al. 2012). Women are far more likely to exhibit environmental sensitivities (80% as opposed to 20% of men) which is thought to be due to their higher body fat to muscle ratio (body burden of toxicants accumulates in fat) and the fact they are exposed to more chemicals in personal care products and cleaning activities (Lipson and Doiron 2006). It has also been reported that those with autism and atopy (asthma and allergies) are especially at risk of developing chemical sensitivities (Steinemann 2019). Exposure to toxicants also varies widely amongst individuals depending upon: past and current environmental exposures; occupation and health and safety practices; place of residence, work and/or school (proximity to vehicle exhaust, industry, mining, waste sites, industrial accidents, golf courses, parks, farms, flight paths, etc.) which is likely to be influenced in part by socioeconomic factors (Tyrrell et al. 2013); use of household products, chemicals and pesticides and appropriate use of safety equipment; and access to clean air, water, food and soil.

4.6. Regulation of toxicants and clinical practice

Failure to properly assess and regulate toxicants means their impact on human health is likely to be underestimated, leading to policies and regulations that fail to adequately protect the public. The wide discrepancies in exposure limits and inability to establish risk, poses significant challenges for clinicians who lack comprehensive clinical guidelines for recognising and treating patients impacted by environmental exposures. The lack of guidelines may explain why environmental sensitivities are largely ignored in clinical practice. Clinicians may either ignore these patients, adopt a polypharmacy approach or refer them on, or take matters into their own hands and make decisions on behalf of individual patients impacted by environmental exposures in the absence of any formal clinical guidelines.

4.7. Summary

Conducting risk assessments and setting exposure standards for toxicants relies heavily on data extrapolated from human epidemiology, animal testing, and laboratory studies and requires comprehensive evaluation of evidence, identification of industry influence and conflicts of interest, whilst also taking into consideration individual needs. Establishing causality between exposure and outcome by employing dose-response analyses is fraught with challenges. These include failure to account for multiple routes of exposure, complex mixtures, non-monotonic dose-responses, transgenerational epigenetic effects and difficulties in accounting for susceptible individuals and populations at risk. In addition, exposure

standards are often developed in consultation with industry, potentially influenced by vested interests and practical considerations. The lack of standardised tools to assess the quality of toxicological studies poses obstacles in evaluating health risks associated with chronic low-level exposure to numerous chemicals throughout a lifetime. Without clinical guidelines, clinicians are largely unaware of the magnitude of the problem and consequently do not have the knowledge or the skills to recognise patients impacted by exposures. Consequently, hazards arising from environmental exposures are likely to be underestimated, potentially leading to policies and regulations that fail to adequately protect the public. Whilst scientific information is fundamental to understanding and managing risk and for forming and implementing appropriate regulations, regulations must account for imperfections in the evidence base that limit the ability to provide definitive answers regarding causality (Krewski et al. 2022).

Chapter 5:
Risk Assessment and Regulation of NIR-EMFs

5.1. Introduction

Adverse health effects associated with ionising radiation are well established, their guidelines are relatively consistent worldwide and they incorporate a margin of safety based on justification of exposure in order to keep doses 'As Low As Reasonably Achievable' (ALARA). In contrast, despite a significant volume of research (human and animal) undertaken in the past two decades, the impact of NIR-EMFs on human health is still the subject of intense debate which has ramifications for risk assessment and regulations. Challenges include the definition of a 'health effect', industry involvement, use of studies that employ simulated emissions under laboratory conditions and heterogeneity between studies. The lack of scientific consensus on safety associated with exposure, has subsequently resulted in a wide divergence in legislated exposure limits in different countries (World Health Organization 2018b) and various countries and organisations have developed exposure limits based on the precautionary principle. The consequent lack of health policy and clinical guidelines has significant ramifications for clinicians who treat patients means clinicians and patients must take matters into their own hands.

5.2. Exposure standards

The Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) are the authority charged with setting the standards for both non-ionising and ionising radiation and their standards have been derived from the International Commission for Non-Ionising Radiation Protection (ICNIRP) guidelines. ICNIRP's guidelines for extra low frequency electromagnetic fields (ELF-EMFs) are based on induced electric currents in the body and their guidelines for radiofrequency electromagnetic fields (RF-EMFs) are based on acute short-term effects of heating of tissue (Commonwealth of Australia 2021; International Commission on Non-Ionizing Radiation Protection 1998, 2010, 2020). The recent ICNIRP guidelines triggered ARPANSA to develop a new standard called 'Standard for Limiting Exposure to Radiofrequency Fields – 100kHz to 300 GHz (RPS S-1)'. Organisations engaged in NIR protection that have adopted the International Commission for Non-Ionising Radiation Protection (ICNIRP) standards include: the European Commission, the World Health Organisation, the International Electrotechnical Commission (IEC), the International

Telecommunication Union, the International Agency for Research on Cancer (IARC), International Labour Organisation and the Australian Radiation Protection and Nuclear Safety Authority (ARPANSA), Health Canada, New Zealand Ministry for the Environment, the Swedish Radiation Protection Authority and the UK Health Protection Agency.

The ICNIRP guidelines for general public exposure to extra low frequency magnetic fields (ELF-MFs) (1 Hz to 100 kHz) is 200 μT (International Commission on Non-Ionizing Radiation Protection 2010).

ICNIRP's guidelines (basic restrictions and reference levels) for radiofrequency exposures are given in terms of certain parameters of the exposure:

1. Personal exposures use the 'Specific Energy Absorption Rate' (SAR) (in W/kg) which quantifies the amount of electromagnetic field power absorbed by biological tissues resulting in thermal effects (International Commission on Non-Ionizing Radiation Protection 2020). SAR is specified over different masses: "SAR_{10g} represents the power absorbed (per kg) over a 10g cubical mass, and whole-body average SAR represents power absorbed (per kg) over the entire body" (International Commission on Non-Ionizing Radiation Protection 2020:486). With regards to general public exposures, the basic restrictions for whole-body average SAR for frequencies between 100 kHz and 300 GHz is 0.08 W/kg averaged over 30 minutes. The basic restriction for local Head/Torso SAR with a frequency range of 100 kHz to 6 GHz is 2 W/kg averaged over a 10 g cubic mass averaged over 6 minutes (International Commission on Non-Ionizing Radiation Protection 2020). To complicate matters, Specific Energy Absorption (SA) (J/kg), is used for brief exposures to electromagnetic fields below 6 GHz where there is not sufficient time for heat diffusion to occur.

2. Environmental exposures use power density or intensity of the incident radiation in W/m^2 which indicates the amount of electromagnetic energy incident upon a unit surface per second (Yakymenko and Tsybulin 2023). Below 6 GHz where EMFs penetrate deep into tissue, SAR is used whilst above 6 GHz, where EMFs are absorbed more superficially, the term 'absorbed power density' (S_{ab}) (W/m^2) is used, even though "… there is uncertainty with regard to the precise frequency for the change from SAR to absorbed power density" (International Commission on Non-Ionizing Radiation Protection 2020:490). (Discussion on frequencies higher than 6 GHz is beyond the scope of this thesis). ICNIRP's reference levels for environmental exposures to RF-EMFs vary according to which part of the body is impacted (ie local vs whole body exposure), exposure duration (time interval), frequency range and

whether exposures occur in the far-field, radiative or reactive near-field zone. These levels use incident power density (S_{inc} in W/m^2), incident E-field strength (E_{inc} in V/m) and incident H-field strength (H_{inc} in A/m). For example, "… frequencies >30 MHz to 300 GHz, personal exposure within the radiative near-field zone is treated as compliant if S_{inc} (…) is below the reference level value. However, for exposure within the >2 to 300 GHz range, within the reactive near-field the quantities applied for the reference level values are treated as inadequate to ensure compliance with the basic restrictions" (International Commission on Non-Ionizing Radiation Protection 2020:495). Reference levels for general public exposure averaged over 30 minutes and the whole body, to electromagnetic fields (100 kHz to 300 GHz) varies from 2 to 10 W/m^2 (10 million μW/m^2) depending on the frequency range (International Commission on Non-Ionizing Radiation Protection 2020:495). In contrast, reference levels for local exposure, averaged over 6 minutes to electromagnetic fields (2 to 6 GHz), is 40 W/m^2 (40 million μW/m^2). Above 6 GHz, incident power density is used as the reference level as RF-EMFs follow the characteristics of plane wave or far-field exposure conditions.

5.3. Challenges assessing risk and setting exposure standards for NIR-EMFs

ICNIRP's guidelines are arduous, difficult to understand and fail to take into consideration the reality that a significant proportion of the global population is exposed to long-term radiofrequency electromagnetic fields at non-thermal levels. Consequently, the guidelines have been met with criticism from researchers and clinicians for failing to ignore a large body of research that has shown RF-EMFs at non-thermal levels may result in significant bioeffects (Altpeter et al. 2000; Blank et al. 2015; Fragopoulou et al. 2010; Johansson and Sage 2010; Morgan et al. 2015). A large database of peer-reviewed studies on RF-EMF health effects, the Oceania Radiofrequency Scientific Advisory Association (ORSAA), led researchers to the conclusion that from a total of 2,266 papers statistically significant biological effects studies involving non-thermal exposures outweighed 'no effect' studies by three to one (Leach et al. 2018).

There are numerous challenges associated with the setting of exposure standards for NIR-EMFs including the definition of what constitutes a 'health effect', and the difficulty in establishing cause and effect, as exposures have multiple sources, are often imperceptible, ubiquitous, and vary greatly over time and distance. Consequently, collecting reliable data on complex and rapidly changing patterns of exposure, whilst minimising recall bias, publication bias and overt errors, is a significant challenge for ongoing large-scale population-based studies. Furthermore, differences in study design (frequency, intensity, modulation and duration of exposure) and the choice to use studies that employ simulated exposures under

laboratory conditions as opposed to real-life exposures, make it difficult to compare studies. In addition, many of the diseases correlated with exposure such as brain tumours, have very long latency periods which take generations to reveal correlations.

5.3.1. Real-life versus simulated exposures

The majority of 'well controlled studies' that form the evidence base used to establish exposure guidelines, are mobile phone studies that use simulated emissions conducted under laboratory conditions (exposure chambers). These studies employ fixed and predictable parameters with no variability that are less likely to be biologically active and more likely to produce misleading 'no effect' findings (Panagopoulos et al. 2021). "While experimental studies employing simulated EMF-emissions present a strong inconsistency among their results with less than 50% of them reporting effects, studies employing real mobile phone exposures demonstrate an almost 100% consistency in showing adverse effects" (Panagopoulos et al. 2015:1).

Studies that employ real-life exposures represent the minority of research, yet they have been shown to be highly and unpredictably variable each moment especially in their intensity, and cause more damage to biological systems, than those conducted under laboratory conditions (Panagopoulos 2019b). The characteristics of wireless communication electromagnetic fields likely to be responsible for the bioeffects arising from non-thermal exposures are polarisation, existence of extra low frequency components (pulsing, modulation, etc), field/radiation intensity, exposure duration and field variability (Panagopoulos 2023a). This led the authors to conclude that the choice to use simulated exposures "…is a serious scientific flaw that may lead to totally devious results with enormous adverse consequences for public health" (Panagopoulos et al. 2015:5). These findings have significant implications for future research, and further support the need to reconsider exposure standards using data extrapolated from studies that employ real-life exposure conditions reflective of the general population's exposure.

5.3.2. Defining health effects

According to ARPANSA and ICNIRP, the only established health effect from RF-EMF is excessive heating caused by high exposure levels (Australian Radiation Protection and Nuclear Safety Agency 2021; International Commission on Non-Ionizing Radiation Protection 2020). However, the definition of 'health effect' lacks specificity and could be deemed to begin at the cellular level when the redox capacity of the cell becomes overwhelmed by persistent and elevated reactive oxygen species that results in a shift in cell signalling pathways (Simkó 2007). It has been suggested that this may lead to health effects from cancer to non-cancer

pathologies arising from low-intensity RF-EMFs (Yakymenko et al. 2016). According to Redmayne (2016):

> *The issue of whether children's RF-EMF exposure is of concern revolves around core beliefs about whether "non-thermal" exposures can cause any effects, and fundamental definitions of a "health effect". Are health effects those which are short-term, well-understood physiological responses, or do they include poorly understood, but repeatedly demonstrated, changes in homeostasis or activated protective and adaptation-compensatory mechanisms effects?* (Redmayne 2016:183).

According to Kryzhanovskiĭ (2004), health is the state of the body where functional dynamic homeostasis remains unaffected, whilst disease is the state of the body where functional dynamic homeostasis is compromised, leading to an inability to perform functions necessary for productive interactions with the environment. Until a consensus regarding what constitutes a 'health effect' arising from exposure to NIR-EMFs can be established, researchers and relevant stakeholders will continue to debate and justify their individual perspectives.

5.3.3. Mechanisms of action by which NIR-EMFs may impact cell biology at non-thermal levels

There are several mechanisms by which NIR-EMF has been shown to impact cell biology. There is compelling evidence that NIR-EMFs result in changes in the waking EEG, in particular, the alpha band frequency (8–13 Hz) (Danker-Hopfe et al. 2019; Ghosn et al. 2015; Hinrikus et al. 2008; Wallace and Selmaoui 2019). Other mechanisms include the enhancement of the permeability of the blood-brain barrier (Benedick 1979; Nittby et al. 2009; Salford et al. 1994; Schirmacher et al. 2000; Sırav and Seyhan 2016; Tang et al. 2015; Wang L-F et al. 2015; Zuev and Ushakov 1993), degranulation of mast cells (Belpomme and Irigaray 2020) and increased inflammatory cytokines (Megha et al. 2015). Whilst the impact of RF-EMF on melatonin has been shown to be inconsistent in animal and human studies, melatonin appears to play a protective (antioxidative) role against radiofrequency induced oxidative stress (Selmaoui and Touitou 2021).

The majority of experimental evidence suggests an increased level of cellular oxidative stress markers induced by RF-EMR exposure arising from changes in redox-related processes through voltage-gated ion channels (Bandara and Weller 2017; Belpomme et al. 2018; Grassi et al. 2004; Lai 2019; Megha et al. 2015; Pall 2013; Panagopoulos et al. 2002; Santini et al. 2018; Stein and Udasin 2020). The latest systematic review examining literature from the last two decades concluded that "…changes in calcium homeostasis, attributable to the voltage-gated calcium channels, were found to be the most commonly reported result of

EMF exposure" (Bertagna et al. 2021:82). Panagopoulos et al. (2023) suggest the modulated and pulsed ELF signals in the radiofrequency carrier waves in combination with intense variability, impacts the voltage gated ion channels in the cell plasma membrane, and disrupts the cell's electrochemical balance. The influence of EMF exposure on genotoxicity however depends on cell type and their homeostatic state. Lymphocytes for example, do not respond to the fields which can be explained by their strong homeostatic activity (Simkó 2007).

The Cellular Stress Response is a unique behaviour of cells following exposure to EMFs (Barati et al. 2021). Redox homeostasis in a cell is achieved if the rate of reactive oxygen species production and antioxidant capacity is in balance (Simkó 2007). An increase in the production of reactive oxygen species (ROS) via its impact on the voltage gated ion channels and subsequent downstream effects, results in the upregulation of antioxidant intermediates, resulting in a protective effect (Barati et al. 2021). Small fluctuations of 20 to 30% in the steady state concentration of ROS are normal (Simkó 2007). If however the production of free radicals persists over time (oxidative stress), redox homeostasis becomes out of balance, resulting in a shift in cell signalling and gene and protein expression (Simkó 2007) which may lead to irreversible cell changes, single and double DNA strand breaks, mitochondrial dysfunction and amplification of the immune response (Bandara and Weller 2017; Dasdag et al. 2015; Fragopoulou et al. 2010; Narayanan et al. 2015; Pall 2013; Simkó 2007; Wyde et al. 2016; Yakymenko et al. 2016). The induced reactive oxygen species and their involvement in cell signalling pathways, explains a range of health effects from cancer to non-cancer pathologies arising from low-intensity RF-EMFs (Yakymenko et al. 2016). Redmayne and Reddel (2021) propose (amongst other things) "…that with repeated RFR exposure the autonomic system (and linked immune and inflammation systems) can shift from becoming dysregulated to dysfunctional…" (Redmayne and Reddel 2021:232).

5.3.4. SAR as a measure to assess non-thermal exposures

SAR is unreliable as a metric to assess non-thermal effects because it fails to consider the most commonly reported result of man-made NIR-EMFs exposure which is attributed to its impact on voltage-gated ion channels (Cellular Stress Response) (Bertagna et al. 2021). Furthermore, SAR is impractical because it cannot be measured directly, and the existing methods for SAR estimation have serious deficiencies because they cannot account for the countless microscopic variations in the physical parameters inherent in living tissue (Panagopoulos et al. 2013; Panagopoulos et al. 2023). Even if the SAR rating was to continue, large animal studies have demonstrated the existing rating should be re-evaluated. The largest animal study ever conducted on RF-EMFs (i.e. the US National Toxicology Program), demonstrated a significant increase in cardiomyopathy and neoplasms in male rats following

19 weeks exposure at 0.2 to 0.29 W/kg whole body SAR for GSM modulation and 0.27 to 0.42 W/kg whole body SAR for CDMA (Falcioni et al. 2018). Using Bayesian modelling averaging a bench mark dose lower limit of 0.2 to 0.4 W/kg was calculated as a point of departure, which means once a ten-fold safety factor is applied, the actual whole body SAR limit for adults should be 2 to 4 mW/kg and for children 0.2 to 0.4 mW/kg (Uche and Naidenko 2021). According to this research, the existing ICNIRP standards should be 40 times lower for adults and 400 times lower for children.

5.3.5. Exposure standards: contradictory, additive, synergistic and antagonistic effects

ICNIRP's dose-response guidelines fail to account for and explain contradictory outcomes observed in experimental studies. Exposure to NIR-EMFs may induce both beneficial effects such as accelerated healing of wounds and injuries and enhancement of chemotherapeutic agents, whilst also enhancing carcinogenesis, cellular or genetic mutations, and teratogenicity (Kostoff and Lau 2017). "… ELF-EMF exposure does not demonstrate a clear dose-response pattern" and "…no threshold can be considered for induction of ELF-EMF biological effects" (Barati et al. 2021:10). The outcome of experimental studies suggest variations in bioeffects arising from EMF exposure are not solely based on intensity and power absorbed by biological tissues, but also appear to depend on the time point of exposure, duration of exposure, cell type and presence of co-stressors (Barati et al. 2021; Grassi et al. 2004).

Whilst epidemiological data on the interaction between electromagnetic fields and chemical toxicants are scant and inconclusive, the combined effect was first raised in 1974 by three Soviet researchers - Danilenko, Mirutenko and Kludrenko - who observed that irradiation of tissue by pulsed radiofrequency sources cause cell membranes to become more permeable to chemical mutagens (Dwyer and Leeper 1978). A systematic review of the combined biological and health effects of electromagnetic fields and at least one other agent highlighted both the beneficial effects (accelerated fracture and wound healing, limb regeneration in amphibians, enhanced drug delivery and bacterial inactivation for prolonged food storage) and the adverse effects of EMFs on biological systems when combined with other agents (Kostoff and Lau 2017). ELF-MFs of at least 3 mT potentiate the impact of other physical and chemical exposures (Juutilainen et al. 2006) and occupational exposures to lead, solvents and pesticides only resulted in an increased risk of glioma when workers were simultaneously exposed to moderate to high levels of ELF-MFs (Navas-Acién et al. 2002). There is also evidence for synergistic interaction of specific electromagnetic patterns (pulsed or physiologically-patterned) and pharmacological agents involving several neurotransmitter systems found to exert potent effects markedly greater than the impact of the drug alone (Whissell and Persinger 2007).

Whilst ELF-EMFs alone are not capable of inducing apoptosis, they have been shown to either potentiate or inhibit apoptotic effects of a co-stressor depending on the timing and duration of exposure (Barati et al. 2021). Short-term ELF-EMF exposure prior to a chemotherapeutic agent, has been shown to significantly inhibit programmed cell death induced by the agent (Grassi et al., 2004). If however exposure to ELF-EMFs is prolonged (>24 hours), apoptotic effects of the chemotherapeutic agent are enhanced (Barati et al. 2021). Barati et al. (2021) suggests this apparent contradiction can be explained with the cellular stress response, whereby the increase in the production of reactive oxygen species (ROS) via its impact on the voltage gated ion channels and subsequent downstream effects, results in the upregulation of antioxidant intermediates, resulting in a protective effect. Conversely, during long term exposure, excess ROS levels overwhelm the antioxidant intermediates which are not capable of coping, thereby promoting apoptotic effects of the chemotherapeutic agent (Barati et al. 2021).

A recent *in vitro* study demonstrated that RF-EMFs dramatically increased black carbon induced toxicity in macrophages which remained high 72 h later for all doses suggesting a prolongation of the innate and inflammatory immune response (Sueiro-Benavides et al. 2021). This issue is also complicated by the fact that cellular stress in the cerebral cortex, the cerebellum or both seems to be more associated with the type of signal than with any additive effects of combined frequencies. This points to the possibility of another mechanism at work when multiple signals act on tissue. Consequently, there is no linear cause-effect relationship, the sub-thermal effects from a combined two-frequency signal must therefore be described as a non-linear biosystem (Salas-Sánchez et al. 2019).

5.3.6. Bias

Recall bias is a common phenomenon in EMF research as a significant proportion of studies investigating personal exposures rely heavily on participants estimating their mobile phone use or using data obtained from service providers. Two large scale population based mobile phone studies - the COSMOS study (Schüz et al. 2011) and the MOBI-Kids study (Sadetzki et al. 2014) - relied on the child or parent's memory as a way to gather exposure data despite the fact exposimeters and mobile phone-based Apps exist on digital devices that claim to accurately estimate personal exposure (Cellraid Ltd. 2015). Despite their limitations, the use of exposure assessment tools in epidemiological studies has been shown to provide significant benefits compared to questionnaires and billing records (Bhatt et al. 2016; Zeleke et al. 2018).

Publication bias is a common phenomenon in electromagnetic field research as evidenced by the growing number of studies and reports that have been withheld from publication (Maisch 2009). The first documented adverse health effects associated with

radiofrequency electromagnetic energy exposure were in military personnel on radar bases during World War II. A report titled ‘Microwave Syndrome’ published in 1970 in the former Soviet Union, and shortly after, a 1971 US government report titled ‘Program for control of electromagnetic pollution of the environment’ both disappeared into the archives and were subsequently withheld from public view (Hecht et al. 2016). In 1994, the Australian Commonwealth Scientific and Industrial Research Organisation (CSIRO) was commissioned to undertake a comprehensive literature review of the biological effects of radiofrequencies used in wireless technologies. The review was authored by Dr Stan Barnett and the funding was derived from the telecommunications industry (Telecom, Optus, and Vodafone) and the report documented adverse health effects arising from power levels well below the existing standards for thermal (tissue heating) effects. The report also called for the establishment of an effective research program to develop safety standards in order to achieve the trust of the public (Commonwealth Scientific and Industrial Research Organisation 1994), yet, the report was subsequently classified ‘Confidential’, and withheld from publication (Maisch 2009). Similarly, in 1996, the German Federal Agency of Telecommunications commissioned researchers to review 1500 Russian studies titled ‘Biological effects of electromagnetic fields on humans in the frequency range of 0 to 3 GHz’. Published in 1997, the report was suppressed by the telecommunications industry (Hecht et al. 2016). “That these findings were not welcome by commercial interests is probably responsible for the fact that the 120-page research report immediately disappeared into the archives of the self-same agency that had commissioned the report in the first place” (Hecht et al. 2016:8). The report was made public as part of a brochure series published by the *Competence Initiative for the Protection of Humanity, the Environment and Democracy* - a registered non-profit society consisting of independent scientists, physicians and lawyers, designed to expose “… a sick government system called health and environmental protection, which exploits the present and future of public health for its own irresponsible political agenda” (Hecht et al. 2016:5).

