AUSTRALIAN GOVERNMENT

AUSTRALIAN RADIATION PROTECTION AND NUCLEAR SAFETY AGENCY

Draft Radiation Protection Standard for Exposure Limits to Electric and Magnetic Fields 0 Hz – 2 kHz

Response from

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Summary

1. EMF Reviews from the NRPB, IARC and WHO have not been subject to the process of blind peer review or public consultation. The California Department of Health Services (CDHS) EMF report of 2002 was issued for public consultation, and the recent EU SCENIHR report is engaged in this process. We therefore welcome the public invitation to respond to the *"Draft Radiation Protection Standard for Exposure Limits to Electric and Magnetic Fields 0 Hz – 2 kHz"* by the Australian Radiation Protection and Nuclear Safety Agency.

2. An analysis of the aggregate data presented in the IARC 2002 and California 2002 reports show that the weight of evidence of positive findings in epidemiological studies for adult leukaemia and adult brain cancer cannot be attributed to chance. The IARC review shows no evidence of having considered the aggregation of results other than subjectively. It has considered individual studies in detail and identified their shortcomings, but this has led to a tendency to fragment and dismiss evidence which is intrinsically highly significant. In conclusion therefore, the data, rather than the assertions made, for both adult leukaemia and adult brain cancer in both the California and IARC Reports agree with each other in indicating an association with EMFs.

3. We further draw attention to the five health outcomes awarded an IARC 2B classification in the California Report: childhood leukaemia, adult leukaemia, adult brain cancer, Amyotropic Lateral Sclerosis (ALS or motor neuron disease) and miscarriage. For childhood leukaemia, the use of a linear no-threshold model, rather than a cut-off in risk below 0.4 μT, would suggest about 60 cases or around 11% of the total incidence might be attributed to EMF in the UK, a similar figure to that published for the USA using a similar model.

4. There are plausible working hypotheses, such as those based on melatonin and the radical pair mechanism which add to the evidence that exposure to power frequency electric and magnetic fields increase the risk of a range of illnesses. We draw attention to relevant research findings in scientific disciplines such as magneto-reception in animal navigation which, so far, fall out of the terms of reference of EMF review committees.

5. The now extensive epidemiological literature on adverse health effects of power frequency EMFs within the normal exposure range around or below one microtesla, indicates that this is the level at which restrictions on exposure might be considered.

6. A cost-benefit analysis taking account of the adverse health effects for which the epidemiological evidence is strongest, significantly alters the balance in favour of active precautionary measures to limit exposure. Specifically, the impact of other diseases is of the order of 100 times greater than that of childhood leukaemia alone.

1. General Comments

1.1 Introductory comments

The authors of the Radiation Protection Standards Document (hereafter referred to as "*the Authors*") have attempted a comprehensive assessment of our current state of knowledge health effects associated with exposure to electric and magnetic fields (EMFs) and how this may impact on precautionary measures against exposure in the home and workplace. They are to be congratulated on this effort and that the Australian Government has seen fit to put this assessment out for public consultation.

Overall, we feel that the potential extent of the adverse health effects associated with exposure to electric and magnetic fields associated with the electricity supply does not appear to be appreciated in this consultation document. Potentially, this has an important impact on the cost-benefit analysis of proposed precautionary measures. We would remind the Authors that the reports from the UK NRPB (now the HPA), IARC and WHO were not sent out for blind scientific peer-review and therefore their reports, however august, must be seen as non-peer-reviewed documents. It is also the case that these bodies contain some overlap in the members of those review bodies and that their deliberations should not be taken as independent.

We should understand that the statutory status enjoyed by these bodies does not mean they are scientifically right. The fallibility of even the most august authorities has been known in science famously through the centuries. It is still alive and well, for example as topically illustrated by the Wegman Report on Climate Change (2006). Recommendation 1 of that Report states:

> "*Especially when massive amounts of public monies and human lives are at stake, academic work should have a more intense level of scrutiny and review. It is especially the case that authors of policy-related documents like the IPCC report, Climate Change 2001: The Scientific Basis,* ***should not be the same people as those that constructed the academic papers.***" [our emphasis]

It is clear from recent experience in the UK, that such bodies often serve a political process. Indeed, if the advisory systems were perfect, there would be no need for the Stakeholder Advisory Group for EMF (SAGE), nor for the Hutton report on Dr Kelly and the Joint Intelligence Services advice on Weapons of Mass Destruction from Iraq, nor for the Phillips report on BSE/CJD, and so on. The very existence of SAGE testifies to the fact that the UK Government is seeking to broaden its advice on EMF from simply that provided by its own statutory body the NRPB/HPA.

Reading the Australian Radiation Protection Standards Document (hereafter referred to as "*the Document*"), we have noted the frequent use of value-added language. For example, there appears to be gratuitous praise of the IARC 2002 Report (e.g. page 77 line 3397/8: "*The review represents an enormous amount of work from many leading researchers in the field.*") and the NRPB 2004 Report (e.g. page 78 lines 3449: "*Many people from AGNIR contributed to this extensive document*"), but gratuitous criticism of the California EMF Program Risk Assessment 2002 (e.g. page 78 lines 3442-5: "*This report was fairly*

controversial and was criticised by, among others, Sander Greenland for its incorrect application of Bayesian decision models and estimation of causality (Program 2002) and AGNIR for its miscarriage conclusions (AGNIR 2002).")

In fact, the California Department of Health Services (CDHS) EMF report of 2002 drew on the 1999 Report of the US National Institute of Environmental Health Sciences, NIEHS which classified both childhood and adult leukaemia as a possible carcinogen and which led to the setting up of the IARC Committee. Unlike the IARC and NRPB Reports, an earlier draft of the California Report was put out for public consultation and the comments attributable to Dr Greenland appear as part of the California Report 345-page Volume 2 compendium of comments received. When all comments were taken into account, the authors of the California Report classed five health outcomes as IARC Class 2B.

We hope therefore that in writing their Document, the authors would wish to avoid value-added judgments.

1.2 Comparison of IARC and California Reports

It has been commented that the IARC and California reports come to different conclusions based on essentially the same body of evidence. We have tried to understand how and why these different conclusions were reached and this is set out in Appendix 1. The findings are summarised briefly here.

In chapter 8 of the California Report, we noted that the results of 43 epidemiological studies of adult leukaemia are tabulated and that 32 of these gave positive odds ratios (i.e > 1.00) and that 11 of these were each statistically significant (at the 95% confidence level) in their own right. Let us surmise that there is no association between EMFs and adult leukaemia. We would then expect an approximately equal number of odds ratios above and below 1.00, according to the normal statistical fluctuations in the data. In fact, the probability of obtaining 32 positive odds ratios out of 43 by chance is exceeding small ($p<0.0007$) and of obtaining 11 that are statistically significant by chance, around 10^{-12}. Such a combination of findings would not occur by chance, so we must look at some other reason.

If epidemiology is to have any value, then for positive findings we consider should causality as a possibility. For each health outcome considered, the California Report set out arguments for and against causality in 14 tables which encompassed the Hill criteria referred to in the Document. Their conclusion to class adult leukaemia as 'IARC Class 2B' was based on the deliberation in these tables as well as the statistical weight of the aggregate data, as indicated above (although this did not include an assessment of the aggregate for statistically significant studies).

We then looked at how the IARC Report assessed the adult leukaemia data. Tables 25, 29 & 30 of the IARC Report list 176 odds ratios from 37 studies, finding 111 positive and 31 statistically significant positive results. Simply combining all the IARC-reported results together gives a statistically strong aggregation, similar to the California Report. This is confirmed when selecting (by objective criteria) one representative result per independent study, as we show in Appendix 1.

An analysis for adult brain tumours again yields similar results between ~~both~~ the California and IARC Reports.

We then sought to determine how IARC reached their overall evaluation, but found little indication of how this was done. On page 334 the Report simply says: "*There was no consistent finding across studies of an exposure-response relationship and no consistency in the association with specific sub-types of leukaemia or brain tumour*."

The IARC review shows no evidence of having considered the aggregation of results other than subjectively. It has considered individual studies in detail and identified their shortcomings, but this has led to a tendency to fragment and dismiss evidence which is intrinsically highly significant. In conclusion therefore, the data, rather than the assertions made, for both adult leukaemia and adult brain cancer in both the California and IARC Reports agree with each other in indicating an association with EMFs.

1.3 Mechanistic understanding of how power frequency magnetic fields may affect health

Considerable advances are being made in our understanding of how fluctuating magnetic fields may affect health. Such advances are occurring from developments across scientific disciplines in general, especially in research fields which fall outside the terms of references of EMF review bodies. Two such areas are addressed below, in section 3 the adverse health effects associated with fluctuations in solar and geomagnetic fields and in section 4 magneto-reception by animals for purposes of navigation. Here we summarise candidate mechanisms by which EMFs may affect health, melatonin and radical pairs.

1.3.1 *Melatonin*

First, we should note that it would be highly unusual for a carcinogen to affect one outcome, namely childhood leukaemia, without also having a bearing on risk for other some other cancers.

