HPA-RPD (formerly National Radiological Protection Board)
Report of an independent Advisory Group on Non-ionising Radiation: Power Frequency Electromagnetic Fields, Melatonin and the Risk of Breast Cancer – February 2006

Critique by

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Summary

Some parts of the Report are satisfactory but the melatonin/cancer connection is not well illustrated considering the large amount of data available. As a result, the Report is rather un-authoritative when it discusses melatonin and cancer. There appears to be scientific misunderstanding and confusion in certain areas and lack of insightful comment. The widely differing concentrations of melatonin in blood, within cells and in certain organs is not discussed nor the reasons for its efficacy as an antioxidant and radical scavenger. The distinction between *electric fields* (EFs), *magnetic fields* (MFs) and *electric and magnetic fields* (EMFs) is not brought out, especially in relation to reported effects of melatonin and circadian rhythm disruption in the human body. The limitations of human volunteer studies involving acute magnetic fields exposures are only briefly discussed. The body of studies for populations chronically exposed to neighbourhood EMFs, including some volunteer studies where exposure was carried out over several days, is not collated in a way which illustrates the overall trend in melatonin suppression/disruption. Reports of melatonin disruption and other adverse health effects resulting from fluctuations in the earth's geomagnetic field are not mentioned. More should have been said about the use of melatonin in the treatment of breast cancer. Important work published in the peer-reviewed literature, of core relevance to EMFs, melatonin and cancer is not cited. While this report contains some useful reading, most evident is the lack of insightful comment at the research level.

2nd March 2006

Summary of specific issues not discussed or otherwise brought out in the AGNIR Melatonin Report

- A description of the widely differing natural concentrations of melatonin in cells, tissues and organs in the body, and its multiple actions, some of which are receptor mediated, making melatonin a broad-spectrum and ubiquitously-acting antioxidant.

- No conclusion drawn from the fact that the body of laboratory-controlled human volunteer studies of melatonin disruption by magnetic fields, appears to have been initiated by the results of Wever (1979) whose studies of circadian rhythm disruption concerned exposure to 2.5 V m^{-1} electric fields.

- In both animal and human volunteer studies, it is those involving longer-term (non-acute) exposures to magnetic fields (in some cases in the presence of electric fields) which have tended to show evidence of melatonin disruption.

- Studies of populations chronically exposed to neighbourhood electric and magnetic fields are consistent in providing evidence of melatonin suppression/disruption, sometimes involving very low field exposures.

- Dose-response issues relating to EMF exposures.

- The work by Blask *et al.* (2005), which was published after the AGNIR Report was compiled, which provides, in an animal model, an explicit demonstration that the normal physiological concentrations of nocturnal melatonin in human blood *per se* suppresses human breast cancer growth.

1. Introduction

This is a critique of what I have gleaned so far from the AGNIR Melatonin Report published on 9th February 2006. The views expressed are not entirely my own. I have taken account of discussions with scientists, especially outside the UK, and I have included copies of e-mails received where appropriate.

I will discuss aspects of the report under the following headings:

2. Melatonin as a radical scavenger and its concentration in the body

Section 3.8.6 on page 67 discusses the relative efficacy of melatonin as a free radical scavenger. Paragraph 2, lines 7 - 10 states: "*Its* [melatonin's] *role as a free radical scavenger at physiological concentrations and hence in vivo is less convincing, as there are many other cellular candidates such as glutathione, vitamin A, or vitamin E that are found in much higher natural concentrations than melatonin, and therefore potentially play a greater role in cellular defence*."

These assertions are not correct and it is evident that there is significant misunderstanding of both the action of melatonin and its concentration in the body. Unlike vitamins A, C and E and glutathione, melatonin enters cells and acts directly on the DNA as an antioxidant and radical scavenger. Therefore, the concentration of melatonin on the DNA is in fact high, while the concentration of vitamin E is much lower. In 2003, the *Journal of Pineal Research* carried an editorial note on this subject: *What constitutes a physiological concentration of melatonin?* (Vol 34, 79-80, 2003). A copy is attached to this critique.