5.3.7. Conflict of interest

Conflicts of interest are common with NIR-EMF research. Several meta-analyses dating from 2000, demonstrated that most government or independent studies find a statistically significant association between AC magnetic field exposure and childhood leukaemia or an elevated risk of at least OR = 1.5, whilst almost all industry supported studies fail to find any significant or even suggestive association (Carpenter 2019). This observation has also been observed in mobile phone studies, whereby studies funded exclusively by industry were less likely to report statistically significant results compared with studies funded by public agencies or charities

(Huss et al. 2007). Consequently the media declares that results are ‘inconsistent’ when in fact they are very consistent if only independent studies are considered (Carpenter 2019).

ICNIRP guidelines for RF-EMFs have come under intense scrutiny for excluding a large body of evidence demonstrating biological effects at non-thermal exposures under the guise of methodological flaws and publication bias (Buchner and Rivasi 2020; Hardell and Carlberg 2020; Pall 2018; Sage and Carpenter 2012; Weller et al. 2020). In addition, ICNIRP has been criticised for close ties to the telecommunications industry and evading the discussion of topics that challenge safety or dismissing them as insignificant (Hardell and Carlberg 2020; Sage and Carpenter 2012; Weller et al. 2020). In 2014, the WHO launched a draft of a monograph on RF fields and health for public comments whereby five of the six members of the Core Group in charge of the draft were affiliated with ICNIRP (Hardell 2017). Such conflict of interest is also highlighted by the fact that agencies charged with responsibility for providing EMR safety advice to the public such as ARPANSA, US Federal Communications Commission, and the UK Health Protection Agency, frequently benefit from selling RF spectrum licenses and champion corporate interest at the expense of public health (Alster 2015; Pall 2018; Starkey 2016). In addition, ICNIRP and WHO’s Environmental Health Criteria Task Group charged with setting exposure standards for NIR-EMFs, have been criticised for allowing researchers funded by telecommunications industry to influence WHO policy thereby providing protection against the need to upgrade distribution systems as well as risks of litigation (Maisch 2006).

5.3.8. Children and electromagnetic fields

Children are uniquely at risk of exposure to the radiation emitted from mobile phones as their head shape and size leads to different areas of peak exposure, their skulls are significantly thinner, their brain and bone marrow have higher conductivity to radiofrequency electromagnetic energy compared to adults, and they have many more hours of cumulative lifetime exposure as exposures begin prenatally and continue throughout early and later life (Christ et al. 2010; Davis et al. 2023; Peyman et al. 2008). Compared with adult models, children experience two to three-fold higher radiofrequency doses to localised areas of the brain when a mobile phone is positioned next to the ear (Fernández et al. 2018). Despite this, very few EMF studies consider the age of first exposure even though higher risks are observed in people who begin mobile phone use before the age of fifteen (Hardell and Carlberg 2015). Despite children’s unique risk of exposure, health outcomes associated with exposure has not yet been defined. A recent systematic review that investigated the health risks of RF-EMF exposure from mobile devices on children and adolescents was unable to draw conclusions

regarding possible effects as most studies displayed methodological weaknesses that limit the internal validity of the results (Bodewein et al. 2022).

5.4. Exposure standards and the precautionary principle

Concerns regarding the biological effects of radiofrequencies and implications for exposure standards, were raised four decades ago. In 1984, the US EPA conducted a comprehensive review of the literature on the 'Biological effects of Radiofrequency Radiation' and concluded that biological effects occur at a SAR of about 1 W/kg and there was sufficient evidence about the relation between RF-radiation exposure and biological effects to permit development of exposure limits to protect the health of the general public (Elder and Cahill 1984). A similar review was conducted and reported by an Australian Parliamentary into Electromagnetic Radiation in 2001 which concluded that:

> *while adverse health effects are not agreed upon, the existence of biological effects associated with radiofrequency radiation is now recognised. For these reasons the Committee Chair recommends a rigorous precautionary approach in all areas of the deployment of wireless technology, that radiofrequency (RF) emissions be kept As Low As Reasonably Achievable (ALARA), and that the expired interim exposure Standard not be adapted to the International Commission on Non-Ionising Radiation Protection (ICNIRP) Guidelines* (Commonwealth of Australia 2001:xv).

Despite these recommendations, the CSIRO was removed from any future involvement in non-ionising research and ARPANSA became the Australian authority to set safety standards for exposure to radiation and adopted the ICNIRP guidelines (Maisch 2009).

ICNIRP's reluctance to consider health effects arising from long-term exposure to RF-EMFs at non-thermal levels, has resulted in divergent exposure standards and policies especially with regards to children's exposure. Approaches vary widely depending on the country, ranging from adopting ICNIRP standard, to adopting ICNIRP standard in addition to providing advice to minimise RF-EMF exposure in children, implementing labelling requirements at the point of sale, or restricting exposure in sensitive sites (Redmayne 2016). There are over 20 countries, regions or cities that take a precautionary approach by setting RF-EMF guidelines that are significantly lower than ICNIRP (Redmayne 2016). For example, the Russian National Committee on Non-Ionising Radiation Protection (RNCNIRP) has a maximum permissible level of 100,000 $\mu W/m^2$ (significantly lower than ICNIRP) as a result of concerns to children's health due to their rapid growth, mobile phone use for longer periods of time, higher conductivity in the brain, smaller head size, thinner skull and smaller distance to the antenna (Grigoriev 2008).

The weight of evidence associating NIR-EMFs with significant biological and adverse health effects, has prompted some governments to adopt their own EMF guidelines that are in some cases thousands of times lower than the existing ICNIRP guidelines, and schools worldwide are taking action to reduce levels of wireless and NIR-EMFs exposure by installing wired connections (Environmental Health Trust 2017). A report commissioned by the Council of Europe urged the scientific community to "…reconsider the scientific basis for the present electromagnetic fields exposure standards set by ICNIRP, which have serious limitations and apply 'as low as reasonably achievable' (ALARA) principles, covering both thermal effects and the athermic or biological effects of electromagnetic emissions or radiation" (Verts 2011:4).

The inadequacies of the exposure guidelines has prompted working groups and industry bodies to develop guidelines for the general public that incorporate a margin of safety and take into consideration the precautionary principle. Guidelines that take into consideration non-thermal effects arising from long term exposure to RF-EMFs, and international conventions such as the United Nations, European Convention on Human Rights concerning the right to a healthy environment and legislation covering Disability, Equality, Equal Opportunities, Health & Safety, and Non-Discrimination, were developed by the BioInitiative Working Group (Sage and Carpenter 2012) released in 2012 and updated in 2020, and the International Guidelines on Non-Ionising Radiation (IGNIR) by the European Association for Environmental Medicine (International Guidelines on Non-ionising Radiation 2021). The BioInitiative Report has an exposure limit to RF radiation between 30 to 60 $\mu W/m^2$ (Sage and Carpenter 2012). IGNIR's limits are based on the time of day, i.e. 100 $\mu W/m^2$ (day time), 10 $\mu W/m^2$ (night time), and 1 $\mu W/m^2$ (sensitive groups i.e. children, the elderly, foetuses, pregnant women, those with comorbidity, body metal work and people with Electromagnetic Sensitivity) (International Guidelines on Non-ionising Radiation 2021). These recommendations are similar to the Building Biology Evaluation Guideline limit of up to 10 $\mu W/m^2$ (IBN, 2015a) and consistent with Panagopoulos' experimental research on fruit flies (Panagopoulos 2012, 2017) and human peripheral blood lymphocytes (Panagopoulos 2019a) which led him to conclude that exposures should be limited to 1,000 $\mu W/m^2$ (short-term) and 10 $\mu W/m^2$ (long term) (local exposures averaged over 6 minutes in the 2 to 6 GHz range) (Panagopoulos 2023a). This is in stark contrast to ICNIRP and ARPANSA's general public reference levels for whole body (averaged over 30 minutes) exposure for radiofrequency fields (100 kHz to 300 GHz) of up to 10 million $\mu W/m^2$ depending on the frequency (Commonwealth of Australia 2021; International Commission on Non-Ionizing Radiation Protection 2020).

With regards to ELF-MF exposure, the International Guidelines on Non-Ionising Radiation maximum exposure is 1 µT (day), 0.3 µT (night) and 0.1 µT (International Guidelines on Non-ionising Radiation 2021). The Building Biology Evaluation Guidelines is up to 0.1 µT

(IBN, 2015a). This is in sharp contrast to the ICNIRP limit of 200 µT (International Commission on Non-Ionizing Radiation Protection 2010).

5.5. Public mean total exposures to NIR-EMFs

Personal exposures to ELF-MFs are fairly consistent amongst studies conducted in various countries, regardless of the location and source. Residential extra low frequency magnetic fields are reported to vary between 0.025 and 0.07 µT in Europe (Salvan et al. 2015), between 0.05–0.06 µT in Australia (Karipidis 2015) and between 0.055 and 0.11 µT in the USA (World Health Organization 2007b). A review involving 25 studies published between 1993 and 2019 concluded the average exposures in homes ranged from 0.02 to 0.4 µT (Baaken et al. 2020). Readings were more likely to be higher in school classrooms with mean exposures at 0.11 µT and 21.67% of classrooms had a magnetic field strength above 0.2 µT (Silangam et al. 2018). The Israeli Ministry of Environmental Protection found more than 60% of schools had at least one classroom with magnetic fields exceeding 0.4 µT (Israel Ministry of Health 2015). ELF-MFs in excess of 0.4 µT were more likely to be found in homes and schools in close proximity to electricity substations, transformers or high voltage power lines (Baaken et al. 2020). Population exposure to ELF-MFs are well within guidelines published by ICNIRP, ARPANSA, the Building Biology Evaluation Guideline and the International Guidelines on Non-Ionising Radiation. Furthermore, residential exposures to ELF-MFs in excess of precautionary guidelines of 0.1 µT are rare except when in close proximity to high powered sources.

Personal exposures to radiofrequency electromagnetic fields (RF-EMFs) are highly variable depending on the source, its location and proximity to the user, time of day and day of the week, and region of the body exposed. A systematic review involving 21 studies conducted in Europe concluded that the population weighted mean total RF-EMF exposure was 8.25 µW/m^2 in homes, 10.31 µW/m^2 outdoors, and 101 µW/m^2 in transportation (trains) (Sagar et al. 2018). In contrast, the median exposure to RF-EMF in a sample of children (8-18 years) from five European countries was 75.5 µW/m^2 with the greatest exposures arising from mobile phone base stations, television, and radio antennas (Birks et al. 2018). A Mexican study recorded stratified mean minimum exposures as 146.5 µW/m^2 in travel and 116.8 µW/m^2 at home, and maximum values at the workplace of 499.7 µW/m^2 (Ramirez-Vazquez et al. 2021). A Spanish University recorded an average maximum value of 205 µW/m^2 inside the classroom (Ramirez-Vazquez et al. 2023). An Australian study recorded the median personal RF-EMF exposures as 115 µW/m^2 (208 mV/m) with the main contributors being downlink and broadcast (Zeleke et al. 2018). An Australian study of kindergarten children concluded that environmental exposures to RF-EMFs (primarily from mobile phone base stations) exceeded personal exposure levels (Bhatt et al. 2017), whilst a cohort study of Swiss adolescents

estimated phone calls contributed 88% to RF-EMF exposure (Foerster et al. 2018). Personal exposures to RF-EMF vary significantly, depending on the source of exposure, location relative to the user and use of digital devices and age, which makes it difficult to compare studies. Whilst these measurements are well within ICNIRP's and ARPANSA's standards, they exceed the Building Biology and International Guidelines on Non-Ionising Radiation guidelines.

5.6. Regulation of NIR-EMFs and clinical practice

The lack of scientific consensus on safety associated with exposure, and wide divergence in legislated exposure limits in different countries, has resulted in the absence of health policies and clinical guidelines in Australia. This is despite the dramatic increase over the past twenty-five years to RF-EMFs at non-thermal levels, which are associated with a range of adverse health effects. The lack of clinical guidelines means most clinicians have no awareness of the issues, and a growing number of frustrated patients are ignored and gaslit by the medical fraternity. Furthermore, the absence of clinical guidelines means discerning clinicians who spend the time to listen to their patients and take comprehensive environmental exposure histories, must take matters into their own hands, and develop the knowledge and the skills over many years to assist these patients. This is further complicated by the challenges establishing individual susceptibility which has not yet been well defined, but is likely to be impacted by device use, exposure duration, frequency, modulation and proximity to the source, amongst other factors. Thus there is a need for public policy makers to recognise RF-EMFs as a potential health risk in susceptible populations, to adopt the precautionary approach and develop clinical guidelines to increase awareness amongst the medical community, as has been done by progressive organisations such as the Austrian Medical Association.

5.7. Summary

Current exposure standards for NIR-EMFs are based on short-term heating effects, and do not take into consideration the global population's exposure to long-term levels at non-thermal effects, which account for the majority of exposures. The mechanism of action by which NIR-EMF at non-thermal levels may induce health effects has been a subject of debate for decades despite the growing number of experimental studies and systematic reviews demonstrating its impact on the EEG, blood brain barrier, and voltage gated ion channels. Furthermore, a significant proportion of EMF studies investigating biological effects, employ simulated exposures under laboratory conditions with fixed parameters that are far less likely to induce

biological effects, as opposed to real-life exposures involving polarised and highly variable fields (Panagopoulos 2023a).

Exposure standards are frequently developed in consultation with industry, involving scientists employed by corporations with vested interests, taking into account what is practicable in the workplace, economic output and future innovations. Conflicts of interest associated with study outcomes abound, resulting in publication bias, cherry picking papers, misrepresenting the balance of evidence and excluding evidence under the guise of methodological flaws.

PART C:
ENVIRONMENTAL MEDICINE AND CLINICAL PRACTICE: A CALL TO ACTION

Chapter 6:
Environmental Medicine and Clinical Practice: A Call to Action

6.1. Introduction

We are entering a new chapter in the practice of medicine. The ‘epidemiological transition’ from traditional infectious diseases to chronic non-communicable diseases (NCDs) brought on by the complex interactions between an individual’s genetics, lifestyle and environmental factors, has significant ramifications for chronic disease management and general medical care. This is especially pertinent as half of all adult Australians have one or more chronic conditions (Australian Bureau of Statistics 2022). Failure to anticipate the inevitable shift to NCDs in countries undergoing rapid transitions, has resulted in health systems struggling to deliver effective interventions for these diseases. NCDs caused by the environment weigh heavily on health services and national household budgets and sustainability of health systems is put at risk if the upstream determinants of disease are not seriously tackled (World Health Organization 2020). The rise in the global population’s exposure to toxicants and manmade electromagnetic fields over the past three decades, have been linked to multiple disease states commonly seen in routine medical practice. During this period, the number of disability adjusted life years due to years lived with disability (YLDs) rose from 20.7% to 33.9% (Vos et al. 2020) and the number of countries where YLDs exceeded years of life lost increased from 1 to 29 countries which is mirrored in these nation’s health expenditures. Low investment in research into underlying causes and therapeutic innovations for key causes of functional health loss is exacerbating this widespread and unacceptable neglect (Murray et al. 2020). The dramatic change in the environmental landscape over the past three decades and its impact on chronic and complex diseases, raises significant challenges for the medical community to better identify, diagnose and treat patients at risk of health effects arising from environmental exposures. This chapter will discuss how Environmental Medicine is defined, and the challenges translating environmental health research into evidence-based healthcare and policy. It will also identify stakeholders who raised concerns for regulatory reform and taken action to mitigate exposures, challenges clinicians face diagnosing and treating patients impacted by environmental exposures, and the need to account for individual variations required to implement the new era of personalised medicine.

6.2. Lessons in history

The history of medical care is littered with examples of missed opportunities, wasted resources and counter-productive policies, due to the inability to effectively assemble and act on available evidence on toxicant exposure (Whaley 2013). Environmental tobacco smoke, asbestos, lead dust, benzene, polychlorinated biphenyls, chlorofluorocarbons, lead and organochlorine pesticides are just some examples where warnings were ignored for decades prior to the emergence of devastating public health issues (Harremoës et al. 2001). History also provides examples of doctors whose observations at the clinical level, in addition to the power of rapid action, resulted in significant improvements in public health despite great criticism from their peers. For example, in the 18th century, British surgeon, Sir Percival Pott, without knowing the cause or mechanism of action, stopped an epidemic of scrotal cancer in chimney sweepers by asking them to improve their genital hygiene (Pott 2002). Furthermore, in 1854, Dr. John Snow who is credited as the first epidemiologist, was able to prevent an outbreak of cholera by dismantling a water pump handle in Broad St, London (Snow 1857) and Dr Alice Stewart identified that a single diagnostic foetal x-ray significantly increased the risk of developing childhood leukaemia (Stewart et al. 1958).

6.3. Environmental medicine: definitions and scope of practice

Environmental medicine (EM) is a specialty field that is not well-defined and has been relegated to specialists outside of general medical practice despite the weight of evidence correlating environmental exposures to conditions routinely seen in general practice and chronic disease causation. In the mainstream scientific literature, environmental medicine is defined as the evaluation, management, and study of detectable human disease or adverse health outcomes from exposure to external physical, chemical, and biologic factors in the general environment (Ducatman 1993; Pope et al. 1995). This is in contrast to occupational clinicians whose definition of environmental medicine varies depending upon the country and include: “exposures arising from industrial activities at a workplace” (Australia), “embrace any influences on health and disease that are not genetic” (UK), or as “that branch of medical science which addresses the impact of chemical or physical stressors on the individual or group in a community or dwelling through evaluation, diagnosis, treatment and control” (USA) (Australasian Faculty of Occupational & Environmental Medicine and Royal Australasian College of Physicians 2012:17). To add to the confusion, public health clinicians define environmental medicine more broadly as “…issues in the physical environment which impact on health. This includes quality of air, water and food…” (Australasian Faculty of Occupational & Environmental Medicine and Royal Australasian College of Physicians 2012:18).

Consequently, environmental medicine has become a specialty field under the guise of 'occupational and/or environmental medicine' and 'public health' with the majority of 'environmental physicians' focusing on public health issues rather than patient-centred clinical practice (Schwartz et al. 2005).

Wide inconsistencies in the definition for the term 'environment', has further ramifications for establishing environmentally attributable risk estimates. For example, researchers and publications that define the environment in the narrow sense (air, water, food, and soil pollutants) tend to have smaller attributable risk estimates, whereas researchers and publications that refer to the environment in the broadest sense (including lifestyle factors, occupational exposures, and pollutants) have consistently larger estimates (McGuinn et al. 2012).

Relegating environmental health to a specialty field is highly problematic when environmental exposures are implicated in many of the conditions seen by clinicians on a daily basis (Institute of Medicine (US) Division of Health Promotion and Disease Prevention 1988). Furthermore, few doctors take adequate occupational or exposure histories or have the tools or expertise to adequately assess or manage these exposures (Bijlsma and Cohen 2018; Politi et al. 2004) and few doctors refer patients to environmental physicians (Herr and Eikmann 2011) and therefore environmental exposures are seldom identified in disease causation (Reuben 2010). Consequently, the cadre of environmental oncologists, researchers and clinicians trained in environmental health are relatively small, which may explain why environmental health is largely excluded from general medical practice and national policy (Reuben 2010).

6.4. Translating environmental health research into evidence-based healthcare and policy

The healthcare environment is multidimensional and complex and there is no single, linear approach to translate evidence into policy and clinical practice. In theory "…environmental health policy and practice [should be] supported by the best available evidence, taking into account the preferences of citizens and the wider public and our own professional judgment" (Barratt et al. 2013:2). Health related organisations and governmental bodies have a duty of care to assess and manage risks associated with environmental exposures by establishing health policies and clinical practice guidelines, yet clearly there are many obstacles that are preventing them from doing so. For example, the challenge to make decisions regarding the strength of evidence and probability of causation when the evidence is inconclusive; the capacity to apply evidence obtained from clinical trials and systemic reviews and account for

individual differences reflected in sub-populations; the ability to make decisions to establish when there is sufficient evidence to act; or how to manage conflicts of interest when members of scientific organisations, governmental bodies and/or journal reviewers are closely aligned with industry who have a vested interest in research outcomes and the setting of exposure standards.

Evidence-based medicine is the cornerstone of medical practice and requires clinicians to shift from traditional and intuition-driven practice to evidence-based practice to incorporate the growing body of research into clinical decision making. “Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. [This involves] integrating individual clinical expertise with the best available external clinical evidence from systematic research” (Sackett et al. 1996:71). This involves 5 steps: 1) asking the question, 2) acquiring the best evidence, 3) appraising the evidence, 4) applying the findings to clinical practice and 5) evaluating the outcomes of change (Sackett 1997). Evidence-based medicine forms the basis for evidence-based practice models with the aim to assess, interpret and apply research into practice to improve patient care, treatment and outcomes within healthcare (Dusin et al. 2023).

Establishing the health impact of environmental exposures is based on evaluation of the available data by expert scientific bodies using a weight of evidence approach, and “… is further strengthened if the results from different types of studies (epidemiology and laboratory) point to the same conclusion” (Australian Radiation Protection and Nuclear Safety Agency 2020:3). This is good in theory, however the divergent evaluation and interpretation of evidence associated with environmental exposures to establish ‘current best evidence’ is fraught with challenges. According to the ‘Hierarchy of Evidence’, systematic reviews and meta-analyses such as PRISMA (Preferred Reporting items for Systematic Reviews and Meta-analyses) have become the gold standard for reviewing the literature and appraising the evidence, and translating environmental health research into policy and clinical practice. However the tools used to assess the quality of a study can lead to inappropriate conclusions and exclude a significant proportion of the available evidence which may lead to significant underestimation of the associated health effects and inadequate support for the regulation of environmental exposures (Eick et al. 2020). Furthermore, there are substantial differences in methodological rigour across systematic reviews (Menon et al. 2022), inconsistencies in risk assessment methods (Chartres et al. 2019) as well as a lack of consensus on methods for the study appraisal, risk of bias tools and best evidence-based practices on health effects of hazardous agents (Eick et al. 2020). For example, differences in risk of bias tools to assess validity of studies and potential biases on the direction of effects such as the IRIS tool use of

subjective indicator for overall study quality, can lead to inclusion of only a subset of studies on the harms of hazardous exposures resulting in inaccurate conclusions (Eick et al. 2020).

Another reason for the divergent evaluation and interpretation of evidence is the selective use of evidence source such as toxicological or epidemiological data that relies entirely on one source or limited analyses of animal toxicity studies which can result in conflicting conclusions (Chartres et al. 2022). Widely accepted methodologies used to inform health decisions and policy such as the Cochrane Collaboration and GRADE (Grades of Recommendation, Assessment, Development and Evaluation) frequently use data that is largely derived from randomised, controlled trials (RCTs). Randomised controlled trials on environmental contaminants are underutilised and practically precluded from the evidence stream due to ethical considerations including concerns regarding intentional human exposure studies posing more than minimal risk (e.g. pesticide testing), withholding potentially effective environmental intervention from the placebo group in controlled studies, and unintentional increase to environmental hazard exposure (Allen et al. 2015; Resnik 2008). Evidence derived from animal studies in the absence of human experimental data, is considered 'weak evidence' by the medical fraternity and outside the comfort zone and time constraints of most clinicians (Woodruff et al. 2011).

