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Public Comments on Developing an Unified Intercarrier Compensation: =====

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Organization Name: null

What concerns me about this is the eventual elimination of landlines.

I see the bit about elimination of identical coverage, which that may fall under, or other areas.

As one of an increasingly large part of the population that have strong emf reactions to wireless communications, i.e. cellphones, wifi, wimax, smart meters, I would like to see clear wording in here for the disabled population that would cause landlines for phone and internet to continue to be made available.

Without this, it will leave many, many of us w/o regular means of useable communication or internet access.

I hope this is seriously taken, as it may well be you or yours that is next in experiencing these problems.

Sincerely,
Robin Ashton

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Your plan to deprive us of land lines and leave us with only cell phones will result in the deaths and illness of millions of Americans. Truly such a plan smells of genocide.

CELL PHONES: Right now, the data shows a 500% rise in the rate of brain tumors, called gliomas, that no patient survives.

DISEASES: There is also a 360% rise in tumors of the eye nearest the ear used for the cell phone, and 26% rise in tumors on the hearing apparatus, and on salivary glands near the ear used for cell phones. This is all hitting the press now, but still in toned-down terms.

Although many studies are American funded and have American scientists, they are mostly being done in Europe and Canada to avoid exposure to Americans. It is like the Tobacco Industry all over again. There are 2000 journal published studies proving danger and the US Navy already performed 6000 studies when EMF was proposed as a method of mass destruction--only of humans--while retaining the infrastructure.

IF YOU TRY TO REMOVE LAND LINES, MANY WILL CONSIDER THAT AN ACT OF WAR TOWARDS THE AMERICAN PEOPLE.

Depriving us of land lines and causing the cancers and neurotoxic effects of low power electromagnetic radiation and microwave of the cell phones is a criminal activity and we will do everything in our power to stop this travesty.

Whatever corporate entity has entered into our government to foist this upon us must be revealed and expurgated.

The scientific community is well aware of not only cancers, but of the affects on hormones, cardiovascular function, the leakage of albumin from brain cells through the blood brain barrier, the sterility in men, the miscarriages in women--all caused by EMF.

There is no doubt in my mind and the mind of many educated persons that this is a plan to cause a massive depopulation and eventuate Big Brother in our lifetime. This

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is a bipartisan issue and will be fought by both parties, and by all generations.

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Preface

There is an old joke with a well-known punch line about a man who has just fallen from the 86th floor of the Empire State Building in New York. As he passes the 30th floor, he is heard saying to himself 'so far, so good'...

Most of us laugh because we know where the man is headed, and that he must know too. But, our laughter usually has a guilty edge. We know that many of us are guilty of occasionally displaying a 'so far, so good' attitude in our own lives. We think of the smoker who says that about the possibility of getting lung cancer or heart disease and who counts on beating the odds because he feels healthy at the moment. That smoker will not find out if he won the bet until many years later, and by then it is often too late. The 'so far, so good' attitude to health is so common that people even kid themselves about it. One smoker told me that smoking would only cut a few years off his life, and that he did not mind losing the last few years because they are usually not much fun anyway.

Unlike the optimist in the joke, whose end is virtually certain, many of us live like the smoker, playing the odds and reassuring ourselves 'so far, so good'. Diseases like cancer usually take many years to develop, and we try not to think how some of the things we do casually can affect the long-term odds by compromising the natural processes that protect us. We rely on our bodies to be strong and resilient all the time. Yet, we know there are limits to the body's natural ability to reverse damage to cells. We also know that there may be gaps in the ability of our genetic endowment to cope with damage. At some level, we all know it is just common sense to try to minimize damage to our bodies and maximize the ability to repair.

These opening paragraphs provide a quick introduction to the theme of this issue of Pathophysiology and a summary of the point of view of its authors. The public is currently interested in possible hazards from radio frequency (RF) due to cellphones, towers, WiFi, etc. The concern is certainly warranted, but we are surrounded by electromagnetic fields (EMFs) of many frequencies, and there are also significant biological effects and known risks from low frequency

EMF. The scientific problem is to determine the nature of EMF interaction with biological systems and develop ways of coping with harmful effects in all frequency ranges, as well as their cumulative effects. The practical problem is to minimize the harmful biological effects of all EMF.

The technical papers in this issue are devoted to an examination and an evaluation of evidence gathered by scientists regarding the effects of EMF, especially RF radiation, on living cells and on the health of human populations. The laboratory studies point to significant interactions of both power frequency and RF with cellular components, especially DNA. The epidemiological studies point to increased risk of developing certain cancers associated with long-term exposure to RF. Overall, the scientific evidence shows that the risk to health is significant, and that to deny it is like being in free-fall and thinking 'so far, so good'. We must recognize that there is a potential health problem, and that we must begin to deal with it responsibly as individuals and as a society.

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EMF effects on DNA

M. Blank and R. Goodman (USA): Electromagnetic Fields Stress Living Cells

Abbreviations: EMF, electromagnetic fields; Hz, hertz (cycles/s the unit of frequency); ELF, extremely low frequency ($3-3 \times 10^3$ Hz) power frequency is 50–60 Hz; RF, radio frequency (band width 3×10^3 to 3×10^{11} Hz); UHF, ultrahigh frequency band the RF sub-division used for cell phones (3×10^8 to 3×10^9 Hz).

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Special Issue on EMF

Bioelectromagnetics, the study of biological effects of electromagnetic fields (EMF), is an interdisciplinary science with a technical literature that is not easily accessible to the non-specialist. To increase access of the public to the technical literature and to the health implications of the scientific findings, the Bioinitiative Report was organized by an international group of scientists and published online at www.bioinitiative.org on August 31, 2007. The report has been widely read, and was cited in September 2008 by the European Parliament when it voted overwhelmingly that the current EMF safety standards were obsolete and needed to be reviewed.

This special issue of Pathophysiology includes scientific papers on the EMF issue by contributors to the Bioinitiative Report, as well as others, and is prepared for scientists who are not specialists in bioelectromagnetics. Each paper is independent and self-contained. To help the reader appreciate how the different subjects contribute to an understanding of the EMF issue, the papers are arranged in groups that emphasize key areas, and the role of science in analyzing the problem and evaluating possible solutions. The subject headings are:

- DNA to show biological effects at the sub-cellular level that occur at very low EMF thresholds and across frequency ranges of the EM spectrum. Interactions with DNA may account for many of the effects of EMF, and they raise the possibility that genetic damage due to EMF can lead to cancer.
- The Brain is exposed to radiation from mobile phone antennas, and laboratory studies show that the radiation causes leakage of the protective blood-brain barrier, as well as the death of neurons in the brain. Radiation emitted from base stations can affect all who are in the vicinity. Epidemiological studies have shown a relation between exposure to mobile phones, base-stations and the development of brain tumors. Some epidemiological studies have significant flaws in design, and the risk of brain cancer may be greater than reported in the published results.
- In addition to the risk of brain cancer, EMF in the environment may contribute to diseases like Alzheimer's dementia and breast cancer in humans, as well as reproductive and developmental effects in animals in the wild. EMF affect the biochemical pathways and immunological mechanisms that link the different organ systems in our bodies and those of animals. The human body can act as an antenna for RF signals, and a small percentage of the population appears to be so sensitive to EMF that it interferes with their daily lives. In addition to the growing presence of EMF signals in the environment, the complexity of the signals may be important in altering biological responses. These are among the many factors that must be considered in approaching EMF safety issues.
- Science as a guide to public policy

Four centuries ago, when Francis Bacon envisioned a course for modern science, he expressed the idea that *knowledge is power that should be applied for the benefit of mankind*. It is in keeping with that ethical standard that the final papers in this issue show how knowledge gained from scientific research can help solve problems arising from EMF in our environment. The first of these papers discusses the Precautionary Principle, its growing acceptance as a rational approach to environmental issues, and how past experience can help us deal with the EMF issue. The second paper, by the editors of the original BioInitiative Report, is an update on how best to deal with the challenge of EMF in the environment and, specifically, the problems accompanying wireless technologies. The last paper describes the most recent in a

series of petitions by scientists demanding that society use our knowledge to deal effectively with the EMF issue.

We trust that the reviews and original research papers will increase awareness of the growing impact of EMF in the environment, and the need for modern society to deal expeditiously with the potential health problems brought to light by EMF research.

Guest Editor

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22 January 2009

Late Lessons from Early Warnings: Towards realism and precaution with EMF?

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Abstract

The histories of some well-known public and environmental hazards, from the first scientifically based early warnings about potential harm, to the subsequent precautionary and preventive measures, have been reviewed by the European Environment Agency in their report "Late Lessons from Early Warnings: The Precautionary Principle 1896–2000". This paper summarises some of the definitional and other issues that arise from the report and subsequent debates, such as the contingent nature of knowledge; the definitions of precaution, prevention, risk, uncertainty, and ignorance; the use of different strengths of evidence for different purposes; the nature and main direction of the methodological and cultural biases within the environmental health sciences; the need for transparency in evaluating risks; and public participation in risk analysis. These issues are relevant to the risk assessment of electro-magnetic fields (EMF). Some implications of these issues and of the "late lessons" for the evaluation and reduction of risks from EMF are indicated.

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Keywords: Late lessons; EMF; Precautionary principle; Evaluating evidence

1. Introduction

The histories of fourteen well-known hazards and their harm, which include some chemicals: tributyl tin (TBT), benzene, polychlorinated biphenyls (PCBs), chlorinated fluorocarbons (CFCs), methyl tert butyl ether (MTBE), sulphur dioxide, (SO₂) and Great Lakes pollution; two pharmaceuticals (diethylstilboestrol (DES) and beef hormones); two physical agents (asbestos and medical X-rays); one pathogen (BSE); and fisheries, have been reviewed by the European Environment Agency [1]. The purpose of the review was to see how societies had used, or not, the available scientific information in order to avoid or reduce hazards and risks, and at what overall cost.

Twelve "Late Lessons" were drawn which attempted to synthesise the very different experiences from the case studies into generic knowledge that can help inform decision making on potential hazards from, for example, GMOs [2,3], nanotechnologies [4], mobile phones [5,6] and such

endocrine disrupting substances as phthalates, atrazine and bisphenol A [7–9]. These emerging issues are all cases for which the luxuries of hindsight are not yet available but where there is some plausible evidence of harm, and where exposures are widespread and generally rising.

The purpose of the twelve late lessons is to help societies to make the most of both past experience and current knowledge in order to anticipate and reduce the impact of future "surprises" from technologies, without stifling innovation.

The "late lessons" are reproduced in Box 1.

2. The early use of precaution

John Graham, who was senior science policy advisor to President Bush, is a critic of the precautionary principle, but has nevertheless noted that:

Precaution, whether or not described as a formal principle, has served mankind well in the past and the history of public health instructs us to keep the spirit of precaution alive and well [10].

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Box 1: "The EEA Twelve Late Lessons"**A. "Identify/Clarify the Framing and Assumptions"**

1. Manage "uncertainty" and "ignorance" as well as "risk".
2. Identify and reduce "blind spots" in the sciences used.
3. Assess and account for all pros and cons of action/inaction.
4. Analyse and evaluate alternative options to the agent/activity under scrutiny.
5. Take account of stakeholder values.
6. Avoid "paralysis by analysis" by acting to reduce hazards via the precautionary principle.

B. "Broaden Assessment Information"

7. Identify and reduce interdisciplinary obstacles to learning.
8. Identify and reduce institutional obstacles to learning.
9. Use "lay" and local as well as specialist knowledge.
10. Identify and anticipate "real world" conditions.
11. Ensure regulatory and informational independence.
12. Use more long-term (i.e. decades) monitoring and research.

Graham might have been thinking of the cholera episode of 1854 in Soho, when precaution did indeed serve the people of London well. Dr. John Snow, a well known but controversial London physician, was called in to investigate the cholera outbreak. He used the spirit of precaution to advise banning access to the polluted water of the Broad St. pump, which he suspected was the cause of a serious cholera outbreak. He based his recommendation partly on the evidence he had gathered from his comparative study of two South London populations, who were separately served by piped or well water; and partly on his innovative spatial epidemiological study of the Soho area which pointed to the Broad St. well as the source of water polluted by faeces. He considered this overall evidence was sufficiently strong to justify advising the precautionary action of removing the water pump handle, so that consumers would be forced to use less convenient but cleaner water supplies. His view was accepted by the local church authorities who administered the area.

