Annex: ‘Non thermal effects and mechanisms of interaction between EMF and living matter: a selected Summary’


(A selected summary, supplemented by information from the ‘Late Lessons From Early Warnings’ EEA project, David Gee, EEA, Feb 18 2011)

This Monograph by the International Commission for Electromagnetic Safety (ICEMS) edited by Giuliani, from the Italian National Institute for Prevention & Safety at Work, and Soffritti, Director of the Cesare Maltoni Cancer Research Centre, Ramazzini Institute, Italy, includes 25 scientific papers in 400 pages and summarises evidence on the non thermal biological effects of EMF. (Page refs are to those in the monograph).

Non thermal effects defined therein are biological mechanisms that are not able to induce a temperature increase higher than 0.01 degrees C (living organism), 0.001 (cells) or 0.0005 (sub-cellular).

By comparison, ANSI, WHO, IEEE & ICNIRP consider that exposures below 0.05 degrees C (0.4 W/kg) are safe for workers, and exposures below 0.01 C (0.08 W/kg) are negligible for the public.

Any biological effects below these levels are considered by these organisations to have no biological significance and to be reversible. (px1)

There is some dispute about the concept of non-thermal effects that, inter alia, involves debates about the focus and nature of the temperature being debated. Guiliani maintains that as the scientific focus shifts from the independent particles of atomic physics to the dependent molecules and greater complexity of biophysics there is a need to see temperature as a feature of the system, not of its components. (p1x)

There a few key issues at the heart of the EMF controversy (both ELF from power lines etc. and the RF from mobile phones etc.).
This selected Summary is constructed around some of these main issues, viz:

- **Scientific paradigms and EMF**
- **Biological plausibility and coherence?**
- **Low dose effects and ‘windows of sensitivity’**
- **The importance of timing for some biological effects and policy actions**
- **Replicability and consistency of research results**
- **Children: more sensitive to EMF than adults?**
- **Cancer epidemiology**
- **Implications of biology for current safety guidelines and test methods**

1. **Scientific Paradigms and EMF**

The current conventional paradigm used by the main authorities on EMF (e.g. IEEE, ICNIRP, WHO, the EU Commission) is based essentially on the thermal effects of EMF. 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’.  

This in turn is based on classical engineering assumptions and theories arising originally from Faraday which assume that energy transfer in biological matter is based on ‘hopping’ along discrete energy levels.

However, this paradigm cannot explain observations such as, for example, ‘photosynthesis, where light absorbing molecules can funnel energy with a near unit quantum efficiency across mesoscopic distances’ (Guiliani, L. p x).

When observations can no longer be explained by existing paradigms, some scientists begin to question the conventional theories and begin the search for new explanations and theories which can better explain the new observations. (See the story of cholera in the London of 1854, which involved new observations about cholera being caused by water pollution rather then by air pollution, which was the dominant paradigm of the day. ‘Late Lessons from Early Warnings’, Introduction, EEA, 2001)

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1 ICNIRP, Guidelines for limiting exposures to time-varying electric, magnetic and electromagnetic fields (up to 300GHz), Health Physics, 74(1998) No. 494-522, p496
When there are no shared biological explanations and understanding about why some experimental observations happen, ‘the scientist faced with choosing between well replicated observations and contrary calculations based on existing theory must always opt for the former’. (Liboff, p. 66).

(This is analogous to the position of Galileo 400 hundred years ago when he published ‘The Starry Messenger’ which contradicted the conventional paradigm that the Earth was stationary and the sun moved round it. His subsequent lifelong house arrest by the Vatican was an extreme example of ‘shooting the messenger’. This has its current counterpart in personal attacks on some scientists who promote the non thermal, low level effects of EMF).

This ‘power of the prevailing paradigm’ means that conventional paradigms are, as is nearly always the case in science, defended vociferously.

Max Planck, the Nobel physicist, noted darkly\(^3\) 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.’)

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’\(^4\).

For example: Professor Ahlbom (Karolinska Institute) said, in 2001, that the asserted association between mobile phones and brain tumours is ‘biologically bizarre’\(^5\).