The challenges and inconsistencies involved in interpreting and establishing the strength of evidence and probability of causation, has meant little of the vast amount of literature published on environmental health finds its way into general medical journals and subsequently into public health policy. This has occurred in spite of the increase in the number of journals dedicated to public health, environmental health and occupational health increasing from 335 in 1999 to 559 in 2019 (Scimago Journal & Country Rank 2020). It has also occurred despite the recognition of environmental exposures in chronic disease causation which has led to the formation of organisations, professional societies and environmental medical associations to address environmental health related issues, over the past three decades.

Despite the underpinning premise that evidence-based medicine considers the needs of individual patients, epidemiological studies can be limited by often failing to take into account the role of individual differences reflected in sub-populations (Alam and Jones 2014). Similarly treatments under investigation in clinical trials were assumed to apply to anyone with the relevant clinically defined condition (Biankin et al. 2015). Applying study outcomes to individuals impacted by environmental exposures is not helpful as they have highly specific needs that require detailed exposure histories. Subsequently citizens concerned about and/or exhibiting adverse health outcomes arising from environmental exposures are often dismissed in clinical practice as the existing medical paradigm does not support the long consultation times required to undertake effective environmental exposure histories. In addition, most

clinicians do not have the underpinning knowledge to diagnose, test or treat these patients. The strong focus on experimental evidence undervalues clinical expertise acquired through experience and practice and relegates health policy into ‘cookie cutter’ approaches. “Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence maybe inapplicable to or inappropriate for an individual patient” (Sackett et al. 1996:72).

To complicate matters, many types of research are non-reproducible and difficult to interpret clinically and often misinterpreted and misunderstood (Sharma 2021). Clinicians have limited knowledge of the evidence based medicine process and research methodology, including study design and interpretation of the results (McAlister et al. 1999; Windish et al. 2007). The sheer volume of evidence assumes clinicians have the time and skill to retrieve, critically appraise and apply medical literature to patient care.

As little of the vast amount of literature on environmental health finds its way into general medical journals, resources and tools to educate clinicians and elicit personal environmental health data in the clinical setting are limited in scope and applicability. The Australian Institute of Health and Welfare acknowledge there are notable gaps in environmental data in the Australian population required to understand the links between the natural and built environments and human health (Australian Institute of Health and Welfare 2020). This may explain why adverse health outcomes arising from environmental exposures are frequently ignored. For example, the Australian NHMRC 2011 Standard for Clinical Practice Guidelines portal does not provide any guidelines on how to assess environmental exposures, despite the fact there are extensive guidelines for conditions like diabetes and brain tumours, which are known to be influenced by environmental exposures. The lack of guidelines is compounded by a lack of conventional pathology tests to assess environmental exposures, and a medical model that does not support long consultation times, which are required to take a comprehensive environmental exposure history. Furthermore, the medical curricula rarely provides the underpinning knowledge to assess, diagnose or treat patients with potential exposures to environmental hazards. The lack of guidance from health agencies and policy makers to assist clinicians to identify environmental exposures, has been met with a growing number of screening questionnaires including:

- CDC’s Agency for Toxic Substance and Disease Registry Taking an Exposure History Guide (Agency for Toxic Substances and Disease Registry 2006),
- Environmental Exposure and Sensitivity Intolerance (QEESI) (Miller and Prihoda 1999),
- Brief Environmental Exposure and Sensitivity Inventory (BEESI) (Palmer et al. 2020),

- Chemical Sensitivity Scale for Sensory Hyperreactivity (CSS-SHR) (Nordin et al. 2004),
- Chemical Odour Sensitivity Scale (COSS) (Bailer et al. 2004) (CGES) and
- World Health Organisation's Pediatric Environmental History (World Health Organization 2012).

Most of these are unlikely to be known by most clinicians and have either not been validated and/or require lengthy periods of time to complete, which may not always be practical in a clinical setting. Consequently, many clinicians and those specialising in idiopathic multimorbidity have developed their own assessment procedures to assess susceptibility or exposure of their patients to environmental toxicants. Such procedures may include extensive historical inquiries (paediatric, occupational, and environmental exposure histories) along with an assessment of their patients' metabolic, nutritional, genetic, and exposure profiles and include unconventional tests performed at pathology laboratories from around the globe. Such assessments may come at considerable expense to their patients and as exposure standards are not available for many biomarkers, these clinicians must interpret the data without the benefit of published normal ranges or specific diagnostic criteria.

6.5. Environmental exposures and the call to action

"Although [family] physicians remain one of the most often accessed and most trusted sources of information about the environment (…) they are rarely trained to understand, act on, or inform the public about these issues" (Gómez et al. 2013:168-169). The need for greater awareness regarding environmental exposure assessments for clinicians was highlighted in 1967 at a conference by the American Medical Association's National Congress on Environmental Health Management, the American College of Clinicians (Selikoff 1985; White 1990), as well as being a focus of the International Federation of Environmental Health in 1991 (O'Brien 1991) and 2013 (O'Connor 2013) and more recently by a group of Australian researchers and clinicians (Bandara et al. 2020).

Both the World Health Organisation (World Health Organization 2002) and the American Academy of Paediatrics (Etzel 2012) recommend that children's environmental health be incorporated into the training for health care providers. This has led to the emergence of educational training programs for health care providers dedicated to managing early-life exposures on health outcomes throughout life[1]. Obstetricians and gynaecologists

[1] Examples of educational programs include: Pediatric Environmental Health Specialty Units (PEHSUs) across the USA and Canada (U.S. Environmental Protection Agency 2023), Child Health and the Environment (CHE) network (Buka et al. 2020),

have also been called upon to advance policy changes for prevention of exposure to toxic chemicals through increasing public knowledge as well as assessing for exposures in light of the irreversible health impacts from chemical exposures in utero (Di Renzo et al. 2015; Tinney et al. 2015). Yet, despite these recent initiatives, obstetrics-gynaecology education has been lacking in environmental health training other than consideration of nutrition, smoking and drinking during pregnancy (Schenk et al. 1996). A report by the International Federation of Gynaecology and Obstetrics recommended that reproductive and other health professionals advocate for policies to prevent exposure to toxic environmental chemicals, work to ensure a healthy food system for all, make environmental health part of health care, and champion environmental justice (Di Renzo et al., 2015). In 2015, the Association of American Medical Colleges developed a webinar on 'Teaching Population Health: Innovative Medical School Curricula on Environmental Health' (Association of American Medical Colleges 2015) outlining the need to educate undergraduate medical students in environmental health which included links to the American College of Medical Toxicology's Environmental Medicine Modules (American College of Medical Toxicology 2015).

Despite the recognised need for clinical education on environmental chemicals and electromagnetic fields, there is a lack of environmental health education in medical undergraduate curricula. Surveys of medical school graduates found that more than one-third of respondents received 'inadequate' instruction in environmental health (Association of American Medical Colleges 2013) and a recent survey, identified that whilst 92% of family medical residents believe environmental health is important, only 18% had any specific training in taking an environmental exposure history (Sanborn et al. 2019). Furthermore only 27.8% of primary care physicians surveyed, were able to correctly recognise health effects related to environmental exposures (Nicotera et al. 2006). The Institute of Medicine has been particularly vocal about the lack of environmental health training as evidenced by the publication of the book 'Role of the Primary Care Physician in Occupational and Environmental Medicine' (Institute of Medicine (US) Division of Health Promotion and Disease Prevention, 1988), and the report 'Environmental Medicine—Integrating a Missing Element into Medical Education' (Pope et al. 1995), which outlined six competency-based learning objectives for medical students. This was further reinforced by the World Health Organisation's report 'Environmental Health and the Role of Medical Professionals' (World Health Organization 1996), which highlighted the medical professionals role in assessing, investigating, diagnosing, monitoring, treating and preventing environmentally-related disorders.

and a series of modules on Children's Environmental Health developed by the World Health Organisation (World Health Organization 2019)

Whilst environmental health is considered important by clinicians, there is a gap between its perceived value and the knowledge, effective teaching and clinical practices necessary for diagnosing exposure-related conditions (Sanborn et al. 2019). The lack of environmental education for clinicians can be seen to be due to competition from other disciplines in increasingly crowded medical curricula, along with a lack of funding and appropriately trained academics (Shanahan et al. 2010). Only 11% of family medical residents believed their supervisors had a good understanding of environmental exposures, and almost half believe taking an environmental exposure history takes up too much time (Sanborn et al., 2019). A significant proportion of undergraduate medical training is devoted to pharmacology as opposed to toxicology (Hays Jr et al. 1992) or environmental health, with the exception of medical toxicology, a specialty field involving acute high dose exposures confined to emergency clinicians (Thompson 2013). Furthermore, nutrition is rarely taught in undergraduate medical training despite the fact that nutritional state has a large and lasting impact on health and affects the metabolism of toxicants in key Phase 1 and 2 metabolic detoxification pathways (Zeliger 2011b).

6.5.1. Governmental agencies concerns about environmental exposures

There appears to be growing governmental concern about environmental electromagnetic exposures, and several countries have implemented restrictions or bans on the use of Wi-Fi. Following a petition by the National Parents' Leadership and the Organisation for ‘Sensible’ Use of Cellular Technology, guided by the precautionary principle, the Israeli Ministry of Education banned the use of Wi-Fi in kindergartens, restricted use in schools and installed equipment to ensure exposure would be as low as possible (Israel Ministry of Health 2015). Cyprus has removed Wi-Fi from elementary schools and France passed a law in 2015, to ban Wi-Fi in kindergartens and childcare centres and restrict students up to the age of 15 from using phones, tablets and smartwatches in school (Pierre Le Hir 2015).

In 2001, an Australian Parliamentary Inquiry into Electromagnetic Fields outlined their concerns for the roll out of Wi-Fi which has largely fallen on deaf ears (Commonwealth of Australia 2001). A report commissioned by the Council of Europe suggested implementation of awareness-raising campaigns targeting children, teenagers and young people of reproductive age on the risks of potentially harmful long-term biological effects of EMFs on environment and health (Verts 2011).

There is a growing movement in various countries to halt the implementation of 5G. Concerns regarding the rollout of 5G and its impact on human health were recently raised by the European Parliament (Karaboytcheva 2020). The House of Representatives (Dutch Parliament) engaged the Health Council of the Netherlands, to publish a report on 5G in 2020

which led to the Council's Standing Committee on Electromagnetic Fields to recommend not using the 26 GHz frequency band for 5G until any potential health risks have been investigated. The council further recommended a cautionary approach by keeping exposures 'as low as reasonably achievable' on the basis that exposure under the latest ICNIRP standards also has the potential to negatively affect health (Health Council of the Netherlands 2020).

6.5.2. Citizens' concerns about environmental exposures

Failure of health agencies and policy makers to limit the global population's exposure to environmental hazards, has led to a sharp increase in public concerns and media coverage associated with manmade electromagnetic fields and toxicants. Two surveys conducted by the European Commission with each involving over 27,000 Europeans, found more than two thirds are concerned about exposure to chemicals in everyday products (household products, clothes, furnishings, electronics, paints, cosmetics) (European Commission 2017) and believe that manmade electromagnetic fields (high voltage power lines, mobile phone masts and mobile phone handsets would affect their health (European Commission 2010). Nearly half are concerned that the current level of regulation and standards in the EU is not strict enough (European Commission 2017). This is despite the implementation of the REACH regulation (Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation) that came into force in June 2007.

The past decade has seen an avalanche of citizen-initiated support groups on social media dedicated to educate the community and assist vulnerable citizens impacted by environmental exposures. These include Stop Smart Meters (in various countries), Stop 5G, Electrosensitivity UK (Electro-Sensitivity UK 2018), The Swedish Association for the Electrohypersensitive (Elöverkänsligas Riksförbund 2020), Multiple Chemical Sensitivity Aware (UK) (MCS Aware Charity for Environmental Illness 2017), Mould Toxic Illness Facebook groups (various countries), Australian National Register of Environmental Sensitivities (The Australian National Register of Environmental Sensitivities 2015), Parents for Safe Technology (Parents for Safe Technology 2023b), Wi-Fi in Schools Australia (Australian Radiation Protection and Nuclear Safety Agency 2023d), Working for Safe Technologies for Nurseries, Schools and Colleges (UK) (WiFiinschools 2018) (UK), Hoc the Wi-Fi (Australia) (HOC the WiFi 2019), Wireless Education (Canada) (Wireless Education 2021), Safe Schools Information Technology Alliance (UK) (Safe Schools Information Technology Alliance 2019) along with many others.

Concerns regarding Wi-Fi in schools has been raised by teachers (UK Professional Association of Teachers) and parents. France, Cypress and Israel have limited or even banned the use of wireless technologies from childcare centres, kindergartens and/or primary schools. Various cities throughout the world have restricted or banned the use of Wi-Fi networks including Salzburg (Austria), libraries in Paris, and the Frankfurt city government until the technology can be proven to be safe (Association Nationale Pour La Securite Sanitaire Dans Les Technologies Sans Fil 2008; Environmental Health Trust 2020; Parents For Safe Technology 2023a; Philips and Philips 2017).

6.5.3. Clinicians and researchers concerns about environmental exposures

The weight of evidence associating electromagnetic fields with adverse health effects, has prompted thousands of doctors, scientists and researchers, teachers as well as various government and non-governmental agencies to sign resolutions and appeals to reclassify RF-EMFS in mobile phone and wireless technologies from Group 2B to Group 1 human carcinogen (Altpeter et al. 2000; Blank et al. 2015; Carlberg and Hardell 2017; Fragopoulou et al. 2010; Informa Healthcare 2006; International Agency for Research on Cancer 2011a; Johansson and Sage 2010; Kelley 2008; Lower House of the German Parliament 2007; Miller et al. 2018; Morgan et al. 2015; Rogers 2002; Verts 2011). The most recent appeal signed by 215 scientists from 40 nations, each of whom had published peer-reviewed studies on electromagnetic fields, called on the United Nations to revoke the existing exposure standards because they do not consider the adverse health effects arising from non-thermal exposures (Blank et al. 2015). In addition, a growing number of independent professional scientific organisations dedicated to providing unbiased scientific advice have arisen, such as the International EMF Alliance (Europe), Oceania Radiofrequency Scientific Advisory Association (Australia), EM-Radiation Research Trust (UK), and the Environmental Health Trust (USA).

Various medical associations and clinicians have formed their own professional organisations with the intention to disseminate and upskill clinicians in the field of environmental medicine. Examples include: American Academy of Environmental Medicine, Australasian College of Nutritional and Environmental Medicine (Australasian College of Nutritional & Environmental Medicine 2023), British Society for Ecological Medicine, European Academy for Clinical Environmental Medicine (European Academy for Environmental Medicine 2023), International Society for Environmentally Acquired Illnesses in the USA (The International Society for Environmentally Acquired Illness 2023), International Society of Doctors for Environment, Physicians for Safe Technologies in the USA (Physicians for Safe Technology 2023), Physicians Health Initiative for Radiation and Environment in the UK (The Physicians' Health Initiative for Radiation and Environment 2023b), Society for the

Advancement of Hormones and Healthy Ageing Medicine in Malaysia (Society for the Advancement of Hormones and Healthy Ageing Medicine in Malaysia 2023), International Board of Clinical Metal Toxicology in Europe (International Board of Clinical Metal Toxicology in Europe 2023), to name but a few. This has resulted in a growing number of conferences in environmental health, with recent ones including 'Environmental and Viral Disrupters' in Australia (Australasian College of Nutritional & Environmental Medicine 2020), 'Radiation Health Conference' in the United Kingdom (The Physicians' Health Initiative for Radiation and Environment 2023a), and EMF Medical Conference in the USA (EMF Medical Conference 2021).

The Bio-Initiative Report was one of the first reports published on the impact of EMFs on human health and prepared by 29 researchers and doctors from ten countries (Sage and Carpenter 2012). In 2012, the Austrian Medical Association published a guideline for doctors as a duty of care for the 'Diagnosis and treatment of EMF-related health problems and illnesses' (Austrian Medical Association 2012), whilst the European Academy of Environmental Medicine published their 'EMF Guideline for the prevention, diagnosis and treatment of EMF-related health problems' (Belyaev et al. 2016). In 2020, the 'Consensus Statement of UK and International Medical and Scientific Experts and Practitioners on Health Effects of Non-Ionising Radiation' was published that was endorsed by 10 medical and 3 scientific organisations in 6 countries involving over 3,500 medical doctors (Mallery-Blythe 2020).

6.6. Challenges clinicians face dealing with environmental exposures

While risk assessment requires the application of multiple scientific fields to public health and regulatory matters, it is up to individual clinicians to determine the relevance of the many issues involved to the current and future health needs of their individual patients. The challenge is how clinicians utilise evidence generated from systematic reviews and meta-analyses and apply them in the context of individual patients whose variants are so unique they represent a minority of the community.

Environmental exposure assessment in clinical practice requires the personalisation of medicine using a complex knowledge base to determine an individual's body burden of toxicants, along with their personal risk factors and health status. Yet, despite the many scientific developments occurring in chemical risk assessment, the discrepancies amongst leading authorities in their interpretation of evidence of harm makes it difficult for clinicians to translate scientific information into clinical practice.

Whilst biomonitoring is an established approach to evaluate the internal body burden of environmental chemical exposures, the use of biomonitoring for exposome research is limited by the high costs associated with quantification of individual chemicals (Go et al., 2015). Interpretation of the presence of chemicals in human tissues has also been the subject of much controversy, as its presence cannot be taken to imply that there will be adverse functional consequences (Darbre 2022a; Herr and Eikmann 2011). For example blood and urine samples generally only reflect recent exposures to toxicants (heavy metals, persistent organic chemicals, organophosphate (OPs) and carbamate pesticides); hair and nails reflect past exposures (pesticides, heavy metals, polychlorinated biphenyls and polyaromatic hydrocarbons), are easily contaminated and difficult to collect in a standardised way; and many other biological matrices such as human milk, saliva, adipose tissue and meconium lack reliable reference values for human populations (Hernández et al. 2019).

To assess environmental exposures in patients, the challenge for clinicians is to ask relevant questions to elicit sources and exposure, identify the most relevant tests and to digest data from multiple streams (traditional medical data, ‘omics’ data and quantified self-data), and place this information in the context of individual patients in a way that has measurable and meaningful outcomes that shift the focus from treating disease, to prevention and wellness.

6.7. Summary

Environmental medicine is a specialty field that is not well-defined, practiced by few, and largely excluded from general medical practice. The history of environmental medicine is littered with numerous examples where the failure to act on available evidence resulted in significant loss of life. Despite the growing volume of published literature associating adverse health effects with environmental exposures, health care systems have fallen short in their ability to translate knowledge into practice. Part of the problem lies with the challenges and inconsistencies involved in interpreting and establishing the strength of evidence and probability of causation when the evidence is inconclusive, the need to account for individual differences reflected in sub-populations, and identifying and managing conflicts of interest from stakeholders closely aligned with industry, who have a vested interest in research outcomes and the setting of exposure standards.

The need to gather sufficient ‘weight of evidence’ and prove causation is difficult to achieve as environmental exposures are extremely complex often involving multiple exposures over the course of a lifetime, from in-utero and cradle to the grave exposures, each varying in their dose, duration and timing of exposure especially during critical windows of development, in addition to compounding and synergistic effects, let alone the need to account

for individual variants. Evidence based medicine which involves utilising current best available evidence in making decisions about the care of individual patients, has a long way to go. The need to develop tools to assist clinicians to measure environmental exposures and provide training on environmental assessment has been overlooked and environmental exposures can be considered an elephant in the room that is largely ignored in practice settings. The inherent limitations of the regulatory framework to assess environmental exposures, and the failure of health agencies, policy makers and regulators to act to manage risk, reflects a broken medical system that is failing clinicians and their patients and has subsequently resulted in a call to action from various stakeholders for regulatory reform. Without clinical guidelines, astute clinicians face many challenges including the time-consuming process of attending conferences, and reading a large body of work generated from systematic reviews and meta-analyses and applying them in the context of individual patients whose variants are so unique they represent a minority of the community. Some medical organisations have taken matters into their own hands and developed clinical practice guidelines specific to environmental exposures. There is a need for concerted action at all levels, including medical educators and journals promoting and publishing papers related to environmental exposures, in addition to individual, organisational and the wider civil society to understand the ‘exposome’ and minimise the extent of exposures on current and future generations.

Chapter 7:

Expert Clinicians' Perspectives on Environmental Medicine and Toxicant Exposures in Clinical Practice: A Qualitative Study

7.1. Abstract

Background: Most clinicians feel ill-equipped to assess or educate patients about environmental exposures, and it is unclear how expert environmental medical clinicians assess these exposures or treat exposure-related conditions. We aimed to explore expert clinicians' perspectives on their practice of environmental medicine to determine the populations and toxicants that receive the most attention, identify how they deal with environmental exposures and identify the challenges they face and where they obtain their knowledge.

Methods: A qualitative study involving semi-structured interviews with sixteen expert environmental clinicians in Australia and New Zealand was conducted. Interviews were recorded and transcribed, and themes were identified and collated until no new themes emerged.

Results: Five dominant themes emerged from 16 interviews: (1) environmental medicine is a divided profession based on type of practice, patient cohort seen and attitudes towards nutrition and exposure sources; (2) clinical assessment of toxicant exposures is challenging; (3) the environmental exposure history is the most important clinical tool; (4) patients with environmental sensitivities are increasing, have unique phenotypes, are complex to treat and rarely regain full health; and (5) educational and clinical resources on environmental medicine are lacking.

Conclusions: Environmental medicine is divided between integrative clinicians and occupational and environmental physicians based on their practice dynamics. All clinicians face challenges in assessing toxicant loads, and an exposure history is seen as the most useful tool. Standardised exposure assessment tools have the potential to significantly advance the clinical practice of environmental medicine and expand its reach across other clinical disciplines.

7.2. Introduction

Epidemiologic studies, breakthroughs in biomarker research and large biomonitoring studies have raised awareness of the impact of environmental exposures and their relationship to chronic illnesses. Yet, whilst most clinicians acknowledge that environmental toxicants affect human health and are frequently asked about exposures by their patients, a lack of environmental health training in medical courses and standardised exposure assessment tools leaves most clinicians feeling ill-equipped to assess or educate patients about toxicant exposures and their consequences (Bijlsma and Cohen 2016; Massaquoi and Edwards 2015; Zachek et al. 2015).

Expert Environmental Medicine (EM) physicians include practitioners who focus on public health and prevention by making inferences on cause and effect of toxicants in populations, and those who diagnose and treat the consequences of environmental exposures in individual patients. EM practitioners not only require skills in clinical medicine, they also require specialised knowledge about the impact of different toxicants on human health; exposure sources and dose estimation; the factors that influence inter-individual variation to toxicant exposures; interpretation of laboratory tests; measures to minimise toxicant exposures; and interventions that treat different sequelae. EM therefore requires the integration of knowledge from diverse fields and the skills to apply this knowledge in a wide variety of circumstances, yet this skill-set is poorly defined and it is unclear how experts navigate from the scientific literature to the needs of their patients.

To date there has been very little literature on the clinical practice of EM and little qualitative research on environmental clinicians' perspectives of their practice. To address this, we undertook a qualitative study of environmental physicians with the aim to determine the nature of EM practice and identify how expert clinicians who specialise in EM deal with environmental toxicant exposures. We further aimed to determine where clinicians obtained their knowledge and skills, the populations and toxicants that receive the most attention, as well as the challenges they face on a daily basis in order to inform the development of resources and tools that can be used by all clinicians.