We know now that Snow's conclusion was accurate. However, his views on cholera causation were not shared by the medical establishment of the day, the Royal College of Physicians and the London Board of Health, who had considered Snow's thesis and rejected it as 'untenable' and biologically

implausible [1]. They believed that cholera was caused by airborne, not water borne, pollution. Their scientific "certainty" was increasingly challenged by Snow and others until Koch in Germany finally isolated the cholera vibrio in 1883, thus removing the last remaining doubt about the veracity of Snow's water pollution hypothesis.

The Snow story illustrates many of the key elements of the PP issue that are relevant to today's health and environment controversies, viz conflicting expert advice; competing scientific paradigms; the strength of scientific evidence needed to justify action; the long time lag between *observing* compelling associations and *understanding* their mechanisms of action; and the pros and cons of being wrong in taking action to remove risks, compared to the pros and cons of inaction.

The histories of TBT, PCBs and the other cases in the EEA "Late Lessons" report provide further illustrations of these points.

3. On paradigms and mechanisms of action

Scientists can cling to their favourite paradigm for decades—as with supporters of the air pollution theory in the cholera example between 1854 and 1883, despite mounting evidence that they are likely to be wrong. This passion for the prevailing paradigm is not uncommon. Max Planck, the Nobel physicist noted darkly that old paradigms only really die out when their promoting professors also die: "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it" [11].

In similar vein, the IPPC has cautioned the scientific authors of its climate change assessment reports against:

a tendency for a group to converge on an expressed view and become over confident in it. Views and estimates can also become anchored on previous versions or values to a greater extent than is justified [12].

This "power of the prevailing paradigm" is relevant to the current controversy over mobile phones, where the dominant view of WHO, the EU, and many others is that EMF-RF (radio frequency) energy has to be sufficiently large to cause the heating of biological tissue if it is to cause significant harm [13–15]. The current ICNIRP guidelines for limiting unacceptable RF exposures are derived from this paradigm and are therefore:

based on short term, immediate health effects, such as stimulation of peripheral nerves . . . and elevated tissue temperatures [13].

This majority view is opposed by those who think that much lower levels of EMF have the potential to cause harm via their capacity to disturb cell signalling or stress response systems that use very small changes in electro-magnetic fields [16–19].

Is the EMF field witnessing one of those shifts in prevailing paradigms that Thomas Kuhn noted had characterised progress in many fields of science? [20]

It can be difficult to accept that something is happening if you do not understand how it can be happening. A major reason why some scientists hang on to their preferred paradigm when evidence against it is mounting is that they need not only to observe a strong association between a cause and an effect but also to understand the mechanisms of biological action that link them. However, this can take decades. From the association between exposure to water polluted with human faeces and cholera, observed by Snow in 1854, to Koch's discovery of the *mechanism of action*, took 30 years of further scientific inquiry.

Such a long time lag between acknowledging compelling associations and understanding their mechanisms of action is a common feature of scientific inquiry, as illustrated by many of the case studies in the EEA report. Biological and ecological understanding about exactly how these exposures caused harm is still absent, decades after the associations were accepted as sufficient to justify preventive actions.

With EMF, there is currently no *established* knowledge about the mechanisms of biological action that could explain the consistent associations between EMF-ELF (extremely low frequency) exposure from overhead electrical power lines and childhood leukaemia. However, there is some evidence of *plausible* biological mechanisms. These include hypotheses concerning "information physics" [21]; melatonin [22]; oxidative stress [19]; indirect effects via cancer promotion; and the radical pair mechanism, which according to the Swedish Radiation Protection Authority, is "*probably the most plausible hypothesised mechanism*" [23]. Some or all of the above mechanisms, possibly in combination with other stressors and genetic configurations, is likely to eventually provide mechanistic explanations for the observed biological effects of EMF-ELF.

Despite this lack of mechanistic knowledge, and a general lack of corroborating animal evidence, the International Agency for Research on Cancer (IARC-WHO) recognised ELF from such magnetic fields as possibly carcinogenic in 2002, based on more than 30 positive epidemiological studies which had been completed since the first "early warning" observation in 1979 [24]. Other scientists do not believe the association between ELF and childhood leukaemias, given the paucity of mechanistic knowledge. However, recent animal and human evidence seems to be filling some of this knowledge gap [25].

The ELF story has parallels with that concerning the ionising X-rays which were routinely given to pregnant women before the early warning of Alice Stewart in the 1950s. She had observed a twofold excess of childhood leukaemias in women given X-rays during pregnancy. Her findings were eventually accepted by the 1970s, despite the continuing absence of knowledge about mechanisms of action: and such routine X-ray exposures were then stopped [26].

The current situation with the EMF-RF exposures from mobile phones is characterised by some positive, yet generally inconsistent epidemiological evidence [27–29], by a general absence of animal evidence; and by little established knowledge of possible mechanisms of carcinogenic action.

The question therefore arises: should actions that seem likely to protect the health of the public have to wait for knowledge about mechanisms of action? The precautionary principle was designed to justify actions to protect the public and the environment in the absence of some significant knowledge, and could be used to justify exposure reductions to EMF, despite current gaps in knowledge.

Could the unfolding story of EMF be a repetition of these earlier histories of ionising radiation exposures where evidence of harm was only "established" some twenty or more years after the first early warning?

4. Early warnings

When dealing with newly emerging hazards it can be helpful to use historical examples to illustrate what a scientifically based early warning looks like. It is often difficult to properly recognise such warnings when they occur.

A good example is that provided by the UK Medical Research Council's Swann Committee in 1969. The Committee was asked to assess the evidence for risks of resistance to antibiotics in humans, following the prolonged ingestion of trace amounts of antibiotics arising from their use as growth promoters in animal feed [30]. They concluded that:

Despite the gaps in our knowledge ... we believe ... on the basis of evidence presented to us, that this assessment is a sufficiently sound basis for action ... The cry for more research should not be allowed to hold up our recommendations' ... 'sales/use of AFA should be strictly controlled via tight criteria, despite not knowing mechanisms of action, nor foreseeing all effects [31].

Despite the gaps in knowledge, the need for much more research, and considerable ignorance about the mechanisms of action, the available evidence was acknowledged by the Swann Committee as sufficient to justify the need for the authorities to restrict the possibility of public dietary exposures to antibiotics from animal growth promoters.

This early warning was initially heeded, but was then progressively ignored by the pharmaceutical companies and regulatory authorities, which wanted more scientific justification for restricting profitable anti-microbial growth promoters. However, the use of antibiotics as growth promoters was finally banned in the EU in 1999, following the lead of Sweden in 1985 [30].

Pfizer, the main supplier of such antibiotics in Europe, appealed against the European Commission decision to ban their product, pleading, *inter alia*, an insufficiency of scientific evidence. They lost the case at the European Court of Justice [32]. This case further clarified the appropriate use and

application of the precautionary principle in circumstances of scientific uncertainty and of widespread, if low, public exposures to a potentially very serious threat.

On EMF there has been a number of early warnings about potential risks at low levels of exposure, culminating in the Bioinitiative report of 2007 [33]. This prompted the EEA to also issue an “early warning”:

Appropriate, precautionary and proportionate actions taken now to avoid plausible and potentially serious threats to health from EMF are likely to be seen as prudent and wise from future perspectives [34].

It is possible that such early warnings, particularly on RF from mobile phones, issued by the EEA and others, will turn out to be incorrect. This will only be established with time, and the hindsight it brings. However, the EEA would rather be wrong in raising concerns that turn out not to be justified, than being wrong in not issuing an early warning if the potentially serious hazards from RF technology turn out to be real. Large numbers of people are potentially exposed to RF, particularly children who are generally more susceptible to the potential harm. Reducing RF exposures in response to a mistaken early warning is preferable to not reducing exposures to a hazard that turns out to be real, and largely irreversible. Moreover, encouraging such reduction could help to stimulate technical innovation.

5. The importance of timing

The issue of time is a critical issue for risk analysis and application of the precautionary principle.

For example, the time from the first scientifically based early warnings (1896 for medical X-rays, 1897 for benzene, 1898 for asbestos), to the time of policy action that effectively reduced damage, was often 30–100 years, during which exposure increased considerably (Table 1).

One consequence of such failures to act in good time (e.g. on CFCs or asbestos) is greater and irreversible damage over longer time periods. For example, extra natural radiation coming through the ozone hole will cause many tens of thousands of extra skin cancers in today's children but the cancers will only peak around the middle of this century because of the long latent period between exposure and effect. Over a decade's worth of extra skin cancers could have been avoided if action had been taken on the first early warning, (which was subsequently deemed robust enough to justify giving the Nobel prize for Chemistry to its authors), rather than on the discovery of the ozone hole itself. Other negative impacts from the damaged ozone hole include eye cataracts and reduced crop productivity.

Such long-term but foreseeable impacts raise liability and compensation issues, including appropriate discount rates (if any) on future costs and benefits. These issues, which involve value and equity choices, need also to be discussed by stake-

Table 1

Late Lessons chapter	Date of first Early Warning	Date of Effective risk reduction action	Years of substantial inaction
Fisheries: taking Stock	1376	1995–2008 “responsible” management: which is not very effective	Hundreds...
Radiation: Early Warnings, Late Effects	1896	1961–1996 UK etc., then EU laws	65
Benzene: occupational setting	1897	1978 Benzene voluntarily withdrawn from most consumer products, US	81
Asbestos: from “magic” to malevolent material	1898	1999 EU ban by 2005	101
PCBs and the Precautionary Principle	1899	1970–80s: EU and US restrictions; phase out by 2010	c. 100
Halocarbons, the ozone layer and the Precautionary Principle	1974	1887–2910 global ban on CFCs + other Ozone depleters	10–30
DES: long-term consequences of pre-natal exposure	1938	1971–1985 US, EU, global ban	30–50
Antimicrobials as growth promoters: resistance to common sense	1969	1999 EU ban	30
SO ₂ : from protection of human lungs to remote lake restoration	1952 (lung) 1968 (lakes)	1979–2001 increasing EU etc restrictions leading to c 90% reduction on 1975 levels by 2010	25–55
MTBE in petrol as a substitute for lead	1960 taste/odour/persistence in water	2000 undesirable in Denmark/California: permitted elsewhere	40+
Great Lakes contamination	1962/3	1970s DDT banned in N America & EU. 2000 debates continue about persistent health damaging pollution	10–7
TBT antifoulants: a tale of ships, snails and imposex	1976–81 French oysters collapse	1982–7 French, UK then NE Atlantic ban; 2008 global ban	5–30
Beef Hormones as growth promoters	1972/3 oestrogen effects on wildlife	1988 EU ban. US continues	16+
Mad cow disease-reassurances undermined precaution	1979–1986	1989 Partial; 1996 total ban	10–17

holder groups. Experience in the climate change field with these long-term issues [35] may be helpful for the EMF issue.

Timing is also a critical issue for the assessment of risks. Many agents seem to be most damaging during sensitive windows of biological opportunity, either at the foetal stage of development [36], or when the host is susceptible because of an immune response deficiency, or of impacts from other stressors.

Timing is relevant to several biological end points as indicated in a review of the evidence on endocrine disrupting substances:

the time of life when exposures take place may be critical in defining dose–response relationships of Endocrine disrupting substances for breast cancer as well as for other health effects [37].

Responding to these issues of timing involves using lower strengths of evidence to justify action at earlier times in the exposure history of the stressors that inflict damage during specific windows of vulnerability, such as during foetal or early childhood development [38]. The wide exposure of children to EMF brings the timing of actions to reduce exposures into critical focus.

6. Knowledge and ignorance, prevention and precaution

The Broad St. pump example, and the other case studies in the EEA report serve to illustrate the contingent nature of scientific knowledge. Today's scientific certainties can be tomorrow's mistakes, and today's research can both reduce and increase scientific uncertainties, as the boundaries of the "known" and the unknown expand (Fig. 1).

It is common to hear the call for "more research" to remove uncertainties before any actions are taken to reduce hazards. However, such further research may not only take many years but tomorrow's knowledge, in addition to removing some uncertainties, is likely to identify previously unknown

sources of both uncertainty and ignorance. These new uncertainties can then be used as reasons for continued inaction on hazard reduction: "paralysis by analysis".

Socrates observed some time ago:

I am the wisest man alive, for I know one thing, and that is that I know nothing [39].

Such an approach to knowledge encourages humility in scientists rather than the hubris demonstrated by those scientists who, for too many years, professed certainties about the absence of harm from X-rays, asbestos, CFCs etc. These "certainties" turned out to be misplaced as knowledge expanded [1].