There are several emerging competing paradigms for the non thermal biological behaviour of EMF. They are based essentially on Quantum Electro-dynamics and informational physics. These more modern theories

\(^3\) M. Planck, Scientific Autobiography and other Papers, Philosophical Library, N York. (1949)
\(^4\) IPPC, Uncertainty Guidance note for authors of the Fourth Assessment report, Geneva. (2005))
are needed to help explain the observations, first made separately by Liboff and Blackman in 1985, that alternating and static magnetic fields can resonate with the cyclotron frequency of some metallic ions in biological tissue e.g. calcium, potassium, magnesium.

Zhadin, in the 90s, then found that these resonant effects of AC magnetic fields also occurred with solutions of alpha amino acids at exposure levels that were 1000 times lower than even the very low levels used by Liboff and Blackman i.e. around 40 nanotesla.

(The Bioelectromagnetics journal would not publish these remarkable results from Zhadin until some biologically plausible mechanism was proffered by him, which came 4 years later, in 1998, when they were published).

His results have since been independently replicated in 3 other laboratories. The results are consistent with the DC magnetic field sensitivities of birds, bees, bacteria, lobsters, sharks, termites, bats etc., which can be around levels of 10-100 nanotesla. (Liboff, p. 51)

2. Biological Plausibility and Coherence?

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 want 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.

Two of the nine widely used Bradford Hill ‘criteria’ for helping to move from association to causality are ‘biological plausibility’ and ‘coherence’ i.e. is the observational evidence compatible with the known science? (See table 1, page 16)

Bradford Hill began his classic 1965 article on causation in environmental health by asking how ‘the’ environmental feature seen to

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be associated with harm could be reliably identified as the cause of that harm.

‘With preventive medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A’.

He described nine characteristics (‘features’ or ‘viewpoints’) of scientific evidence that, if taken together, could help scientists to move with some confidence from association to causation.

It is clear the biological plausibility and coherence are dependent on the stock of current scientific knowledge, which is always vulnerable to advances in science. These two criteria do not therefore provide robust evidence for dismissing new evidence. If new evidence is compatible with known science then it can provide a more robust basis for accepting the evidence.

This illustrates the asymmetrical nature of all of the Bradford Hill ‘criteria’ i.e. if the criteria are present, from high quality studies, they can be a robust basis for accepting an observed association as real, but if absent they cannot necessarily be a robust basis for dismissing the association, especially in the context of meta causality and complexity. Bradford Hill pointed this out in 1965 but it is frequently forgotten by those who wish to dismiss early warnings by using the absence of the criteria as evidence of no association.

The possible biological explanation for the Zhadin results mentioned earlier was based on the idea that water (which makes up about 70% of the mass, and 99% of the molecules, of living matter) has two components, one ‘coherent’, the other ‘incoherent’ (with respect to molecular movements) and these differ both from each other and from water as a whole in terms of, for example, their viscosity and oscillation damping.

Living organisms are complex systems in which millions of molecular components interact with large amounts of water and display configurations that are quite different from the one assumed when they are isolated i.e. the systems have ‘emergent properties’ that arise only at the level of the system and which cannot be predicted from the individual parts.
Understanding the role of biomolecules in such biological systems can only begin when the two main matrices that determine their functions, water and electromagnetic fields, are taken fully into account, as Albert Szent-Gyorgyi pointed out in 1957.

‘Given the basically electromagnetic character of this organisation it is not surprising that living organisms are able to interact with external electromagnetic fields in a non thermal way’. (Del Guidice E. Guiliani L, p. 14)

‘Water performs important functions in determining the shape and function of proteins … (providing) flexibility to the proteins … (and) catalysing the chemical reactions with oxygen that produce the energy for living matter’.

The EMF scientific literature does now have several candidates for the biological explanation for non thermal effects, such as the combined free radical pair/oxidative stress mechanism. (Giorgiou, C.D., p. 64 and p. 103 for a diagramme illustrating this). Oxidative stress is implicated in cancer and neurogenerative diseases such as Parkinsons and Alzheimers.

There are also several other possible biological explanations for low dose, non thermal effects of EMF, such as: chemical kinetic effects, stochastic resonance, electrically induced phase transitions, cyclotron resonance, resonant transport of ions, coherence effects, signal averaging rectification, parametric resonance, ion interference, coherent excitations, alterations of metastable water states, effects of torsion fields and combinations of the above. (p. 158)

The biological reality of the non thermal effects of EMF means that it can also be used for therapeutic benefits, as with the more energetic, ionising X radiations. EMF is now used to treat some bone fractures and diseases. (p. 120). And as ELF effects on human and rat cells (maturation and differentiation) have been demonstrated, this could possibly lead to a ‘simple and safe biotechnological tool to improve cardiac regenerative potential’ (Ledda et al, p. 145).