7.3. Methods

A qualitative study was performed that involved a series of one-on-one, in-depth, semi-structured interviews with clinicians with an undergraduate degree in medicine who were identified as experts in the field of EM. Ethics approval was obtained from the RMIT University Human Research Ethics Committee BSEHAPP 25-15.

7.4. Participant selection

Potential participants were identified by contacting doctors (via phone and/or email) known to be prominent in the field of EM through their speaking at conferences, lecturing in postgraduate courses, and membership of either the Australasian College of Nutritional and Environmental Medicine (ACNEM) or the Australasian Faculty of Occupational and Environmental Medicine (AFOEM), which are the only two Australian medical organisations with 'Environmental Medicine' in their title. Some of the participants were known to the researchers prior to commencement of the study through mutual participation in conferences. This was followed by a snowball recruitment campaign whereby participants were asked to identify further experts. To be recruited, a phone call was undertaken with prospective participants to confirm details of the study, confirm they had an undergraduate medical degree in medicine and that they were affiliated with ACNEM or AFOEM. Doctors listed on the ACNEM and AFOEM websites were emailed and invited to participate in the study. A follow-up phone call was made to those who responded to explain the nature of the research and invite them to participate. All prospective participants were then emailed a *Project Information Statement* and contacted to make an appointment for an interview. Clinicians were not compensated for their time.

7.5. Survey design

A series of open-ended questions was developed by the authors to determine:

- Where EM clinicians obtained their knowledge
    - The institutions and associations to which they belonged
    - The journals, websites and books they used
    - The educational and clinical resources they used
- The nature of their EM practice
    - The type of diseases they treated
    - How much time they spent with patients
    - The cost of consultation and tests
    - The populations and toxicants they pay the most attention to
    - The situations where they have the greatest success and challenges
- How they assess environmental exposures
    - The most effective tools they use to assess chemical exposures
    - The type of tests they undertake and how they interpret them

7.6. Interview process

All interviews were conducted via Skype audio by the first-named author between September 2015 and June 2016 during which the clinicians provided informed consent. There were no other participants present during the interview and no follow-up interviews. Nine interviews were conducted whilst the clinician was at their workplace, and the remaining seven interviews were conducted after hours. General questions (tell me about your practice) were asked at the beginning of the survey to initiate the conversation, gain the participant's trust and familiarise them with the interview process. Open-ended questions were developed to give the participant the freedom to explain their responses and identify new themes.

The interviews were recorded and transcribed and a preliminary analysis of the initial interviews was undertaken to explore new lines of inquiry that emerged from the interview process. In this way, new questions were developed and explored with the next interviewee as specific themes became apparent. Recruitment of clinicians continued until no new themes emerged, and saturation had been reached (i.e. no new information or themes were introduced from subsequent interviews). Transcripts were not returned to participants for comment or correction and participants did not provide feedback on the findings.

7.7. Analysis

NVivo 11.3 software program was used to document specific themes within each interview. They were then analysed by the authors to identify the dominant themes that emerged from the data that were common across the entire cohort. The results were reported according to published guidelines for reporting qualitative research (Tong et al. 2007).

7.8. Results

A total of sixteen clinicians participated in the study: eleven from ACNEM and five from AFOEM with thirteen based in Australia and three in New Zealand. The average length of Environmental Medical practice was twenty years. The range for length of practice was 8 to 43 years (mean of 20 years).

The themes that emerged from the data analysis were:

1. EM is a divided profession
2. Clinical assessment of toxicant exposures is challenging
3. The environmental exposure history is the most important clinical tool

4. Patients with environmental sensitivities are increasing, have unique phenotypes, are complex to treat, and rarely regain full health
5. Educational and clinical resources on EM are lacking

7.8.1. Theme 1: EM is a divided profession

The strongest theme is that clinicians identified as experts in the field of EM can be classified into two distinct groups: Integrative Medical Practitioners (IPs), and Occupational and Environmental Physicians (OEPs). This classification is based on the nature of their employment (corporate vs patient-centred), the patient populations dealt with, the type of diseases they see, the type of toxicants they were concerned about[2], and their views on the role of nutrition and genetics in toxicant exposures. Comments from clinicians that illustrate the differences between IPs and OEPs are presented in Table B1.

The nature of employment between the two groups was distinct with the IPs being general medical practitioners (n = 9) and paediatricians (n = 2) who worked in private practice, averaged five or more patients per day, and were directly renumerated by their patients. In contrast, the OEPs had a history of employment by large companies and received a salary from an employer or an agreed fee to conduct medico-legal work and worked either as company physicians to assess and monitor the health of workers, advisors in government departments, emergency physicians in hospitals, or as medico-legal experts. The average cost (in Australian dollars) of an initial consultation with an IP was $421, although this varied from $280 to $630. The average subsequent consultation cost was $269, with the lowest at $150 and highest at $360. The one OEP who had a part-time practice seeing patients (referred to by GPs) charged $270 for a consultation (initial and subsequent). It was not possible to quantify the remaining four OEPs cost as most were not paid for individual consultations and instead received a salary or an agreed fee to conduct medico-legal work.

The OEPs primarily deal with adult men with musculoskeletal disorders and diseases arising from occupational exposures to heavy metals, asbestos, coal dust, beryllium, pesticides, or solvents such as benzene, diesel, and isocyanates. This was distinctly different to the IPs whose patients actively sought their expertise to address chronic, complicated ill-defined conditions involving multiple systems characterised by long-term fatigue (Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, and fibromyalgia), allergy intolerances, digestive disorders and chronic autoimmune, metabolic and/or neurological conditions. Sleep disturbances were ubiquitous amongst their patients. Many IPs along with both of the

[2] Clinicians agreement was based on independent opinion that manmade toxicants are harmful.

paediatricians were also seeing children with learning, developmental and behavioural issues and recurrent infections.

Whilst all clinicians agreed toxicants are harmful, there was a stark difference in the type of toxicants they were concerned about. OEPs were primarily concerned about acute and chronic exposures to toxicants arising from the workplace or hobbies where linear dose-response relationships are well described. In contrast, the IPs were concerned about long-term exposure to low-level toxicants in food, the workplace and the home environment and their combined effects. The two groups also differed in their perspectives on nutrition. OEPs considered nutrition as fringe medicine, not related to toxicant exposure except where the evidence was conclusive such as mercury in fish, pesticides in fruit and contamination of food with lead dust. In contrast, all the IPs highlighted food as the most important source of toxicant exposure and as a treatment to build resilience against environmental insults.

Whilst all clinicians acknowledged that genetics was important, most of them did not do genetic testing. None of the OEPs conducted genetic testing due to the costs involved, clinical uncertainty, lack of knowledge on gene variants, and because of the ethics involved in discriminating against people. In contrast, four of the IPs conducted genetic testing, but only in a small minority of their patients with chronic, idiopathic environmental sensitivities.

7.8.2. Theme 2: Clinical assessment of toxicant exposures is challenging

Comments from clinicians that highlight the challenges associated with the assessment of assessing toxicant exposures are presented in Table B2. IPs noted that EM requires long consultation times that limits the number of patients that can be seen, leading to long waiting lists and high costs, which are compounded by the costs of specialised laboratory tests not covered by third party reimbursement. Toxicant testing and other laboratory tests were also noted to present challenges with clinicians stating that laboratory testing is often unreliable or unavailable and lack standard clinical approaches.

The OEPS reported their most significant challenge with toxicant testing was the difficulty in establishing cause and effect. This limited the number of tests they undertook as they were more likely to use tests with established scientific evidence and reference ranges. In contrast, half of the IPs were more likely to undertake controversial tests that lacked clinical meaning such as hair mineral analysis, digestive stool analysis, organic acids test, provoked challenge urine test, food sensitivity tests, lymphocyte sensitivity test, liver detoxification profiles, tests for specialised inflammatory markers associated with biotoxin exposure, and tests to detect persistent organic pollutants or tick-borne diseases. The remaining IPs did not undertake additional toxicant testing on the basis that there were no established reference ranges and that exposures could be determined from the patient's history.

7.8.3. Theme 3: The environmental exposure history is the most important clinical tool

It was agreed by all clinicians[3] that the environmental exposure history is by far the most important clinical tool to assess toxicant exposures which is consistent with a growing number of articles on the topic (Marshall et al. 2002; Nicotera et al. 2006; Pope et al. 1995; Sanborn et al. 2019). The average time clinicians spent taking an exposure history in the first consultation was 90 minutes although this varied from 1 to 3 hours. Some clinicians used formal questionnaires that patients completed prior to attending their first consultation, whilst others relied on the patient's responses to guide their questioning. Clinicians' comments on the relevance and characteristics of an environmental exposure history are presented in Table B3.

The exposure history encompassed a variety of questions about the patient's occupational, dietary, dental, drug, lifestyle, hobbies, and place history. Whilst there were many similarities in the type of questions that clinicians asked, the OEPs spent more time obtaining a detailed occupational history through the course of the patient's working life, whilst the IPs spent a significant portion of their time obtaining a comprehensive dietary history. Place history was considered to be important by both groups, however where the OEPs focused on locations resulting in significant exposures such as mining, IPs were more likely to ask about exposures to traffic-related air pollutants, pesticides and other industrial toxicants based on where the patient worked, lived, or went to school. Furthermore, IPs were seeing an increasing number of patients who raised the issue of mould and EMF exposures in their home, which they were unable to assist with, because they had no training to address mould related issues.

7.8.4. Theme 4: Patients with environmental sensitivities are increasing, have unique phenotypes, are complex to treat, and rarely regain full health

Where IPs readily accepted and treated patients with chronic idiopathic environmental sensitivities, OEPs were more likely to attribute symptoms to psychological factors on the basis that linear dose-response relationships could not explain their symptoms, and they did not want to create alarm. Consequently, most of the information about patients with environmental sensitivities was derived from the interviews with IPs and their comments, their unique characteristics, and the complexities involved in treating them (Table B4).

[3] Clinicians' agreement was based in response to the leading question "what is the most important clinical tool to assess environmental exposures".

Several IPs noticed a significant increase in the incidence and awareness of environmental sensitivities like allergies, chemical sensitivities, neurodevelopmental disorders in children and mould-related illnesses over the past ten years. IPs also noticed their patients were well informed about their illness and potential triggers (chemicals, mould, and electromagnetic fields), and hence more likely to seek advice than those with limited knowledge of their condition.

Some clinicians provided a detailed description of the characteristics of patients diagnosed with environmental sensitivities attributed to environmental exposures. Where two OEPs noticed that the majority of patients with chemical sensitivities had a history of allergies, IPs were more likely to provide a detailed description of their personality traits. Three IPs noticed that patients with a Scottish/Irish descent were more likely to experience food (gluten, salicylates) and environmental sensitivities. Another feature observed by some IPs was that these patients were more likely to have gene variants in methylation and detoxification enzymes, or specific haplotypes (HLA DRB-1, HLA-DQ) that made them more susceptible to mould toxins and gluten.

Patients with idiopathic, multi-morbid diseases including Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Electromagnetic Hypersensitivity, and autism were said to be the most difficult to treat due to challenges in limiting their exposures to everyday toxicants and EMFs, and poor tolerance to treatment, resulting in few of these complex patients regaining full health. Furthermore, all their patients had chronic and persistent sleeping difficulties which had multiple downstream effects that made it difficult for them to gain a full recovery.

7.8.5. Theme 5: Educational and clinical resources on EM are lacking

Clinicians' comments on the lack of resources available on EM and the limitations in their training, is listed in Table B5. Clinicians reported acquiring their knowledge on environmental toxicants over many years through a great many sources which included formal postgraduate qualifications; online journals and websites; conferences and workshops made available through their respective associations, government organisations and institutes (Australia, US and UK); collaboration with peers; discussions with patients; as well as conducting searches on PubMed and Google Scholar. Training also varied considerably across clinicians with no single resource or training program being recognised as comprehensive or an industry standard.

7.8.5.1. Formal and informal training

All interviewed clinicians had an undergraduate medical degree and twelve had postgraduate qualifications. Six IPs had postgraduate qualifications in nutrition (two had a Masters degree), two were registered paediatricians one of which also had a Masters in Public Health, and all the IPs had undertaken the ACNEM primary course yet most acknowledged it was more focused on nutrition and limited with respect to EM. All the OEPs had undergone a four-year training program to be affiliated with AFOEM and all had at least one postgraduate Masters degree in public health, epidemiology, health administration or toxicology, with one having a PhD in chemistry. Despite this training, two OEPs acknowledged that EM is an emerging field that is still developing.

7.8.5.2. Online journals

Online journals and databases were seen as an important resource for most clinicians with Google Scholar, SNPedia and PubMed listed as the most useful search engine databases. Whilst eight journals were mentioned as good resources on environmental health, Environmental Health Perspectives was the only journal mentioned more than once (by three IPs). The OEPs mentioned various journals in Occupational or Occupational and EM (US, UK, Scandinavia), however no journal was mentioned by more than one OEP. Apart from The Lancet mentioned by one IP, no other general medical journals were mentioned as a useful resource.

7.8.5.3. Conferences, workshops and webinars

Local and international conferences conducted by the following associations or institutes were cited as a useful source of information: Australasian Faculty of Occupational and EM; Australasian College of Nutritional and EM; International Board of Clinical Metal Toxicology (The Netherlands); Australian College of Medical Nutrition; American Academy of EM (USA); Autism Research Institute (USA); Mind foundation (Australia); Clinical Education (UK) and the Institute of Functional Medicine (USA).

7.8.5.4. Websites and books

The OEPs focused on websites and textbooks relevant to occupational medicine and toxicology, whilst the IPs mentioned websites and textbooks dedicated to functional medicine and specific environmental hazards like mould and chemicals in consumer products. The only websites that were mentioned more than once was the Environmental Working Group website

(mentioned by three IPs) and the Surviving Mould website (mentioned by three IPs). Healthy Home Healthy Family was the most frequently cited textbook (mentioned by three IPs). Refer to Tables B6 and B7.

7.8.5.5. Peers, colleagues, patients and other experts

Peers, colleagues and patients were often mentioned as an important resource for information on EM. Numerous researchers and authors were mentioned by IPs as important sources of information. For example, four IPs who specialised in mould mentioned Dr Ritchie Shoemaker's work and papers. The paediatricians mentioned Philippe Grandjean and Philip Landrigan's work; clinicians who specialised in multiple chemical sensitivity mentioned William Rea's work; two IPs mentioned Sarah Myhill and Paul Cheney's work on Chronic Fatigue Syndrome; Jean Munro was mentioned for her work in nutritional medicine; John McLaren Howard for his work on neurolipid research and Joseph Pizzorno's for his work on detoxification. One of the IP's had acquired much of their knowledge on environmental toxicants through nutraceutical reps. One OEP mentioned government departments, laboratories, and tertiary institutions as a good resource for up-to-date information on toxicants.

7.9. Discussion

The perspectives of clinicians working at the coalface of EM provide insights on the current clinical practice of EM and outline many challenges for EM clinicians including dealing with multifactorial diseases that are poorly defined, making assessments without standard assessment tools, interpreting lab investigation without comparative data or established cause and effect relationships, and a lack of educational resources and defined education pathways. It also appears that EM is divided based on training and practice settings between top-down population-based approaches, and bottom-up patient-based approaches to medicine. This is reflected in the two main organisations to which the interviewed clinicians belong, which clearly divide the profession between specialist doctors in the field of integrative medicine (the IPs) and occupational and EM (the OEPs). These groups differ in the type of patients and the diseases they see, the type of toxicants they are concerned about, differences of opinion on the role of nutrition, and the type and number of pathology tests they use.

The difference between the two groups may be explained by their education and their different practice dynamics. All the IPs had studied nutritional medicine and were working from a bottom-up approach to assess and treat multi-morbid disease in the absence of clear evidence. These doctors were seeing mainly women with idiopathic environmental

sensitivities, patients with neurodegenerative disorders and children with neurodevelopmental disorders, and considered chronic responses to low-dose exposures in susceptible individuals. In contrast, the OEPS all had formal training in occupational medicine and were employed by industry and insurance companies on a top-down approach to deal with occupational exposures with an emphasis on musculoskeletal disorders, noise, asbestos, toxic metals, coal dust and various solvents in mostly adult male workers. These doctors considered linear-dose response relationships as the gold standard in establishing adverse health effects and were sceptical of patients with chemical sensitivities and 'fringe' doctors who use nutritional approaches and laboratory testing with uncertain clinical meaning.

While these differences give an appearance of a divided profession, there were strong similarities across all clinicians including, agreement that the most important tool for assessing environmental exposures is an exposure history. Clinicians also agreed that EM is an emerging science with few established experts, and that risk assessment is challenging in the absence of standardised data collection tools or guidelines for toxicant testing. Thus, clinicians questioned the value of tests with uncertain accuracy and clinical significance, and favoured taking an exposure history over toxicant testing despite acknowledging that this took considerable time to obtain. While the elements of an exposure history varied amongst clinicians, they generally included questions about the patient's occupation (from the moment they began their first job), hobbies, lifestyle factors, diet, dental record, and drug history. Several IPs stressed the importance of place history and asking questions about the patient's working, school and living residence and their proximity to toxicants and manmade electromagnetic fields in the ambient and indoor environment. It is noteworthy that despite its importance, most clinicians were not taught to take an exposure history in their undergraduate or postgraduate training. This is consistent with a report that only 20% of US paediatricians received training in environmental history taking (Kilpatrick et al. 2002).

While all clinicians commented on the difficulties associated with exposure monitoring, clinicians acknowledged that patients with environmental sensitivities have unique phenotypes. The significant increase in the number of patients presenting with environmental sensitivities such as allergies (food and aeroallergens), neurodevelopment disorders and mould-related disorders observed by several IPs, is consistent with a large body of research that has seen a dramatic increase in the prevalence of allergic diseases (Ellwood et al. 2017; Nutten 2015; Platts-Mills 2015; Prescott and Allen 2011; Wang et al. 2016) learning and behavioural disorders (Australian Institute of Health and Welfare 2017; Polanczyk et al. 2014; Thomas et al. 2015) and mould-related disorders (Antova et al. 2008; Fisk et al. 2010; Mendell et al. 2011; Shoemaker et al. 2014; Shoemaker and House 2006; Thrasher et al. 2016). Clinicians also observed that patients are more likely to seek help earlier on, are more

informed about toxicants, and more likely to undertake some preliminary online research prior to their consultation. In addition to noting that environmental intolerances appear to be increasing, clinicians also acknowledged that they are difficult to diagnose, complex to treat, and that patients with environmental sensitivities rarely regain full health with almost all their patients exhibiting chronic and persistent sleep disorders. This is consistent with a growing body of evidence on the complexities in diagnosing and treating patients with environmental intolerances such as Chronic Fatigue Syndrome, Multiple Chemical Sensitivity and Systemic Exertion Intolerance Disease, Sensitivity-Related Illness, Idiopathic Environmental Intolerances, Fibromyalgia, Electromagnetic Hypersensitivity and Sick Building Syndrome (Belyaev et al. 2016; Castro-Marrero et al. 2017; Clayton 2015; De Luca et al. 2010; Haney et al. 2015; Smith et al. 2015).

Despite the interviewed doctors all having extensive training in fields such as clinical medicine, public health, epidemiology, nutrition and occupational medicine, many still felt inadequate to call themselves ‘experts’ or ‘environmental physicians’. Part of the problem stems from their realisation that environmental exposure assessment at an individual level requires knowledge of highly complex clinical domains from genetics, nutrition, geomedicine, microbiomics and exposomics, which are not widely taught or integrated into clinical practice. Furthermore, environmental practitioners must diagnose and provide medical and nonmedical management for environmental diseases, translate new research results to practice, and make complex causal inferences (Schwartz et al. 2005).

The complexities of EM are compounded by a lack of established educational resources, and the challenge to identify any single resource or training program that provides the knowledge they feel they need to practice EM. Consequently, clinicians were left to navigate their own unique path to acquire their EM knowledge using a collage of sources including journals, books, websites, conferences, webinars and discussions with peers and patients. Remarkably only one medical journal was mentioned as a useful resource, which highlights the lack of information on EM in general medical journals.

Perhaps the greatest challenge for general medical practice, is that most chronic diseases maybe caused or exacerbated by environmental exposures (Bijlsma and Cohen 2016; Orešič et al. 2020; Schmitt et al. 2021), yet clinicians are not provided with the underpinning knowledge or the skills required to practice EM which is relevant to all fields of medicine. There is therefore a need to inform all clinicians about toxicant exposures and adverse health effects and educate them about the factors that influence individual susceptibility to toxicant exposures. This may be achieved through the development of standardised environmental exposure surveys and other tools to assess, monitor, and map exposures and their health effects. It will also require the inclusion of EM education in standard

medical curricula and post-graduate training and the publishing of information about EM in general medical textbooks and medical journals, which is a need that has been voiced by numerous organisations and researchers over many decades (Gehle et al. 2011; Herr and Eikmann 2011; Institute of Medicine (US) Division of Health Promotion and Disease Prevention 1988; Le Moal and Reis 2011; O'Brien 1991; O'Connor 2013; Pope et al. 1995; White 1990; World Health Organization 1996).

EM is a complex field that requires an integration of top-down and bottom-up approaches to understand potential sources of toxicant exposures and their health impacts, monitor and mitigate individual exposure profiles and risk factors, and evaluate measures to minimise exposures and their effects. These tasks are not only relevant to all clinicians, they also require engagement from the wider community, including policy makers and individual citizens and the tools to achieve this are becoming widely available to the community. There are now multiple community-led, citizen-science campaigns and 'crowd-in-the-cloud' projects enabling the general community to participate in scientific projects that monitor exposures to toxicants at a personal level (Hindmarsh 2013; Pocock et al. 2014; Turner et al. 2017), collect data on the occurrence of disease geographically (Nethery et al. 2014), identify the sources and impact of different exposures, and assess the efficacy of public health campaigns and individual treatment protocols and expand environmental health literacy (Finn and O'Fallon 2017). Such efforts will be greatly assisted through the development of standardised environmental exposure tools that combine medical and exposure history data with biomarker information along with data from the growing number of environmental sensors. This has implications for all future clinicians, educators, and patients at large and will change the way that EM is practiced in future.

7.10. Limitations

Whilst this paper has identified clear themes, our research has several limitations. Qualitative research has inherent limitations, which include the biases we bring as clinician researchers who decide on the questions to ask and how responses are interpreted. The study population was limited to Australia and New Zealand and the finding of two distinct groups clearly arose from the organisations from which participants were recruited. Our findings therefore may not be representative of Environmental Medical clinicians elsewhere and we cannot be sure that the inclusion of additional participants from other sources would not have led to additional or different themes emerging.

7.11. Conclusion

EM is relevant to all fields of medicine, yet it is currently a divided profession practiced by occupational and environmental physicians using public health approaches in workplace settings, and integrative practitioners using patient-centred approaches in private practice settings. Clinicians practicing EM face many challenges in assessing environmental exposures in the absence of comprehensive educational resources, definitive laboratory tests, established dose-response relationships or exposure history tools and due to the complex, integrative and rapidly changing nature of the field, few practitioners consider themselves 'EM experts' despite having extensive postgraduate training and many years of clinical experience.

While there is widespread agreement that an exposure history is the most useful clinical tool for assessing toxicant exposures, there are no standardised tools for this, leaving EM clinicians to develop their own approaches to assess the growing number of patients with environmentally-related disorders. Further efforts directed at the development of standardised exposure assessment tools have the potential to significantly advance the clinical practice of EM and expand its reach across clinical disciplines. The ability to engage patients and the community at large in assessing and monitoring the extent and impact of toxicant exposures has further potential to integrate knowledge about individual susceptibility, lifestyle and work choices, and toxicant exposures, and usher in a new era of personalised medicine that considers the impact of the environment on the health of populations and individuals.