The apparent disparate set of adverse health outcomes associated with EMF exposure, ranging thorough childhood leukaemia, adult leukaemia and brain cancer, certain neurodegenerative diseases to miscarriage and depression, could all be linked by disruption of the nocturnal production of melatonin in the pineal gland. The wide ranging properties of melatonin as a powerful antioxidant have been extensively researched and there is a detailed mechanistic understanding of these properties (see example reviews in Reiter 1998, Reiter and Tan 2003, Tan *et al.* 2006, Anisimov 2003).

Henshaw & Reiter (2005) pointed out that studies of populations chronically exposed to EMFs from electricity supply, show consistency in demonstrating disruption in the nocturnal production of melatonin in the pineal gland. Effects were particularly evident in the presence of magnetic field transients or switching and/or the additional presence of magnetic fields. In a more recent study by Davies *et al.* (2006), involving 115 women volunteers, a 0.8 μT magnetic field source was placed under the bed while the women slept. Melatonin disruption was measured by monitoring the metabolite 6-OHMS in morning urine samples. A statistically significant reduction in melatonin with the applied magnetic field was observed.

Juutilainen and Kumlin (2006) found evidence that occupational exposure to magnetic fields by day affected the sensitivity of the pineal gland to light exposure that night. While the observation is based in small numbers, it is potentially significant to the detailed mechanism by which magnetic fields may disrupt pineal melatonin.

Melatonin is highly protective of oxidative damage to human blood cells (Vijayalaxmi *et al.* 1996, 1998a, b) and studies in animals have shown melatonin to be highly protective of oxidative damage to the fetus (for example Wakatsuki *et al*.1999a, b and 2001a, b; Okatani *et al*. 1997). There is good evidence to suggest that much of childhood leukaemia involves a two-hit process, the first occurring *in utero* followed by a second in childhood. It could therefore be postulated that melatonin disruption by magnetic fields increases childhood leukaemia risk (Henshaw & Reiter 2005).

Melatonin is known to control seasonal breeding in animals. The human fetus does not have its own source of pineal melatonin, rather this is derived from the mother via the placenta. Thus, in women, serum melatonin levels increase throughout pregnancy, and are particularly high at term (Nakamura *et al.* 2001). Given the demonstrative protectiveness of melatonin to the fetus in animals, it is feasible therefore that melatonin disruption by magnetic fields could affect miscarriage risk.

1.3.2 *The radical pair mechanism (RPM)*

As discussed in the Document on page 98, section 1.1, magnetic fields can increase the lifetime of free radicals by acting on radical pairs, altering the ratio of their triplet to singlet spin states in what is known as the Low Field Effect, LFE.

(i). *Radical Pair Mechanism per se*

Juutilainen *et al.* (2006) reviewed 65 laboratory studies where various biological cells were exposed *in vitro* to both EMFs (specifically magnetic fields) simultaneously with known carcinogens (e.g. ionising radiation or chemicals). The overall percentage of studies where induced biological effects were greater in the presence of magnetic fields was so high that the authors calculated that the probability of this occurring simply by chance was less than 1 in 10,000. Indeed, they pointed out that if the results were to be explained in terms of researchers failing to publish negative findings, then there would have to be some 900 such pieces of (unpublished) research. In practice, this is inconceivable.

The findings of Juutilainen *et al.* (2006) support the radical pair mechanism in which such fields increase the lifetime of free radicals in the body and therefore their opportunity to produce oxidative damage. This is the mechanism by which animals detect tiny changes in the Earth's magnetic field ~0.1 μT for the purposes of navigation.

More recently, Mairs *et al.* (2007) using a relatively new and highly sensitive method of detecting chromosome damage, have shown that 1 mT magnetic fields cause damage to brain tumour cells both with and without the presence of a known carcinogen. The observation is particularly relevant, given the association between EMF exposure and brain cancer.

(ii) *Radical Pair Mechanism and magneto-reception in animals*

As described in more detail in section 4 below, animals across a wide range of species detect tiny changes in the Earth's magnetic field for the purposes of navigation. This is achieved by magneto-receptors in the eye, identified as cryptochromes which produce light-dependent radical pairs whose spin states are modified by changes in ambient magnetic fields, which are then detected by the brain. This may provide a pathway by which changes in magnetic fields (50/60 Hz would constitute a slow change in this context) affect the pineal gland, disrupting its nocturnal production of melatonin (onset delay, peak level, or total production).

1.4 Electric field effects – corona ion emission from high-voltage powerlines

Draper *et al.* (2005) carried out the largest ever survey of childhood leukaemia in relation to proximity to high voltage powerlines. Taking the address at birth of cases in England & Wales during the period 1962 – 1995, the authors found increased incidence up to 600 m from powerlines. Such a distance is well beyond the range of the direct electric and magnetic field from powerlines but is within the range of corona ion emission, as discussed in Fews *et al.* (1999, 2004) and Henshaw (2002). Recent studies by Knox (2005a, b, 2006) suggest strong links between air pollution and childhood cancer in the UK, supporting the notion that corona ion charging of inhaled pollutant aerosols may increase childhood leukaemia risk. Some powerlines emit sufficient corona to account for the Draper *et al.* findings. What remains uncertain is whether this was the case for all powerlines in England & Wales during the period 1962 – 1995.

More is said below about the corona ion model in response section 1.4 page 99, lines 4491-4504 on electric fields and particulates.

1.5 Cost benefit analysis of precautionary measures

We do not think it is rational to base an assessment of the cost impact of precautionary measures on childhood leukaemia alone, when most of the hypothesised mechanisms and their supporting evidence relates to biological systems involved in many diseases, rather than exclusively to childhood leukaemia.

A short summary is given here of the cost-benefit analysis of precautionary measures presented in Appendix 2 below. The following table gives the total impact on society, in thousands of pounds per year per 1,000 exposed population, from EMF exposure for five '*what-if*' scenarios, as calculated in:
http://www.electric-fields.bris.ac.uk/volume1ocarroll.pdf. The impact of other diseases is of the order of 100 times greater than that of childhood leukaemia alone.

	CL alone[1]	NIEHS 2[2]	CDHS 5[3]	CDHS 11[4]	12 diseases[5]
With credibility factors	4	70	146	679	716
With definite causation	5	122	246	1899	2629

[1]Childhood leukaemia; [2]Childhood and adult leukaemia; [3]as 2 plus adult brain cancer, ALS and miscarriage; [4]full list in CDHS 2002; [5]as 4 plus depression.

2. Specific comments

We will first draw attention to a given statement in the Document, followed by our response to it.

1. Statement: Foreword page i para 3: "There is currently a level of concern about electric and magnetic field exposure, which is not fully dispelled by existing scientific data. It is true that data regarding biological effects, at levels below the limits specified in the Standard, are incomplete and inconsistent. The health implications for these data are not known and such data could not be used for setting the levels of the Basic Restrictions in the Standard."

Response: We would challenge the assertion in the final sentence. There is a substantial body of epidemiological literature indicating a range of adverse health effects at normal exposures, let's say below one microtesla. This gives an indication of where exposure standards should be drawn.

We can take the example of coffee which is also a Class 2B carcinogen. The ICNIRP exposure limit of 100 μT is 250 times higher than the 0.4 μT above which a doubling of associated childhood leukaemia risk is acknowledged. So, would we be comfortable with drinking 250 cups of coffee per day? In fact health advice is to limit coffee intake.

2. Statement: Foreword page i bottom para: "...there are costs involved in adopting precautions and the science does not establish even indicative parameters on which a precautionary approach might be based."

Response: A similar response to above, adverse health effects are reported around or below 1 μT, so this is the area for setting limits on exposure.

3. Statement: Page 23 – References

Response: The California Department of Health Services (CDHS) EMF report of 2002 is missing from the references list. While it is quoted elsewhere, it should also be quoted here alongside the other reports quoted.

4. Statement: page 29, line 1218-19 re IARC: "No such association has been established in the case of adult cancers, or of non-cancer diseases."

Response: In the light of our analysis presented above and in Appendix 1 below, we consider this statement to be wrong. The data presented in the tables in the IARC Report itself, do support an association for adult leukaemia and adult cancer.

5. Statement: Page 29 lines 1225-8: "Magnetic fields *per se* cannot be regarded as having been unequivocally established as causative because there is:

1. a lack of supporting evidence from the bulk of animal experiments

2. a lack of a credible and accepted biophysical induction mechanism
3. no clear dose-response
4. uncertainty on what the appropriate exposure metric may be."