And weak combined magnetic fields reduced a key cause of Alzheimer’s disease viz Amyloid-B in mice, indicating its possible therapeutic role in early neuronal degeneration. (Bobkova, N.V. et al, p. 235)

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7 Tigrek, S., Barnes , F. ‘Water structures and effects of electric and magnetic fields’, p. 25-50
As in the paper of Vedruccio (p.126), H. Fricke and S. Morse, 1926, in their paper "The electric capacity of malignant tumors of the breast" reported that "malignant tumors have a greater polarizability than normal breast tissues or benign tumors".

This fact was apparently forgotten until the end of the last century, when this electric feature of malignant cell has been fruitfully used to design an electro medical device - that we could name bioscanner for the early detection of tumors. (One of these devices, designed by the author of the paper, Vedruccio, has passed clinical tests and it is now used in many hospitals, e.g. in the Policlinico of Sapienza University of Rome).

The therapeutic use of EMF has a long history, from first century AD, when electric fish were used to cure headaches and gout, to Paracelsus, who studied the medical use of lodestone, and to Sir Kenelm Digby who described the magnetic cure of wounds. (p. 120)

3. Low dose effects and ‘windows of sensitivity’

Non thermal effects from EMF do not generally produce the classical linear dose response that Bradford Hill regarded as one of the 9 features of evidence that could help move from an observed association to an inferred causal relationship.

The experimental evidence on EMF shows instead a ‘window’ of responses to magnetic intensities which are often absent at higher and lower intensities.

The ‘window of sensitivity’ in the EMF field is similar to the ‘low dose’ effects of some endocrine disrupting and other chemicals, such as BPA, where low exposures have biological effects that are absent from higher doses.

The field intensities detectable by animals are very low: the racing pigeon can detect changes as little as 100-1000 times lower than predicted from engineering calculations; and honey bees are estimated to be 10 times more sensitive to magnetic fields than the pigeon. The scalloped hammerhead shark meanwhile can detect changes in electric fields as low as 0.5 microvolts /m. (p. 53/4)

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If this ‘window’ of sensitivity is not taken into account when interpreting epidemiological results then important biological effects can be dismissed.

For example, the significant association of acute lymphoblastic leukemia in children exposed to ELF from powerlines with magnetic field strengths of 0.4-0.499 microtesla was not observed at either lower or higher field intensities in the 1997 Linet study. This was interpreted by Linet as showing ‘little evidence’ of an effect because of the absence of effects in the other 6 categories of field intensity. (Liboff, p. 52).

Other studies since confirmed this association of children living near power lines and leukemia, first observed in 1979. Such exposures were classified by the IARC as a 2B possible carcinogen in 2002.

4. The Importance of Timing for some Biological Effects and Policy Actions

These ‘windows of sensitivity’ to EMF are also often dependent on the timing of the exposure and therefore on the stage of development of the biological matter being irradiated.

That ‘the timing of the dose’ is at often more important than the dose itself is a well known scientific phenomena that was learnt the hard way via the histories of some medicines.

For example the pregnancy pill, thalidomide, caused gross deformities in the new born only when the mother took the pill within a small time window of several days in the early part of the pregnancy.

Another pregnancy pill, DES, later caused vaginal cancer in the adult daughters, again mainly when taken in the first 3 months of pregnancy9.

There is now also a large and growing body of evidence that demonstrates the extra sensitivity of the developing foetus to environmental stressors.

This can help explain the developmental origin of many diseases10, such as cancer and diabetes, which can sometimes be caused by very lower levels of exposure when delivered to the foetus.

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It follows from this that prevention of such diseases must begin at earlier times in the exposure of the foetus and need to be justified by lower strengths of evidence, if lifelong harm is to be prevented\textsuperscript{11}. Such harm is often irreversible and sometimes multi-generational causing lifetime personal and societal costs that can not be offset by any benefits to the individual from intra-uterine exposures.

Thus biology, economics, equity and morals all justify early actions to prevent developmental and reproductive harm.