PART D:
DISCUSSION AND CONCLUSION

Chapter 8:
Discussion and Conclusion

8.1. Overview

The aims of this thesis were to explore the role of exposure to toxicants and NIR-EMFs in chronic disease, and assess how expert clinicians in the field of environmental medicine deal with these exposures. These objectives were achieved through a narrative review, a qualitative study involving semi-structured interviews with expert clinicians in the field of environmental medicine, and a double blind, randomised, placebo-controlled, crossover study investigating the impact of radiofrequencies on sleep structure and sleep quality. There were several themes that emerged from this research:

1. Environmental exposures are increasing and contributing to the global burden of chronic diseases.
2. Wi-Fi enabled devices (e.g. baby monitors) may have clinically relevant impact on sleep quality in real-world scenarios.
3. Regulation of toxicants and NIR-EMFs is inadequate.
4. Translating environmental health research into evidence-based healthcare is challenging.
5. Various stakeholders are raising concerns regarding environmental exposures.
6. Environmental Medicine is not well-defined and educational resources for clinicians are lacking.
7. Environmental sensitivities are increasing, and expert clinicians face significant challenges to diagnose and treat patients impacted by environmental exposures.
8. The environmental exposure history is the most important clinical tool for assessing environmental exposures.

The outcome of this research revealed that while environmental exposures are increasing and contributing to the growing number of chronic diseases typically seen in clinical practice, most clinicians are unaware of the magnitude of the problem and very few practice Environmental Medicine. The absence of clinical guidelines and public health policy have subsequently impacted multiple stakeholders including patients, and clinicians who are trying to do the right thing, but are hampered by a fragmented system that continues to ignore their needs. The root of the problem appears to lie with the concept of Evidence Based Medicine and the need

to establish causation, in addition to industry's influence on the regulations and setting of exposure standards that demand economic output be considered. Until a cost-risk-benefit analysis is undertaken that includes the real costs of environmental exposures on human health, the true cost to society and government health systems is unknown. Whilst much work needs to be done, emerging technologies and a call to action by various stakeholders, indicates that change is forthcoming. This section will discuss the implications of these findings and provide suggestions to address the issues.

8.2. Environmental exposures are increasing

The literature review provided many sources that document the dramatic increase in the global population's exposure to toxicants and man-made NIR-EMFs over the past four decades. Large population biomonitoring studies conducted in multiple countries show all individuals are at risk despite location, class, race and socioeconomic status. These studies also reveal widespread chemical exposures from the 'womb to the tomb' with levels in humans and wildlife that are known to cause adverse health effects. Since wide-band microwave signals (3G onwards) were incorporated into mobile phones and the use of Bluetooth and wireless technologies became prevalent, most of the global population has also been exposed to RF-EMFs on a continuous basis. This exposure is anticipated to increase dramatically with the rollout of the infrastructure and satellite technology required to support 5G and the fourth industrial revolution including the Internet of Things.

Despite the complexities and challenges involved in correlating environmental exposures to adverse health outcomes, the literature review revealed that toxicants and NIR-EMFs are contributing to the chronic disease burden in developed countries. Toxicants and, in particular, persistent organic pollutants like pesticides are associated with an extensive and growing list of chronic diseases from neurodevelopmental to neurodegenerative disorders across a lifespan. Furthermore, a growing number of systematic reviews and meta-analyses have identified statistically significant associations between AC magnetic fields in excess of 0.3 μT and childhood leukaemia, and between RF-EMFs, sleep disturbances and brain tumours. Whilst IARC classified AC magnetic fields and Radiofrequencies as a Group 2B possible human carcinogen (International Agency for Research on Cancer 2002, 2011b), a substantial number of epidemiological and mechanistic studies have strengthened the association between RF-EMFs and brain tumours. The increase in the global population's exposure to toxicants and NIR-EMFs is also associated with a rise in the prevalence of patients with multimorbid chronic diseases and extensive symptoms involving multiple organ systems. In the past decade, the prevalence of self-reported chemical sensitivity has increased over 300% and medically diagnosed multiple chemical sensitivity (MCS) is estimated to impact

around 12.8% of the US population (Steinemann 2018a). In contrast, most countries do not recognise Electromagnetic Hypersensitivity as a medical condition, and the European Parliament are calling on the World Health Organisation to recognise it as a medical condition especially since biomarkers such as circulating autoantibodies against O-myelin, histaminemia, oxidative/nitrosative stress-related biomarkers and abnormal urine profile (6-hydroxymelatonin sulfate/creatinine ratio) have been identified (Belpomme and Irigaray 2020).

The literature review also revealed an association between exposure to RF-EMF and sleep disturbances. This is important because the incidence of insomnia coincides with the rollout of Wi-Fi enabled technologies, and sleep disturbances are a risk factor for mortality and many chronic diseases. The qualitative survey with expert clinicians further identified insomnia as being ubiquitous amongst patients with environmental sensitivities and the outcome of the crossover pilot study using a 2.45 GHz device (baby monitor), revealed RF-EMF exposure resulted in a statistically significant and clinically meaningful reduction in sleep quality with reduction in PIRS-20 scores ($p<0.05$) and a statistically significant increase in EEG power density in the higher frequencies (gamma, beta and theta bands) during Non-Rapid Eye Movement (NREM) sleep ($p<0.05$). Further large-scale investigations over longer periods of time, are required to confirm these findings that include signal features emitted from Wi-Fi enabled devices such as modulation, field strength, resonance, pulsing nature, polarisation and power flux density, however, until further studies can verify or provide contrary evidence, caution needs to be exercised when placing RF-EMF devices in bedrooms.

8.3. A new paradigm in translating environmental health research into evidence-based healthcare

Evidence based medicine (EBM) is the cornerstone of medical practice, and evidence-based practice models ultimately lead to public health policies. Despite the volume of research associating environmental exposures with a growing number of chronic diseases, very little is published in medical journals or translated into public health policy or clinical practice. Part of the problem appears to lie with the need to establish probability of causation and evidence of harm, which takes decades and, for a significant proportion of environmental hazards with long latency periods, difficult to prove as the outcome is influenced by multiple confounding factors and individual susceptibility. This influences the data that is used to regulate toxicants and NIR-EMFs, and subsequently translated into public policy and clinical practice guidelines. Despite the EBM model, the history of medical care is littered with numerous examples of missed opportunities, wasted resources and counter-productive policies due to the failure to act when hindsight has revealed there was sufficient evidence to cause harm as was the case

with asbestos, lead and environmental tobacco smoke. Sir Austin Bradford Hill, the famous epidemiologist reminds us that "… [we] must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so" (Hill 1965:296). The failure to act on the available evidence, has meant astute clinicians who are required to diagnose and treat patients impacted by environmental exposures have to take matters into their own hands.

Risk assessment and the setting of exposure standards is a complex undertaking that requires careful evaluation of the available evidence, identification of industry influence, conflicts of interest, and the need to take timely action. Advances in science have provided a better understanding of the complex nature of chronic disease causation beyond the paradigm of single factor relationships. Many diseases are the outcome of the complex interplay between genes and multiple risk factors over the course of a lifetime. Establishing the magnitude of an association as Bradford Hill suggests, has been replaced with statistical significance using data from multiple scientific disciplines. To ensure a consistent and transparent systematic approach, data from multiple evidence streams (human, animal, surveillance, and mechanistic data) need to be considered collectively and integrated for environmental hazard identification that poses potential public health risks (Chartres et al. 2022; Krewski et al. 2022). Randomised controlled trials on environmental exposures have significant ethical, logistical and economic limitations that need to be taken into consideration. In contrast, the use of mechanistic studies that provide a mode of action, further contributes to the overall weight of evidence thereby lessening the need for repetition among numerous observational studies (Fedak, 2015). Whilst the body of epidemiologic studies on EMFs and many individual toxicants are limited and conflicting, mechanistic studies provide a mode of action at a cellular level and strengthen causal inference in a more efficient manner than human studies and should therefore be given high priority. In light of the impact of EMFs on the cellular stress response, and toxicants demonstrated to initiate or contribute to the progression of disease via epigenetic and/or defined metabolic pathways, I believe there is sufficient evidence to warrant stricter exposure limits and the development of public health policies and clinical practice guidelines for environmental hazards.

Achieving better outcomes for patients impacted by environmental exposures requires the medical community and policy makers to be aware of the complexities of establishing cause and effect, and the need to integrate multiple evidence streams (not just randomised controlled trials) to be used when establishing evidence of harm. There is also a need to raise awareness amongst the medical community by prioritising publication of environmental health research with actionable outcomes in clinically-related medical journals. For example, there is a growing volume of research to suggest that long-term use of a mobile phone on one side of

the head for at least 30 minutes per day over ten years (cumulative exposure >1640 h) may increase the risk of brain tumours (Prasad et al. 2017). This research is relevant to clinicians who could counsel patients to use caution when using a mobile phone and encourage texting (instead of placing the phone next to the head), using loudspeaker, using corded earpieces, using Skype or Voice over Internet Protocol that is hardwired, or using a corded phone and keeping the phone away from vital organs during transport.

Translating environmental health research into evidence-based care will require new ways to assess risk and interpret evidence of harm. Scientists are currently exploring new ways to strengthen the interpretation of evidence of harm and chemical risk assessment through the refinement and codification of methodological approaches for systematic review and meta-analysis tailored to the specificities of environmental health (Rooney et al. 2014; Sheehan and Lam 2015; Woodruff and Sutton 2014). To date there have been several attempts at establishing a broadly applicable methodology for systematically evaluating evidence on environmental health hazards and thereby inform policies, and support transparent decision-making based on the best available data (Whaley 2013). These include the Office of Health Assessment and Translation Handbook (OHAT) (National Toxicology Program 2015), Navigation Guide (Woodruff & Sutton, 2014), Collaboration for Environmental Medicine (CEE); Conduct of Systematic Reviews in Toxicology and Environmental Health Research (COSTAR), Grading of Recommendations, Assessment, Development and Evaluations (GRADE), and Reporting Standards for Systematic Evidence Syntheses in Environmental Research (ROSES).

Despite the challenges translating environmental health research into evidence-based healthcare and policy, Chartres et al. (2022:17) propose the following recommendations to address the divergent evaluations of evidence to support health-protective actions against hazardous agents;

1. Make better use of existing data and information. Engage all stakeholders including populations impacted by exposures early on; incorporate the cumulative impacts of environmental and social threats; and provide comprehensive data on environmental releases of all toxic pollutants and population characteristics that may highlight vulnerabilities.
2. Ensure timeliness. The strength of evidence needed to justify practical actions is context specific and takes into consideration plausible consequences of inaction; evaluate and regulate chemicals as ‘classes’ to facilitate timely protection and prevent regrettable substitutions (ie replacing restricted chemicals with similar chemicals that are not yet restricted).

3. Increase transparency and consistency and use systematic reviews to increase transparency, minimise bias, and increase rigor in scientific evaluation and risk assessment.
4. Minimise the influence of financial conflicts of interest by requiring full disclosure that includes stricter disclosure policies in research design, conduct, publication, peer review and policy development, as well as increasing funding from both public and private sources.

8.4. Regulation of NIR-EMFs needs to account for non-thermal effects

EMF research and the thermal-only paradigm has been the subject of intense debate for decades and has not translated into actionable outcomes for clinicians or the population. The heterogeneity between studies makes it difficult to compare studies due to differences in study design, timing and duration of exposures, the type of frequency used, modulation, power density, field strength, pulsing nature, challenges in controlling extraneous confounding factors, bias, and the laboratory or clinical context involved. Furthermore, the use of simulated studies conducted under laboratory conditions, do not reflect real-world population exposures and are less likely to demonstrate bioeffects. The use of different statistical methods amongst studies leads to statistically different results thus impacting the strength of an association. Consequently, despite decades of research, most studies display methodological weaknesses that limit the internal validity of the results, and systematic reviews are unable to draw conclusions. Waiting for conclusive evidence, whilst exposing the population to an ever-increasing amount of radiation that is known to trigger cellular changes that may predispose to chronic health issues, is not in the best interest of public health.

There are various inadequacies with the current regulation of NIR-EMFs including the absence of standards to account for long-term exposure to radiofrequency electromagnetic fields at non-thermal levels which account for the majority of exposure; inadequacies of the thermal-only effects paradigm, which fail to ignore a large body of research that demonstrate significant bioeffects at non-thermal exposures; inability to establish what constitutes a ‘health effect’; failure to explain contradictory outcomes observed in experimental studies; and industries influence in the setting of exposure standards and research outcomes. Failure to adequately regulate NIR-EMFs has been met with fierce criticism from various medical groups, researchers, and citizens and subsequently resulted in the publication of various appeals such as the Seletun Statement (Johansson and Sage 2010), the International EMF Scientists Appeal (Blank et al. 2015) and the 2020 Consensus Statement of UK and International Medical and Scientific Experts and Practitioners on Health Effects of Non-Ionising Radiation (Mallery) to recognise the health effects arising from non-thermal exposures.

Experimental studies demonstrate ‘health effects’ arising from exposure to non-thermal levels begins at the cellular level when the redox capacity of the cell becomes overwhelmed by persistent and elevated reactive oxygen species and results in a shift in cell signalling pathways. The irreversible cell changes, DNA strand breaks and mitochondria dysfunction that subsequently ensue, is likely to reflect shifts in the autonomic nervous system from becoming dysregulated to dysfunctional with repeated radiofrequency radiation exposure (Redmayne and Reddel 2021). Given this understanding, exposure standards should incorporate a margin of safety ‘as low as reasonably achievable’ (ALARA) similar to that used for ionising radiation, yet standards that encompass long-term exposure to non-thermal levels and account for susceptible populations by adopting the precautionary principle seem to be a long way off.

With this in mind, it is proposed that Radiofrequency Electromagnetic Fields and Alternating Current Magnetic Fields be reclassified as a Group 1 known human carcinogen by the International Agency for Research on Cancer. The existing ICNIRP limit of 200 μT (International Commission on Non-Ionizing Radiation Protection 2010) for ELF-MFs should be replaced with the International Guidelines on Non-Ionising Radiation limit of 1 μT (day), 0.3 μT (night) and 0.1 μT (International Guidelines on Non-ionising Radiation 2021). Near field exposures for RF-EMFs should adopt a whole body SAR limit of 4 mW/kg (adults) and 0.4 mW/kg (children) which is 40 times lower for adults and 400 times lower for children than the existing ICNIRP limit (Uche and Naidenko 2021). Far field exposure standards that incorporate non-thermal effects should be adopted such as described in the BioInitiative Report ie 30 to 60 μW/m^2 (Sage & Carpenter, 2012) or the International Guidelines on Non-Ionising Radiation limit of 100 μW/m^2 (day time), 10 μW/m^2 (night time), and 1 μW/m^2 (sensitive groups) (IGNIR, 2021). This is in stark contrast to ICNIRP and ARPANSA’s general public reference levels for whole body (averaged over 30 minutes) exposure for radiofrequency fields (100 kHz to 300 GHz) of up to 10 million μW/m^2 depending on the frequency (Commonwealth of Australia 2021; International Commission on Non-Ionizing Radiation Protection 2020).

EMF research that is funded by governments, organisations or philanthropists free from conflict of interest, will enable researchers (not the funder) to establish the research question, ensure all research is published to prevent publication bias and enable them to test the validity and reproducibility of biomarkers and testing methods used by clinicians. Profit-based funding models that favour treatment over prevention, and/or funding obtained from industry or any stakeholder that is likely to be impacted financially by the outcome, could therefore be avoided. It is further proposed that journal reviewers and editors of journals (not just authors of publications) disclose conflict of interest and relationship to industry. Future studies should reflect real-world conditions and be conducted over longer periods of time taking into

consideration the totality of exposure using personal monitoring devices and mapped to health effects (Apps). Methodologies could also consider exposure dosimetry, placement of exposure devices that are well-defined, consistent, and consider signal features such as modulation, field strength, resonance, pulsing, polarisation and power flux density.

8.5. New horizons in chemical risk assessment

The review highlighted the inadequacies of the existing regulatory and risk assessment frameworks for toxicants which fail to protect vulnerable populations, account for multiple routes of exposure, mixture effects and transgenerational epigenetic effects. It also neglected to address timing of exposure during critical windows of development or individual human risk factors such as age, gender, genetics, nutrition, psychosocial determinants, and comorbidities. The review further identified the challenges and complexities involved in risk assessment including conflicts of interest with industries who influence data collection and the establishment of exposure standards. Whilst the existing chemical risk assessment has many challenges and limitations, advances in artificial intelligence and biochemical and computational technologies have resulted in the emergence of genomics, epigenomics, proteomics and metabolomics, that enable the screening of chemical mixtures at the molecular level and the development of more sensitive and specific methodologies for biological monitoring of combined exposures (Chung and Herceg 2020; Hernández et al. 2019; Vrijheid 2014). If advances in bioinformatics that encompass computational toxicology, toxicogenomics and systems biology are taken into account, it may become possible for scientists to uncover how environmental chemicals lead to toxicity and vastly improve toxicity testing. High-resolution metabolomics (HRM) that uses ultra-high resolution mass spectrometry with minimal sample preparation can support high-throughput relative quantification of thousands of environmental, dietary, and microbial chemicals and measure metabolites in most endogenous metabolic pathways, thereby providing simultaneous measurement of environmental exposures and their biologic responses (Go et al. 2015). Once this is achieved, exposure standards for toxicants could implement the precautionary principle and take sensitive groups into consideration.

Epigenetics has taken centre stage in the study of chronic diseases such as cancer, obesity, diabetes, and neurodegeneration; however, its integration into the field of environmental health sciences and toxicology is relatively new (Perera et al. 2020). Epigenetics has attracted significant attention in oncology because DNA methylation can reflect dysregulated gene expression patterns such as global hypomethylation in tumoural cells, that occurs early during the pathogenesis of cancer. A significant body of work has already been developed to determine the pathways deregulated in cancer, tumour subtypes

and drug resistance (Galardi et al. 2020) and determine diagnostic markers in cervical cancer (Schmitz et al. 2018), colorectal cancer (Li et al. 2020; Raut et al. 2020), thyroid malignancies (Zafon et al. 2019) and breast cancer (Ishihara et al. 2018). However, the uptake of these findings into general medical practice has been slow.

Whilst environmental epigenomics and toxicoepigenomics are still in their infancy, epigenetic signatures arising from exposure to a wide range of environmental toxicants have been identified even after cessation of exposure, and are proving to be useful biomarkers, molecular predictors of disease and disease progression (Chung and Herceg 2020). These biomarkers of exposures include DNA modifications (5-methylcytosine and 5-hydroxymethylcytosine), Transposable elements (Alu, LINE-1, IAP elements), Histone marks (H3K27me3, H3K4me3, H3K27Ac, H3K4me1, H3K9me3) and ncRNA (miRNA, lncRNA, piRNA, circRNA) (Perera et al. 2020). This field will rapidly advance once cell-type-specific epigenomic maps are developed for all tissue and cell types which is currently underway by various groups from the International Human Epigenome Consortium, to the ENCODE Project Consortium and the National Institutes of Health Roadmap Epigenomics Program (amongst others). In addition, the TaRGET program (Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription) is providing useful data on the impact of environmental exposures on the epigenome, however once the epigenetic state is identified, questions remain as to whether it will be an adverse event or an early adaptive response (Chung and Herceg 2020).

Chemical risk assessment can be vastly improved by gaining data on the totality of exposures across the lifespan (Lioy and Rappaport 2011). The ability to assess and identify early-life environmental exposures and their impact on later health outcomes is limited by the costs required to conduct large population prospective studies with long-follow up durations, short half-lives of some toxicants, and lack of biomarkers to capture inter-individual differences (Schrott et al. 2022). To assess the health consequences of lifetime exposure to environmental chemicals, various projects to improve toxicity testing are underway including Evidence-Based Toxicology Collaboration (Hoffmann and Hartung 2006), PROMETHEUS project by the European Food Safety Authority (European Food Safety Authority 2015), Chemical Management Plan Risk Assessment Toolbox by Health Canada (Government of Canada 2016), Integrated Risk Information System (IRIS) and Tox21 by the joint US EPA and Food and Drug Administration. Other initiatives include the National Institute of Environmental Health Sciences (Attene-Ramos et al. 2013; Shukla et al. 2010), ToxRTool by the European Commission (Schneider et al. 2009) and REACH (Registration, Evaluation Authorisation and Restriction of Chemicals) by the European Chemicals Agency and KIimisch Ring Test (Klimisch et al. 1997). REACH is regulated by the European Union and was designed to

promote alternative methods for assessing chemicals that may impact human health, whilst placing the burden of proof on manufacturers to demonstrate a product's safety prior to releasing their products and technology into the marketplace (European Chemicals Agency 2023). Further developments to improve toxicity testing based on animals include a new design from the National Research Council for cellular-response networks that take into consideration advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology thereby allowing scientists to uncover how environmental chemicals may lead to toxicity (National Research Council 2007). Emerging tools like the maximum cumulative ratio will further help to identify a person's cumulative exposure to multiple chemicals over a lifetime (Han and Price 2013).

Emerging technologies are also providing a mechanism to clinically assess a patient's allostatic load. Predictive modelling involving methylation scores and machine learning approaches, have identified epigenomic biomarkers of exposure (primarily obtained from cord blood samples at birth) that are detectable across the lifespan across a range of exposure domains (Schrott et al. 2022). Renewed interest in the placenta as a potential biomarker of transgenerational exposure and its contributions to long-term human health and disease was initiated by the National Institutes of Health: Human Placental Project following evidence of its impact on the health of the mother (Fisher 2015; Lacroix et al. 2013) and foetus (Barker et al. 1990; Barker and Thornburg 2013; Kroener et al. 2016; Rees and Inder 2005). Prospective follow-up birth cohorts to examine the effects of early life programming will also be important (Grandjean et al. 2015).

8.6. Stakeholders and citizen science

The need for greater awareness regarding environmental exposures began five decades ago when clinicians united across the globe to form medical groups dedicated to environmental medicine. The sheer number of community support groups currently dedicated to environmental exposures is staggering and reflect a fragmented medical system. Furthermore, the weight of evidence associating EMFs with adverse health effects has prompted thousands of doctors and researchers to sign Resolutions and Appeals to reclassify EMFs in mobile phone and wireless technologies from Group 2B to Group 1 known human carcinogen. Despite this, healthcare policies around the world largely ignores their pleas and continues to purport NIR-EMFs as safe. The qualitative research survey identified that despite frustrations due to the constraints of the medical system, Environmental Medical practitioners dedicate enormous amount of resources, time and finances to upskill their knowledge in continued support of their patients.

The impact of environmental exposures ultimately requires action at many levels, and patients and the community. Thus, civil society, including non-government organisations and civilian advocates can play a vital role in shedding light on the nature, extent and impacts of exposures. As such, citizen science or 'participatory urbanism' is an emerging field that shows great promise in the scope of environmental awareness and regulation (Paulos et al. 2009). This became evident as early as the 1960s when a citizen science project revealed widespread contamination from radioactive fallout from atomic weapon testing through the analysis of strontium 90 in baby teeth collected from around the world, leading to the signing of the Partial Nuclear Test Ban Treaty in 1963 (Logan 1964).