Response:

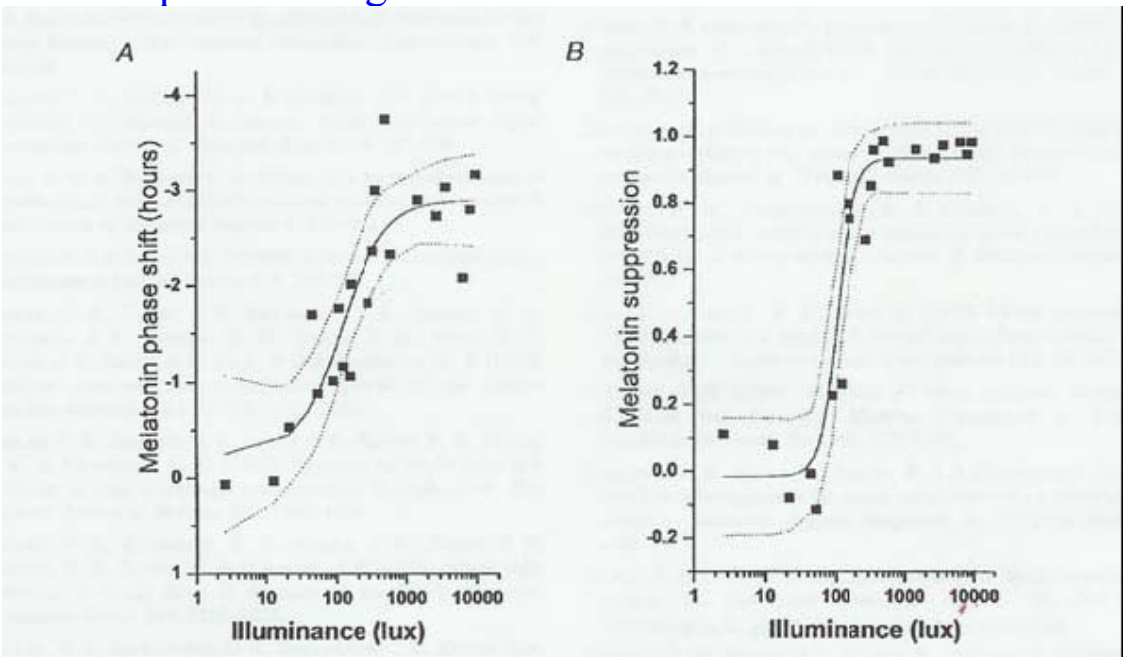
1. It should be emphasised that there is no animal model for acute lymphoblastic leukaemia, ALL, the common form of leukaemia in childhood. Therefore, it is of course the case that findings of particular relevance to childhood leukaemia have not been seen in animals.

2. It is an assertion to claim "a lack of a credible and accepted biophysical induction mechanism". Accepted by whom? The statement fails to give credit to the significant advances in understanding biological interactions with EMFs and of the working hypotheses such as melatonin and the radical pair mechanism.

3. The statement "no clear dose-response" is a fallacy. The problem is that we don't know what the dose-response looks like, so we do not know when we have not got one!

For example, it is often claimed that studies looking for melatonin disruption effects from EMF exposures fail to find a dose response effect. The graphs below show the dose-response of melatonin for visible light taken from Zeitzer *et al.* (J. Physiol. 2000, 526, 695-702). Looking at the right-hand graph, melatonin is fully suppressed over a wide range of illuminance, from around 200 - 20,000 lux. This of course corresponds to the daytime period. In the evening, as light falls below approximately 200 lux the nocturnal production of melatonin begins to rise (i.e. the suppression falls) and is complete at around 20 lux. Therefore, the pineal response to visible light is not at all linear, rather it is a 'switch' effect.

Dose response for light



Zeitzer *et al*. J Physiol (2000) 526, 695-702

4. Re Exposure metrics. There is indeed a debate as to which exposure metric or metrics are relevant to health effects from EMF exposures. Henshaw & Reiter (2005) found that effects on melatonin disruption were more pronounced when switching or transient of magnetic fields were present. This concurs with other findings. For example, page 316 of Kumlin *et al.* (2005) provides a discussion of the results of research carried going back to the 1980s. Here is one extract:

> "It may be hypothesized that MF exposure stimulates pineal cells so that they are more receptive to signals from the biological clock. Another possibility is the stimulation of retinal photoreceptors so that stronger signals of light variations reach the pineal gland. According to studies reported by Olcese *et al*. (1985, 1988) and Reuss and Olcese (1986), retinal photoreceptors of rats might be capable of responding to a magnetic field. Reuss and Olcese reported that exposure to dim red light at night is a necessary predisposing factor for magnetic fields to inhibit the melatonin production in the mammalian pineal gland. These findings suggest that the MF signal goes to the pineal gland through the eyes. Recently, exposure to a 60 Hz MF has been reported to modulate the diurnal rhythm of the pain threshold in mice. The authors concluded that MFs are acting on the system that is associated with the environmental light-dark cycle. Thoss *et al*. (1999) reported changes in oscillations of visual sensitivity in human volunteers after artificial changes in the direction of earth's magnetic field."

The suppression of pineal melatonin by light has been extensively characterised. If 50/50 Hz magnetic fields affect the response of the pineal gland to light, then this is potentially a most important finding.

6. Statement: Page 29, lines 1233-1236: "Without results of further exposure assessment studies in Australia, it is hard to say how many cases per year of childhood leukaemia could result from residential EMF. Given overseas results and some studies here, it is unlikely to be more than a very small number of cases per year.

Response: This report appears to be working on the assumption that childhood leukaemia risk occurs only above 0.4 μT. In public health risk assessment, it would be normal to apply the linear no-threshold model of steadily reducing risk down to zero excess risk at zero exposure. This is the practice for agents such as radon and chemical carcinogens.

Thus, for the US, Wartenberg 2001 performed such an analysis, concluding that the total number of childhood leukaemia cases attributable to EMFS would be about 11% of the USA total. We have carried out a similar analysis for the UK which suggests around 60 cases out of a total of around 500 cases per year, coincidentally also around 11%.

7. Statement: Page 77, lines 3390-3428 – the IARC Review

Response: As discussed above in section 1.2 and below in Appendix 1, The data actually presented in the IARC report gives the same statistical message as for the California Report. This is not surprising given that both reports draw on the same body of epidemiological evidence.

8. Statement: Page 78, lines 3441-45 – re criticisms of the California Report

Response: In fact, the California Report drew on the 1999 Report of the US National Institute of Environmental Health Sciences, NIEHS which classified magnetic fields as a possible carcinogen for both childhood and adult leukaemia and which led to the setting up of the IARC Committee. Unlike the IARC and NRPB Reports, the California Report was put out for public consultation and, as stated above, the comments attributable to Dr Greenland appear as part of the California Report 345-page Volume 2 compendium of comments received. When all comments were taken into account, the authors of the California Report classed five health outcomes as a Class 2B.

The comments by the AGNIR related to the miscarriage paper by Li *et al.* (2002) and not to the issue of miscarriage as assessed in the California Report, which was based on 37 studies.

The AGNIR made a number of errors in its criticism of the Li *et al.* study. In a statement on the NRPB website late February 2002, the AGNIR claimed that the findings could be explained by nausea during pregnancy which modified the behavior of pregnant women in a way that made them more prone to exposure to EMFs. However, they had failed to read a letter in the March 2002 edition of Epidemiology (Vol. 13, No. 12, page 238/9), which was readily available in hard copy form several days before the AGNIR posted it comments, which described how they had indeed investigated nausea and found it not to be a confounding factor in their findings of an association between miscarriage and MF exposure.

A number of us pointed out the AGNIR error and the website content was changed, but there was no update concerning the date of posting or an admission of this error. However, the corrected AGNIR comments also contained errors which again were later changed. The final set of comments were at best weak and not of a nature which affected the findings of Li *et al.* (2002).

Overall, the behaviour of the AGNIR in its response to the Li *et al.* (2002) paper was unprofessional.

9. Statement: Page 79-80, lines 3525-3553, with special reference to the following extracts:

"There does not appear to be any new convincing evidence either to discount or to strengthen assumptions of causality between EMF and childhood leukaemia,.....Elwood has also recently drawn attention to possible over-interpretation of the consistency in the pooled analyses: firstly because the individual studies that provided the most cases to the pooled analyses did not themselves support an association and secondly because the positive results only arose with less sophisticated measures of exposure that had to be used in the analyses, together with post hoc cut-offs, to ensure a common exposure framework across studies (Elwood 2006)."

Response: The paper by Dr Elwood (2006) has been firmly rebutted by Professor Leeka Kheifets *et al*. (2006). In paragraph 2 of their introduction, these authors say of the Elwood paper:

"First, the three studies were misinterpreted as ''negative'' because they found no statistically significant association, when in fact they did supply evidence for an association. It is unfortunately common to confuse lack of significance with lack of evidence or lack of positive association, but as well documented in textbooks [Royall, 1997; Rothman and Greenland, 1998, Ch. 12] it is a fallacy nonetheless, for the significance reflects numbers in categories as much as strength of the association. In reality, 11 of 12 studies used by Greenland et al. exhibit positive associations across a wide variety of analyses, as have three subsequent studies [Greenland and Kheifets, 2006]. Almost any association can be made to appear unstable and violate dose-response by dividing the extreme categories too finely, as Elwood does by using a 0.5 microtesla upper category. When analyzed using stable categories, however, results from the 15 studies are remarkably consistent, and remain positive when various bias adjustments are made [Greenland and Kheifets, 2006]. And as Greenland et al. showed, taking account of matching factors only increased the association.

For example, although the UKCC study provided 33% of all cases (1,073/3,247) in the Ahlbom et al. pooled analysis, it contributed only 9% of the cases (4/44) exposed to ≥4 mG, and has fewer cases ≥4 mG than 4 of the 12 studies in Greenland et al. [2000]."

In any case, the findings of the pooled analyses of a doubling of the risk of childhood leukaemia in relation to magnetic fields exposure above 0.3/0.4 μT has since been supported by two further studies, notably the UK study by Draper *et al* (2005) and the Japanese National Study by Kabuto *et al.* (2006). Mejia-Arangure *et al.* (2007) have reported increased risk of leukaemia in children with Down Syndrome with magnetic field exposures ≥0.6 μT (OR = 3.7, 95% CI = 1.05 – 13.1). Down children have a higher risk of leukaemia compared with other children (some reports suggest a 20-fold increase). An association with magnetic fields would have implications for schools for Down Syndrome children.