5. Replicability and Consistency of research results

‘Consistency’ of research results is a third, often used, ‘criterion’ or ‘feature’ of evidence, from Bradford Hill. However, like all of his nine features of evidence (see table 1, page 16) it is more robust if present, than if absent, especially in the context of multi-causality, biological complexity and gene/environment interactions, including epigenetics.

Bradford Hill pointed this out in 1965 but his advice has largely been forgotten, even though this asymmetry is stronger now, given our increased knowledge of biological complexity.

Prof. Needleman\textsuperscript{12}, who provided the first of what could be called the second generation of early warnings on lead in petrol in 1979, has also observed that:

‘\textit{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.}’

However, despite the biological complexities, the \textit{epidemiological} evidence on mobile phones and head cancers is now reasonably consistent-see below.


\textsuperscript{12} Needleman, H.L., Making Models of Real World events: the use and abuse of inference, Neurotoxicology and Teratology, 17(3). (1995)
However, the absence of consistency and replicability in many experimental results is more prevalent: there are many examples of positive and negative studies which have not been replicated.

It appears that biological complexity is likely to be a major reason for this inconsistency, as the number of parameters that are relevant to EMF study outcomes, and which have to be reproduced exactly if studies are to have any chance of replicability and consistency, is very large.

‘Most reviews of the experimental studies do not include analysis of various biological variables and physical parameters when comparing the data on non thermal microwave effects (NTMW) from different studies. As a result, a misleading conclusion is often made that MW at NT levels produce no reproducible effects’. (Belyaev, I. p. 208)

These parameters include: carrier frequency and modulation, polarisation, intermittence and coherence time of exposure, static magnetic field, electromagnetic stray fields, genotype, gender, age, physiological and individual traits, including immune status and oxidative stress, cell density during exposure, duration and timing of exposure, power density and specific absorption rate.

Even small differences in magnetic flux density changed the developmental rate of tadpoles when exposed to weak 50 Hz magnetic fields. (Severini M , Bosco, L, p. 247)

Blackman (US EPA) also commented on these complexities of the EMF/biological interface (see below, p. 15)

**Bi-directional effects of MW** need also to be taken into account in replication studies. For example, different exposures to microwaves can either increase or decrease growth rate of yeast cells; radiation damages in mice; respiratory burst of neutrophils in mice; and condensation of nucleoids in E.coli cells and human lymphocytes.

Similarly, when ELF was administered before well known genotoxic agents the number of malformed eggs in avians was reduced while the opposite happened when ELF was administered after the genotoxic agent. (p. 249)

In addition, most studies of MW effects have not used exposure metrics that mimic real exposures; and the widespread exposure of most
populations to EMF radiations means that ‘it is almost impossible to select unexposed control groups’.

This absence on unpolluted controls will, in general, dilute any biological effects observed in epidemiological studies such that it is reasonable to conclude that ‘studies may be inconclusive, if results are negative, or may underestimate the hazard, if positive’. (Belyaev, I., p. 210)

It follows that most ‘negative’ studies are actually ‘non-positive’ because the biological and exposure complexities are such that it is very hard to establish robust negative effects with much confidence.

This is another example of the asymmetry in the evidence that arises from biological complexity.

The first large scale rodent experiment from prenatal life to death using powerline radiation of 50 MHz in combination with a low dose of gamma radiation has produced positive preliminary results for malignant mammary tumours in female rats. (Soffritti M. et al p. 232) 30 years ago the first epidemiological evidence of breast cancer in male telephone company workers was published (Matanoski G.M. et al Lancet 1981, 337-737), but studies since have been inconclusive.

Cognitive functions including effects on memory have been demonstrated in rodents and ‘considering that memory functions are similar in mice and humans with respect to the hippocampus, we may assume that upon using the mobile phone in contact with the head a person may experience cognitive deficits’. (Fragapuolo F., Margaritis, L., p. 269).

Some support for subtle effects on the brain was recently published.13

The overall evidence on reproductive effects from EMF is mixed. ‘Overall the results obtained to date through the epidemiological approach do not raise strong concern for human reproductive health from the usual occupational and environmental EMF exposure levels’. (Talamanca et al, p. 387).