The potential for participatory citizen science has expanded enormously since the 1960s. Consumer's appetite for health information is evident by the availability of more than 350,000 health-related mobile applications (Aitken and Nass 2021) and the fact that 45-58% of mobile phone users have downloaded at least one health app (Krebs and Duncan 2015; Paradis et al. 2022). Furthermore, genomic profiling is now available for as little as $99 from companies like 23andMe who have databases with millions of clients. With more tools at their disposal, citizens are no longer passive recipients of health care and can make informed health-care decisions and take a more proactive approach. Furthermore, the advent of the internet along with rapid advances in cell computing, wearable devices, nano-biosensors, lab on a chip technology, geographical information systems, the internet of things, big data analytics and cloud computing, represent disruptive innovations that promise to create a fundamental shift in biological discovery. Such advances, which enable the real-time measurement of physiological and psychological states along with environmental measures, offer the ability to better predict, detect and prevent disease brought on by chemical exposures and thus radically accelerate our understanding of the health impact of environmental chemical exposures (Marcus 2009).

Widespread adoption of information technology applications requires behavioural adaptations on the part of clinicians, organisations, and patients (Baker 2001) and the ability of technology designers to build better tools and platforms that allow patients to share data with their doctors in order to augment existing medical knowledge and practices (Neff 2013). Whilst citizen science has the potential to build important bridges between scientists, clinicians and the public, with positive outcomes for all (Louv et al. 2012), clinicians need to be receptive to the shift in the information available to the public and be capable of answering questions and directing patients to credible and reliable resources where appropriate (Kurup 2010). Engaging volunteers in rigorous science, global-scale citizen science projects also provide an excellent opportunity to promote awareness, and educate and empower individuals and

clinicians to find solutions to problems that would otherwise be overwhelming (Louv et al. 2012).

The ongoing release of new technologies to create smart homes, schools and workplaces, creates an imperative to upskill all stakeholders including clinicians, schools, trades and the population at large, on the potential health effects arising from long-term exposure to RF-EMFs at non-thermal levels and effective ways to mitigate exposure whilst embracing the benefits of living in a technological society. Concerning the protection of children, recommendations by the Council of Europe suggest "…targeted information campaigns aimed at teachers, parents and children to alert them to the specific risks of early, ill-considered and prolonged use of mobiles and other devices emitting microwaves; (…) ban all mobile phones, DECT phones or Wi-Fi or WLAN systems from classrooms and schools…" (Verts 2011:4). The outcome of the Parliamentary Inquiry into Electromagnetic Fields suggest the government "… considers developing material to advise parents and children of the potential risks associated with mobile phone use… [and] enable community groups to have greater input into the siting of antenna towers…" (Commonwealth of Australia 2001:xxv).

The National Construction Code does not yet provide recommendations to architects, builders and electricians on how to construct dwellings, schools and workplaces that minimise exposure to NIR-EMFs. Such recommendations could include avoiding smart meters in close proximity to bedrooms and living spaces, installing ports in every room so they can be hardwired, and the capacity to switch off all fields in bedrooms at night which can be achieved by installing a demand switch in the meter panel that shuts off circuits that supply the bedrooms. Similarly, town planners could be educated to ensure housing developments are not at risk of exposure to elevated fields arising from proximity to high voltage transmission lines, tram and distribution lines, substations and mobile phone base stations. Dwellings should also be a distance away from toxicants arising from proximity to traffic-related air pollution, flight paths, mining, ports, coal trains, bus/taxi terminals, manufacturing, golf courses, turf farms and farming that incorporates aerial spraying for example.

8.7. Environmental medicine as a medical speciality

The failure of regulatory authorities to adequately manage risk, in addition to the widespread and growing number of toxicants, use of mobile phones and rollout of Wi-Fi enabled technology across the globe, provides clinicians with unique and important roles to play in identifying and preventing environmental exposures, yet few are adequately prepared for this (McClafferty et al. 2015). EM is virtually unknown as a medical speciality in its own right due to its fragmented definition which varies depending on the viewpoint of the industry (public health, occupational and environmental medicine and integrative medicine), and the

observation that it has been relegated to a relatively small group of clinicians outside of general medical practice, most of whom focus on public health issues rather than patient-centred clinical practice. I propose a more appropriate definition for Environmental Medicine taking into consideration the underpinning knowledge and skills Environmental Medical Physicians (EMPs) will need to acquire as described in this section:

> *Environmental Medicine recognises, evaluates and manages hazards in the environment that may impact human health, with the aim to establish root cause(s) and susceptibility, and provide advice and treatment specifically tailored to the needs of individuals.*

Establishing Environmental Medicine as a specialty that is differentiated from occupational medicine and public health, will go along way towards recognising and managing environmental exposures. This will require specific training in a cluster related knowledge, skills and attitudes in the fields of genomics, nutrigenomics, microbiology, hygiene, toxicology, occupational health, public health, epidemiology and, from a clinical perspective, nearly all fields, as well as general medicine, paediatrics and oncology. However, there are many obstacles that hinder this process including:

- the complexities involved in integrating data from numerous emerging fields,
- time constraints imposed on clinicians,
- educational requirements,
- the need for population and individual biomonitoring,
- the lack of clinical assessment tools,
- pathology facilities and adequate risk-based regulation,
- profit based funding models that favour treatment over prevention, and,
- the lack of political will to implement changes in how we produce, monitor and regulate chemicals.

8.7.1. Environmental medicine, personalised medicine and genetic testing

Environmental exposures are unique for each individual and reflect their specific risk factors, health status and susceptibilities, along with their burden of toxicants (including biotoxins and stealth infections) and current and cumulative exposure to NIR-EMFs. Conducting environmental assessment at the clinical level is an extremely challenging task, and education of EMPs requires the knowledge and the skills to recognise, evaluate and manage patients impacted by environmental exposures along with the ability to adopt clinical genetic testing. Personalised medicine will require measurements obtained at the individual level whilst also

utilising the data and learning retrieved from the rest of the population (Tebani et al. 2016). The challenge will be integrating data from numerous emerging fields.

Following sequence completion of the Human Genome Project in 2003 in conjunction with the rapid advances in bioinformatics, the ‘omics’ fields exploded onto the scene, challenging our understanding of the nature and cause of disease, whilst also shifting the focus to what it means to be well. Clinical genetic testing has transformed from being centred on mutation detection for Mendelian disorders like sickle cell disease to personal genomic data as a way to predict ancestry and assess disease risk. Various medical disciplines have begun to explore and adopt the application of gene variants into the diagnosis and treatment of various diseases including oncology (Horak et al. 2022; Saliba et al. 2022), neurology (Dratch et al. 2023) and cardiology (Ingles et al. 2018). Whilst the brunt of these discoveries has yet to infiltrate clinical practice (because it takes an average of 17 years to incorporate scientific discovery into clinical practice (Committee on Quality of Health Care in America 2001), the ramifications of these findings will provide more precise treatment for individuals and issue a new era in personalised medicine.

While genetic testing is providing greater understanding of disease risk, the clinical application of targeted genomic sequencing is fraught with challenges. Very few of the one million plus SNPs identified in genome wide association studies have clear functional implications and actionable outcomes that are relevant to mechanisms of disease (Bland 2015). Rapid sequencing and analysis technologies to accurately detect genomic variants remains disorganised owing to the technical and conceptual difficulties faced in evaluation (Ha et al. 2023), and characterising the genes in the context of the molecular pathophysiology of the disease is challenging (Karczewski and Snyder 2018). Furthermore, genomics and metabolomics are constricted by data quality and integrity, reproducibility and the need to include large sample sizes, let alone the need to upskill a new medical workforce (Tebani et al. 2016). In addition, the accuracy of laboratory analysis of genetic information and interpretation of results may vary amongst direct-to-consumer genetic testing companies depending upon their quality control standards (National Health and Medical Research Council 2011).

Despite the use of genetic testing in specialist medical disciplines, clinical guidelines for genomic testing are still in their infancy and, there is often little understanding of the effect of individual alleles, many of which appear to be non-sense mutations but may later prove to be of clinical relevance especially in the context of other alleles, epialleles and environmental exposures (Katsanis and Katsanis 2013). Despite the remarkable advances in the field of genomics in the past twenty years, concerns have been raised about the lack of knowledge and skills in genetic and genomic testing, interpretation of test results, communication of

results to patients and families, and basic genetic counseling amongst general non-academic clinicians (Botkin et al. 2015; Sawhney et al. 2014). A recent survey of physicians highlighted they did not feel their medical training was adequate to produce the necessary competency in medical genetics and genomics, despite understanding its importance in general medical practice (French et al. 2023) and clinicians perceive the analysis of genetic data requires considerably more time and work with uncertain outcomes (Neff 2013). This was confirmed by our findings whereby clinicians acknowledged that genetics was likely to be important, however most of them did not undertake genetic testing due to the costs involved, clinical uncertainty, lack of knowledge on gene variants, and because of the ethics involved in discriminating against people.

Clinical genomics requires an understanding of the ethical, legal and social considerations associated with genomic profiling including employment and health insurance non-discrimination, patient's rights and anxiety, informed consent, disclosure, microarray screening for pregnancy, cost/benefit ratio, drawbacks versus perceived benefits, genetic counselling, protection of privacy and data protection (Chow-White et al. 2015; Nys 2002; Solomon 2015). Clinicians will therefore need educational programs that target relevant scientific, clinical, ethical, legal, and social topics and support systems that address structural and systemic barriers to the integration of genetic medicine into clinical practice and the time to keep abreast of advances (Botkin et al. 2015).

Genetic testing may provide an insight into one's susceptibility, however it is only one facet of Personalised Medicine. Former director of the U.S. National Institutes of Health, Francis Collins, coined the phrase 'genetics loads the gun and the environment pulls the trigger'. Establishing an individual's risk to environmental exposures based on the presence of low penetrance genes (SNPs) alone is limited unless it is combined with the potential epigenetic effects of pathological, developmental, dietary and environmental chemical exposure history across the lifespan (Barrett et al. 1997). The concept that the phenotype is the consequence of gene-environment interaction was highlighted by Archibald Garrod in 1902 who suggested that individual differences in genetics could play a role in variation in response to drugs, and that this effect could be further modified by the diet (Garrod 1902). Breast cancer risk provides a good example. Whilst the aetiology of breast cancer is still not fully understood, there are several known risk factors including: the age of menarche/parity/menopause; family history of breast cancer; length of time of breast feeding; body mass index; drugs (hormone replacement therapy, oral contraceptive pill); exercise; alcohol intake; and cigarette smoking (Hankinson et al. 2004; Johnson et al. 2011). Given that the prevalence of gene mutations (BRCA1, BRCA2) for women diagnosed with breast cancer are low (5.3% and 3.6% respectively) (Lerner-Ellis et al. 2015), it has been suggested that

low-penetrance susceptibility genes combined with environmental factors may be important risk factors (Zhang et al. 2010). Advances in genomics have identified several gene variants (Single Nucleotide Polymorphisms (SNPs)) in key detoxification pathways that maybe associated with breast cancer susceptibility (Kumar et al. 2015; Meplan et al. 2013; Oliveira et al. 2010; Šarmanová et al. 2004; Ünlü et al. 2008). However, few of these variants (COMT, CYP1B1, GSTP1, MnSOD, MTHFR) have been shown to contribute to breast cancer risk individually except when these polymorphisms are combined (Cerne et al. 2011), or in the presence of relevant environmental chemical and lifestyle exposures (Lin et al. 2005; Liu et al. 2012). This is significant in light of the fact that unique populations of various ethnicity have been shown to have polymorphic variants in detoxification enzymes, which may predispose them to increased adverse health effects from environmental chemical exposures (Piacentini et al. 2011; Vogel et al. 2011). For example, despite the low incidence of breast cancer amongst Asian women (Ziegler et al. 1993), a meta-analysis to determine the role of MTHFR C677T polymorphism in breast cancer risk, showed a strong significant association between TT genotype and breast cancer which is far more prevalent in the Asian population compared with the Caucasian population (Kumar et al. 2015). This may explain why US-born Asian women have an almost two fold higher incidence of invasive breast cancer than foreign-born Asian women (Gomez et al. 2010), implying that epigenetic effects involving lifestyle, dietary, and/or environmental factors are likely to play a role. The findings may explain why so many risk factors have been implicated in breast cancer and other chronic diseases, and yet a causal relationship has not been definitively established.

Clinicians interviewed in the qualitative survey all agreed that the most effective way to assess exposures is to undertake an environmental exposure history, which takes an average of 90 minutes (1 to 3 hours) to complete. As a result of the time required, most clinicians couldn't bill through the conventional Medicare system, which significantly increases the cost for patients many of whom have already seen multiple practitioners. Many of the clinicians were frustrated with the existing medical model whose 7-minute consultations were geared towards acute conditions, and penalised clinicians for spending 'too much time' with patients presenting with chronic, multimorbid diseases. Some Integrative Clinicians were concerned about being deregistered for taking up too much time with their patients and undertaking tests and treatments that were not considered evidence-based, but felt they had no other options as the conventional medical testing and treatments had failed their patients. To address these concerns, standardised exposure assessment tools and Apps that quantify mean exposures to RF-EMFs could be developed to engage the community in quantifying environmental and individual exposures and enable the patient to become aware of and modify their behaviour.

A comprehensive environmental exposure history App could incorporate individual susceptibility and data from paediatric, environmental, geographical, dietary, occupational and lifestyle sources and be used to screen all patients suspected to be impacted by environmental exposures to assess their toxic load. EMPs could use such digital tools to quantify exposure and educate the patient on how to mitigate exposure. This would need to encompass:

- Establishing the *patient's inherent susceptibility* to environmental toxicants and electromagnetic fields through assessment of their demographics, ethnicity, socioeconomic status, comorbidities, nutritional and genomic profile.
- *Family history* that includes previous generations.
- Undertaking a detailed *place history* that includes places of residence and work across the lifespan and throughout the week including primary modes of transportation and an assessment of the patients living and working conditions.
- Undertaking an *obstetric, paediatric, environmental, dental, dietary and occupational exposure* history in additional to pharmaceutical and recreational drug use and general lifestyle factors including the use of chemicals in the home and garden, cooking utensils, cleaning methods, personal care products and consumer goods.
- Undertaking a *family history* that includes previous generations.
- A detailed *symptom history* that includes a timeline from the perinatal period and enquiry into multiple organ systems.
- *Physical examination* to look for physical signs of metabolic, neurological, reproductive, or other disease and co-morbidities.
- A *digital diary* to identify the use and cumulative exposure to various Wi-Fi enabled digital devices in the home, school and workplace.
- Writing support letters to assist environmentally sensitive patients with a range of medical and social welfare services (including in-home support) as well as appropriate referrals to specialists and allied health practitioners (Martin 2017). This may involve networking with building biologists to assess the patient's home and/or workplace proximity to ambient exposures to toxicants (e.g., golf courses, farms, flight paths etc) and electromagnetic field exposures (mobile phone base stations, distribution lines, wind turbines etc).
- A consideration of *external data sources* such as personal monitors that track and quantify exposures, geographical information systems and governmental or non-government environmental pollution reporting, ambient air monitoring, drinking water quality and any crowd-sourced data.

EMPs should also be upskilled in the understanding and implementation of emerging technologies and biomonitoring tests to assess the allostatic load in their patients that also takes into consideration population data. For example, biomolecular adducts formed when a xenobiotic or its metabolite binds to biological molecules (DNA or proteins), are a useful tool to assess exposures to non-persistent chemicals in blood such as organophosphates and aromatic amines before clinical consequences appear (Sogorb et al. 2014). Genome-wide association studies, in contrast to single nucleotide polymorphisms (SNPs) are also likely to provide an important tool to identify the 'susceptible biomarkers' to environmental chemicals (Bhattacharjee et al. 2013). EMPs will be required to interpret test results and have knowledge of sources of exposure to educate patients on how to prevent future exposures.

The time required to collate and interpret this data, and existing time constraints imposed on clinicians, would require the public and private health insurance to compensate EMPs for the time required to undertake a proper environmental exposure history. Politicians and the corporate sector would also need to support the dissemination and implementation of this type of service in accordance with clinical guidelines based on existing literature including the Guideline of the Austrian Medical Association for the diagnosis and treatment of EMF related health problems and illnesses (EMF Syndrome) (Austrian Medical Association 2012); the EUROPAEM EMF guideline 2016 for the prevention, diagnosis and treatment of EMF-related health problems and illnesses (Belyaev et al. 2016); and Belpomme and Irigaray's Electrohypersensitivity as a newly identified and characterised neurologic pathological disorder: how to diagnose, treat and prevent it (Belpomme and Irigaray 2020).

While citizen science and mobile technology have the potential to engage the wider community in monitoring and reducing exposures to environmental pollutants, a lack of integration between data sources and big health data streams is a key challenge. Incorporating 'big data' arising from traditional medical data, 'omics' data and quantified self-data to routine clinical care will be a formidable and challenging task, yet this is vital for the emergence of personalised medicine that is predictive, personalised, preventative, and participatory (4Ps). Recent developments in the field of systems biology, innovative breakthroughs in biomedical research encompassing the 'omics' fields, and advances in mobile sensing, peer-to-peer networks and, big data, may provide tools that future clinicians can use to assess environmental exposures in their patients and the advent of personalised medicine. Systems biology uses computational mathematical tools that promise to unify multiple data sets-personal, clinical, genomic, geographical, and environmental data and provide the foundation for personalised medicine where the patient becomes an integral part of the identification and modification of disease related risk factors and the clinical decision-

making processes takes advantage of the most up-to-date scientific knowledge (Payne and Marsh 2012).

8.7.2. Undergraduate medical training and environmental medicine

Environmental exposures are implicated in many of the conditions seen by clinicians on a daily basis, yet the tools and expertise to adequately manage these exposures are not widely taught or available to general practitioners (Institute of Medicine (US) Division of Health Promotion and Disease Prevention 1988). Furthermore, few doctors collect adequate occupational or exposure histories (Bijlsma and Cohen 2018; Politi et al. 2004) or refer patients to environmental physicians (Herr and Eikmann 2011) and therefore environmental exposures are seldom identified as contributing to disease causation (Reuben 2010). In addition to the development of a postgraduate course in environmental medicine to create EMPs, basic principles of Environmental Medicine need to be integrated into the undergraduate medical programs in order to recognise patients impacted by environmental exposures and enable them to refer on to EMPs. The complex and ubiquitous nature of environmental exposures requires medical curricula to integrate environmental medicine education with pathophysiology, history taking and physical examination skills during pre-clinical years (Merritt 1999), as well as knowledge and skills in a broad range of scientific and public health fields, including training and experience in general clinical medicine, paediatrics and oncology. Even basic training in Environmental Medicine can be effective as indicated by a well received 6-hour online foundational Environmental Health Course developed to recognise, assess and prevent environmental health exposures (McClafferty et al. 2015). A multi-phase environmental medicine program integrated with medical curriculum has been implemented by Wayne State School of Medicine, where during preclinical years environmental lectures are incorporated as part of basic sciences and public health courses (Merritt 1999). During subsequent clinical years, students are introduced to exposure history taking and examined on a broad spectrum of environmental associated health effects including chemical exposures such as pesticides and lead as well as electromagnetic radiation (Merritt 1999).

Ultimately the challenges presented by environmental exposures are far greater than those that can be faced by clinicians, as they affect all people and indeed all life on earth. Risk assessment requires the application of multiple scientific fields to public health and regulatory issues. In addition, a medical school syllabus "…will require input from medical practitioners, public health professionals, environmental scientists, ecologists, and policy experts [which] will require physicians to embrace multi- and transdisciplinary work alongside professionals from many backgrounds (…) to develop greater fluency in the language of these affiliated fields" (Gómez et al. 2013:171). There is a need therefore for concerted action at all levels

including actions by individual patients, clinicians, medical educators, regulators, government and non-government organisations, corporations and the wider civil society in order to understand and minimise the extent of toxic exposures on current and future generations.

8.8. Conclusion

Environmental exposures, including exposure to toxic chemical and non-ionising radiation electromagnetic fields, are ubiquitous amongst the global population and may contribute to a significant burden of chronic diseases typically seen in everyday clinical practice. Despite this, environmental medicine is not clearly defined with only a small subset of clinicians practicing environmental medicine and very few feel their expertise is adequate to consider themselves as experts. Clinicians practicing environmental medicine face significant challenges in diagnosing conditions that often present with idiopathic, multimorbid diseases, and treating patients who are difficult to treat and rarely regain full health. Clinicians are also constrained by a medical model that does not provide the required underpinning knowledge and skills to recognise patients impacted by environmental exposures, or compensate practitioners for the time required to take an environmental exposure history, which is widely acknowledged as the most important clinical tool for assessing toxic exposures.

The challenges faced by clinicians are compounded by challenges faced by patients who are exposed to multiple toxic chemicals along with NIR-EMFs that may impair sleep thereby reduce their resilience to other stressors. The results of the randomised controlled trial using a baby monitor to assess the effects of a 2.45 GHz radiation on sleep revealed that this radiation, which uses the same frequency as many Wi-Fi enabled digital devices, may have a clinically relevant adverse impact on sleep quality in real-world scenarios. Further large-scale real-world investigations with specified dosimetry are required to confirm these findings. Until future studies verify or provide evidence contrary to these findings, caution should be exercised when using RF-EMF devices such as baby monitors in bedrooms and adjacent rooms.

While various stakeholders from citizens, researchers and clinicians are raising concerns about environmental exposures, few clinicians recognise environmental exposures due to inadequacies of the existing education and regulatory systems, and delays in translating environmental health research into evidence-based healthcare and clinical practice. This situation is slowly changing and developments in toxicogenomics, bioinformatics and systems biology along with advances in mobile sensing, peer-to-peer networks, big data and innovative methodologies for systematic review and meta-analyses, are providing tools that can help quantify exposures and inform clinical assessment and mitigation strategies.

Considering the complexities of these issues raised by environmental exposures, there is a need for concerted action at all levels, including actions by individual patients, clinicians, medical educators, regulators, government, and non-government organisations, corporations, and the wider civil society, to understand the ‘exposome’ and minimise the extent of toxic exposures on current and future generations. Clinical environmental risk assessment may provide a bridge between multiple disciplines that uses new technologies to herald in a new era in personalised medicine that unites clinicians, patients, and civil society in the quest to understand and master the links between the environment and human health.

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Appendices

Appendix A: Publications

List of Publications

Bijlsma N, Cohen MM. Environmental chemical assessment in clinical practice: unveiling the elephant in the room. *International Journal of Environmental Research and Public Health.* 2016;13(2):181.

Bijlsma N, Cohen MM. Expert clinician's perspectives on environmental medicine and toxicant assessment in clinical practice. *Environmental Health and Preventive Medicine* 2018;23(1):19. doi:10.1186/s12199-018-0709-0.

Bijlsma, N. (Chapter 2: Environmental Medicine). Hechtman, L. (2020). *Advanced Clinical Naturopathic Medicine*. Elsevier Health Sciences

List of Draft Publications

Bijlsma N, Kennedy, G, Conduit, R, Cohen, M. Does radiofrequency radiation impact sleep? A double-blind, placebo-controlled, crossover pilot study. *Submitted, under review.*

Bijlsma N, Kennedy G, Cohen, M, Conduit R. Should non-ionising radiation electromagnetic fields be addressed in clinical practice? *In draft.*

Appendix B: Presentations and Awards

Presentations

1. ATMS. Environmental Medical Conference. 22 October 2023. Sydney. Australia.
2. ACIIDS. Environmental Exposures. 3 September 2023. Sydney. Australia.
3. HEAT Ageing Conference. 17-19 August 2023. Bangkok, Thailand.
4. NIIM. Advances in Integrative Medicine and Healthcare. 7th Annual Symposium. 25 & 26 November 2022. Richmond, Melbourne.
5. ACNEM. Environmental Medicine. 27 & 28 November 2021. Virtual Event
6. MTHFR Conference. 13-15 July 2018. Chicago. USA
7. ACNEM. Environmental Medicine. 5 & 6 May 2018. Melbourne. Australia
8. AIMA. Environmental Medicine. 14 & 15 April 2018. Auckland, New Zealand
9. ACNEM. Environmental Health. 29 & 30 July 2017. Brisbane. Australia
10. A4M Anti-Ageing and Aesthetic Medical Conference. 8 & 9 September 2016. Thailand, Bangkok.
11. AIMA. Children's Environmental Health. 28 & 29 March 2015. Auckland, New Zealand.