Many great scientists since Socrates have also displayed much humility in the face of acknowledged ignorance. Isaac Newton provided an elegant illustration of this towards the end of his life of discoveries:

to myself I seem to have been only like a boy playing on the seashore, and diverting myself now and then, finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me [40].

This was an early lesson in humility that seems to have been lately forgotten by many of the scientists and politicians who deal with hazards to the public and environment.

The distinction between uncertainty and ignorance also has significant implications for risk analysis and management [41]. Uncertainties arise, inter alia, from the known gaps in knowledge, from imprecise exposure sampling and monitoring; and from the assumptions and simplifications of models used to describe complex reality. Scientists involved in regulatory risk assessments try to take account of some of these uncertainties by using arbitrary safety factors to arrive at "acceptable" exposure limits.

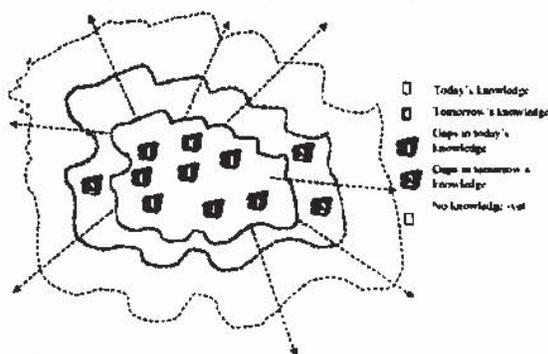
Acknowledging ignorance, however, involves acknowledging the unknown unknowns, as well as the sometimes unknowable unknowns that arise from complex and unpredictable biological and ecological systems and the random variations that are common to them [42,43]. It is obviously not possible to just use safety factors applied to "known" associations to account for such lack of knowledge.

States of ignorance are also the source of new scientific discoveries as well as of unpleasant "surprises" such as the mesothelioma cancer from asbestos, the hole in the ozone layer, or the reversed sexuality in the sea snails contaminated by the TBT biocide in marine anti-fouling paints [44].

Foreseeing and preventing hazards in the context of ignorance presents particular challenges to decision-makers. Ignorance ensures that there will always be surprises, and at first sight it looks impossible to do anything to avoid, or mitigate, them. However, there are some measures that could help minimise the consequences of ignorance and the impacts of surprises:

- using the intrinsic properties of potential stressors as generic predictors for unknown but possible impacts e.g.

*Knowing' and not knowing: A dynamic expansion.....



....and "complexity" increases.

Fig. 1. Knowing and not knowing both expand.

the persistence, bioaccumulation and spatial range potential of chemical substances [45];

- reducing specific exposures to potentially harmful agents on the basis of credible 'early warnings' of initial harmful impacts, thus limiting the size of any other 'surprise' impacts from the same agent, such as the asbestos cancers that followed asbestosis; and the PCB neurotoxicological effects that followed its wildlife impacts;
- promoting a diversity of robust and adaptable technological and social options to meet human needs, which then limits technological 'monopolies' (such as those of asbestos, CFCs, PCBs etc.), and therefore reduces the scale of any 'surprise' from any one technological option;
- accepting significant biological and ecological effects, such as inflammatory responses, or changing sex ratios, as sufficient evidence of potentially adverse effects to justify hazard reduction, without waiting for the adverse effects themselves to arrive;
- using more long-term research and monitoring of what appear to be "surprise sensitive sentinels", such as frogs, bees and foetuses, in order to identify "early warnings" earlier;
- using scenarios and stakeholder involvement to help foresee and anticipate implications of particular technological and social pathways.

Some of these approaches are relevant to EMF.

The distinction between *prevention* and *precaution* is also important. Preventing hazards from "known" risks is relatively easy and does not require precaution. Banning smoking, or asbestos, today requires only acts of *prevention* to avoid the well-known risks. However, it would have needed *precaution* (or foresight, based on a lower strength of evidence), to have justified exposure reductions to the then uncertain hazards of asbestos exposure in the 1930s–50s, or of tobacco smoke in the 1950s–60s.

Such precautionary acts then, if implemented successfully, would have saved many thousands of lives and, in the case of asbestos, stimulated innovation in the insulation and other asbestos using industries decades earlier than has been the case.

Similarly, it would need precaution to justify reducing exposures to an IARC category two carcinogen, such as EMF, but only prevention to avoid the cancer risk from a class one carcinogen, such as ionising radiations, where the evidence for action is very well established.

There has been much debate generated by the different meanings attached to these and other terms commonly used in debates on hazards, such as "prevention", "precaution", "risk", "uncertainty" and "ignorance". Table 2 attempts to clarify these definitions, using some of the "Late Lessons" case studies as illustrations.

There is also frequent confusion between the *strength of evidence* needed to justify any action to reduce risks, and the *type of action* deemed to be appropriate: the two are not directly connected. For example, there is very strong evi-

dence that cars harm people, but they are not banned from most places. In contrast, slight evidence of possible birth defects arising from taking a pregnancy pill would usually be sufficient to justify banning that pill.

7. The precautionary principle: some definitions and interpretations

The Vorsorgeprinzip, (the "precautionary", or "foresight") principle, only emerged as a specific policy tool during the German debates on the possible role of air pollution as a cause of "forest death" in the 1970–80s.

An increasing awareness of ecological complexity and uncertainty during the 1980–90s led to debates on the Vorsorgeprinzip shifting from Germany to the international level, initially in the field of nature conservation [46] but then particularly in marine pollution, where an overload of data accompanied an insufficiency of knowledge [47]. This absence of knowledge generated the need to act with precaution to reduce the large amounts of chemical pollution entering the North Sea.

Since then over 60 international treaties, including the Third North Sea Ministerial Conference, 1990, have included reference to the precautionary principle, or, as the Bush negotiators prefer to say, the precautionary approach. (A recent legal review points out that there is little, if any practical difference between these two concepts [48].)

The Treaty of the European Union cites the precautionary principle thus:

Community policy on the environment ... shall be based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should, as a priority, be rectified at the source, and the polluter should pay [49].

Although only cited in the environment part of the EU Treaty, the precautionary, prevention and polluter pays principles also apply to health and consumer affairs, as European Court of Justice decisions have made clear [50].

Unfortunately, these principles, as well as the important and legally required *proportionality principle*, which limits disproportion between the costs and benefits of precaution or prevention, are not defined in the EU Treaty. However, their usage has been clarified in over 100 court cases [48].

A definition of the precautionary principle that is often cited by supporters and detractors alike is that from the The North Sea Declaration, which calls for:

action to avoid potentially damaging impacts of substances, even where there is no scientific evidence to prove a causal link between emissions and effects (my emphasis).

Critics of the precautionary principle claim that this definition appears to justify action even when there is "no scientific evidence" that associates exposures with effects. However, the N. Sea Conference text clearly links the words "no scien-

Table 2
Towards a clarification of key terms.

Situation	State and dates of knowledge	Justification for action
• Risk	Known' impacts; 'known' probabilities e.g. asbestos 1999	<i>Prevention</i> : action taken to reduce known hazards e.g. eliminate exposure to asbestos dust
• Uncertainty	'Known' impacts; 'unknown' probabilities e.g. antibiotics in animal feed and associated human resistance to those antibiotics 1999	<i>Precautionary Prevention</i> : action taken to reduce exposure to plausible hazards e.g. ban antibiotic growth promoters
• Ignorance	'Unknown' impacts and therefore 'unknown' probabilities e.g. the 'surprise' ozone hole from (CFCs), pre-1974	<i>Precaution</i> : action taken to anticipate, identify and reduce the impact of 'surprises'

Source: Amended from the "Late Lessons" report, EEA 2001.

tific evidence" with the words "to prove a causal link" (my emphasis).

We have already seen with the Broad St. pump example that there is a significant difference between the evidence needed to show an "association" between a pollutant and its harm, and evidence which is robust enough to "prove" a causal link, which requires a very much higher strength of evidence. Bradford Hill pointed this out in his classic paper on association and causation in public health which he wrote at the height of the smoking controversy [51].

The N. Sea Declaration says that the absence of the strong evidence needed to support causality is not a valid reason for inaction where there is widespread and potentially hazardous exposures and some plausible evidence of potential harm.

Despite increasing use of the precaution principle there is still much disagreement and discussion about its practical application. This is particularly due to the absence of an EU definition in regulatory texts, and to disputes over the sufficiency of scientific evidence needed to justify public policy action.

For example, many "definitions" of the precautionary principle or approach in the 60 or so Treaties and Conventions that now include this concept use a triple negative: that is, they identify the *absence* of strong scientific evidence (e.g. of "full" certainty") as a reason that *cannot* be used to justify *not* acting. And they do not specify what a sufficiency of evidence would be that could justify taking action.

Some other widely cited definitions of the precautionary principle, notably the Wingspread and UNESCO definitions, are rather long, and include items that are not strictly part of a definition, such as the *process* by which decisions are taken (i.e. participatory, or not); and the allocation of the *burden of proof* to risk makers or risk takers: the latter is a separate issue that societies have dealt with without recourse to the precautionary principle.

For example, European and other societies have long placed the pre-market burden of establishing reasonable grounds for the safety of medicines, pesticides, nuclear plants and large construction projects on those who wish to provide such products or projects. Other potentially harmful agents, such as the 100,000 or so existing chemicals in consumer products, have been placed on the market without such pre-market burdens. Although pre-market testing or assessment is more precautionary than post market surveillance, it does not require justification from the precautionary principle.

There have been further definitions and clarifications of the precautionary principle from, for example from the EU Council of Ministers; in EU case law; and in the regulation establishing the new European Food Safety Authority, EFSA [52].

The judgement of the European Court of Justice in the BSE case illustrated a general definition which many authoritative commentators consider contains most of the necessary elements of the precautionary principle:

Where there is uncertainty as to the existence or extent of risks to human health, the institutions may take protective measures without having to wait until the reality and seriousness of those risks become fully apparent [53].

The WHO Declaration from the Fourth Ministerial Conference on Environment and Health [54] also refers to the precautionary principle. An explanatory background paper recommends that the principle:

should be applied where the possibility of serious or irreversible damage to health or the environment has been identified and where scientific evaluation, based on available data, proves inconclusive for assessing the existence of risk and its level but is deemed to be sufficient to warrant passing from inactivity to policy alternatives [55].

A recent report from the Health Council of the Netherlands on the precautionary principle provides a clear and cogent summary of the issues raised by its use [56].

However, there remains an absence of a clear definition at EU level so the European Environment Agency (EEA), in response to the debates on the precautionary principle since its 2001 report, has produced a working definition of the precautionary principle.

The Precautionary Principle provides justification for public policy actions in situations of scientific complexity, uncertainty and ignorance, where there may be a need to act in order to avoid, or reduce, potentially serious or irreversible threats to health or the environment, using an appropriate level of scientific evidence, and taking into account the pros and cons of action and inaction [8].

The definition is proving useful in promoting a shared understanding of the precautionary principle. It is explicit in specifying both uncertainty and ignorance as contexts for applying the principle; it is couched in the affirmative rather

than the negative; and it explicitly acknowledges that a case specific sufficiency of scientific evidence is needed to justify public policy actions, given the pros and cons of action or inaction.

The definition also explicitly widens the conventionally narrow, and usually quantifiable, interpretation of costs and benefits to embrace the wider and sometimes unquantifiable, “pros and cons”. Some of these wider issues, such as loss of public trust in science, are unquantifiable, but they can sometimes be more damaging to society than the quantifiable impacts: they therefore need to be included in any comprehensive risk assessment.

But what is “an appropriate strength of evidence” that would justify taking action under the precautionary principle to reduce exposures and risks?

8. Establishing evidence for action

All serious applications of the precautionary principle require some plausible evidence of an association between exposures and current, or potential, impacts.

For example, the Communication from the EU on the precautionary principle [57] specifies that “reasonable grounds for concern” are needed to justify action, but it does not say that these grounds will vary with the specifics of each case: nor does it explicitly distinguish between risk, uncertainty and ignorance.

The strength of scientific evidence that would be appropriate to justify public action clearly must vary with the pros and cons of being wrong with action or inaction in the specific circumstances of each case. These circumstances include the nature and distribution of potential harm; the justification for, and the benefits of the agent or activity under suspicion; the availability of feasible alternatives; and the overall goals of public policy. Such policy goals can include the achievement of the “high levels of protection” of public health, of consumer safety, and of the environment, required by the EU Treaty.

The use of different strengths of evidence for different purposes is not a new idea.