However, studies of male infertility amongst military personnel and amongst attendees at male infertility clinics, from Norway, Hungary, Poland and the USA, show a consistent pattern of possible damage,

which, when combined with the animal evidence, ‘raises serious concern’ and indicates the need for further research. (p. 389).

Studies of pregnant women provide evidence that is ‘either absent or weak’ (p. 394), although one study, which is the only one with measured exposures, showed increased miscarriage rates when there was a total or maximum exposure above 16 mG.

A more pronounced effect was observed when the exposure was in the first 9 weeks of gestation. (p. 394). Based on analogous evidence from other reproductive stressors (e.g. X rays; DES), this is likely to be the most sensitive period for these effects.

**Experimental evidence** on reproductive effects shows ‘possible damage to the male reproductive system at doses similar to those encountered in our environments’. (p. 399).

Animal studies on females also show possible damage, such as increases in mortality, reduced litter size, and low birth weight.

Inconsistent results and the absence of an accepted mechanism of action make interpretation of the evidence difficult. Given that current exposures to the public is a ‘massive experiment’ it is of concern that studies on possible lifetime effects of EMF exposures to the foetus and new born are rare.

### 6. Children: more sensitive to EMF than adults?

Children are, in general, more sensitive to exposures to the RF from mobile phones than adults, as pointed out by the UK National Radiological Protection Board in 2002 (Stewart report) and again in 2004. As the existing public safety limits are based on an adult male head this is a cause for concern, especially as about half of the RF radiation from the phone is absorbed by the head (p. 303).

Children’s skulls are thinner, and their brains are less dense and more fluid than adult brains. Children’s brains also have higher electrical permittivity and conductivity which means that they can absorb 50-100% more RF energy than the adult head (Table 2, p 310/1, Han, Y.Y., Gandhi, O.P., DeSalles, A., Herberman R.B., Davies, D.L., p. 301-318).

Recent studies by Wiart (2008) for French Telecom, and Kuster (2009), shows that ‘a given signal is absorbed about twice as deeply into the
bone marrow of the head and cortex of a child in contrast with that of an adult, even though systemic absorption may not differ substantially’. (p. 312)

The recent change in the recommendation from IEEE to average EMF exposures over 10 grams of the head, compared to 1 gram before, when estimating SAR (Specific Absorption Rate) values, leads to a less stringent protection for both adults and children. (p. 312).

Other changes in the test guidelines for head absorption allow RF exposures that are 8-16 times higher than previous guidelines. (p. 312 and table 2, p. 313)

In addition to absorbing proportionately more radiation than adults for the same exposure, the brains of children are more sensitive to that radiation because their brains are still in developmental stages compared to adults e.g. less neural integration and myelination until about the twenty years old. (p. 312)

7. Cancer Epidemiology

For ELF (e.g. from power lines) the International Agency for Research on Cancer concluded in 2002 that this exposure was a 2b (possible) carcinogen, based on sufficient epidemiology from more than 30 positive epidemiological studies since the first ‘early warning’ observation in 1979. However, there was inadequate animal evidence and unclear mechanisms of action. IARC will review the evidence on ELF and on RF for the first time in May 2011.

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 two fold excess of childhood leukaemia in women given X rays during pregnancy. Her findings were eventually accepted some 20 years later, despite the continuing absence of knowledge about mechanisms of action: and such routine X ray exposures were then stopped.  

The evidence from studies of workers exposed to high (i.e. usually ‘from 20/10 W/m2, with peaks of 10-30 W/m2, for 1-2 hours per shift, compared to the public 24 hour exposure to usually an average of below

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0.1 W/m²’ (p. 359). RF microwave radiation (e.g. to radar workers, metrologists, mobile phone technicians, and plane flight workers etc) is inconsistent.

However, it provides ‘a coherent pattern of data’ on various cancers, particularly those of the blood (hematopoietic) system (p. 361).

(Exposures of other workers to EMF can be considerable in modern offices and ‘it is strongly recommended that periodic EMF exposure measurements should be done’ particularly to identify hot spots of high exposures from photocopiers etc. (p. 379)

For the public exposure to RF from mobile phones, the evidence on head cancers is now consistent for those exposed for longer than 10 years.

Both the Hardell studies and the Interphone studies indicate potential head tumour risks of between 1.5 -2.0 times the normal rates for head tumours (but up to 5 times for the younger groups in the Hardell study), particularly for gliomas and acoustic neuromas which are generally on the same side of the head used when phoning. (Hardell, p. 363).