Awards

2016 RCT Scholarship, RMIT University

2016 Jacka Foundation Scholarship

Appendix C: Search Strategy for EMF and Sleep Disturbances

Methodology

The methodology for the review of evidence on electromagnetic field (EMF) exposure association with sleep disturbances from evidence-based reviews (EBRs) followed PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines (Moher et al. 2015).

General Search Strategy

The electronic databases of PubMed, Scopus, Cochrane Library, EMF-Portal (https://www.emf-portal.org/en) and GreenFile (access via EBSCOhost) were searched from 2000 to 2021 inclusive. In addition, citations and references of relevant studies were manually searched. The search terms for the topic on EMF associated with sleep disturbances included population, exposure and outcome which were applied to PubMed and Scopus databases. The term EMF was combined with the relevant outcome of sleep disturbances and applied to the other three databases (Cochrane Library, EMB-Portal and GreenFile). Searches were limited to human and the English language. The search strategy was limited to only evidence-based reviews including systematic reviews, scoping reviews, meta-analyses, and pooled-analyses while excluding expert opinions, commentaries, narrative reviews and animal or preclinical studies. As the overarching aim of this study was to collect published evidence on EMF exposures for individuals affected by sleep disturbances, therefore the review of evidence included only peer reviewed EBR such as systematic reviews and meta-analyses while grey literature such as trial registries and thesis were not searched.

General Eligibility Criteria

In general, reviews that did not report on evidence related to non-ionising radiation exposures or only provided expert opinion or commentaries were excluded and any review with a focus on animal studies or mechanistic review were deemed ineligible. Reviews that reported on findings from studies on sleep disturbances such as insomnia or sleep disorders associated with exposure to any level or dose of non-ionising radiation sources (see above) for any duration were included.

General Study Selection Process and Data Abstraction

Records identified through database searches were exported into the Endnote X9 reference management software followed by deduplication of all records and exporting to excel for screening. The title and abstracts of potential articles were screened according to the eligibility criteria for each topic. This was followed by screening full text based on inclusion and exclusion criteria before data extraction. Relevant data extracted from identified studies included first author and publication year, review design (systematic review or meta-analysis), number and type of studies in the review, focus of the study, exposure characteristics (e.g. level or dose), main findings including exposure categories and conclusions of the reviews.

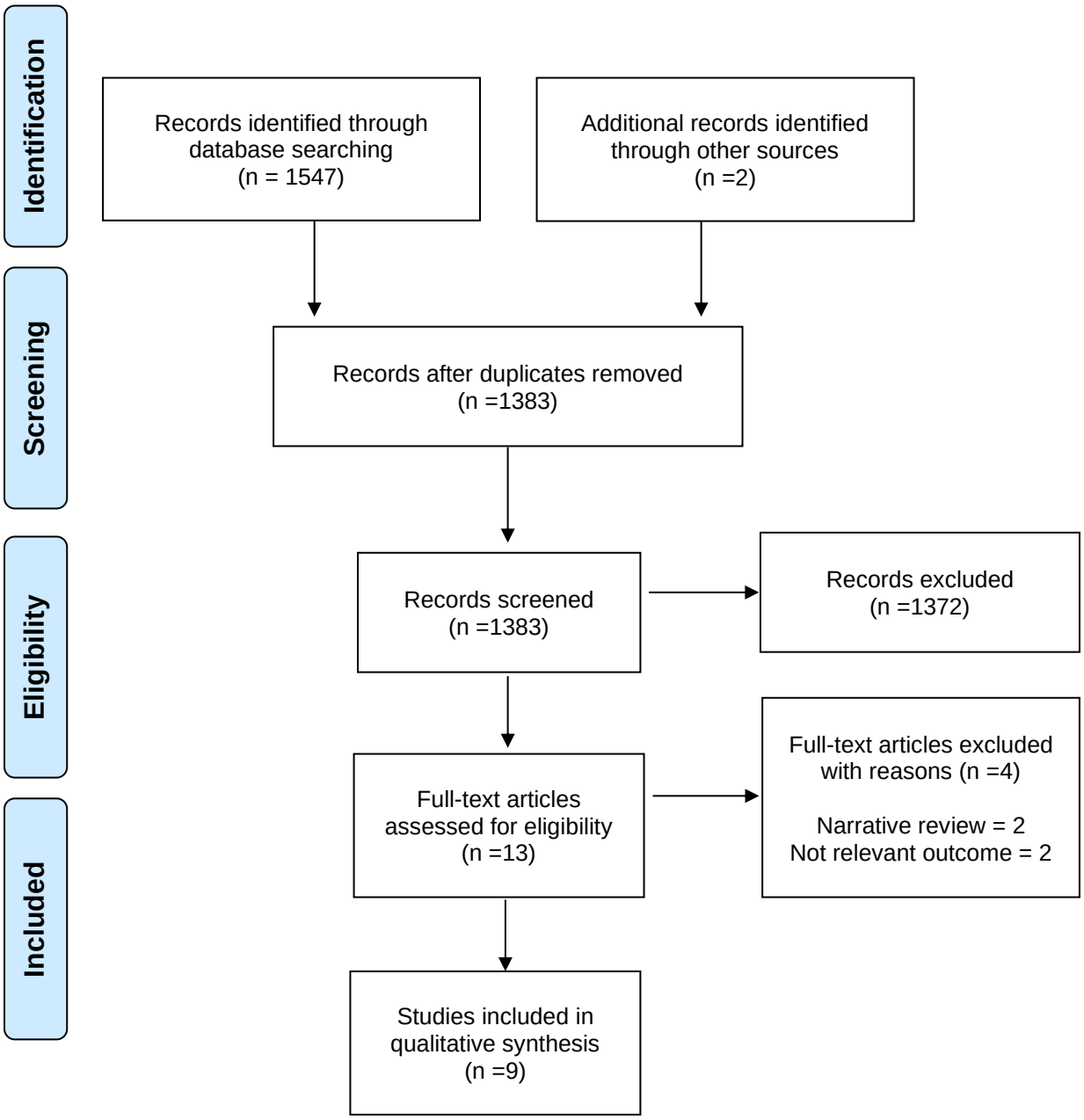
Table 1. PubMed key search terms for electromagnetic field and sleep disturbances

Key terms	Search terms
Population	Adult OR 'young adult' OR Child* OR 'adolescent'[Mesh] OR 'Humans'[Mesh]
Int/Exposure	'Electromagnetic fields'[Mesh] OR 'Environmental Exposure'[Mesh] OR 'Magnetic Fields'[Mesh] OR 'Magnetic field exposure' OR 'wire codes' OR 'Radiation, Nonionising'[Mesh] OR 'non-ionising' OR 'non-ionising' OR 'power line exposure' OR 'residential power line' OR 'power lines' OR 'high voltage' OR 'mobile phone' OR 'smart meters' OR 'portable wireless device' OR 'base stations' OR Wi-Fi OR '5G technology' OR 'laptop computer' OR 'Cell Phone'[Mesh] OR 'cell phone base stations' OR radiofrequenc* OR 'Occupational Exposure'[Mesh] OR 'wireless phone' OR RF-EMF
Outcome	'Sleep Stages'[Mesh] OR 'Sleep'[Mesh] OR 'Sleep, REM'[Mesh] OR sleep* OR 'sleep electroencephalogram ' OR 'Sleep EEG' OR 'slow wave sleep' OR 'sleep quality' OR 'sleep duration' OR 'Polysomnography'[Mesh] OR 'sleep loss' OR 'sleep disturbance' OR 'disturbed sleep' OR 'sleep disorder' OR 'NREM sleep' OR 'REM sleep' OR Insomnia OR 'primary insomnia' OR 'acute insomnia' OR 'secondary insomnia' OR 'chronic insomnia' OR polysomnograph* OR 'sleep efficiency' OR 'sleep latency' OR 'sleep time' OR 'sleep staging'

Table A2*. Search strategy for Scopus on electromagnetic field and sleep disturbances*

No.	Search term combination
#1	Adult OR 'young adult' OR Child* OR 'adolescent' OR 'Humans'
#2	'electromagnetic field' OR 'environmental exposure' OR 'magnetic fields' OR 'magnetic exposure' OR 'non-ionising' OR 'non-ionising'
#3	sleep* OR 'sleep quality' OR 'sleep disturbance' OR 'sleep disorder' OR Insomnia
#4	#1 AND #2 AND #3
#5	#4 plus Filters: Publication Year 2000-2021
#6	'systematic review' OR 'meta-analysis' OR 'meta analysis' OR 'pooled analysis'
#7	#5 AND #6
#8	#7 plus Filter publication type (article and review)

Figure A1. *PRISMA flow chart for study on the impact of EMF on sleep disturbances*



Appendix D: Chapter 4 Tables. Expert Clinicians Perspective on Environmental Exposures

Table B1. *Environmental medicine is a divided profession*

Area of difference	Clinician	Quotes
Nature of employment	OEPs	I've never worked in the private clinical area as a fee-charging professional.
		A lot of our fellows do medical-legal work and don't do much work in the environment space.
		We do more work-related than actual environmental toxins.
		We reviewed the use of copper beryllium in the aviation industry and did some complex tests including lymphocyte proliferation test to look for adverse consequences.
		Most court cases I do, are usually exposures to substances that are used in workplaces.
		I do two days with private cases, referred to me by general practitioners which includes workers compensation in motor vehicle accidents assessments. It has an emphasis on musculoskeletal medicine, but from time to time, I will see some cases with Multiple Chemical Sensitivity.
		There are very few people out there who can find us and see us as environment medicine specialists. I don't get many referrals, may be one a month and people somehow they find their way to me, maybe even less.
		You have to walk this very fine line where you have to tell the management to do things and you have to tell the workers to wear their hearing plugs and masks. So you're not very popular with anybody. Most of us are more closely aligned with the management side. Our job is to really protect the workers, but I think a lot of us have moved too far to the right. I think I was a bit too critical at one stage and so I lost my job.

Area of difference	Clinician	Quotes
		You've got to understand that the older guys have been welded to these management of the coal and gas. That's where their money is coming from all their life, and they're not going to start turning on their companies just yet and start advising them to close down.
	IPs	The patients that I see have seen seven or eight different doctors and have been examined to death and nothing has come out of that.
		The basis of my practice is chronically ill people, who do not fit into a clear medical diagnostic category.
		I see more kids with, rather than an obvious diagnosis, just a splattering of all sorts of things not quite right.
Type of diseases seen	OEPs	Mainly chronic neck pains and chronic back pains from a work injury. So it's much more musculoskeletal than environmental unfortunately.
		A lot of our fellows are heavily involved in musculoskeletal injuries, noise, slips, trips and falls.
		A lot of our doctors will be doing noise exposure history. They'll [the worker] be deaf from being at work and just take down the history and do the audiometry and send in for their compensation.
		The work I do with mining in New South Wales is a couple of cases of pneumoconiosis in coal miners.
	IPs	The basis of my practice is chronically ill people, who do not fit into a clear medical diagnostic category... [they] suffer [from] persistent inflammation, immunological dysregulation and neurological responses which are hyper-responses.
		Chronic and complicated, ill-defined conditions like Chronic Fatigue and tiredness, chronic allergy intolerances, persistent sleep disturbances and autoimmune dysfunction.

Area of difference	Clinician	Quotes
		A mixture of the real kind of severe multiple chemical sensitivities, which I see a number of, where they come in, with a proper mask on the whole time, because they didn't get through the waiting room to my office without being affected, to the much milder versions of that.
		Kids who are affected, but not full on the spectrum… we're just seeing a bigger cohort of those more subtly affected.
		Multiple sclerosis, Motor Neuron Disease, Parkinson's disease, those would probably be the ones I see most, and neurological dysfunctions that don't necessarily get a name because they are somewhat atypical.
		I see quite a few kids that live in a house with mould.
		If a child presents with explosive behaviour, or problems with focus, attention and judgement, the first thing I do is make sure it's not a reaction to chemicals.
Toxicants of concern	OEPs	The environment means different things to different people. What we're talking about is a workplace environment.
		You can have significant environmental exposures, but by and large, it's the ones we know about, you know, the lead, the mercury, the radioactive stuff. Most of these are heavy metals.
		I'm doing a coal [medico-legal] case at the moment for coal dust.
		I'm looking at people who were aircraft fitters and maintainers who in the course of their duly entered fuel tanks and were exposed to the various combinations of military aviation turbine fuel.
		Exposures to substances that are used in workplaces like caustic or acid substances… also occupational exposures that are carcinogenic substances.
		Solvents and pesticides are still one of the issues that comes up, but much less than it did in the 1990's because of a shift to 'softer' chemicals, implementation of OH&S regulations and changes in the method of application (moon buggies rather than aerial application).
		Hormone disrupting chemicals are not a consideration in our industry.

Area of difference	Clinician	Quotes
		We don't deal with the long-term… because this is what normal life is. None of these very, molecular or unseen chemical injuries are being monitored, because that's still really research.
		If you're talking about the millions of chemicals that are produced, not many actually have good known studies. Gold standard studies are rare as hen's teeth on what these things actually do to people.
		I have been struggling with things like electromagnetic radiation and so on. And those arguments have gone on for thirty years or more, without any definitive answers really.
	IPs	It's the very ubiquitous ones that people are routinely eating and drinking, without thinking much about it, just because of it being in the water supply and food.
		I think the biggest issue with environmental toxic load, is the amount of processed food that we eat, including foods stripped of nutrition, foods stripped of fibre, foods laced with food chemicals, foods dowsed in pesticides. Foods using abnormal hydrogenated toxic oils. I think that is actually our biggest danger.
		Most people expect toxins are outdoors, but most of the toxins are indoors.
		Mould is very common; chemicals and some degree of heavy metal exposures are very common as well. So, it seems to be that the mix of it all, the toxic synergy creates a bad result, rather than any single substance on its own.
		I see quite a few kids that live in a house with mould… you get them out of that house and they get better.
		There was a period in the early 1980's, where the organochlorine pesticides heptachlor and chlordane were required by law to be used under the slabs of homes as a termite treatment, and lots and lots of people got sick.
		If I've got someone with really intractable hormonal issues, breast or prostate cancer, I'd be looking for exposure to plastics and pesticides and some of those xenoestrogens.

Area of difference	Clinician	Quotes
		Problems with metal allergy, not just metal toxicity. So, if you take inorganic mercury from dental amalgams, it can be a mitochondrial poison, it can inhibit a vast array of enzymes.
		Plenty of times I've been looking for external toxins, there's nothing around and then the whole process unravels and it turns out that they have a fear of spiders and they've had the house completely sprayed (with pesticides) in every single room.
		Children eat a lot of fish, particularly Asian children, so much higher rates of mercury toxicity.
		All of those children [with neurobehavioural disorders] will have a proportion of their problem due to foods and chemicals.
		If you figure out that this child is reacting to a food, or a chemical and you remove that food or chemical, then, on review, you can untick all those boxes … how I regard those children, is not as having autism or ADHD, that is, really, as having food and chemical sensitivities, that express themselves with those conditions.
		I see much more of the indoor air pollutants and much less of the agricultural chemicals.
Role of nutrition in toxicant exposures	OEPs	There's a fringe thing called nutritional medicine... it's not really recognised.
		There is this serious discrepancy here, between Occupational and Environmental Medicine and this fringe group who call themselves Environmental Medical practitioners.
		I don't spend my time talking about nutritional enhancement of their condition, whatever that is.
		With people that don't have a recognised problem such as an allergy, nutrition is unlikely to play a role.
		I stick to the big things like fish and mercury, pesticides in fruit and lead exposures if they haven't washed their hands this may potentially contaminate the food.
	IPs	Nutrition is your backbone in biochemistry; if you've got good nutrition, you've got a level of resilience against environmental insults, if you've got poor nutrition, you have less resilience.

Area of difference	Clinician	Quotes
		When you go from healthy food to processed food, you are doing two things: you're decreasing the nutrients and at the same time increasing the toxins, and this changes the whole balance of survival.
		If a person is low in calcium and iron, they have a greater affinity to absorb lead. Likewise, if a person is deficient in Vitamin C and selenium, they have a greater affinity for absorbing mercury.
		If you eat a healthy diet, high in antioxidants, you're more likely to be able to detoxify and get rid of those toxins… if you eat an organic diet, you reduce your pesticide load; when you eat fish, you are more likely to be exposed to heavy metals and other pollutants. So, nutrition has a huge amount to do with that.
		If the body has optimum nutrition, then the toxic load is less likely to be problematic.
		Certain toxins bind up our enzymatic pathways and create nutritional deficiencies. So nutrition is really important for protecting you against toxic exposure.
		Zinc and manganese are very important for upregulating metallothionein, and in protecting you against heavy metal exposure.
		If the child is iron deficient, they have increased absorption of lead and often have pica symptoms, of eating the dirt.
		Food is probably the first one because I know how toxic gluten is… it is associated with inflammation.
		The biggest issue with environmental toxic load, is the amount of processed food that we eat, including foods stripped of nutrition and fibre, foods laced with food chemicals, foods dowsed in pesticides. Foods using abnormal hydrogenated toxic oils. I think that is actually our biggest danger.

Area of difference	Clinician	Quotes
Attitude towards genetic testing	OEPs	There's a huge reluctance in Occupational and Environmental Medicine to do genetic testing because of the implications, discriminating against people on the basis of genetic predisposition to problems. Are we in the position to actually do the testing and make those decisions? No, that's very contentious.
	IPs	People with the HLA DRB-1 and the HLA-DQ test do put them into a category that makes perfect sense about why the person reacted [to biotoxins in a water-damaged building]. I really do think that the idea of checking the genetics and susceptibility will be a big thing, once we understand why those particular chromosomal changes predispose a person towards more toxic injury than others. The genes that I usually look out for would be the methylation genes, the glutathione-related genes, the Phase I and Phase II hepatic detox pathway genes, the acetylation genes of glucuronidation pathways, the Metallothionein gene and PON-1 (Paraoxonase-1). I have a sense that neurological sensitivity and methylation disorders and hypersensitivity to toxins, are different aspects of the very same thing, of the very heightened response of the central nervous system to particular inputs.

Table B2. *Clinical assessment of toxicant exposures is challenging*

Key challenges	Clinician	Quotes
Lack of clinical guidelines	IP	It would be great to have a standardised data collection tool for environmental exposure history. It would make an enormous difference to outcomes. I've got a patient today with high bisphenol and phthalate levels. What do you do about it, besides stopping the exposure? So then, the question is, when they've got all these things and they've stopped the exposure and they are still very sick people, how do you go about dealing with that?
Limitations of laboratory testing	OEP	The frustrating thing with Environmental Medicine is actually trying to find the tests which can actually show that what they (the patient) have got is real. You would counsel (the patient) against over testing and wasting public money. Most of them you don’t have tests for. Testing is really difficult. I have a very limited array of tests. If you’re trying to test for things like benzene exposures and stuff, you really have to catch that at the time they’re exposed because very quickly you don’t get many metabolites left in the system from solvent exposures. It’s far too expensive for my patients to do that. I use blood for heavy metals and obviously that only picks up the products that are long-term exposures that bioaccumulate like lead, cadmium, and nickel. I just don’t feel like I have the tools to do a better job.
	IP	There's a lot of rubbish pathology that goes on, where we don't have good standards, where we accept almost any kind of result as proof of poison and abnormalities, and we don't have good, validated ways of understanding how to measure the toxins. So we don't have good surrogate markers, because no one can agree on what a marker of a toxic exposure does.

Key challenges	Clinician	Quotes
		The whole question of the testing… it's really a mind-field that's very hard to get your head around.
		Standard medical labs do not measure anything that are specific to environmental toxins or exposures.
		In my area of medicine [CFS/MCS], physical examination is terribly disappointing. It doesn't really show much at all and that's part of why people get ignored in this area. They can have neurological and immunological impacts and the physical examination looks and feels just the same as any other person.
		Although we wanted to believe that the Australian labs were doing it properly, clearly they weren't, when they had five-fold differences in one-split sample which they thought were different patients.
		I used to use porphyrin tests, but I found that the results were so inconsistent, that I just stopped.
		I don’t test for chemicals. I just do the functional liver detoxification profile and get their livers working properly to get rid of the chemicals.
Difficulty in establishing cause and effect	OEP	In case of putative or suspected cause, until there's sufficient scientific evidence supporting, relating the possible cause and the effect... that's where dose-response relationships are important, whether there's a plausible biological mechanism that can explain the mechanism from the exposure. It’s important not to create alarm.
		It’s hard to quantify these health risks. I think what happens in a lot of companies is you do what you’re regulated to do, and then you just report what you can. There’s a lot of uncertainty in everything we do.
		We simply don’t have enough data to make strong conclusions unfortunately.
		You have to be a little bit careful in this area otherwise you can get a [bad] reputation. You need to be a little bit cautious that you stick with science as much as possible. But there are a lot of areas where the science isn’t that great.

Table B3. *The environmental exposure history is the most important clinical tool*

Features	Clinician	Quotes
Importance of an environmental history	OEP	It's quite a long, drawn-out question and answer process that follows no specific format, because then I go along and choose the questions I want to ask, to determine what their alleged level of exposure is and what has been the responses by their body to that exposure, and what measurements they've had.
	IP	History, history, history is the most important tool to use. I tell the patient, it's all in the history. Let's spend some time getting it down and also that we're not going to get this right in, like, the first appointment, it might take several appointments. Because we couldn’t rely on the Australian laboratories, we stopped testing and went entirely on history. It’s important to ask a very detailed history: occupational, hobbies, recreational, nutritional, environmental exposures, even down to things like chemical use in the house, indoor air pollution, external air pollution etc. It's becoming less and less value to do toxin checking and much more valuable to say, Is your history one of exposure to toxins and if so, what is the generalised approach that we could do, to safely protect and unload you from whatever the likely historical toxins are. The first thing is to have an awareness of the possibility [of toxicant exposure]. The second is to ask a good history. And then trying to find out what tests could be done and what treatments could be used or who to refer to.
Challenges of long consultations	OEP	In 90 minutes, you can actually really get to understand a person and their risk of exposures and whether in fact this might be something that is related to occupational or environmental exposures.