For example, a high strength of evidence such as “beyond all reasonable doubt” is used to achieve good science where A is generally accepted as causing B only when the evidence is very strong. Such a high level of proof is also used to minimise the costs of being wrong in the criminal trial of a suspected murderer, where it is usually regarded as better to let several guilty men go free, when reasonable doubt about their guilt cannot be eliminated, than it is to wrongly convict an innocent man.

However, in a different trial setting, where a citizen seeks compensation for harm that is possibly due to negligent treatment at work, the courts in many European and other societies will use a lower strength of evidence, commensurate with the costs of being wrong in this different situation. An already injured party is given the benefit of

the doubt by the use of a medium level of proof, such as “balance of evidence, or probability”. This is justified on the grounds that it is more acceptable to give compensation to someone who was *not* treated negligently than it is to *not* provide compensation to someone who was treated negligently. The “broad shoulders” of insurance companies are seen as able to bear the costs of mistaken judgements rather better than the much narrower shoulders of an injured citizen.

In each of these two illustrations it is the nature and distribution of the costs of being wrong that determines the strength of evidence that is “appropriate” to the particular case, based essentially on ethical grounds. The choice of an appropriate strength of evidence in each case is therefore a societal not a scientific issue.

This has long been recognised. Bradford Hill, cited above, drew attention to the social responsibility of scientists whose work involves public health. He concluded his classic 1965 paper on association and causation in environmental health with a “call for action” in which he also proposed case specific and differential strengths of evidence.

His three illustrative examples ranged from “relatively slight” to “very strong” evidence, depending on the nature of the potential impacts and of the pros and cons of being wrong. These varied between a possibly teratogenic medicine for pregnant women; a probable carcinogen in the workplace; and government restrictions on public smoking or diets [51].

In the field of cancer, the International Agency for Research on Cancer also uses several types of scientific evidence to categorise their strengths of evidence on carcinogens [58].

Identifying an appropriate strength of evidence has also been an important issue in the climate change debates. The International Panel on Climate Change (IPCC) discussed this issue at length before formulating their 1995 conclusion that “on the balance of evidence” mankind is disturbing the global climate. They further elaborated on this issue in their 2001 report where they identified seven strengths of evidence that can be used to characterise the scientific evidence for a particular climate change hypothesis. By 2007 the evidence for human induced climate change had strengthened to a “reasonable certainty” [59].

Table 3 provides the middle 5 of these strengths of evidence from the IPCC and illustrates their practical application to a variety of different societal purposes.

In the risk assessments of EMF published so far there has been little explicit discussion about the choice of the strength of evidence used in the assessments. The vague term “no established evidence” is often used to characterise the absence of some strength of evidence that would convince the particular scientists doing the risk assessment that a hazard existed. There is little if any discussion about for whom the evidence is said to be not established (risk takers or risk makers), nor about for what purpose (warning labels, or low cost exposure reductions, for example.).

Table 3
Different levels of proof for different purposes.

Different levels of proof for different purposes: some examples and illustrations			
Probability	Quantitative descriptor (Probability bands based on IPCC 2001)	Qualitative descriptor	Illustrations
100% probability	Very likely 90–99%	<ul style="list-style-type: none"> • “Statistical significance” • “Beyond all reasonable doubt” 	<ul style="list-style-type: none"> • Part of strong scientific evidence for “causation” • Most criminal law. And the Swedish Chemical law, 1973, for evidence of “safety” of substances under suspicion-burden of proof on manufacturers • Food Quality Protection Act, 1996 (US) • To justify a trade restriction designed to protect human, animal or plant health under World Trade Organisation Sanitary and Phytosanitary (SPS) Agreement, Art. 2.2, 1995
	Likely (66–90%)	<ul style="list-style-type: none"> • “Reasonable certainty” • “Sufficient scientific evidence” 	<ul style="list-style-type: none"> • Intergovernmental Panel on Climate Change 1995 & 2001 • Much Civil and some administrative law
	Medium Likelihood (33–66%)	<ul style="list-style-type: none"> • “Balance of evidence” • “Balance of probabilities” • “Reasonable grounds for concern” • “Strong possibility” 	<ul style="list-style-type: none"> • European Commission Communication on the Precautionary Principle 2000 • British Nuclear Fuels occupational radiation compensation scheme, 1984 (20–50% probabilities triggering different awards up to 50% + ; which then triggers full compensation)
	Low Likelihood (10–33%)	<ul style="list-style-type: none"> • “Scientific suspicion of risk” • “Available pertinent information” 	<ul style="list-style-type: none"> • Swedish Chemical law, 1973, for sufficient evidence to take precautionary action on potential harm from substances-burden of proof on regulators • To justify a provisional trade restriction under WTO SPS Agreement, Art. 5.7 where “scientific information is insufficient”
	Very Unlikely (1–10%)	<ul style="list-style-type: none"> • Low risk • “Negligible and insignificant” 	<ul style="list-style-type: none"> • Household fire insurance • Food Quality Protection Act, 1996 (US)

Source: EEA (2002).

An exception is the Californian EMF-ELF risk assessment which was much more transparent and explicit about these critical issues [60].

Establishing a sufficiency of evidence for whom, and for what purpose, involves value judgements: such issues therefore require public participation.

9. Public participation in risk analysis

Choosing an appropriate strength of evidence for a particular case is not a scientific issue but a social choice. It is therefore necessary to involve the public in decisions about serious hazards and their avoidance: and to do so for all stages of the risk analysis process, as recommended by several authoritative bodies during the last 10 years [61,62,63,64,56,65]. Three of the “twelve late lessons” of the EEA report (numbers 5, 9 and 10 in Box 1) also encourage the involvement of stakeholders at all stages of risk analysis.

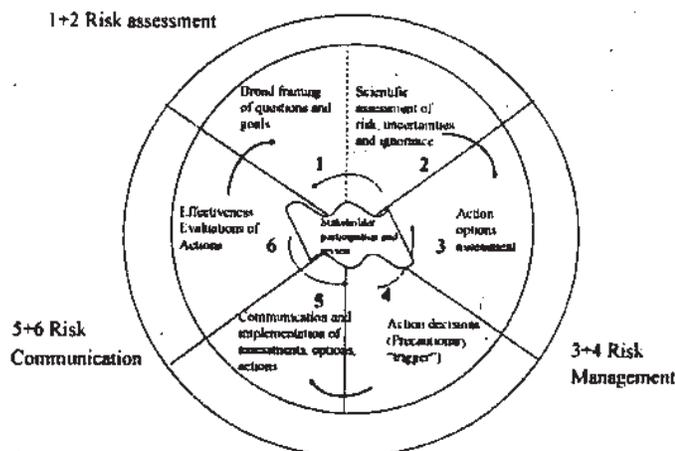
Fig. 2 based on the above reports, illustrates the iterative nature of risk assessment, risk management, and risk com-

munication; the links between them; and the involvement of stakeholders at every stage, albeit with different intensities.

The existing International and European arrangements for risk analysis, and for the setting of public exposure limits for EMF and other issues such as food [66], do not seem to reflect these recommendations for opening up the process of risk analysis, including risk assessment, to stakeholder participation. Instead they largely retain the older, linear approach where risk assessment is separated from risk management and communication and where communication is largely one way, i.e., from scientists to managers to the public.

The best available science is therefore a necessary but not a sufficient condition for sound public policy making on potential threats to health and the environment, such as from EMF. Where there is scientific uncertainty and ignorance “it is primarily the task of the risk managers to provide risk assessors with guidance on the science policy to apply in their risk assessments” [67]. The content of this science policy advice, as well as the nature and scope of the questions to be addressed by the risk assessors, need to be formulated by the

A Precautionary Framework for Risk Analysis.



Source: EEA, based on US Presidential Commission on Risk (1997), Royal Commission on Environmental Pollution (1988), Codex Alimentarius 07, IRC/ICCS 06, NAS 04

Fig. 2. A Precautionary risk analysis framework.

risk managers and relevant stakeholders at the initial stages of the risk analysis, as indicated in Fig. 2.

It is not easy to involve the public in all stages of risk analysis and in helping to set associated research agendas and technological trajectories [68,69]. However, there are some useful experiences, in both Europe and the USA, with focus groups, deliberative polling, citizens juries, and extended peer review, which are exploring appropriate ways forward [70,71].

The SAGE stakeholder process in the UK, which focused on ELF from power lines, provides a useful illustration of stakeholder engagement [72].

Public participation is particularly essential when future technological and social pathways, and associated hazards, are unpredictable: being wrong together is more socially robust than letting experts alone make the mistakes.

But why are there enough "mistakes", from delayed policy actions to prevent serious harm, to fill several volumes of Late Lessons reports?

10. False positives and false negatives

The fourteen case studies in the Late Lessons Report are all examples of "false negatives" in the sense that the agents or activities were regarded as not harmful for many years before evidence showed that they were harmful. Attempts were made to include a "false positive" case study in the report (i.e. where actions to reduce potential hazards turned out to be unnecessary), but neither authors nor sufficiently robust examples were found.

Providing evidence of "false positives" is more difficult than with "false negatives" [73]. For example, how robust, and over what periods of time, does the evidence on the absence of harm have to be before concluding, with con-

fidence, that a restricted substance or activity is without significant risk?

Volumes 2 of "Late Lessons", which the EEA will publish in 2009, will explore the issues raised by false positives, including lessons to be learned from such apparent false positives as the EU ban on food irradiation and the hazardous labelling of saccharin in the US [74].

But why are there so many "false negatives" that have been so damaging to health or environment? And how might this be relevant to EMF?

The first Late Lessons volume of case studies provided two main answers: the bias within the health and environmental sciences towards avoiding "false positives", which thereby generates more "false negatives"; and the dominance within societal decision-making of short term, specific, economic and political interests over the longer term, diffuse, and overall welfare interests of society. The latter point needs to be further explored, particularly by the political sciences: the current and increasing dominance of the short term in markets and in parliamentary democracies makes this an urgent issue.

Since the publication of "Late Lessons" the EEA has further explored the second cause of "false negatives" i.e. the issue of bias within the health and environmental sciences. Table 4 lists eighteen common features of methods and culture in the environmental and health sciences and shows their main directions of error. Most tend towards generating "false negatives".

Table 3 is derived from papers presented to a conference on the precautionary principle organised by the Collegium Ramazzini, the EEA, the WHO and NIEHS in 2002 [75]. It tries to communicate the main directions of the biases within the environmental and health sciences which decision makers and the public should be aware of as they debate the evidence on emerging hazards such as EMF.

Table 4
ON BEING WRONG: Environmental and health sciences and their main directions of error.

Scientific studies	Some methodological features	Main ^a directions of error-increases chances of detecting a:
Experimental Studies (Animal Laboratory)	<ul style="list-style-type: none"> • High doses • Short (in biological terms) range of doses • Low genetic variability • Few exposures to mixtures • Few Foetal-lifetime exposures • High fertility strains 	<ul style="list-style-type: none"> • False positive (negative for low dose effects) • False negative • False negative • False negative • False negative • False negative (developmental/reproductive endpoints)
Observational Studies (Wildlife & Humans)	<ul style="list-style-type: none"> • Confounders • Recall bias • Inappropriate controls • Non-differential exposure misclassification • Inadequate follow-up • Lost cases • Simple models that do not reflect complexity 	<ul style="list-style-type: none"> • False positive (negative with multi-causality?) • False positive • False positive/negative • False negative • False negative • False negative • False negative
Both Experimental and observational studies	<ul style="list-style-type: none"> • Publication bias towards positives • Scientific cultural pressure to avoid false positives • Low statistical power (e.g. From small studies) • Use of 5% probability level to minimise chances of false positives • Much scrutiny of positive studies cf. negative studies 	<ul style="list-style-type: none"> • False positive • False negative • False negative • False negative • False negative

^a Some features can go either way (e.g. inappropriate controls) but most of the features mainly err in the direction shown in the table.

11. Towards realism about complex reality

Max Planck observed that "reality is . . . just a very thin slice of that vast range of what our thoughts try to encompass" [76]. EMF scientists and risk assessors need not only to take account of the false negative/positive biases described above but they should also take more account of "that vast range" of other realities which characterise the EMF issue. These include multi-causality; thresholds; timing of dose; sensitive sub-populations; sex, age, genetics, and immune status of the host; cumulative exposures to EMF and other stressors; information physics; effects below the thresholds of such "acute" impact as tissue heating; non-linear dose-response relationships; "low dose" effects; the absence of unexposed controls; and the effects arising from disturbing the balance between opposing elements in complex biological systems, i.e. the "harmony of opposites" which Heraclitus noted many centuries ago.