10. Statement: page 80, lines 3560-85 re breast cancer

Response: The study by Forssen *et al.* (2005) is indeed a large one. 20,400 cases of breast cancer were involved and the overall odds ratio for women exposed to 0.3 μT or more was 1.01 (95% CI: 0.93 – 1.10). However, the study could be considered to have three weaknesses: (i) the exposure assessments were based on job title which is a very crude method of assessing exposure and Forssen *et al.* acknowledge the possibility of exposure misclassification; (ii) this study concerns daytime exposure only, and so would not test the hypothesis that nocturnal melatonin disruption by EMFs may affect breast cancer risk (data on exposure to light-at-night, which suppresses nocturnal melatonin production, in night shift workers show increased risk of breast cancer) and (iii) the study by Forssen *et al.* is in a single Swedish population who enjoy good dark winter nights where nocturnal melatonin production might be less disrupted compared with populations in other developed countries. In the meta-analysis of EMF breast cancer studies by Erren (2001), it is interesting to observe that for all studies at higher latitudes (52º – 59º) the odds ratios obtained are close to the null, but for those at moderate latitudes (38º - 46º) positive odds ratios are observed, the average in this latitude band being 1.26. This limited evidence might be indicative of a latitude effect due to day length or due to interactions with the Earth's geomagnetic field.

The study by Forssen *et al.* has been commented upon by Erren (*Am J Epidem*. 2005; 162: 389-395), who also discusses melatonin, commenting on the problems of confounding with exposure to light-at-night as well as other methodological issues.

In summary, the study by Forssen *et al.* (2005), while indicating a low breast cancer risk from EMF exposure in the more northerly latitude of Sweden, does not justify that EMF is most likely not a risk factor for breast cancer.

11. Statement: page 81, lines 3649-56 re suicide & depression

Response: Melatonin disruption is linked to increased risk of both depression and suicide. The references below cite 7 studies of depression and 9 studies of suicide supporting an association with EMF exposure.

12. Statement: page 81-2, lines 3658-79 re Cardiovascular disease

Response: The cited paper by Feychting *et al.* (2005) is an example of not considering data outside the terms of reference of EMF and health. In fact, there are reports of cardiovascular problems associated with exposure fluctuations in solar and geomagnetic fields (see Palmer *et al.* 2006).

13. Statement: page 84, lines 3797-99: "While there are many studies providing evidence of association between various EMF metrics and various diseases, it is only when these associations are considered to be causal that they should be used to set quantitative standards."

Response: This is an assertion which was described as "absurd" by Dr Chris Portier, Deputy Director of the NIEHS and author of the US 1999 NIEHS EMF Report, at a recent enquiry into a powerline development in Connecticut (see Microwave News January 2007). It is obvious that the reported health effects are occurring at exposures around or below 1 μT.

14. Statement: page 84, lines 3800-09: "One fairly standard framework for assessing causality is that proposed by Bradford-Hill (Hill 1965), outlined above, who suggested that satisfying the criteria of: strength and consistency of association; a dose-response effect; plausibility; and temporality, would be a reasonable guide to assuming causality. Because most of these are absent in most EMF disease associations (as explained more fully elsewhere (e.g. (Karipidis 2006)), the possibility of causality can only be tenuous, as exemplified by the IARC conclusion. For childhood leukaemia and ELF there is strength, some consistency and also temporality, but so far, no dose response (only the cut-point above and below either 0.3 or 0.4 μT) and not much plausibility."

Response: Many of the assertions in this statement are simply wrong: (i) there is strength and consistency in the aggregate data for a number of health end points such as the five identified in the California report, including within the IARC Report itself, but this was never addressed by IARC; (ii) as explained above, since we do not know what form of dose-response to

expect, we do not know when we have not got one; (iii) There is progress in mechanistic understanding not acknowledged in this statement, adding to the plausibility of the epidemiological findings.

15. Statement: page 98, lines 4449-4460 re magnetochemistry

Response: The authors are to be congratulated for including this section. It could be expanded significantly and further information here is given above in section 1.3.2 and in section 4 below.

16. Statement: page 99, lines 4491-4504 re electric fields and particulates

There has been much misunderstanding of the electric field/corona ion work at Bristol. The issue has little to do with radon. In our 1996 and 1999 papers, we were looking at the effect of 50 Hz electric fields on pollutant aerosol particles in the atmosphere. When radon-222 decays, it produces decay product atoms which they themselves are radioactive, with combined halve-lives less than one hour. In air, such atoms attach to airborne particles of air pollution (they attract clusters of molecules within 100 ns and then attach to aerosols within a few minutes). As explained in our papers, since we have sensitive methods for detecting radon decay products in air, we were therefore, using radon decay product aerosols simply as markers of aerosol behaviour in general and not of radon *per se*.

One of us (DLH) is particularly critical of one aspect of the AGNIR report on corona ions (NRPB 2004). The report on corona ions arose from our work at Bristol suggesting that corona ion emission from high voltage powerlines may lead to increased exposure to air pollution in those living near powerlines and in particular may in part account for the increased incidence of childhood leukaemia seen in the vicinity of powerlines. This is most notable in the recent UK report by Draper *et al* 2005. The AGNIR invited DLH to give oral and written evidence on this corona ion work on 3rd December 2001. This evidence included our risk assessment that corona ions may be responsible for increased incidence of certain illnesses near powerlines, notably annually 200 – 400 excess cases of lung cancer, 2000 – 3000 excess cases of air pollution associated illnesses such as asthma and aggravated allergies and 2 – 6 excess cases of childhood leukaemia. This risk assessment was published in 2002 in the peer-reviewed journal *Medical Hypotheses* (Henshaw 2002). Prior to publication of the AGNIR report I was sent a draft copy, extending up to paragraph 137. We at Bristol expressed our approval of the report, because in the version we were sent it acknowledged the factual nature of the phenomenon of corona ion emission from high voltage powerlines and of the model we had proposed. In particular, it accepted that airborne particles which had been electrically charged by corona ions were more likely to be trapped in the lung when inhaled.

However, when the report was published in 2004 we found that further paragraphs had been added, and that the report actually extended to paragraph 165. We were most surprised that nowhere in the report was the paper by Henshaw (2002) cited, nor the risk assessments therein. Instead, amongst the added paragraphs, paragraph 146 mentions lung cancer near powerlines and makes some very general unsubstantiated statements to the effect that the AGNIR thinks that there is unlikely to be an increased risk in lung cancer.

Our work continues to be misunderstood. In a paper by Jeffers (2006), the author fails to understand that his calculations do indeed support the corona ion model. In particular, the author has assumed that complete charging of aerosols by corona ions is needed to produce increase health risks. This is not the case. Referring to the paper, on page 4, left-hand column, para 4, last two lines, it states: "*...in Boltzman equilibrium and 0.1 μm diameter particles carry an average of 0.67 charges. Exposure to the power-line corona would increase this to 0.78 charges."* This represents a 16.4% increase in charge. In Henshaw (2002) I also assumed a 16% increase in charge state, which based on existing research would be expected to increase lung deposition by 30%. In other words, the Jeffers' calculations agree exactly with the values used for estimates of increased health risk.

17. Statement: Page 104, lines 4763-4774 & page 108, lines 4993-5006 & page 108, lines 5018-5028 Melatonin

Response: There is a great deal that could be said concerning these sections and we have already made a number of comments concerning melatonin.

There are difficulties with volunteer experiments exposed to laboratory-generated fields. Henshaw& Reiter (2005) says:

"*However, while these volunteer studies have been carefully designed and well-controlled, they nevertheless have a number of drawbacks: (i) the relatively small number of volunteers limits the ability statistically to resolve changes in melatonin secretion against the natural variations between individuals; (ii) exposures have tended to be for short periods compared with chronic exposures in real populations when the evidence in animals suggests that several days or weeks of exposure are required before effects on melatonin secretion become manifest; (iii) laboratory generated exposures may not contain features such as transients or rapid on/off changes in magnetic fields which have been shown effective in demonstrating melatonin suppression in animals and (iv) volunteer studies have not included exposure to electric fields which may also factor in melatonin disruption*."

As already stated, Henshaw & Reiter (2005) reviewed 14 studies of exposure to neighbourhood/environmental fields, comprising 12 studies for power frequency and 2 for fluctuations in the GM fields. Consistent evidence of melatonin disruption (changes in onset of the nocturnal rise, peak, or total overnight melatonin) was found, especially where switching of magnetic fields and/or electric fields were also present.

The following two sections concern areas of science which would normally fall outside the terms of reference of committees investigating the health effects of exposure to power frequency electric and magnetic fields.