I have raised this point with Professor Russ Reiter of the University of Texas Medical Center who gave the keynote address on melatonin at the CHILDREN with LEUKAEMIA Conference on the causes of childhood leukaemia in London in September 2004. Professor Reiter is widely regarded as the world-most leading expert on melatonin. The first of two e-mails received from him on 13/2/06 is given below:

Dear Denis

You are absolutely correct. In the blood, vitamin E is in higher levels than melatonin. However, when one compares melatonin's ability to protect DNA from oxidative damage relative to that of vitamin E, melatonin is significantly better. Unless they can prove the vitamin E is in higher concentrations than melatonin in the IMMEDIATE vicinity of DNA, they really do not know what they are talking about. This is a common error even among free radical biologists. Blood concentrations are irrelevant when one is worried about protection within cells. The highest concentrations of vitamin E within cells are in the lipid-rich environments, e.g., membranes. The environment around DNA is an aqueous environment; there is not much vitamin E present as a consequence.

It was great to hear from you. I send very best personal regards.

Russ Reiter

----- Original Message -----
From: "Denis Henshaw" <D.L.Henshaw@bristol.ac.uk>
To: <reiter@uthscsa.edu>
Sent: Monday, February 13, 2006 9:42 AM

The remaining bottom part of paragraph 2 of section 3.8.6 states: "*There is some evidence that the overall antioxidant activity of blood is correlated with melatonin content, at least in chicks (Albarran et al, 2001). Correlation does not of course establish causality. It is difficult to reconcile the fact that most melatonin produced is excreted as aMT6s, whereas if the molecule was oxidised other primary metabolites would be likely (eg N-acetyl N-formyl 5-methoxykynurenamine).*"

I have raised further questions with Professor Reiter, in relation to both the above and to vitamin A and glutathione. The text of an e-mail reply received on 21/2/06 is given below:

Dear Denis
The issue of antioxidants is a complex one because of their compartmentalization and there different modes of action. In reference to your questions.

What I said for vitamins E and C also applies to vitamin A and glutathione (GSH).

AFMK does appear in the urine in low quantities; it functions as a scavenger and is then converted to N1-acetyl-5-methoxykynuramine (AMK); so the half life of AFMK is presumably very short although this has never been measured directly.

In reference to our work with Dr Vijayalaxmi [**see below**], it presumably would have required much higher concentrations of vitamins E and C to achieve the same level of protection. In a similar situation, vitamin E and C concentrations had to be 60-70 higher than that of melatonin to achieve the same level of protection as that of melatonin (see: Qi W, Reiter RJ, Tan DX, et al. Environ Health Perspect 2000; 108: 399-402).

[unlike other antioxidants] Melatonin does scavenge 2 hydroxyl radicals and is converted to cyclic 3-hydroxymelatonin, which is also a scavenger. When melatonin scavenges other reactants it is converted to AFMK and eventually to AMK. Thus there is a cascade of reactions that allows melatonin to scavenge several reactants. (see: Tan DX et al, Endocrine J 1993; 1: 57-60 and Hardeland R. Endocrine 2005; 27: 119-130).

What you should mention is that melatonin is a powerful antioxidant because of its multiple actions. 1) Melatonin as well as its metabolites are all free radical scavengers. 2) Melatonin stimulates GSH synthesis by stimulating its rate-limiting enzyme, gamma-glutamylcysteine synthase; GSH is an important intracellular antioxidant. 3) Melatonin stimulates several antioxidative enzymes including SOD, GPx and GRd which greatly increase the potential of melatonin as an antioxidant (see Rodriguez C et al, J Pineal Res 2004; 36: 1-9). 4) Melatonin prevents electron leakage from the mitochondrial respiratory

chain thereby reducing free radical formation (see Leon J et al J Pineal Res 2005; 38: 1-9 and the Hardeland reference above).

The multiple actions of melatonin, some of which are receptor mediated, make melatonin a broad-spectrum and ubiquitously-acting antioxidant.

I hope this info is helpful.