In the EMF debate these complexities are often subsumed under many simplifying assumptions. For example, the WHO review of power line ELF states that:

Based on known physical principles and a simplistic biological model, many authors have argued that average magnetic fields of 0.3–0.4 micro tesla are orders of magnitude below levels that could interact with cells or tissues and that such interactions are thus biophysically implausible [77].

In the context of expanding scientific knowledge, the "implausibility" of biological interactions may not be a robust basis on which to dismiss positive epidemiological or experimental observations, especially when the biological models being used are "simplistic".

The case studies in the EEA report illustrate the surprises that arise from real life ecological and biological complexities and which may carry some lessons for the EMF debate. For

example, the unfolding of the TBT story was accompanied by an increased appreciation of scientific complexity. This arose from the discoveries that the known acute effects provided no indication of the chronic impacts that were caused by very low doses (i.e. in parts/trillion); that high exposure concentrations were found in unexpected places e.g. in the marine micro-layer; and that bioaccumulation in higher marine animals, including sea-food for human consumption, was much greater than expected. The early and prescient actions on TBT exposure reduction in France and the UK in 1982–85 were based only on a medium 'strength of evidence' for the 'association': evidence that was sufficient to infer 'causality', or to identify 'mechanisms of action' came much later.

We were lucky with TBT: a highly specific, initially uncommon impact (imposex) was quickly linked to one chemical, TBT. This is not likely to happen with the multi-causal and more common impacts such as neurodevelopmental diseases and dysfunctions, or cancers, which are the more complex impacts from EMF that are under suspicion.

Some key lessons from the DES story are also relevant to EMF exposures [78].

These include the realisation that the absence of visible and immediate teratogenic effects is not robust evidence for the absence of reproductive toxicity; and the timing of the dose clearly determined the poison, in contrast to the conventional dictum in toxicology, articulated by Paracelsus, that 'the dose determines the poison'.

DES is now a well-studied compound, with over 20,000 publications, yet many doubts persist about its mechanisms of action more than 30 years after it was banned on compelling observatory evidence that has since become more so. If we still have few biological certainties about DES after so much time and research, what should our attitude be towards relatively little understood hazards, such as other endocrine disrupting substances and EMF?

The scientists and risk assessors of EMF need not only to acknowledge the “surprises” that arise from complex realities but also the asymmetry of measurement precision between gene typing and environmental exposure assessment. As Vineis has observed, such asymmetry is likely to lead to an underestimation of the effects of environment and an overestimation of the effects of genes in the gene/environment interactions that are involved in most public health issues, including EMF [79].

The research implications arising from multi-causality, and from the systemic interactions between genes, host conditions and environmental stressors, seem not to have been fully recognised in the environmental and health sciences.

Sing has noted that:

neither genes nor their environments, but their interactions, are causations . . . pretending that the aetiology of common diseases like CHD, cancer, diabetes and psychiatric disorders are caused by the independent actions of multiple agents is deterring progress [80].

He went on to call for:

“research that reflects the reality of the problem” and notes that “a reductionist approach that has no interest in complexity discourages imaginative solutions . . . we need an academic environment that puts greater value on how the parts are put together”.

Such a systems approach to multiple and cumulative stressors seems to be largely absent from much research and risk assessment of EMF. Recent progress in dealing with cumulative stressors in the chemical field may be of use to EMF scientists [81].

12. Towards transparency in evaluating “weight of evidence”

Since 1965 overall evaluations of scientific evidence for policy making on health hazards has often, implicitly or explicitly, been based on the nine, “Bradford Hill Criteria”, which Bradford Hill actually called “features” of evidence [51]. These were produced in response to the smoking and health controversy of the 1960s.

One of the apparently more robust of the nine “criteria”, consistency of research results, which is a much discussed issue in the current EMF debate, may not be so robust in the context of multi-causality, complexity and gene/host variability.

Prof. Needleman, who provided the first of what could be called the second generation of early warnings on lead in petrol in 1979, has subsequently observed that:

Consistency in nature does not require that all or even a majority of studies find the same effect. If all studies of lead showed the same relationship between variables, one would be startled, perhaps justifiably suspicious [82].

It follows that the *presence* of consistency of results between studies on the same hazard can provide some of the robust evidence needed to establish a causal link, but the *absence* of such consistency may not provide very robust evidence for the absence of a real association. In other words, the “criterion” of consistency is asymmetrical, like most of the other Bradford Hill “criteria”.

This is relevant to the current position with EMF where consistent research results are not generally available. Such inconsistency is to be expected, particularly at this relatively early stage in the complex biological and physical story of EMF.

There is great scope for legitimate differences of view about this and other implications of the complexity, uncertainty and ignorance that characterise the EMF debate. Judgements need to be made, for example, about the weights to be placed on the presence or absence of features of the evidence, such as consistent research results, mechanisms of action, and animal evidence. There is therefore likely to be wide divergences of scientific opinions between different groups of scientists who evaluate the same stock of scientific knowledge during their risk assessments.

For example, in 2000, the UK National Radiological Protection Board set up the Stewart Committee to evaluate the evidence on mobile phones. It concluded that the evidence for safety was not great; that the evidence for harm was weak, but that this was to be expected at this early stage in the history of mobile phones; that the numbers of people, especially young people, exposed was widespread and rising; and that the precautionary principle was relevant, and justified the recommendation that mobile phones ought not be used by children under 16, except in emergencies [5].

During the same year, a radiation advisory Committee under the Dutch Health Council, comprising similarly qualified scientists, evaluated the same stock of knowledge and concluded that the evidence for safety was robust; that the evidence for harm to RF exposure was largely absent; that children were not more sensitive to RF exposures from mobile phones than adults; and that the precautionary principle was not relevant: no action on exposure reduction was therefore justified [83].

In order to tease out the different and largely hidden assumptions and inferential rules adopted by the two committees, the EEA organised a workshop in May 2008 at which representatives of the two committees explained how they came to such divergent opinions. They were joined by scientists who had produced different evaluations of essentially the same knowledge in three other case studies: ELF from power lines; the plastics chemical, bisphenyl A; and pesticides spray drift.

A brief report summarising the EEA workshop, and containing an eighteen-point checklist that identifies the main reasons for such divergences of view is now available [84].

There appears to be very few risk assessments of EMF that are transparent about how their largely implicit assumptions, judgements and rules of inference affected their conclusions.

An exception is the Californian Department of Health Services evaluation of the possible risks from ELF power line exposures [60]. This report was transparent about its graduated approach to strengths of evidence, about the weights that the individual scientist involved in the assessment placed on different types of evidence, and their types of argumentation and their rules of inference. The assessment was longer and more resource consuming than other EMF risk assessments but its transparency, and stakeholder involvement in agreeing the approach to evaluating the evidence, seems to have produced a more socially and scientifically robust assessment. The recent report from the US National Academy of Sciences on Risk Assessment strongly recommends such transparency and stakeholder involvement, especially at the crucial problem framing stage [65].

13. Conclusion

The successful application of available scientific knowledge and of the precautionary principle to public policy-making on health and environment involves several issues that have been identified in, or have arisen from, debates over some late lessons from early warnings that the EEA has identified. Such issues include the contingent nature of knowledge; approaches to uncertainty, ignorance and "surprises"; appropriate strengths of evidence for policy actions; the biases in the environmental health sciences; public participation in risk analysis and in choices over innovation pathways; and the need for more realism and transparency in the evaluation of evidence about complex ecological and biological realities.

These issues are particularly relevant to the potential hazards that are now emerging from, *inter alia*, nanotechnology, where scientific ignorance predominates [85]; from the non-ionising radiations arising from the use of mobile phones and power lines; and from endocrine disrupting substances. Such issues require new approaches that, *inter alia*, involve elements of what has been called post normal science [86].

The capacity of "homo sapiens" (who should perhaps be called, with less hubris, "homo stupidus" as few, if any other species, consciously destroy their habitats) to foresee and forestall disasters, appears to be limited, as the EEA reports on late lessons illustrate.

Societies could, however, with more humility in the face of uncertainty and ignorance, heed the late lessons and, aided by a wider, yet wise application of the precautionary principle, anticipate and minimise hazards. In so doing they would stimulate more participatory risk analysis and governance; the use of more realistic and transparent systems science; and the development of more socially robust and technologically diverse technological and social innovations.

Three main scenarios seem to face us with EMF, particularly with the RF from mobile phones. The first is similar to the case studies in the EEA reports on late lessons, where much avoidable harm was not prevented. The second is where

precautionary actions to reduce EMF exposures avert much potential harm, whilst stimulating more sustainable innovation in the production and use of mobile phone technologies and energy systems. And the third is where such precautionary actions to reduce exposures are taken but they turn out to have been unnecessary, if reasonable, given the state of knowledge today. The choice is ours: to act or not to act, as Shakespeare might have said.

Disclaimer

The views expressed are those of the author and do not represent the views of the EEA or its Management Board. The author has no competing financial interest in the matters dealt with.

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Electromagnetic fields stress living cells

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Abstract

Electromagnetic fields (EMF), in both ELF (extremely low frequency) and radio frequency (RF) ranges, activate the cellular stress response, a protective mechanism that induces the expression of stress response genes, e.g., HSP70, and increased levels of stress proteins, e.g., hsp70. The 20 different stress protein families are evolutionarily conserved and act as 'chaperones' in the cell when they 'help' repair and refold damaged proteins and transport them across cell membranes. Induction of the stress response involves activation of DNA, and despite the large difference in energy between ELF and RF, the same cellular pathways respond in both frequency ranges. Specific DNA sequences on the promoter of the HSP70 stress gene are responsive to EMF, and studies with model biochemical systems suggest that EMF could interact directly with electrons in DNA. While low energy EMF interacts with DNA to induce the stress response, increasing EMF energy in the RF range can lead to breaks in DNA strands. It is clear that in order to protect living cells, EMF safety limits must be changed from the current thermal standard, based on energy, to one based on biological responses that occur long before the threshold for thermal changes.

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Keywords: DNA; Biosynthesis; Electromagnetic fields; ELF; RF

1. Electromagnetic fields (EMF) alter protein synthesis

Until recently, genetic information stored in DNA was considered essentially invulnerable to change as it was passed on from parent to progeny. Mutations, such as those caused by cosmic radiation at the most energetic end of the EM spectrum, were thought to be relatively infrequent. The model of gene regulation was believed to be that the negatively charged DNA was tightly wrapped up in the nucleus with positively charged histones, and that most genes were 'turned off' most of the time. Of course, different regions of the DNA code are being read more or less all the time to replenish essential

proteins that have broken down and those needed during cell division.

New insights into the structure and function of DNA have resulted from numerous, well-done laboratory studies. The demonstration that EMF induces gene expression and the synthesis of specific proteins [1,2] generated considerable controversy from power companies, government agencies, physicists, and most recently, cell phone companies. Physicists have insisted that the reported results were not possible because there was not enough energy in the power frequency range (ELF) to activate DNA. They were thinking solely of mechanical interaction with a large molecule and not of the large hydration energy tied up in protein and DNA structures that could be released by small changes in charge [3]. Of the biologists who accepted such results [4], most thought that the EMF interaction originated at, and was amplified by, the cell membrane and not with DNA.

It is now generally accepted that weak EMF in the power frequency range can activate DNA to synthesize proteins. An EMF reactive sequence in the DNA has been identified [5] and shown to be transferable to other gene promoters [6]. This DNA sequence acts as an EMF sensitive antenna

Abbreviations: EMF, electromagnetic fields; Hz, hertz; ELF, extremely low frequency; RF, radio frequency; MAPK, mitogen activated protein kinase; ERK1/2, extracellular signal regulated kinase; JNK, c-Jun-terminal kinase p38MAPK; SAPK, stress activated protein kinase; NADH, nicotinamide adenine dinucleotide dehydrogenase; ROS, reactive oxygen species.