3. Adverse health effects associated with fluctuations in solar and geomagnetic fields

The natural geomagnetic field of the Earth is far from static. Superimposed on the quasi-static, latitude dependent field, ranging from approximately 20 to 60 μT, are fluctuations on short-term time-scales. The so-called Schumann resonances, with principal ELF frequencies 7.8, 14.2, 19.6, 25.9, 32 and 41 Hz arise from cavity oscillations in the ionosphere induced by solar and global lightning activity. Some of these frequencies coincide with the frequency of certain brain rhythms. Other fluctuations, varying between 5 and 500 nT occur as a result of geomagnetic storms and are described over three hour periods by K-indices. This is in addition to nano-tesla changes resulting from the natural diurnal variations due to solar activity.

A range of adverse health effects not dissimilar to those associated with ELF EMFs have been reported as associated with fluctuations in the Earth's geomagnetic field. These have been partially reviewed by Ward (2006):
http://www.electric-fields.bris.ac.uk/Volume2%20Appendix1&2.pdf

A more comprehensive review has been made by Palmer *et al.* (2006).

This body of data provides information on adverse health effects of ELF EMF exposure by way of analogy and plausibility.

4. Animal navigation in the Earth's geomagnetic field

Many animal species are known to navigate by sensing small changes in the Earth's magnetic field. Birds have been identified as having compass and magnetic intensity information, the latter, attributed to magnetite in their beaks, enabling changes as low as 10 nT to be detected. Ritz *et al.* (2004) identified robins as possessing compass information by means of a radical pair mechanism involving detection of field changes as low as 84 nT. In a recent review, Wiltschko and Wiltschko (2006) described this mechanism in birds as due to an array of magneto-receptors, consisting of photopigments, postulated to be cryptochromes, situated in the right eye (Cryptochromes are also found in the human retina). For magneto-reception to occur, visible light of a particular wavelength initiates radical pair production from which magneto-reception occurs from the detection of the ratio of singlet to triplet spin states. It would appear that in birds these photopigment arrays constitute the necessary mechanism for amplifying magnetic field interaction with a single pair spin state to a signal of sufficient amplitude to be interpreted and registered by the brain.

How do these finding relate to adverse health effects of ELF EMFs in humans? They demonstrate a biological mechanism for the detection of low intensity magnetic fields (in the tens of nT regime), and one which involves one of the candidate mechanisms for adverse health effects of ELF field exposure. The finding that in birds magneto-reception occurs in the eye, at the site of the newly discovered ganglion cells which signal the pineal gland to

produce nocturnal melatonin, is intriguing (Berson *et al.* 2002, Hattar *et al.* 2002). Equally intriguing, in salamanders the magneto-receptors have been found to be located in the pineal gland itself (Deutschlander *et al*. 1999, Adler & Taylor 1980). With time-scales of microseconds, the radical pair mechanism will not discriminate between static or power frequency fields, thus extending the mechanism, to the existing body of work on the adverse effects of power-frequency magnetic fields. This does not mean that the quasi-static field from power supply will be dwarfed by the geo-magnetic field, for the evidence relates to animals detecting *changes* in the geo-magnetic field. The alternating fields from power supply therefore may fall within the scope of bio-detection.

An important principle for ELF and RF fields is that if a signal or exposure can be detected, in principle it can have an effect. This is an '*information effect*' – one which needs only the energy necessary to transmit the information, not the energy to create an energetic effect directly. Such information effects might be suspected where there are intricate control systems and in-built amplification mechanisms. It sometimes seems as though the established review bodies have been unable to consider such information effects and have been prejudiced by a supposed implausibility of energetic effects.

Appendix 1

Aggregating epidemiological evidence: comparing two seminal EMF reviews

(Statistical comparison of the reviews of epidemiological studies of adult leukaemia from the California Department of Health Services (CDHS) EMF Report (2002) and the International Agency for Research on Cancer, IARC Report (2002).)

Summary

Two seminal reviews (IARC 2002, CDHS 2002) of possible health effects from power-frequency EMFs reached partly different conclusions from largely similar epidemiological evidence. These differences can have an impact on precautionary policy.

We examine the statistical aggregation of results from individual disparate studies. Without consistent exposure metrics, the advantage of meta-analysis and pooling to estimate magnitude of effect and confidence limits is lost. However, counting positive results and statistically significant results yields important information with p-values reflecting the overall strength of evidence.

Representative results from 33 independent adult leukaemia studies tabled by IARC yielded 23.5 positives ($p \approx 0.01$) and 9 significant-positives ($p < 10^{-7}$). From 43 representative results from CDHS, there were 32 positive ($p < 0.001$) and 14 significant-positives ($p < 10^{-12}$). There were no significant-negative results in either list. Results for adult brain cancer gave a similar, but less clear, message.

Results for childhood leukaemia suggests they are not stronger, numerically, than those for adult leukaemia, and that formal pooling of coherent studies shows a stronger association than aggregating all the studies.

CDHS did not note the number of significant positives, but noted the meta-analytic summary and the number of positives, forming a view about the strength of these findings. IARC shows no evidence of considering the aggregation of results other than subjectively. It considered individual studies but this led to a tendency to fragment and dismiss evidence which is intrinsically highly significant. We make recommendations for future reviews.

1. Introduction

The key purpose behind this paper is to try to understand how two seminal reports from major health bodies, reviewing the possible health effects of exposure to power frequency electric and magnetic fields (EMFs), reached different conclusions from what was largely the same body of evidence. While there are constitutional and procedural differences between the review bodies, we have focused on a striking difference in how they went from critical review of the many individual studies of EMF health effects to a summative assessment of the overall weight of evidence.

The review bodies were the International Agency for Research on Cancer (IARC), an agency of the World Health Organization, and the California EMF Program team of the California Department of Health Services (CDHS). Both published the reports of their reviews of EMFs and health in 2002. Both rated power-frequency EMFs as "*possibly carcinogenic to humans*" (the IARC class 2B), on the basis of epidemiological evidence relating to childhood leukaemia. In respect of all other cancers IARC concluded the epidemiological evidence was "*inadequate*", whereas CDHS concluded it was "*limited*" for four other health outcomes, including two cancers. The "*limited*" assessment supports class 2B for the agent.

There have been other reviews, before and since 2002. For example, the NRPB reviews in the UK have consistently recognised the possibility of cause of cancer, but did not use a formal classification system for assessment. Some reviews never reached publication, for example in the US the NCRP review in 1995, though its conclusions were leaked. The subject of power-frequency EMFs has been controversial. In the 1990s there were calls to halt research funding on the basis that any potential risk had been dismissed. However, the evidence of adverse health effects has persisted to the point that precaution against exposure to EMFs is now being considered.

The US National Institute of Environmental Health Sciences (NIEHS) EMF-Rapid programme concluded in 1998 that the evidence for both childhood and adult leukaemia supported a 2B classification. Two key pooled analyses, Ahlbom *et al.* (2000) and Greenland *et al.* (2000) reinforced concerns, showing, by statistical aggregation, that the fragmented findings for childhood leukaemia became stronger when pooled, the former revealing a 2-fold increase in risk associated with time-weighted average magnetic field exposures above 0.4 μT, the latter a 1.7-fold increase above 0.3 μT.

When IARC made its formal 2B classification in 2002 against this background, a basis was set for precautionary policy which is under development in several countries and in the WHO. Policy based on the risk of childhood leukaemia alone tends to be limited, because the normal incidence is comparatively rare and the attributable risk very small. The question of additional risk of other diseases then becomes important. Hence the California review, by recognising five health outcomes corresponding to the 2B classification, challenges the limitation of proportionate precautionary measures to those of very low cost.

An understanding of the differences between these seminal reviews is therefore important to the present development of precautionary policy for EMFs.

2. The two seminal EMF health reviews of IARC and CDHS

Both IARC (2002) and CDHS (2002) evaluated the possible risks to public health from EMFs at supply frequency. CDHS considered only power-frequency EMFs, whereas IARC considered other frequencies but specifically assessed power frequency (or ELF). IARC assessed carcinogenic risk whereas CDHS assessed both carcinogenic and other health outcomes. Nevertheless the two reviews had a large area of common ground in the body of evidence relating to power-frequency fields and various cancer outcomes.

The formative work for IARC 2002 was carried out at a Working Group meeting in June 2001. The CDHS programme extended over several years with *Consultation Draft 3* published in April 2001. IARC (2002) did not refer to recent CDHS drafts but did refer to an earlier progress review (Neutra *et al*. 1996). The final report CDHS 2002 referred to IARC (2001 in press) and particularly addressed the question of their differing conclusions.

IARC (2002) listed some 800 references, covering both ELF (mainly power-frequency) and static fields. CDHS listed some 400 references (ELF only).

The IARC classification system formally combines assessments of evidence in humans (essentially epidemiology) and evidence in animals. Both reviews were agreed in assessing the evidence in animals as "*inadequate*". A particular difficulty in relation to childhood leukaemia is that animal studies could be considered inappropriate since there is no animal model for acute lymphoblastic leukaemia, the common leukaemia type in children. Both reviews were agreed in assessing the evidence in humans in relation to childhood leukaemia as "*limited*", and hence were led by the formal classification system to the overall IARC 2B assessment.

CDHS 2002 uses another formal system of assessment, a "*qualitative Bayes*" approach, which is a central feature of the review and an interesting innovation. However, for the purpose of comparison, they also provide assessments on the IARC classification system. The five health outcomes identified by CDHS as each warranting IARC 2B classification of EMFs were childhood leukaemia, adult leukaemia, adult brain cancer, miscarriage and amyotrophic lateral sclerosis (ALS), a form of motor neurone disease.