Features	Clinician	Quotes
		We're taught to ‘Take a good history’. I would challenge most doctors now, they don't. They've got four minutes to see a patient, they're supposed to see forty a day, get them in, get them out. If there's something more complex, they say Oh, I'll tell you what to do, let's get a blood test done here, or Let's see how you go, take these two pills and I'll see you in two weeks, if you're not better. And then they hope in two weeks, that they're going to find more time, but they don't.
	IP	90 minutes allows me to give an hour to the history taking portion and half an hour for examination. That's really what’s needed to conduct a proper environmental history. With the existing system, the history-taking part has to be done in about two minutes, then you have to get the blood pressure on and the script, or the investigation printed within five minutes and then your 'closing statement' is six, or seven minutes. There's no way you're going to pick up anything deeper in that time… and it's just enough history to work out which medication or investigation may be. So, that is a big problem. The system isn't really set up for doctors' seeing patients for a long period of time. And if you claim for a long consultation, they complain.
Occupational history	OEP	You need to go through what is this person exposed to through the whole course of their working life. I would tease it out, detail by detail, according to the history given, whether it was volatile organic solvents, whether it was dust, whether it was asbestos, whether it was diesel fumes. So, it would become an individualised, personal question-and-answer, to get a measure of what the exposure has been, in both the long-term and in the short-term, resulting in the symptoms as expressed by the individual. You ask people what they are exposed to, then you look at specific heavy metals or chemicals in the workplace. If somebody was making or refurbishing old thermometers, then test for mercury. If they’re working on bearings or grinding in a machine workshop, you’d

Features	Clinician	Quotes
		probably do lead and cadmium. If they're doing spray painting for corrosion control on a metal aircraft, then you do chromium. So, you tailor it to the environment.
		If you were a painter, preparing, or getting rid of lead paint in old houses, first of all you scrape the old paint and then you burn it. And if you don't do it properly, you could be exposed to significant lead levels from the old paint.
	IP	If they have listed a job involving the use of chemicals, farming, soldering, or various things like that, I'll specifically ask what personal protection they use.
		I've noticed that some of the parents with autistic children are often very intelligent people in high end academic jobs, but not in great locations like an oil rig and things like that.
		People working around swimming pools and golf course greenkeepers, were getting sick with the same illness' that the farmers in the Central Coast were getting years ago.
Place history	OEP	Mount Isa mines in Queensland and Port Pirie in South Australia they've shown quite significant spread [of lead dust], many kilometres from the stacks and waste dumps.
	IP	Where they've lived as children, renovations of houses, all those kinds of things don't actually come out unless you ask that.
		You need to investigate the house for lead paint, or eating antique furniture, being bathed in an old bath.
		Where were you born, where did you grow up, what were your early life experiences and exposures, or potential exposures, to toxins, what was your health like in childhood, early adulthood and adulthood?
		I get them to map out on Google maps where they live, go to school and where they work. I draw a sausage shape around their home, and go half a kilometre sideways and one kilometre each endwise and find out what is the vicinity of golf courses, industrial areas, service stations, main roads, airports, farms, bowling greens, parks…? What are the prevailing summer and winter winds? although wind direction is not useful in hilly areas.

Features	Clinician	Quotes
		And so, we basically just stare at the map on the places where they used to live and work, and where they currently do live and work. It's a useful thing for identifying where very sensitive people should buy houses or rent. In relation to the Chronic Fatigue Syndrome cluster around Botany Bay, we identified hot-spots for hexachlorobenzene at Botany Bay and dioxin and PCB exposure around Homebush Bay. What school did you go to, where was it? Lots of the toxicological assaults come from the schools, which can be situated on hills, or beside main roads and kids get plenty of exposure to cleaning agents and traffic fumes, pesticides and just about everything there. And then, half the schools seem to have the old, unflued gas heating systems through all of winter… volatile organic chemical exposure and respiratory irritants are high.
Dietary history	IPs	So, tell me a bit about the chemical reaction you are concerned about. When was it, how long was it, how long after the exposure, the duration of the effects? What did those effects, i.e. was it gas, or the neurological, you know, childhood, behavioural. And then I just try and map it out. Then you go on to the next one. What was the next environmental reaction which your child had? And then you just slowly build up a picture of the person, and then I go through the artificial chemicals and colours, additives and preservatives as well as the natural colours, flavours, preservatives, like salicylates. And then, I go through the family history as well, that's very important. I look for genetic predisposition and for chemical sensitivity. If they are salicylate-sensitive, they'll usually have a reaction to other chemicals, to artificial colours, flavours, additives. And the typical child, you know, the blond-haired, blue-eyed freckly, or red head,...If you see someone like that and they're of Scottish origin and they've got behavioural problems, that's the first thing I go to.

Table B4. *Patients with environmental sensitivities have unique phenotypes, are complex to treat, rarely regain full health and are becoming more prevalent*

Key challenges	Clinician	Quotes
Attitude towards patients with environmental sensitivities	OEPs	We (OEPs) don't deal with the long-term… because this is what normal life is. None of these very, molecular or unseen chemical injuries are being monitored, because that's still really research. There often is a lot of worry and psychological overlay with all of these cases, as they've been hunting around for months to find out what's wrong with them. You have to be a little bit careful in this area otherwise you can get a [bad] reputation. You need to be a little bit cautious that you stick with science as much as possible. But there are a lot of areas where the science isn't that great. Dose-response relationships are important. Whether there's a plausible biological mechanism that can explain the mechanism from the exposure... It's important not to create alarm. I've seen a few multiple chemical sensitivity cases and you know most people write them off, but I tend to feel that there's something going on there. There may be a psychological overlay; I don't deny that, but there's often a triggering event. There's only a few of us that drifted more towards a better understanding of patients holistically.
	IPs	The canaries are the ones that are set up early on in life to have more difficulty dealing with the environment, because in terms of liver and cellular detox, they're not that well-equipped for the environment. So, in terms of the bell-shaped curve, they're at one end. And then the rest of us are in the rest of the bell-shaped. And then there's the bulldozer, these guys go through life, and they smoke and drink and they spray everything, and you have to run them over at ninety. Could it be overexposure therefore causation because the dosage was high enough, or could it be failure of elimination, because in the genetic diversity of the human race, some people are just crappy at clearing drugs, pills, potions and pesticides out of their system.

Key challenges	Clinician	Quotes
		As you go through life, many things you'll get over. But other things are there as a toxic record, if you like. Toxic Load. So, it's kind of the building blocks. And you get to a point, where it takes just a small event, whether it's a viral infection, or some other toxic event, that pushes them through their ability to compensate and then they can go off in various directions, whether it's chronic fatigue, autoimmune disease, degenerative disease, cancer, they are just options thereafter.
Observations of patients with environmental sensitivities	IP	I didn't think see those allergies ten years ago.
		The whole ADHD has been kind of like a tsunami in the making in recent times.
		The increased number of people with mould-related illness… I do see more of what I now appreciate biotoxin exposures, rather than all pesticides, poisons, and other types of toxins.
		They've become a lot more difficult; more chronic illness, more environmental intolerances, more food intolerances and allergies, persistent sleep disturbances, more chemical sensitivity… a rise of auto-immune diseases.
		The biggest thing that has changed is the degree of education. The patients are much more aware and now they are far more likely to seek advice and tend to come earlier.
		Thankfully patients are getting more informed about ideas and will often come in, rather than I've got something terrible happening and I've got no idea what it's about, they will often be saying, I've got some terrible problems and I'm wondering about this, that and the other.
	OEP	Greater awareness of the population generally...I think GPs are becoming more aware of things like MCS and fibromyalgia… and for which patients were often rubbished thirty years ago.
Observations of phenotypes of patients with	OEP	The majority of people with Multiple Chemical Sensitivity have got some sort of an allergic, or highly reactive predisposition.
		It’s not so much how much toxin they've been exposed to; it's the individual response to that which becomes important.

Key challenges	Clinician	Quotes
environmental sensitivities		One-fifth of the population who are already predisposed, develop this neuropathic pain, for which they have become a hypervigilant responder. They will give you a history of childhood asthma, maybe long-standing hayfever, working out in the farm areas with their exposures there.
		A lot of these people have an allergic background, and I think that shows that they're at risk to (environmental) sensitisation.
	IP	These patients are extraordinarily sensory-sensitive in every way… they tend to be artistic, highly creative, able to read another person, very sensitive to another person's emotions. When I go on their history, sometimes it's he was a normal kid, but he was very, very sensitive to whatever things are around.
		The blond-haired, blue-eyed freckly, or red-haired child of Scottish or Irish descent whose got behavioural problems are much more prone to salicylate sensitivity. And usually, if they are salicylate-sensitive, they'll usually have a reaction to other chemicals, to artificial colours, flavours, and additives.
		People of Scottish-Irish descent are much more sensitive to gluten than other people.
		The Irish for celiac disease, the Chinese for lactose intolerance is quite common.
		These are the individuals who come in wearing white gloves and masks over their face. They're all very, very detailed-minded, perfectionists in their views on life.
		Sensitivity to smells and sensitivity to sound, to all of the senses, out of a group has an extraordinary advantage: that you hear the tiger, you know the poison in the plum, you become, effectively, the early warning radar. Their hypersensitivity might be a bit over the top, but it keeps them out of harm's way at a much higher rate than others... this may explain why the cancer rate in my patients is almost zero.
Observations of genotypes of patients with	IP	Some people are just crappy at clearing drugs, pills, potions, and pesticides out of their system. And those who have it remain for a long period of time, may have vulnerabilities.

Key challenges	Clinician	Quotes
environmental sensitivities		People with the HLA DRB-1 and the HLA-DQ test do put them into a category that makes perfect sense about why the person reacted (to biotoxins in a water-damaged building).
		I have a sense that neurological sensitivity and methylation disorders and hypersensitivity to toxins, are different aspects of the very same thing, of the very heightened response of the central nervous system to particular inputs.
		A reaction to chemicals implies they have some sort of genetic defect in their Phase II detoxification pathways.
		The canaries are the ones that are set up early on in life to have more difficulty dealing with the environment, because in terms of liver and cellular detox, they're not that well-equipped for the environment. So, in terms of the bell-shaped curve, they're at one end. And then the rest of us are in the rest of the bell-shaped. And then there's the bulldozer, these guys go through life and they smoke and drink and they spray everything and you have to run them over at ninety.
Difficulties treating environmental sensitivities	IP	The more symptoms and systems involved and the more chronic the illness, the more challenging it is especially people with multiple chemical sensitivity, because then they have difficulty tolerating the treatment as well.
		Complicated chronic fatigue together with chemical sensitivity, pain, and persistent sleep disorders… and severe neuroimmune dysfunctions. Those are the hardest to treat.
		Very few people that I see get cured for Chronic Fatigue Syndrome … maybe 90% or more of the Chronic Fatigue Syndrome and chemically sensitive people, never go back to the level of health that you would expect from a fit and healthy person of their age, but they adapt well and are able to go back to life and do things with the knowledge of their limitations.
		Autism is clearly the hardest of the neurodevelopmental problems, complex neurodevelopmental disorders.
		Older severely autistic are the most challenging and also the severely allergic, especially with anaphylactic type reactions.

Key challenges	Clinician	Quotes
		Epilepsy, that's probably the most difficult one.
		I've got a patient today with high bisphenol and phthalate levels. What do you do about it, besides stopping the exposure? So then, the question is, when they've got all these things and they've stopped the exposure and they are still very sick people, how do you go about dealing with that?

Table B5. *Educational and clinical resources are lacking*

Resources	Clinician	Quotes
Education process	IPs	Difficult education process, everyone develops in their own way.
		There is no one single organisation I think of as the best. And that's why I go around to lots of different organisations and learn from all different sources.
		The resources just cover fragments and they specialise in one area. I find it very hard to find one organisation who does the whole picture. You have to put the fragments together.
AFOEM training	OEPs	My college has been very slow at developing the Environmental Medical side but they’re working on it, but we're not getting there fast.
		Recently admitted fellows would not have very much training in chemical exposures, even at workplaces.
		The newer fellows (OEPs) really don't know where to submit samples to for analysis.
ACNEM training	IPs	Good introductory course.
		Limited in their scope.
		We need a lot more in-depth teaching.
		It is probably the most comprehensive program at the moment [in Australia], but compared to what you can learn from abroad, from the States, it's not as comprehensive.
Journals	OEP	Many of the things that come up as an expert witness in court, require me to do quite a bit of research with Dr Google and the online journals.
	IP	I haven't found any [journals] that are very useful. I usually do searches and just try and pick up general articles when I am researching a particular topic.
Textbooks	IPs	I'm not aware of a really good environmental health textbook. Is there one?

Resources	Clinician	Quotes
		I've got toxicology textbooks, but they tend to be far more involved with acute toxicity, rather than chronic, often low-level toxicity… a lot of what I think we see, is to do with the latter.
Peers	IPs	80% of what I learn, comes from a colleague emailing me, or passing on a paper from some source and then I go and read it and move on from the references there.
		I went to the Australian Society of Environmental Medicine annual meeting now disbanded. About fifty to sixty other doctors would gather and talk and get lectured to and then go out and try to apply that elsewhere. So, the education was primarily through that group.
Patients	OEPs	Now I just learn from each case that I see. I still have a long way to go. There aren't a lot of experts in this area.
		I teach general practitioners to listen much more to the patient, rather than get into your standard position of physical medicine.
	IP	I have my little army of a few thousand chemically sensitive, chemically poisoned, affected people. And I'm forever getting notices and emails, Did you see that? Here's the biomarkers of chemical sensitivity, Here's what organochlorines do. There's the glyphosate paper.

Table B6. *Websites used as a resource by clinicians on environmental medicine*

Organisation	**Website URL**	**Number of mentions**
Environmental Working Group (USA) and their database Skin Deep	http://www.ewg.org/ http://www.ewg.org/skindeep/	X 3 (IP)
Surviving Mould (USA)	https://www.survivingmould.com/	X 3 (IP)
Autism Research Institute (USA)	https://www.autism.com/	X 2 (IP)
Environmental Health News Above the Fold (daily news feeds) (USA)	http://www.environmentalhealthnews.org/	X 1 (IP)
U.S. Environmental Protection Agency	https://www.epa.gov/	X 1 (OEP) X 1 (IP)
Agency for Toxic Substances and Disease Registry (USA)	https://www.atsdr.cdc.gov /	X 1 (OEP)
REACH (Registration, Evaluation, Authorisation, and restriction of Chemicals) (Europe)	http://ec.europa.eu/environment/chemicals/reach/reach_en.htm https://echa.europa.eu/regulations/reach	X 1 (OEP)
Harvard (T.H. Chan) School of Public Health	https://www.hsph.harvard.edu/	X 1 (Paed)
U.S. National Library of Medicine	https://www.nlm.nih.gov/	X 1 (OEP)
UK Health and Safety Executive	http://www.hse.gov.uk/	X 1 (OEP)

Organisation	Website URL	Number of mentions
International Program on Chemical Safety. Environmental Health Criteria Monographs.	http://www.inchem.org/pages/ehc	X 1 (OEP)
International Labor Organisation	http://www.ilo.org/global/lang--en/index.htm	X 1 (OEP)
Public Health England (UK)	https://www.gov.uk/government/organisations/public-health-england	X 1 (OEP
EnHealth (Australia)	http://www.eh.org.au/resources/knowledge-centre/enhealth-national-documents	X 1 (OEP)
Safe Work Australia	http://www.safeworkaustralia.gov.au/sites/SWA	X 1 (OEP)
National Industrial Chemicals, Notification & Assessment Scheme (Australia)	https://www.nicnas.gov.au/	X 1 (OEP)
US National Institute of Occupational Safety and Health (USA)	https://www.cdc.gov/niosh/about/default.html	X 1 (OEP)
Occupational Safety and Health Administration (USA)	https://www.osha.gov/	X 1 (OEP)
Friends of the Earth	http://www.foe.org/	X 1 (IP)

Table B7. *Books on environmental medicine*

Title	Author	Year	Number of mentions
Healthy Home Healthy Family	Nicole Bijlsma	2018	X 3 (IPs)
Chemical sensitivity. Volume 4.	William Rea	1998	X 2 (IPs)
Surviving mould	Ritchie Shoemaker	2010	X 2 (IPs)
Environmental disasters. A chronicle of individual, industrial and governmental carelessness.	Lee Davis	1998	X 1 (OEP)
Occupational medicine	Carl Zenz	1994	X 1 (OEP)
Four volume encyclopedia of occupational health and safety.	International Labor Organisation (ILO)		X 1 (OEP)
Hunter's diseases of occupations (10th ed)	Peter Baxter and Tar-Ching Aw	2010	X 1 (OEP
Toxic metals and antidotes. The chelation therapy handbook. (2nd ed)	E. Blaurock Busch. MTM Publishing.	2012	X 1 (IP)
Clinical metal toxicology (12th ed)	Prof Peter van der Schaar	2015	X 1 (IP)
Casarett & Doull's Toxicology. The basic science of poisons. (8th ed).	Curtis Klaassen		X 1 (IP)
Textbook of functional medicine	The Institute for Functional Medicine	2010	X 1 (IP)
Textbook of natural medicine (4th ed)	Joseph Pizzorno and Michael Murray	2012	X 1 (IP)
Detox or die	Sherry Roger	2002	X 1 (IP)

Appendix E: Ethics Approval

RMIT University

Science Engineering and Health College Human Ethics Advisory Network (CHEAN)
Plenty Road
Bundoora VIC 3083
PO Box 71
Bundoora VIC 3083
Australia
Tel. +61 3 9925 7096
Fax +61 3 9925 6506
• www.rmit.edu.au

27th July 2015

Marc Cohen
Building 202 Level 4, Room 16
School of Health Sciences
RMIT University

Dear Marc

BSEHAPP 25-15 COHEN-BIJLSMA Environmental Chemical Assessment in Clinical Practice

Thank you for submitting your amended application for review.

I am pleased to inform you that the CHEAN has approved your application for a period of **18 Months** from the date of this letter to **27th January 2017** and your research may now proceed.

The CHEAN would like to remind you that:

All data should be stored on University Network systems. These systems provide high levels of manageable security and data integrity, can provide secure remote access, are backed up on a regular basis and can provide Disaster Recover processes should a large scale incident occur. The use of portable devices such as CDs and memory sticks is valid for archiving; data transport where necessary and for some works in progress.
The authoritative copy of all current data should reside on appropriate network systems; and the Principal Investigator is responsible for the retention and storage of the original data pertaining to the project for a minimum period of five years.

Please Note: Annual reports are due on the anniversary of the commencement date for all research projects that have been approved by the CHEAN. Ongoing approval is conditional upon the submission of annual reports failure to provide an annual report may result in Ethics approval being withdrawn.

Final reports are due within six months of the project expiring or as soon as possible after your research project has concluded.

The annual/final reports forms can be found at:
www.rmit.edu.au/staff/research/human-research-ethics

Yours faithfully,

Dr Falk Scholer

Deputy Chair, Science Engineering & Health
College Human Ethics Advisory Network

Cc CHEAN Member: Margaret Lech School of Electrical & Computer Engineering
Student Investigator/s: Nicole Bijlsma s9711185 School of Health Sciences RMIT University
Other Investigator/s: Liza Oates School of Health Sciences RMIT University

RMIT UNIVERSITY

Human Research Ethics Committee (HREC)
Research and Innovation office
NH&MRC Code: EC00237

Notice of Approval

Date:	**24 January 2019**
Project number:	**21794**
Project title:	***An investigation of electromagnetic field exposure on sleep quality and cognitive function in healthy adults.***
Risk classification:	**More than low risk**
Chief investigator:	**Dr Russell Conduit**
Approval period:	From: **24 January 2019** To: **31 December 2020**

The above application has been approved by the RMIT University HREC as it meets the requirements of the *National statement on ethical conduct in human research* (NH&MRC, 2007).

The following documents have been reviewed and approved:

Title	Version	Date
21794 Conduit appn		3 January 2019
21794 Clinical trial protocol	V2	3 January 2019
21794 Recruitment advertisement		3 January 2019
Screening tool mechanism		3 January 2019
21794 PICF		24 January 2019
PIRS 20 Instrument		3 January 2019

The following documents have been noted:

Title	Date
ANZCTR Registration	3 January 2019
Actigraph feature	3 January 2019
Zmachine Patient Guide	3 January 2019

RMIT UNIVERSITY

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Terms of approval:

1. Responsibilities of chief investigator/principal investigator[4]
It is the responsibility of the above chief investigator to ensure that all other investigators and staff on a project are aware of the clinical protocol and terms of approval and to ensure that the project is conducted as approved by HREC. Approval is valid only whilst the chief investigator holds a position at RMIT University.

2. Amendments
Approval must be sought from HREC to amend any aspect of a project. To apply for ethics approval of an amendment use the Request for Amendment Form, available on the RMIT Human Research Ethics website and submitted to the HREC secretary. Amendments must not be implemented without first gaining approval from HREC.

3. Adverse events
You should notify the HREC immediately (within 24 hours) of any serious or unanticipated adverse effects of the research on participants, and unforeseen events that might affect the ethical acceptability of the project. This notification can be made via email: humanethics@rmit.edu.au Following notification, an Adverse Event Report will need to completed and submitted.

4. Annual reports
Continued approval of this project is dependent on the submission of an annual report. Annual reports must be submitted by the anniversary of approval (24 January 2019) of the project for each full year of the project. If the project is of less than 12 months duration then a final report only is required.

5. Final report
A final report must be provided within six months of the end of the project. HREC must be notified if the project is discontinued before the expected date of completion.

6. Monitoring
Projects may be subject to an audit or any other form of monitoring by the HREC at any time.

7. Retention and storage of data
The investigator is responsible for the storage and retention of original data according to the requirements of the *Australian code for the responsible conduct of research* (2018) and relevant RMIT policies, including those relating to Research Data Management and Information Management.

8. Special conditions of approval
Nil.

9. Other conditions of approval

I. The clinical trial must be conducted in a way that is consistent with National Statement and Good Clinical Practice Guidelines (GCPs). For information on GCPs in an Australian context please refer to *The Australian Clinical Trial Handbook: A simple, practical guide to the conduct of clinical trials to*

[4] The Chief Investigator, Co-ordinating Principal Investigator or Lead Investigator is the person with overall responsibility for the research project. For projects conducted at multiple sites, the Principal Investigator is the person with responsibility for managing the research project at each site.

Human Research Ethics Committee (HREC)
Research and Innovation office
NH&MRC Code: EC00237

International standards of Good Clinical Practice (GCP) in the Australian context

II. The chief investigator is required to register and maintain registration of this clinical trial on the Australian and New Zealand Clinical Trial Registry (ANZCTR): http://www.anzctr.org.au/ Clinical trials must be prospectively registered, that is before the first participant is recruited.

III. Where clinical trials use an unapproved therapeutic good they must be notified to the Therapeutic Goods Administration (TGA) via the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) scheme. Such notifications must be made subsequent to HREC approval and prior to the use of the goods, and via the RMIT account administered by Research Governance. Recruitment may not commence until the CTN or CTX has been notified to the TGA.

IV. A Clinical Trial Research Agreement (CTRA) is required for sponsored collaborative and/or multisite clinical research. A copy of the final CTRA must be provided to the HREC when it is available.

In any future correspondence please quote the project number and project title above.

Prof Stephen Bird

Chairperson

RMIT HREC

cc: Dr Peter Burke, HREC secretary

Dr Adrian Schembri, Associate Supervisor

Ms Nicole Bijlsma, Research Student

Register a trial

Acknowledgment | Step 1: Titles & IDs | Step 2: Health condition | Step 3: Intervention/exposure
Step 4: Outcomes | Step 5: Eligibility | Step 6: Study design | Step 7: Recruitment
Step 8: Funding & Sponsors | Step 9: Ethics & Summary | Step 10: Contacts | Step 11: Data sharing statement
Step 12: Summary Results | Review & Submit

Request number	376315
Current page	Review

VIEW TRIAL AT REGISTRATION

VIEW HISTORY

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SUBMIT

Registration number	ACTRN12621000213842
Ethics application status	Approved
Date submitted	1/12/2020
Date registered	3/03/2021
Date data sharing statement initially provided	3/03/2021
Date results information initially provided	3/03/2021
Type of registration	Retrospectively registered