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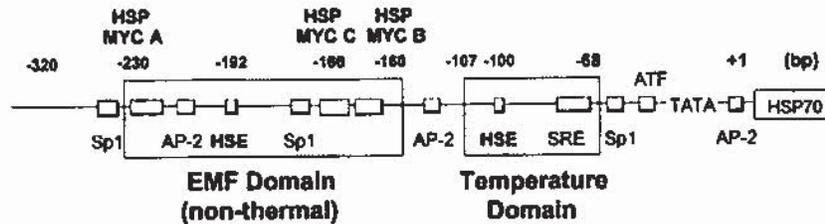


Fig. 1. Diagram of the HSP70 promoter showing the two different DNA sequences that have been identified as activated by EMF (non-thermal) and by thermal stimuli, respectively. The EMF domain contains three nCTCTn consensus sequences (electromagnetic response elements; EMRE), and differs from the consensus sequence (nGAAn) in the temperature or thermal domain.

that responds to EMF when transfected into reporter genes. Research at the more energetic levels of power frequency [7] and in the RF [8] ranges has shown that exposure to EMF can lead to breaks in the DNA strands. Therefore, DNA can no longer be considered unaffected by environmental EMF levels. It can be activated and damaged by EMF at levels that are considered safe [9]. The vulnerability of DNA to environmental influences and the possible dangers associated with EMF, had been underscored by discovery of EMF activation of the cellular stress response in the ELF range [10,11]. The cellular stress response is an unambiguous signal by the cell that EMF is potentially harmful.

2. Physiological stress and cellular stress

Discussions of physiological stress mechanisms usually describe responses of the body to pain, fear, 'oxygen debt' from muscle overexertion. These responses are mediated by organ systems. For example, the nervous system transmits action potentials along a network of nerves to cells, such as adrenal glands, that release rapidly acting agents such as epinephrine and norepinephrine and slower acting mineralocorticoids. These hormones are transported throughout the body by the circulatory system. They mobilize the defenses to cope with the adverse conditions and enable the body to 'fight or flee' from the noxious stimuli. The defensive actions include changes in heart rate, breathing rate, muscle activity, etc.

In addition to the responses of organ systems, there are protective mechanisms at the cellular level known as the cellular stress response. These mechanisms are activated by damage to cellular components such as DNA and protein [12], and the responses are characterized by increased levels of stress proteins [13] indicating that stress response genes have been upregulated in response to the stress.

The first stress response mechanism identified was the cellular reaction to sharp increases in temperature [14] and was referred to as 'heat shock', a term that is still retained in the nomenclature of the protective proteins, the hsps, heat shock proteins. Stress proteins are designated by the prefix 'hsp' followed by a number that gives the molecular weight in kilodaltons. There are about 20 different protein families ranging in molecular weight from a few kilodaltons to over

100 kD, with major groups of proteins around 30 kD, 70 kD and 90 kD.

Research on the 'heat shock' response has shown that hsp synthesis is activated by a variety of stresses that are potentially harmful to cells, including physical stimuli like pH and osmotic pressure changes, as well as chemicals such as alcohol and toxic metal ions like Cd^{2+} . EMF is a recent addition to the list of physical stimuli. It was initially shown in the power frequency (extremely low frequency, ELF) range [13], but shortly afterwards, radio frequency (RF) fields [15] and amplitude modulated RF fields [16] were shown to activate the same stress response.

Studies of stress protein stimulation by low frequency EMF have focused on a specific DNA sequence in the gene promoter that codes for hsp70, a major stress protein. Synthesis of this stress protein is initiated in a region of the promoter (see Fig. 1) where a transcription factor known as heat shock factor 1 (HSF-1) binds to a heat shock element (HSE). This EMF sensitive region on the HSP70 promoter is upstream from the thermal domain of the promoter and is not sensitive to increased temperature. The binding of HSF-1 to HSE occurs at -192 in the HSP70 promoter relative to the transcription initiation site. The EMF domain contains three nCTCTn myc-binding sites -230, -166 and -160 relative to the transcription initiation site and upstream of the binding sites for the heat shock (nGAAn) and serum responsive elements [5,6,17,18]. The electromagnetic response elements (EMREs) have also been identified on the c-myc promoter and are also responsive to EMF. The sensitivity of the DNA sequences, nCTCTn, to EMF exposures has been demonstrated by transfecting these sequences into CAT and Luciferase reporter genes [6]. Thus, the HSP70 promoter contains different DNA regions that are specifically sensitive to different stressors, thermal and non-thermal.

Induction of increased levels of the major stress protein, hsp70, by EMF is rapid, within 5 min. Also it occurs at extremely low levels of energy input, 14 orders of magnitude lower than with a thermal stimulus [10]. The far greater sensitivity to EMF than to temperature change in elevating the protective protein, hsp70, has been demonstrated to have potential clinical application, preventing injury from ischemia reperfusion [19–21]. George et al. [22] have shown the non-invasive use of EMF-induced stress proteins improved hemodynamic parameters during reperfusion

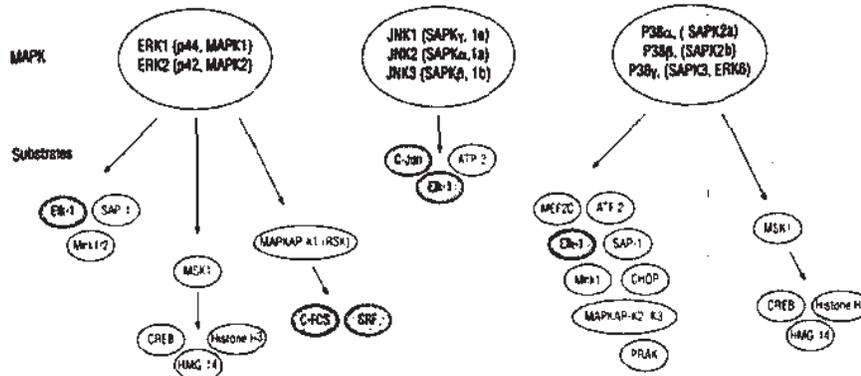


Fig. 2. The four mitogen activated protein kinase (MAPK) signaling cascades identified to date are: extracellular signal regulated kinase 1/2 (ERK), c-Jun-terminal kinase (JNK), p38MAPK and stress activated protein kinase (SAPK). Elements of the three MAPkinase pathways that have been identified as activated by EMF are shown as the shaded circles.

following ischemia. This effect occurred in the absence of measurable increased temperature.

3. EMF interaction with signaling pathways

EMF penetrate cells unattenuated and so can interact directly with the DNA in the cell nucleus, as well as other cell constituents. However, biological agents are impeded by membranes and require special mechanisms to gain access to the cell interior. Friedman et al. [23] have demonstrated that the initial step in transmitting extracellular information from the plasma membrane to the nucleus of the cell occurs when NADH oxidase rapidly generates reactive oxygen species (ROS). These ROS stimulate matrix metalloproteinases that allow them to cleave and release heparin binding epidermal growth factor. This secreted factor activates the epidermal growth receptor, which in turn activates the extracellular signal regulated kinase 1/2 (ERK) cascade. The ERK cascade is one of the four mitogen-activated protein kinase (MAPK) signaling cascades that regulate transcriptional activity in response to extracellular stimuli. The elements of the three

MAPK signaling cascades implicated in exposures to ELF and RF are highlighted in Fig. 2.

The four MAPK cascades are: (1) ERK, (2) c-Jun-terminal kinase (JNK), (3) stress activated protein kinase (SAPK) and (4) p38SAPK. Each of the cascades is composed of three to six tiers of protein kinases, and their signals are transmitted by sequential phosphorylation and activation of the protein kinases in each of the tiers. The result is activation of a large number of regulatory proteins, which include a set of transcription factors, e.g., c-Jun, c-Fos, hsp27 and hsp70. Activation of the stress response is accompanied by activation of specific signal transduction cascades involved in regulating cell proliferation, differentiation and metabolism [24–26]. The MAPK pathways have been characterized in several cell types [24,27–30]. Exposure to non-thermal ELF as well as thermal RF affects the expression of many cellular proteins [23–25] (Fig. 3).

The elevated expression of these protein transcription factors participate in the induction of various cellular processes, including several that are affected by cell phones, e.g., replication and cell-cycle progression [25,31] and apoptosis [32]. RF fields have been shown to activate specific transcription factor binding that stimulate cell proliferation and induce stress proteins [25,33]. It has been reported [31] that within 10 min of cell phone exposures, two MAPKinase cascades, p38 and ERK1/2, are activated. Both ELF and RF activate the upregulation of the HSP70 gene and induction of elevated levels of the hsp70 protein. This effect on RNA transcription and protein stability is controlled by specific protein transcription factors that are elements of the mitogen MAPK cascade.

EMF also stimulate serum response factor which binds to the serum response element (SRE) through ERK MAPK activation and is associated with injury and repair *in vivo* and *in vitro*. The SRE site is on the promoter of an early response gene, c-fos, which under specific cellular circumstances has oncogenic properties. The c-fos promoter is EMF-sensitive; a 20 min exposure to 60 Hz 80mG fields significantly increases c-fos gene expression [34]. The SRE accessory protein,

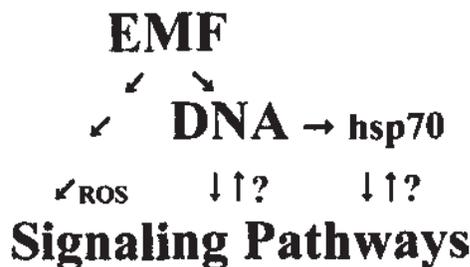


Fig. 3. The signaling pathways and the stress response are activated by EMF. The activation mechanisms discussed in the text are indicated by arrows. In the stress response, DNA activation leads to hsp synthesis and may be due to direct EMF interaction with DNA. The signaling pathways are activated by reactive oxygen species (ROS) that are probably generated by EMF. Possible interactions between the pathways, DNA and hsp are indicated with question marks. In any case, EMF leads to activation of all the processes shown.

Elk-1, contains a growth-regulated transcriptional activation domain. ERK phosphorylation potentiates Elk-1 and trans-activation at the *c-fos* SRE [29].

During the past twenty years, the growing use of cellular phones has aroused great concern regarding the health effects of exposure of the brain to 900 MHz RF waves. Despite claims that the energy level is too low to induce changes in DNA and that the devices are safe, the non-thermal effects that have been demonstrated at both ELF and RF exposure levels can cause physiological changes in cells and tissues even at the level of DNA. Finally, it should be mentioned that some of the pathways described in this section also have roles in protein synthesis via RNA polymerase III, an enzyme in oncogenic pathways [35] and could, therefore, provide a mechanistic link between cancer and EMF exposure.

4. Cells affected by the stress response

Reviews on EMF and the stress response have appeared for the ELF range [13] and for the RF range [36]. The most recent review was published online in section 7 of the Bioinitiative Report [9], and it summarized both ELF and RF studies, mainly at frequencies 50 Hz, 60 Hz, 900 MHz and 1.8 GHz. The citations in that review were not exhaustive, but the different frequencies and biological systems represent the diversity of results on stimulation of DNA and stress protein synthesis in many different cells. It is clear that the stress response does not occur in reaction to EMF in all types of cells, and sometimes because of the use of tissue cultured cell lines, even the same cell line can give opposite results in the same laboratory [37].

Many different types of cells have been shown to respond to EMF, both *in vivo* and *in vitro*, including epithelial, endothelial and epidermal cells, cardiac muscle cells, fibroblasts, yeast, *E. coli*, developing chick eggs, and dipteran cells (see Bioinitiative Report [9], section 7). Tissue cultured cells are less likely to show an effect of EMF, probably because immortalized cells have been changed significantly to enable them to live indefinitely in unnatural laboratory conditions. This may also be true of cancer cells, although some (e.g., MCF7 breast cancer cells) have responded to EMF [38,39], and in HL60 cells, one cell line responds to EMF while another does not [24]. Czyz et al. [16] found that p53-deficient embryonic stem cells showed an increased EMF response, but the wild type did not.

A broad study of genotoxic effects (i.e., DNA damage) in different kinds of cells [40] found no effects with lymphocytes, monocytes and skeletal muscle cells, but did find effects with fibroblasts, melanocytes and rat granulosa cells. Other studies [41,42] have also found that the blood elements, such as lymphocytes and monocytes are natural cells that have not responded. Since mobile cells can easily move away from a stress, there would be little selective advantage and evolutionary pressure for developing the stress response. The lack of response by skeletal muscle cells is related to the need

Table 1
Biological thresholds in the ELF range.