This paper compares the bases of epidemiological evidence in the two reviews, specifically for adult leukaemia and adult brain cancer. Considering the aggregate value of the evidence should have some bearing on its formal assessment and should illuminate the differences in the reviews' conclusions.

3. Statistical aggregation of disparate findings from epidemiological studies

It is not unusual to find a range of reasonably independent epidemiological studies, each with its limitations and statistically weak findings, but nevertheless with an overall tendency to indicate a possible effect. One way of aggregating the evidence from such studies is by meta-analysis or pooling, which may be defined in slightly different ways. This has the advantage of estimating the magnitude of an effect and providing confidence limits from the aggregate evidence. Such estimates are most meaningful when aggregating on a like-for-like basis with

regard to exposure metric, specificity of cases, relevant subsets of population and study methods.

Sometimes the evidence is more disparate, so that only limited numbers of similar studies can be pooled to give very meaningful estimates of parameters such as risk estimates representing magnitude of a possible effect. For example, in the context of EMF, the majority of studies have been concerned with the effects of exposure to magnetic fields. Studies may vary according to type of exposure (residential, occupational), subsets of population (gender, race, age, susceptibility), exposure metric or proxy (measurement, proximity, job title, average, peak), or risk measure (Odds Ratio or Standardised Incidence Rate) and so on.

While taking account of the caveats and qualifications relating to significance and hypothesis testing, as discussed for example in Rothman and Greenland, 1998, chapter 12, it is nevertheless possible to make some assessment of the strength of aggregate disparate evidence. This may be useful in supporting formal assessment of evidence, in comparing different aggregate sets of studies and in comparing different conclusions reached by review bodies.

This paper illustrates two simple methods of aggregation: counting numbers of positive findings and counting numbers of statistically significant positive findings. The more disparate the studies and findings considered, the blunter the implied hypothesis, whose negation is the null hypothesis under examination. For example, aggregating both residential and occupational studies implies a hypothesis that both "exposures" are causal risk factors for the specified disease. That is more demanding than a choice of either sharper hypothesis with a more consistent exposure. It is not the purpose of this paper to provide a formal analysis of sharp, blunt and compound hypotheses.

4. General comparison of evidence bases for adult leukaemia

IARC selected and tabled results including OR or SIR with CI data from 37 (33 independent) human epidemiology studies for adult leukaemia, and CDHS did so for 43. However, despite the reviews' publication in the same year and despite the common reference to previous reviews, these sets of studies had surprising differences. Both reviews identify residential and occupational studies specific to adult leukaemia. IARC's 37 included 6 residential whereas CDHS's 43 only included 2 residential.

The 43 studies listed by CDHS are derived principally from the same reference source (Kheifets *et al.* 1997a). Of the 41 occupational studies, 17 are included in the IARC tables for adult leukaemia, 18 are not (of which 5 are however listed in IARC's references), and the other 6 refer to similar studies by the same authors (e.g. with different dates), so may overlap.

Of the 32 occupational studies considered by IARC, after deducting 17 common and 6 similar studies, there remain 9 which are not in CDHS. Of the 6 residential studies listed by IARC (Table 25), only one (Severson 1998) is listed in the CDHS table for adult leukaemia. The second residential study listed by CDHS is Wertheimer & Leeper 1982, which is not in IARC's Table 25.

Of the 41 occupational studies listed by CDHS, there are two sets of multiple studies from the same source (three from Theriault *et al.* 1994 and two from Tynes *et al.* 1994; the

bibliography lists two studies by Theriault *et al.* 1994 and two by Tynes *et al.* 1994). IARC lists three studies by Theriault *et al.* 1994, in Quebec, France and Ontario, and a fourth updating paper by Miller *et al.* 1996.

Both reviews take account of the caveats and qualifications in the various studies, and comment on their shortcomings, and draw on previous reviews in that respect. Neither review body is unaware of these qualitative considerations. Both are aware of the potential for bias and confounding and both address this specifically. Their conclusions however do give different weight to the human epidemiology studies in aggregate; this was the main observation in the CDHS comparison of the two reviews and reasons for their differences. This paper examines the statistical aggregation of evidence for the two reviews' sets of studies.

5. Statistical aggregation of the CDHS set of adult leukaemia studies

In the CDHS set of adult leukaemia studies, there are similar relative risks or odds ratios for the residential and the occupational studies. While the exposures are disparate between residential and occupational studies, the strengths of association are similar. The summary table (fig. 8.1.1, page 121) combined one odds ratio (OR) result, with its 95% confidence interval (CI), from each of the 43 studies. Taking all 43 studies together, the meta-analytic summary was OR = 1.2 with CI = 1.12 - 1.24. (The CI was given in the draft 3 CDHS report but not in the final version). The summary notes that 29 had OR > 1 with $p \leq 0.01$. That is, in aggregate the occurrence of positive results is statistically significant at a 99% confidence level. The selection of studies and of results from each study was derived principally from a previous reviewer (Kheifets *et al.*) and adopted by CDHS in preference to introducing their own selection. Hence the 43 results were taken as independent.

There were 6 results with OR = 1.00 within the truncation of the report. It is more appropriate to count such results as half negative and half positive, as that would give an unbiased estimate of the true value (50%) under the null hypothesis. Some studies in other sets have a coarser truncation to only one decimal place, with a more substantial truncation bias. While CDHS deploy what they call the sign test, they use a biased version of it which substantially understates the strength of evidence. In the above, including results with OR = 1.00 as half positive and half negative gives 32 positive results with $p < 0.001$, which is highly significant.

A much stronger statistical observation, not made by CDHS, is the number of significant positive results. They are results with 95% confidence intervals wholly above 1. Although the intervals may be based on two-sided p-values of 0.05, they invariably correspond to one-sided values of 0.025 for positive results. There are no significant-negative results in the reviewers' lists for adult leukaemia. Whether the confidence limits have been calculated by a fully frequentist approach or by inference from sample to whole population, each occurrence of a significant-positive result will have, by the same statistical model as used in the calculation, a probability $p < 0.025$.

There are 9 such occurrences, that is strictly significant-positive results from the 43 listed results, with lower confidence limit (CL) strictly > 1, plus 5 results with lower CL = 1.00, and no significant negatives. The significance boundary is different from the 50-50 split for simple positives, so that a marginal occurrence with lower confidence limit equal to 1 might now be counted as with $p = 0.025$ for the occurrence. Although the truncation may slightly

bias an estimate of a true value under a null hypothesis, it will be a good approximation as long as the truncation error (here 0.005) is small compared with OR - 1, which it is.

Therefore, such marginal occurrences of significant-positives should reasonably be fully counted as instances with p = 0.025, giving 14 in all. As long as these results are independent, and considering only random error and not bias or confounding (which have been addressed in the reviews), the probability of 14 such results out of 43 can be calculated by the cumulative binomial distribution as about 10^{-12}, which is extremely significant. Even that is conservative, for most of the separate p-values will be strictly less than 0.025. Even if the 5 marginal occurrences were only counted as halves there would still be 11.5 occurrences with aggregate p-value approximately 10^{-8}, which is still extremely significant, although that would not be the appropriate form of counting.

Although CDHS did not note the number of significant positives, they did note the meta-analytic summary and the number of positives, and formed a view about the strength of these findings which led them to give them greater weight than, seemingly, did IARC. The aggregation of the studies considered by CDHS is summarised in Table 1.

Table 1. Aggregation of the adult leukaemia (AL) studies considered by CDHS (2002).

CDHS / AL (1 per study)	No. of ORs	Positives	p-value for positives	Significant Positives	p-value for sig-pos*
Residential	2	2	0.25	1	0.049
occupational	41	30	0.002	13	1×10^{-11}
Total	43	32	0.001	14	1×10^{-12}

*One-sided, p <0.025

6. Statistical aggregation of the adult leukaemia results chosen by IARC.

IARC discusses a range of adult leukaemia studies and selects 37 studies with ORs or SIRs with CI data for summary description in Tables 25, 29 and 30. The Tables list some 176 results including multiple results from single studies, and including both high and low exposure categories. These are not independent, e.g. some are totals of other results for sub-types of leukaemia, so aggregating them by cumulative binomial distribution would not be valid.

It is surprising however, not least since low exposure categories may dilute the overall apparent significance, that simply lumping all the IARC-reported results together (omitting only base or reference levels) would show an apparent strong aggregation, with 111.5 positive results and 31 significant-positives out of the 176. If the results were independent, those counts would have p-values of 0.0003 and 3×10^{-15} respectively, which we note for reference when considering the effect of selecting more independent subsets of results. Truncated marginal ORs or lower CLs are again counted as explained above for CDHS.