Tumours in the region of the temporal lode are most common. This is the part of the brain that, in general, receives most radiation from the phone. A recent review of 110 phone models showed that exposure to radiations is generally higher in the temporal lobe, which is a part of the brain that is near to the ear.

Since publication of the Ramazzini monograph the lead author for the Interphone study, Cardis E., and another Interphone author, have published a review of both the Hardell and Interphone results.

They have concluded that ‘The overall balance of the above-mentioned arguments (about biases and effects) however, suggests the existence of a possible association’. These results ‘are of concern’ as even a small risk at the individual level will represent a considerable public health issue. The adoption of such simple and low cost exposure reduction methods such as texting, hand free kits and/or the loudspeaker mode ‘could substantially reduce exposure’... the adoption of such precautions, particularly among young people, is advisable’.

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8. Implications of biology for current safety guidelines and test methods

Current guidelines on EMF safety from IEEE and ICNIRP (endorsed by the EU) are only based on short term EMF exposures that are high enough to cause thermal effects. These are inadequate to provide protection to the public against long term effects from lower levels of exposure. Neither do they account for the pulse-like exposures modulated at low frequencies that are common from the modern 2G and 3G appliances. (p. 314)

Blackman of the US EPA has observed elsewhere that:

‘These (current) standards rely primarily on biological responses to intensities within an arbitrarily defined engineering based frequency bands, not biologically based response bands, and are solely based ion energy deposition determinations. Current standards have ignored modulation as a factor in human health impacts and thus are inadequate in the protection of the public in terms of chronic exposure to some forms of ELF modulated RF signals…particularly new technologies that are pulse modulated and heavily used in cellular telephony’. ¹⁷

The biological evidence concerning the non thermal effects of EMF (indications of head cancer, permeability of the brain/blood barrier (p. 319, 333); expression of shock proteins; genotoxic damage, neurological, and possibly reproductive effects), though still limited and controversial, is sufficient, on a precautionary basis, to justify biologically based and lower safety limits for the public.

Such evidence also justifies more realistic test methods for RF absorption from RF.

Recommendations for such lower limits have been proposed by the BioIntiative group; the Selatun Scientific Panel¹⁸ and others. These have been adopted in some cities and regions of Europe.

Whilst the state of the science does not predict obvious choices of particular lower limits it does allow the choice of pragmatically based and more biologically relevant limits which would provide better protection of health.

¹⁸ Reviews on Environmental Health V 25 n 4, 2010
David Gee, Feb 24\textsuperscript{th} 2011.
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<th>Criteria</th>
<th>Example</th>
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<tr>
<td>1. Strength of the association?</td>
<td>John Snow found 71 cholera deaths per 1000 houses served by polluted water but only 5 per 1000 houses served with sewage-free water (London, 1854).</td>
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<tr>
<td>3. Specific effects?</td>
<td>In 1959, the then rare cancer, mesothelioma, was observed to kill children in S. Africa who played on asbestos waste tips without there being increases in other causes of their death.</td>
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<td>4. Temporality?</td>
<td>‘Is the cart coming before the horse’? The DES exposure of mothers occurred before rare cancers in their daughters were observed (USA, 1970).</td>
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<td>5. Biological gradients?</td>
<td>Does effect increase with dose, if such exposure measurements are available? E.g. TBT exposure from boats and imposex in snails (UK, 1986).</td>
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<tr>
<td>6. Biological plausibility?</td>
<td>Depends upon the ‘knowledge of the day’, cannot be robust, as the observation may be new. E.g. PCB contamination of eagles, (Sweden, 1966).</td>
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<tr>
<td>7. Coherence?</td>
<td>Is the evidence coherent with general known factors? E.g. radiation damage from X-rays (USA, 1904). Also dependent on the knowledge of the day.</td>
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<td>8. Experiment (reversibility)?</td>
<td>Does prevention prevent? E.g. a reduction of SO2 eventually leads to less lake/forest acidification (Sweden, 1998).</td>
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<tr>
<td>9. Analogy?</td>
<td>E.g. collapsing fish stocks from over-fishing in different areas e.g. California sardine collapse, 1942 was a useful lesson for other fish stocks.</td>
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