Biological system	Threshold (μT) ^a	Reference
Acceleration of reaction rates		
Na,K-ATPase	0.2–0.3	Blank and Soo [49]
cytochrome oxidase	0.5–0.6	Blank and Soo [43]
ornithine decarboxylase	~2	Mullins et al. [58]
malonic acid oxidation	<0.5	Blank and Soo [59]
Biosynthesis of stress proteins		
HL60, Sciarra, yeast,	<0.8	Goodman et al. [11]
breast (HTB124, MCF7)	<0.8	Lin et al. [39]
chick embryo (anoxia)	~2	DiCarlo et al. [60]
Breast cancer (MCF7) cell growth		
block melatonin inhibition	0.2 < 1.2	Liburdy et al. [38]
Leukemia epidemiology	0.3–4	Ahlbom et al. [61] Greenland et al. [62]

^a The estimated values are for departures from the baseline, although Mullins et al. (1999) and DiCarlo et al. (2000) generally give inflection points in the dose–response curves. The leukemia epidemiology values are not experimental and are listed for comparison.

to desensitize the cells to excessive heating during activity. Unlike slow muscle fibers that do synthesize hsp70, cells containing fast muscle fibers do not synthesize hsp70 to protect them from over-reacting to the high temperatures reached during activity.

5. EMF–DNA interaction mechanisms: electron transfer

The biochemical compounds in living cells are composed of charges and dipoles that can interact with electric and magnetic fields by various mechanisms. An example discussed earlier is the generation of reactive oxygen species (ROS) in activation of the ERK signaling cascade. The cellular stress response leading to the synthesis of stress proteins is also activated by EMF. However, the specific reaction is not known, except that it is stimulated by very weak EMF. For this reason, our focus has been on molecular processes that are most sensitive to EMF and that could cause the DNA to come apart to initiate biosynthesis. We have suggested that direct EMF interaction with electrons in DNA is likely for the following reasons:

- The largest effects of EMF would be expected on electrons because of their high charge to mass ratio. At the sub-atomic level, one assumes that electrons respond instantaneously compared to protons and heavier atomic nuclei, as in the Born-Oppenheimer Approximation. The very low field strengths and durations that activate the stress response and other reactions (Table 1) suggest interaction with electrons, and make ion-based mechanisms unlikely.
- Weak ELF fields have been shown to affect the rates of electron transfer reactions [43,44]. A 10 μT magnetic field exerts a very small force of only $\sim 10^{-20}$ N on a unit charge,

but this force can move an isolated electron more than a bond length, ~ 1 nm, in ~ 1 nanosecond.

- There is a specific EMF responsive DNA sequence that is associated with the response to EMF (Fig. 1), and that retains this property when transfected
- Displacement of electrons in DNA would cause local charging that has been shown to lead to disaggregation of biopolymers [45].
- As the energy in an EMF stimulus increases, there is an increase in single strand breaks, followed by double strand breaks, suggesting an interaction with EMF at all energy levels [46].

Effects of EMF on electrons in chemical reactions were detected indirectly in studies on the Na,K-ATPase [47], a ubiquitous enzyme that establishes the normal Na and K ion gradients across cell membranes. Electric and magnetic fields, each accelerated the reaction only when the enzyme was relatively inactive. It is reasonable to assume that the threshold response occurs when the same charge is affected by the two fields, so the velocity (v) of the charge (q) could be calculated from these measurements and its nature determined. Assuming both fields exert the same force at the threshold, the electric (E) and the magnetic (B) forces should be equal.

$$F = qE = qvB. \quad (1)$$

From this $v = E/B$, the ratio of the threshold fields, and by substituting the measured thresholds [48,49], $E = 5 \times 10^{-4}$ V/m and $B = 5 \times 10^{-7}$ T ($0.5 \mu\text{T}$), we obtain $v = 10^3$ m/s. This very rapid velocity, similar to that of electrons in DNA [50], indicated that electrons were probably involved in the ion transport mechanism of the Na,K-ATPase [47]. An electron moving at a velocity of 10^3 m/s crosses the enzyme ($\sim 10^{-8}$ m) before the ELF field has had a chance to change. This means that a low frequency sine wave signal is effectively a repeated DC pulse. This is true of all low frequency effects on fast moving electrons.

Studies of effects of EMF on electron transfer in cytochrome oxidase, ATP hydrolysis by the Na,K-ATPase, and the Belousov–Zhabotinski (BZ) redox reaction, have led to certain generalizations:

- EMF can accelerate reaction rates, including electron transfer rates
- EMF acts as a force that competes with the chemical forces in a reaction. The effect of EMF varies inversely with the intrinsic reaction rate, so EMF effects are only seen when intrinsic rates are low. (This is in keeping with the therapeutic efficacy of EMF on injured tissue, while there is usually little or no effect on normal tissue.)
- Experimentally determined thresholds are low ($\sim 0.5 \mu\text{T}$) and comparable to levels found by epidemiology. See Table 1.
- Effects vary with frequency, with different optima for the reactions studied: The two enzymes showed broad fre-

quency optima close to the reaction turnover numbers for Na,K-ATPase (60 Hz) and cytochrome oxidase (800 Hz), suggesting that EMF interacted optimally when in synchrony with the molecular kinetics. This is not true for EMF interactions with DNA, which are stimulated in both ELF and RF ranges and do not appear to involve electron transfer reactions with well-defined kinetics.

Probably the most convincing evidence for a frequency sensitive mechanism that involves stimulation of DNA is activation of protein synthesis in striated muscle. In this natural process, specific muscle proteins are synthesized by varying the rate of the (electrical) action potentials in the attached nerves [51]. The ionic currents of the action potentials that flow along and through the muscle membranes, also pass through the muscle cell nuclei that contain the DNA codes for the muscle proteins. Two frequencies were studied in muscle, high (100 Hz) and low (10 Hz) frequency, corresponding to the frequencies of the fast muscles and slow muscles that have different contraction rates and different muscle proteins. In the experiments, either the fast or slow muscle proteins were synthesized at the high or low frequency stimulation rates corresponding to the frequency of the action potentials. The clear dependence of the protein composition on the frequency of the action potentials indicates a relation between stimulation and activation of DNA in muscle physiology. The process is undoubtedly far more complicated and unlikely to be a simple electron transfer reaction as with cytochrome oxidase. It is more probable that an entire region of DNA coding for a group of related proteins is activated simultaneously.

A mechanism based on electron movement is in keeping with the mV/m electric field and μT magnetic field thresholds that affect the Na,K-ATPase. The very small force on a charge ($\sim 10^{-20}$ N) can affect an electron, but is unlikely to have a direct effect on much more massive ions and molecules, especially if they are hydrated. Ions are affected by the much larger DC electric fields of physiological membrane processes. The low EMF energy can move electrons, cause small changes in charge distribution and release the large hydration energy tied up in protein and DNA structures [3]. Electrons have been shown to move in DNA at great speed [50], and we have suggested that RF and ELF fields initiate the stress response by directly interacting and accelerating electrons moving within DNA [52,53].

A mechanism based on electron movement also provides insight into why the same stress response is stimulated by both ELF and RF even though the energies of the two stimuli differ by orders of magnitude. A typical ELF cycle at 10^2 Hz lasts 10^{-2} s and a typical RF cycle at 10^{11} Hz lasts 10^{-11} s. Because the energy is spread over a different number of cycles/second in the two ranges, the energy/cycle is the same in both ELF and RF ranges. Since electron movement occurs much faster than the change of field, both frequencies are seen by rapidly moving electrons as essentially DC pulses. Each cycle contributes to electron movement at both

frequencies, but more rapidly at the higher frequency. The fluctuation of protons between water molecules in solution at a frequency of about 10^{12} Hz [54] gives an indication of the speed of electron movement, and may suggest an upper limit of the frequency in which sine wave EMF act as DC pulses.

6. DNA biology and the EM spectrum

Research on DNA and the stress response has shown that the same biology occurs across divisions of the EM spectrum, and that EMF safety standards based on cellular measures of potential harm should be much stricter. These data also raise questions about the utility of spectrum sub-divisions as the basis for properly assessing biological effects and setting separate safety standards for the different sub-divisions. The frequencies of the EM spectrum form a continuum, and division into frequency bands is only a convenience that makes it easier to assign and regulate different portions of the spectrum for practical uses, such as the different design requirements of devices for EMF generation and measurement. Except for the special case of the visual range, the frequency bands are not based on biology, and the separate bands now appear to be a poor way of dealing with biological responses needed for evaluating safety. The DNA studies indicate the need for an EMF safety standard rooted in biology and a rational basis for assessing health implications.

DNA responses to EMF can be used to create a single scale for evaluation of EMF dose because:

- The same biological responses are stimulated in ELF and RF ranges.
- The intensity of EMF interactions with DNA leads to greater effects on DNA as the energy increases with frequency. In the ELF range, the DNA is only activated to initiate protein synthesis, while single and double strand breaks occur in the more energetic RF and ionizing ranges.

A scale based on DNA biology also makes possible an approach to a quantitative relation between EMF dose and disease. This can be done by utilizing the data banks that have been kept for A-bomb exposure and victims of nuclear accidents, data that link exposure to ionizing radiation and subsequent development of cancer. Utilizing experimental studies of DNA breaks with ionizing radiation, it is possible in principle to relate cancer incidence to EMF exposures. It should be possible to determine single and double strand breaks in a standard preparation of DNA, caused by exposure to EMF for a specified duration, under standard conditions. Although many studies of DNA damage and repair rates under different conditions would be needed, this appears to be a possible experimental approach to assessing the relation between EMF exposure and disease.

7. The stress response and safety standards

Most scientists believe that basic research eventually pays off in practical ways. This has certainly been true of EMF research on the stress response, where EMF stimulated stress proteins have been used to minimize damage to ischemic tissues on reperfusion. However, more importantly, biological effects stimulated by both ELF and RF have shown that the standards used for developing safety guidelines are not protective of cells.

First and foremost, it is important to realize that the stress response occurs in reaction to a potentially harmful environmental influence. The stress response is an unambiguous indication that cells react to EMF as potentially harmful. It is therefore an indication of compromised cell safety, given by the cell, in the language of the cell. The low threshold level of the stress response shows that the current safety standards are much too high to be considered safe.

In general, cellular processes are unusually sensitive to fields in the environment. The biological thresholds in the ELF range (Table 1) are in the range of 0.5–1.0 μ T—not very much higher than the ELF backgrounds of ~ 0.1 μ T. The relatively low field strengths that can affect biochemical reactions is a further indication that cells are able to sense potential danger long before there is an increase in temperature.

EMF research has also shown that exposure durations do not have to be prolonged to have an effect. Litovitz et al. [55,56], working with the enzyme ornithine decarboxylase, showed an EMF response when cells were exposed for only 10 s to ELF or ELF modulated 915 MHz, providing that the exposure was continuous. Gaps in the sine wave resulted in a reduced response, and interference with the sine wave in the form of superimposed ELF noise also reduced the response [57]. The interfering effect of noise has been shown in the RF range by Lai and Singh [46], who reported that noise interferes with the ability of an RF signal to cause breaks in DNA strands. The decreased effect when noise is added to a signal is yet another indication that EMF energy is not the critical factor in causing a response. In fact, EMF noise appears to offer a technology for mitigating potentially harmful effects of EMF in the environment.

EMF research has shown that the thermal standard used by agencies to measure safety is at best incomplete, and in reality not protective of potentially harmful non-thermal fields. Non-thermal ELF mechanisms are as effective as thermal RF mechanisms in stimulating the stress response and other protective mechanisms. The current safety standard based on thermal response is fundamentally flawed, and not protective.

Finally, since both ELF and RF activate the same biology, simultaneous exposure to both is probably additive and total EMF exposure is important. Safety standards must consider total EMF exposure and not separate standards for ELF and RF ranges.

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Electromagnetic fields and DNA damage

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Abstract

A major concern of the adverse effects of exposure to non-ionizing electromagnetic field (EMF) is cancer induction. Since the majority of cancers are initiated by damage to a cell's genome, studies have been carried out to investigate the effects of electromagnetic fields on DNA and chromosomal structure. Additionally, DNA damage can lead to changes in cellular functions and cell death. Single cell gel electrophoresis, also known as the 'comet assay', has been widely used in EMF research to determine DNA damage, reflected as single-strand breaks, double-strand breaks, and crosslinks. Studies have also been carried out to investigate chromosomal conformational changes and micronucleus formation in cells after exposure to EMF. This review describes the comet assay and its utility to qualitatively and quantitatively assess DNA damage, reviews studies that have investigated DNA strand breaks and other changes in DNA structure, and then discusses important lessons learned from our work in this area.