In order to obtain a more independent set of results for aggregation, select at most one representative result from each study, using a common set of selection criteria:

- Omit studies and results which do not record either the OR or the CI.
- Where there are multiple results for sub-types of leukaemia, select only the total or "all leukaemias" results, if available, so that sub-type results are not repeated. While this loses specificity, and so may dilute findings, the alternative would be to apply the same specificity throughout all selected studies. Likewise, take Theriault *et al.* 1994 combined cohort results, not the separate ones for France, Quebec and Ontario.
- Where there are separate results tabled for different exposure bands from the same study, select only the highest band, so that the most relevant test to detect an effect (positive or negative) is used. That will typically be with a cut point at 0.2 μT, which is lower than the principal categories of Ahlbom *et al.* and Greenland *et al.* for childhood leukaemia.
- Where there are separate results for different occupations, select the results for the occupation likely to be most exposed, and if that is not known, select the most populous result.
- Where there are different results for males and females, and no combined gender results, select the most populous results (usually males). While this loses specificity, the alternative would be to seek separate results for males (or females) throughout all selected studies.
- Where the choice remains ambiguous on the above criteria, and yet would make a difference, select an appropriate balance, e.g. half positive and half negative.
- Where two papers from the same source draw on the same data set but analyse it in different ways, select only one result using the above criteria.

We emphasise that these are our selection criteria. They were not applied by either of the review bodies.

Such a selection leads to the summary in Table 2. While still showing highly significant results, selection has moderated, not exaggerated, the strength of the crudely aggregated original data. For example, the results would have been slightly stronger if the significant-positive finding by Alfredson *et al.* (1996) for 10 lymphocytic leukaemia cases for ages 20 - 64 years were included; while some significant information was lost, the objective selection criteria chose 20 all-leukaemia all-ages cases instead.

Table 2. Aggregation of studies of adult leukaemia in IARC (2002) on the basis of selection criteria to identify one representative result per study

IARC / AL (1 per study)	No. of ORs	Positives	p-value for positives	Significant positives	p-value for sig-pos
Residential cohort	5	3.5	0.19 - 0.5	2	0.0059
occupational case-control	17	11.5	0.07 - 0.17	4	0.0007
occupational	11	8.5	0.03 - 0.11	3	0.002
Total	33	23.5	0.007 - 0.018	9	1×10^{-7}

Further selection may be made according to the additional criteria:

- Omit results which give low cumulative exposures in μT-years, typically below average 0.2 μT.
- Omit occupational studies which give no estimate of exposure.

This gives the results in Table 3.

Table 3. Aggregation of studies of adult leukaemia in IARC (2002) on the basis of additional selection criteria to identify results with comparable exposures

IARC / AL (select results)	No. of ORs	Positives	p-value for positives	Significant positives	p-value for Sig-Pos
Residential Cohort	4	3.5	0.06 - 0.31	2	0.0036
occupational case-control	4	4	0.0625	2	0.0036
occupational	5	4	0.1875	2	0.0059
Total	13	11.5	0.002 - 0.01	6	3.6×10^{-7}

As would be expected, the effect of our selection is to reduce numbers of results admitted, and to reduce p-values, while increasing the percentage both of positive results and of significant-positive results.

IARC also summarises 4 studies of electric fields (EF) and adult leukaemia (Table 31). Leaving out the baseline (reference) exposure bands, there are 23 ORs of which 13 are positive, with 2 significant positives and no significant negatives. The p-values are 0.34 for the positives and 0.11 for the significant positives. Selection of high exposure results does not substantially change the picture. These studies do not give the same kind of message as the magnetic field results.

7. Comparison of reviews for adult brain cancer

CDHS again addresses the question of aggregation, citing 32 studies for adult brain cancer in Table 9.1.1, comprising 29 for occupational and 3 for residential exposures, and listing one representative result for each study (OR or other risk measure, with confidence limits). CDHS refers to a meta-analysis by Kheifets of the 29 occupational studies with overall OR of 1.2 (95% CI: 1.1 - 1.3) and to numbers of positive results and numbers with OR above 1.2. CDHS did not count numbers of significant results.

In Table 9.2.2 CDHS includes 7 additional studies to the 32 in Table 9.1.1 but gives confidence intervals for only 5 of them. One study combines residential and occupational exposure, and one is for electric fields (with a significant positive result). While CDHS discusses these additional 7 studies, they are not included in its aggregation (and make little overall difference to it). Our summary for the 32 cited studies is given in Table 4.

Table 4. Aggregation of studies of adult brain cancer in CDHS (2002)

CDHS/ brain (1 per study)	No. of ORs or risk measures	Positives	p-value for positives	Significant positives	p-value for sig-pos
Residential	3	2	0.5	0	1.0
occupational	29	23	0.001	6	7×10^{-5}
Total	32	25	0.001	6	0.0001

While these aggregations are not as strong as those for adult leukaemia, they are highly significant.

IARC selects 38 studies with brain cancer results for setting out in its main tables, of which 5 are residential (Table 26), 15 are occupational cohort studies (Table 29) and 18 are occupational case-control studies (Table 30). The respective numbers of results with risk measures and confidence intervals are 24, 32 and 53, that is 109 in all, but these include repetition of sub-type results in totals and include low-exposure as well as higher-exposure results from the same studies.

These studies include two (Spinelli 1995 and Ronneberg *et al.* 1999) which are for exposures to static magnetic fields. They would have been better excluded when assessing results for ELF (principally power-frequency) fields, as the two exposures are quite different. However, the CDHS lists also included one of these studies, Spinelli 1995, with results for both brain cancer (positive) and for leukaemia (negative). IARC includes these plus the negative results from Ronneberg *et al.* 1999. In treating CDHS and IARC comparably, these inappropriate results are here left in. The effect is slight, by way of diluting any overall findings.

Of the 109 crude results, 71 are positive and 16 are significant-positive. That would be highly significant under a null hypothesis for independent results. There are also 3 significant-negative results, each with the upper confidence limit just on 1.0. That would not be remarkable under a null hypothesis for 109 independent results ($p = 0.51$), but could be under a stronger alternative test hypothesis with a positive association.

One significant-negative result is for a low-exposure category residential study in Table 26; that study is declared for "nervous system" cancer rather than brain cancer *per se* but it is included in Table 26 which is for brain cancer. The other two significant-negatives are in Table 29 and are for males, while they are accompanied by non-significant positives for females; the selection criteria chose the more populous males, though if males and females were combined the significance would be lost. One significant-positive result was similar but the other way round, being just significant-positive for males alongside a non-significant negative for the less populous females. Some significant-positives listed for Cocco *et al.* 1999 in Table 30 may look suspicious at first sight, as three are reported as having OR as 1.2 (95% CI = 1.1-1.2), which seem odd but could be accounted for by round-off from, for example, 1.17 (1.11-1.24) consistent with the usual log-normal model.

Applying our selection criteria obtains a more independent set of results, at most one per study, although as noted above it selects more populous male studies which would be partly countered by female studies. One study remained ambiguous and offered alternative opposite results of fairly equal weight (in Table 29, the Floderus *et al,* 1994, study of engine drivers or railway workers from the sixties or seventies); it was represented here as half positive and half negative. The result of selecting one result per study is summarised in Table 5.

Table 5: Aggregation of studies of adult brain cancer in IARC (2002) on the basis of selection criteria to identify one representative result per study

IARC/ brain (1 per study)	No. of ORs	Positives	p-value for positives	Significant positives	p-value for sig-pos
residential cohort	5	3	0.5	0	1.0
occupational case-control	15	9.5	0.15 - 0.3	3	0.0057
occupational	15	10	0.15	3	0.0057
total	35	22.5	0.04 - 0.09	6	0.0002

At this point the selection process has greatly weakened the aggregate evidence, largely because so many stronger results were in subsets. The selected evidence remains significant, if marginally so, and should not be dismissed, although it would not have the same statistical weight in assessment as that for adult leukaemia. In addition, the significance of the number of significant-positive results is tempered by the existence of three marginal significant-negatives in the crude data set, two of which survived selection of one result per study.

Applying the extra set of selection criteria loses even more strength of evidence, as so many of the brain cancer studies do not have an exposure assessment in terms of field strength. The result, in Table 6, has now lost significance, bearing in mind that one significant-negative result was also selected.

Table 6: Aggregation of studies of adult brain cancer in IARC (2002) on the basis of selection criteria to identify results with comparable exposures

IARC / brain (select results)	No. of ORs	Positives	p-value for positives	Significant positives	p-value for sig-pos
residential cohort	5	3	0.5	0	1.0
occupational case-control	4	3	0.3	2	0.0036
occupational	5	3	0.5	0	1.0
total	14	9	0.2	2	0.047

8. Comparison with evidence on childhood leukaemia

The same approach to aggregation may be applied to the CDHS set of 19 studies for childhood leukaemia listed in Table 8.1.2. As with other health outcomes, CDHS applies its "sign test" and observes the 16 positive results out of 19, citing p = 0.0004 although our cumulative binomial calculation for 16 or more out of 19 gives p = 0.002. CDHS does not consider the number of significant results (3 out of 19; p = 0.01). There were no significant negative results and no results for OR or CLs truncated to 1.00.

IARC tables detailed results for childhood leukaemia for 14 childhood leukaemia studies in Tables 18, 19 and 23, comprising 10 residential exposure studies and 4 relating to use of domestic appliances. Applying the same processes as for adult leukaemia, we find out of 14 results (one per study) there are 13 positive and 3 significant-positive results, with p-values of 0.0009 and 0.005 respectively.