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1. The comet assay for measurement of DNA strand breaks

DNA is continuously damaged by endogenous and exogenous factors and then repaired by DNA repair enzymes. Any imbalance in damage and repair and mistakes in repair result in accumulation of DNA damage. Eventually, this will lead to cell death, aging, or cancer. There are several types of DNA lesions. The common ones that can be detected easily are DNA strand breaks and DNA crosslinks. Strand breaks in DNA are produced by endogenous factors, such as free radicals generated by mitochondrial respiration and metabolism, and by exogenous agents, including UV, ionizing and non-ionizing radiation, and chemicals.

There are two types of DNA strand breaks: single- and double-strand breaks. DNA single-strand breaks include frank breaks and alkali labile sites, such as base modification, deamination, depurination, and alkylation. These are the most commonly assessed lesions of DNA. DNA double-strand breaks are very critical for cells and usually they are

lethal. DNA strand breaks have been correlated with cell death [1–5], aging [6–8] and cancer [9–13].

Several techniques have been developed to analyze single- and double-strand breaks. Most commonly used is micro-gel electrophoresis, also called the 'comet assay' or 'single cell gel electrophoresis'. This technique involves mixing cells with agarose, making microgels on a microscope slide, lysing cells in the microgels with salts and detergents, removing proteins from DNA by using proteinase K, unwinding/equilibrating and electrophoresing DNA (under highly alkaline condition for assessment of single-strand breaks or under neutral condition for assessment of DNA double-strand breaks), fixing the DNA, visualizing the DNA with a fluorescent dye, and then analyzing migration patterns of DNA from individual cells with an image analysis system.

The comet assay is a very sensitive method of detecting single- and double-strand breaks if specific criteria are met. Critical criteria include the following. Cells from tissue culture or laboratory animals should be handled with care to minimize DNA damage, for instance, by avoiding light and high temperature. When working with animals exposed to EMF *in vivo*, it is better to anesthetize the animals with CO₂ before harvesting tissues for assay. Antioxidants

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such as albumin and sucrose, or spin-trap molecules such as α -phenyl-*tert*-butyl nitron (PBN), should be added during dispersion of tissues into single cells. Cells should be lysed at 0–4 °C to minimize DNA damage by endonucleases. Additionally, antioxidants such as tris and glutathione, and chelators such as EDTA, should be used in the lysing solution. High concentrations of dimethylsulfoxide (DMSO) should be avoided due to its chromatin condensing effect. Treatment with proteinase K (PK; lyophilized DNase-free proteinase-K from Amresco is ideal) at a concentration of 0.5–1 mg/ml (depending upon cell type and number of cells in the microgel) should be used for 1–2 h at 37 °C to reveal all possible strand breaks which otherwise may go undetected due to DNA–protein crosslinks. Longer times in PK will lead to loss of smaller pieces of DNA by diffusion. Glass slides should be chosen based on which high resolution agarose (3:1 high resolution agarose from Amresco is ideal) will stick well to the slide and on the ability of the specimen to be visualized without excessive fluorescence background. Choice of an electrophoresis unit is important to minimize slide-to-slide variation in DNA migration pattern. A unit with uniform electric field and buffer recirculation should be used. Electrophoresis buffers should have antioxidants and chelators such as DMSO and EDTA. DNA diffusion should be minimized during the neutralization step by rapidly precipitating the DNA. Staining should employ a sensitive fluorescent dye, such as the intercalating fluorescent labeling dye YOYO-1. A cell-selection criteria for analysis should be set before the experiment, such as not analyzing cells with too much damage, although, the number of such cells should be recorded.

There are different versions of the comet assay that have been modified to meet the needs of specific applications and to improve sensitivity. Using the most basic form of the assay, one should be able to detect DNA strand breaks in human lymphocytes that were induced by 5 rad of gamma-ray [14,15].

2. Radiofrequency radiation (RFR) and DNA damage

In a series of publications, Lai and Singh [16–19] reported increases in single- and double-strand DNA breaks, as measured by the comet assay, in brain cells of rats exposed for 2 h to a 2450-MHz RFR at whole body specific absorption rate (SAR) between 0.6 and 1.2 W/kg. The effects were blocked by antioxidants, which suggested involvement of free radicals. At the same time, Sarkar et al. [20] exposed mice to 2450-MHz microwaves at a power density of 1 mW/cm² for 2 h/day over a period of 120, 150, and 200 days. Rearrangement of DNA segments were observed in testis and brain of exposed animals. Their data also suggested breakage of DNA strands after RFR exposure. Phillips et al. [21] were the first to study the effects of two forms of cell cellular phone signals, known as TDMA and iDEN, on DNA damage in Molt-4 human lymphoblastoid cells using the comet

assay. These cells were exposed to relatively low intensities of the fields (2.4–26 μ W/g) for 2–21 h. They reported both increased and decreased DNA damage, depending on the type of signal studied, as well as the intensity and duration of exposure. They speculated that the fields may affect DNA repair in cells. Subsequently, different groups of researchers have also reported DNA damage in various types of cells after exposure to cell phone frequency fields. Diem et al. [22] exposed human fibroblasts and rat granulosa cells to cell phone signal (1800 MHz; SAR 1.2 or 2 W/kg; different modulations; for 4, 16 and 24 h; intermittent 5 min on/10 min off or continuous). RFR exposure induced DNA single- and double-strand breaks as measured by the comet assay. Effects occurred after 16 h of exposure to different cell phone modulations in both cell types. The intermittent exposure schedule caused a significantly stronger effect than continuous exposure. Gandhi and Anita [23] reported increases in DNA strand breaks and micronucleation in lymphocytes obtained from cell phone users. Markova et al. [24] reported that GSM signals affected chromatin conformation and γ -H2AX foci that co-localized in distinct foci with DNA double-strand breaks in human lymphocytes. The effect was found to be dependent on carrier frequency. Nikolova et al. [25] reported a low and transient increase in DNA double-strand breaks in mouse embryonic stem cells after acute exposure to a 1.7-GHz field. Lixia et al. [26] reported an increase in DNA damage in human lens epithelial cells at 0 and 30 min after 2 h of exposure to a 1.8-GHz field at 3 W/kg. Sun et al. [27] reported an increase in DNA single-strand breaks in human lens epithelial cells after 2 h of exposure to a 1.8-GHz field at SARs of 3 and 4 W/kg. DNA damage caused by the field at 4 W/kg was irreversible. Zhang et al. [28] reported that an 1800-MHz field at 3.0 W/kg induced DNA damage in Chinese hamster lung cells after 24 h of exposure. Aitken et al. [29] exposed mice to a 900-MHz RFR at a SAR of 0.09 W/kg for 7 days at 12 h per day. DNA damage in caudal epididymal spermatozoa was assessed by quantitative PCR (QPCR) as well as by alkaline and pulsed-field gel electrophoresis. Gel electrophoresis revealed no significant change in single- or double-strand breaks in spermatozoa. However, QPCR revealed statistically significant damage to both the mitochondrial genome and the nuclear β -globin locus. Changes in sperm cell genome after exposure to 2450-MHz microwaves have also been reported previously by Sarkar et al. [20]. Related to this are several publications that have reported decreased motility and changes in morphology in isolated sperm cells exposed to cell phone radiation [30], sperm cells from animals exposed to cell phone radiation [31], and cell phone users [32–34]. Some of these *in vivo* effects could be caused by hormonal changes [35,36].

There also are studies reporting no significant effect of cell phone RFR exposure on DNA damage. After RFR-induced DNA damage was reported by Lai and Singh [16] using 2450-MHz microwaves and after the report of Phillips et al. [21] on cell phone radiation was published, Motorola funded a series of studies by Roti Roti and colleagues [37] at

Washington University to investigate DNA strand breaks in cells and animals exposed to RFR. None of the studies reported by this group found significant effects of RFR exposure on DNA damage [38–40]. However, a different version of the comet assay was used in these studies. More recently, four additional studies from the Roti-Roti laboratories also reported no significant effects on DNA damage in cells exposed to RFR. Li et al. [41] reported no significant change in DNA strand breaks in murine C3H10T1/2 fibroblasts after 2 h of exposure to 847.74- and 835.02-MHz fields at 3–5 W/kg. Hook et al. [42] showed that a 24-h exposure of Molt-4 cells to CDMA, FDMA, iDEN or TDMA-modulated RFR did not significantly alter the level of DNA damage. Lagroye et al. [43,44] also reported no significant change in DNA strand breaks, protein–DNA crosslinks, and DNA–DNA crosslinks in cells exposed to 2450-MHz RFR.

From other laboratories, Vijayalaxmi et al. [45] reported no increase in DNA strand breaks in human lymphocytes exposed *in vitro* to 2450-MHz RFR at 2.135 W/kg for 2 h. Tice et al. [46] measured DNA single-strand breaks in human leukocytes using the comet assay after exposure to various forms of cell phone signals. Cells were exposed for 3 or 24 h at average SARs of 1.0–10.0 W/kg. Exposure for either 3 or 24 h did not induce a significant increase in DNA damage in leukocytes. McNamee et al. [47–49] found no significant increase in DNA breaks and micronucleus formation in human leukocytes exposed for 2 h to a 1.9-GHz field at SAR up to 10 W/kg. Zeni et al. [50] reported that a 2-h exposure to 900-MHz GSM signal at 0.3 and 1 W/kg did not significantly affect levels of DNA strand breaks in human leukocytes. Sakuma et al. [51] exposed human glioblastoma A172 cells and normal human IMR-90 fibroblasts from fetal lungs to cell phone radiation for 2 and 24 h. No significant changes in DNA strand breaks were observed up to a SAR of 800 mW/kg. Stronati et al. [52] showed that 24 h of exposure to 935-MHz GSM basic signal at 1 or 2 W/kg did not cause DNA strand breaks in human blood cells. Verschaevae et al. [53] reported that long-term exposure (2 h/day, 5 days/week for 2 years) of rats to 900-MHz GSM signal at 0.3 and 0.9 W/kg did not significantly affect levels of DNA strand breaks in cells.

3. Extremely low frequency electromagnetic fields (ELF EMF) and DNA damage

To complete the picture, a few words on the effects of ELF EMF are required, since cell phones also emit these fields and they are another common form of non-ionizing EMF in our environment. Quite a number of studies have indicated that exposure to ELF EMF could lead to DNA damage [54–69]. In addition, two studies [70,71] have reported effects of ELF fields on DNA repair mechanisms. Free radicals and interaction with transitional metals (e.g., iron) [60,62,63,69] have also been implicated to play a role in the genotoxic effects observed after exposure to these fields.

4. Some considerations on the effects of EMF on DNA

From this brief literature survey, no consistent pattern of RFR exposure inducing changes in or damage to DNA in cells and organisms emerges. However, one can conclude that under certain conditions of exposure, RFR is genotoxic. Data available are mainly applicable only to radiation exposure that would be typical during cell phone use. Other than the study of Phillips et al. [21], there is no indication that RFR at levels that one can experience in the vicinity of base stations and RF-transmission towers could cause DNA damage.

Differences in experimental outcomes are expected since many factors could influence the outcome of experiments in EMF research. Any effect of EMF has to depend on the energy absorbed by a biological organism and on how the energy is delivered in space and time. Frequency, intensity, exposure duration, and the number of exposure episodes can affect the response, and these factors can interact with each other to produce different effects. In addition, in order to understand the biological consequence of EMF exposure, one must know whether the effect is cumulative, whether compensatory responses result, and when homeostasis will break down. The contributions of these factors have been discussed in a talk given by one of us (HL) in Vienna, Austria in 1998 [72].

Radiation from cell phone transmission has very complex patterns, and signals vary with the type of transmission. Moreover, the technology is constantly changing. Research results from one type of transmission pattern may not be applicable to other types. Thus, differences in outcomes of the research on genotoxic effects of RFR could be explained by the many different exposure conditions used in the studies. An example is the study of Phillips et al. [21], which demonstrated that different cell phone signals could cause different effects on DNA (i.e., an increase in strand breaks after exposure to one type of signal and a decrease with another). This is further complicated by the fact that some of the studies listed above used poor exposure procedures with very limited documentation of exposure parameters, e.g., using an actual cell phone to expose cells and animals, thus rendering the data from these experiments as questionable.

Another source of influence on experimental outcome is the cell or organism studied. Many different biological systems were used in the genotoxicity studies. Different cell types [73] and organisms [74,75] may not all respond similarly to EMF.

Comment about the comet assay also is required, since it was used in many of the EMF studies to determine DNA damage. Different versions of the assay have been developed. These versions have different detection sensitivities and can be used to measure different aspects of DNA strand breaks. A comparison of data from experiments using different versions of the assay could be misleading. Another concern is that most of the comet assay studies were carried out by experimenters who had no prior experience with this technique and mistakes