On this assessment of the value of the listed sets of studies, the evidence for adult leukaemia appears more significant than that for childhood leukaemia. However, we have not taken into account consistency of exposure type or measurement, nor of magnitude of apparent effect such as represented by ORs. CDHS refers to Wartenberg 2001 with a meta-analytic summary OR of 1.3 (1.0 - 1.7) for childhood leukaemia. This might reasonably be compared with the meta-analytic summaries cited for adult leukaemia of 1.2 (1.12 - 1.24) and for brain cancer of 1.2 (1.1 - 1.3) with reference to Kheifets *et al.* (1997a). There is not much difference between all three cancer groups at this level of meta-analysis.

The two more selective pooled analyses for childhood leukaemia, with ORs of 1.69 (1.25 - 2.29) for exposures above 0.3 μT by Greenland *et al.* (2000) and 2.00 (1.27 - 3.13) for exposures above 0.4 μT by Ahlbom *et al.* (2000) provide stronger results by focusing on fewer more coherent and comparable studies. Although the adult leukaemia and brain

cancer studies may be more disparate than those entirely residential studies pooled for childhood leukaemia, it would seem plausible that if they had better exposures measurements which could be used for selection, the result would also be to strengthen the overall finding.

9. Conclusions

There is a risk that review bodies, however august, may overlook the statistical weight of aggregate evidence in a collection of disparate studies which are individually inconclusive. It would be helpful in improving confidence in their reviews and assessment decisions if the issue of aggregation of disparate evidence could be seen to be addressed explicitly, preferably by a formal pooled analysis or meta-analysis to give an overall risk estimate, or if that is not available at least by the sort of significance analysis which we have demonstrated in this paper.

In aggregating evidence by the simple significance analysis we illustrate, when using the "sign test" (counting numbers of positive results), odds ratios reported as truncated at 1.0 or 1.00 etc. should be counted as half positive and not discounted. Counting numbers of significant results in this case gives stronger information than the simple sign test. If using the cumulative binomial distribution to assess the significance of numbers of positive results or of significant-positive results, it is important that the individual results are independent. We have suggested a set of selection criteria to produce at most one result per study for this purpose. However, one disadvantage of this approach is that a genuine raised risk in a particular cancer sub-type, could become lost in considering all subtypes in one group, for example *all leukaemia*, or *all brain cancer*.

The CDHS has addressed the aggregation of results, using the sign test and referring to external meta-analytic summaries, but it has not considered counts of significant results. The IARC review shows no evidence of having considered the aggregation of results other than subjectively. It has considered individual studies in detail and identified their shortcomings, but this has led to a tendency to fragment and dismiss evidence which is intrinsically highly significant.

Review bodies have a right to dismiss evidence on rational grounds, taking into account potential bias, confounding and methodological limitations as well as statistical strength, but should not do so without being seen also to take statistical aggregation into account.

The CDHS review, quite apart from its interesting and innovative qualitative Bayes approach, offers a useful complementary insight into the weight of epidemiological evidence in human studies. It adds a perspective which the mainstream international review bodies seem to have overlooked.

The differences in the conclusions of the IARC and CDHS reviews are not explained by differences in the sets of studies they considered. Their overlapping data sets on adult leukaemia, while surprisingly different in the studies included, both represent a highly significant body of aggregated evidence. In the case of brain cancer, the crude sets of data both appear highly significant in aggregate, though our selection criteria applied to the IARC data produced only a marginally significant aggregate result.

It is debatable whether the IARC classification system should be used to distinguish between specific diseases, since it seems to be designed to classify agents. It would be reasonable for the IARC classification to refer to evidence on childhood leukaemia in reaching a 2B classification. The additional evidence on adult leukaemia and brain cancer might then add further support, when taken in addition to childhood leukaemia.

By separating the evidence in humans for "all other cancers" (besides childhood leukaemia) and summarily classifying it as "inadequate" (section 5.5 page 338) IARC may be seen as effectively promoting a hypothesis that EMFs may be a cause of childhood leukaemia alone and of no other cancers. That is how we see policy makers interpreting it. We do not think this is rational for complex multi-causal diseases, especially bearing in mind evidence for possible systemic effects which could affect causation of several diseases. IARC does not seem to have addressed the question of compound hypotheses.

This exclusive attribution of the IARC 2B classification to childhood leukaemia has repercussions in precautionary policy, as manifest in the draft WHO Precautionary Framework (2006). Owing to its rarity, childhood leukaemia has relatively little impact on society and its avoidance relatively little benefit, compared with the substantially more prevalent adult leukaemia and brain cancer, as well as the other outcomes rated as 2B by CDHS.

An earlier review by the NIEHS 1999 had associated both adult and childhood leukaemia with a 2B classification, and both the IARC and CDHS reviews were informed by this. Given the extent and aggregate strength of the evidence for adult leukaemia, both in itself and in comparison with that for childhood leukaemia, it is difficult to see a clear division which would support an exclusive hypothesis of carcinogenicity of EMFs for childhood leukaemia but not for adult leukaemia.

10. Recommendations

The following recommendations are made for future reviews of EMF health effects

(i) IARC and other review bodies should incorporate expressly into their methodology some assessment of aggregate value of disparate evidence. Such assessment should not itself determine the overall assessment decision, but it is better to be aware of the nature of the aggregated data.

(ii) A focused pooled analysis should be undertaken for adult leukaemia to parallel, as far as possible, those of Ahlbom *et al.* and Greenland *et al.* for childhood leukaemia.

(iii) Advisory bodies considering precautionary policy relating to EMFs should take into account both the IARC and CDHS reviews, including the failure of IARC to demonstrate any assessment of aggregate value of evidence.

(iv) The WHO EMF team, in forming its Precautionary Framework, should expressly address the impact of possible health outcomes other than childhood leukaemia, noting especially their relatively high incidence compared with childhood leukaemia, and giving particular attention to the five outcomes classified by CDHS as corresponding to IARC class 2B.

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Full references are not reproduced here for every study mentioned in the reviews, since references appear in the reviews themselves and their mention in this paper is concerned only with how they are counted in the reviews.

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Appendix 2

DRAFT – Version 1 29/6/06: Adverse health effects associated with exposure to ELF electric and magnetic fields – assembly of scientific evidence and discussion of possible public health impact - Summary

M. J. O'Carroll[1] & D. L. Henshaw[2] with help from J. Close, J. Ward, S. Limb, E. Ainsbury, A. Buckley, P. Keitch, J. Matthews and M. Wright. [1]University of Sunderland, Garden House, Welbury, Northallerton, DL6 2SE, UK. [2]H H Wills Physics Laboratory, University of Bristol, Tyndall Avenue, Bristol, BS8 1TL, UK

The summary below is taken from a 160-page draft document which assesses the scientific evidence for the range of adverse health effects which have been associated with exposure to power frequency electric and magnetic fields. The document also carries out cost impact analysis for the UK population on the basis of a number of "*what if*" scenarios. The main conclusion, given in the first table, shows that when illnesses other than childhood leukaemia are considered, it becomes cost-beneficial to consider active remedial measures to reduce exposure to power frequency electric and magnetic fields.

The full document (in three volumes) may be accessed at:
http://www.electric-fields.bris.ac.uk/ocarroll.html

Summary

The following table gives the total impact on society, in thousands of pounds per year per 1,000 exposed population, from EMF exposure for five '*what-if*' scenarios, as calculated in a moderate and transparent way in section 2.3 of the main document. The impact of other diseases is of the order of 100 times greater than that of childhood leukaemia alone.

	CL alone[1]	NIEHS 2[2]	CDHS 5[3]	CDHS 11[4]	12 diseases[5]
With credibility factors	4	70	146	679	716
With definite causation	5	122	246	1899	2629

[1]Childhood leukaemia; [2]Childhood and adult leukaemia; [3]as 2 plus adult brain cancer, ALS and miscarriage; [4]full list in CDHS 2002; [5]as 4 plus depression.

We do not think it is rational to base an assessment of cost impact on childhood leukaemia alone, when most of the hypothesised mechanisms and their supporting evidence relates to biological systems involved in many diseases, rather than exclusively to childhood leukaemia. The decreasing 'Degree of Certainty' [as described in CDHS 2002] with greater numbers of diseases is however reflected in the credibility factors. Therefore, while there remains considerable uncertainty and imprecision in such assessments, it seems sensible to give consideration to the above scenarios and multiple outcomes, without adopting any one as definitive.

The next table shows the numbers of ELF-EMF epidemiological studies covered in major reviews to 2002, as explained in section 2.2. This shows that, on the basis of numbers of studies and their statistical strength, there is stronger evidence for some other diseases than for childhood leukaemia.

Disease	Studies	Positives	Significant positives	Significant negatives
Childhood leukaemia	19	16	3	0
Adult leukaemia	43	32	11	0
9 other diseases	150	110	36	1
Total	212	158	50	1

Since 2002 there have been many new studies increasing knowledge of potential mechanisms. Important earlier studies have been overlooked in the major reviews, for example the results of Schuz *et al.* (2001) showing stronger associations of childhood leukaemia with nocturnal exposure, with its implications for the melatonin hypothesis.

In addition, we note two substantial areas of established and relevant research which have also been largely overlooked: solar and geomagnetic activity (S-GMA), which includes ELF exposure and bio-detection of magnetic fields by migrating birds and other animals. Both give firm implications for biological effects of very low fields. The first reinforces implications of ELF EMFs for various diseases. The second reinforces implications for biological mechanisms by which this may be possible.

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