Russ Reiter
----- Original Message -----
From: "Denis Henshaw" <D.L.Henshaw@bristol.ac.uk>
To: "'Russel J. Reiter'" <reiter@uthscsa.edu>
Sent: Monday, February 20, 2006 5:58 AM
Subject: From Denis Henshaw - further quick questions

As can be seen, there is a substantial body of knowledge concerning the efficacy of melatonin as a radical scavenger. One important set of data is provided by the work of Dr Vijayalaxmi, also at the University of Texas Medical Center, which was also presented at the CHILDREN with LEUKAEMIA Conference in September 2004. She has carried out experiments both in mice and in human blood *in vivo* on the ability of melatonin to act as a protector of damage from ionising radiation (Vijayalaxmi *et al.* 1998a & b, 1999; Badr *et al.* 1999). In Vijayalaxmi *et al.* (1998a) human volunteers took a single oral dose of 300 mg of melatonin. Blood samples were taken at 5-10 mins before and at 1 & 2 h following melatonin administration and exposed to 1.5 Gy gamma radiation. The blood taken at 1 & 2 h showed significant decreases (in the range 53 – 70%) in various types of chromosome damage in lymphocytes compared with the blood sample taken just prior to melatonin administration.

A second set of data concerns the literature on melatonin and glutathione referred to in Prof Reiter's e-mail. The following papers may be of interest: Barlow-Walden *et al.* 1995; Rodriguez *et al.* 2004; Martín *et al.* 2000; Pieri *et al.* 1994.

I am surprised that the AGNIR Report says so little about melatonin as a radical scavenger, given that this has a fundamental bearing on melatonin and cancer. The major misunderstandings in this area significantly affects the whole tone of the Report and its conclusions.

I received a second e-mail from Professor Reiter on 13/2/06 on his general views of the Report. An edited text is given below:

Dear Denis
I now have examined the report of the Advisory Council and I find it not especially satisfying. Some parts are satisfactory but the melatonin/cancer connection is not well illustrated considering the large amount of data available. This surely relates to
……
……
…… It is easy to see that the article deals primarily with melatonin and circadian rhythms.
[paraphrase] D.E. Blask is a leader in melatonin and cancer research. His paper that appeared in Cancer Research in Dec 2005 is especially important. However, I would not have expected citation

of this work because the material was written before the article appeared. However, Blask's earlier work should have received more ink. As a result, the report is rather unauthoratative when it discusses melatonin and cancer. Best regards.

Russ Reiter

----- Original Message -----
From: "Denis Henshaw" <D.L.Henshaw@bristol.ac.uk>
To: <reiter@uthscsa.edu>
Sent: Monday, February 13, 2006 9:42 AM

3. Invited peer-reviewed evidence and other peer-reviewed material

3.1 Henshaw & Reiter (*Bioelectromagnetics,* Supp **7**, S86-S97, 2005)

On 27th April 2005 I was invited to give oral evidence to the AGNIR Melatonin Sub-committee. This evidence summarised the findings described in an invited paper at the World Health Organisation meeting on EMF and Child Health, held in Istanbul in June 2004. The paper was written jointly with Professor Russ Reiter of the University of Texas Medical Center and was subsequently published in peer-reviewed form by Henshaw & Reiter in *Bioelectromagnetics* in 2005 (Supp **7**, S86-S97). Whereas human volunteer experiments have provided equivocal evidence of melatonin disruption following acute exposure to laboratory-controlled magnetic fields, 12 studies, comprising (i) studies in volunteers exposed to magnetic fields for several days and (ii) populations exposed to neighbourhood fields have, taken together, found a consistent pattern of melatonin suppression/disruption. The effect is particularly evident when magnetic field switching and/or electric fields are present.

The Henshaw & Reiter paper is not cited in the Report, nor are their findings discussed, including a description of the properties of melatonin as an antioxidant and radical scavenger in paragraphs 4, 5 & 6 of the Introduction.

The press release accompanying publication of the AGNIR Melatonin Report carries as the final sentence of the headline paragraph: "*In addition, EMFs do not appear to affect the production or biological action of the hormone melatonin*". This is not correct; indeed the opposite is the case. Whatever one's view of the data, the evidence to date does suggest that EMFs affect melatonin. In fact, despite the caveats given, this observational fact is acknowledged in the Report in section 7.3 paragraph 4 sentence 2 with the words: "*Although, most of the published studies have found some significant results……*"

3.2 Erren (*Bioelectromagnetics,* Supplement **5**, S105-S119, 2001)

Erren (2001) reviewed 43 publications on a possible association between EMF and breast cancer. His pooled analysis found a relative risk of 1.37 (95% CI = 1.11 – 1.71) in men and 1.12 (95% CI = 1.09 – 1.15) in women. The excess risk in women is small but given the high incidence of breast cancer, the finding is of public health significance. However, this is at the lower end for those cancers where a link with EMF exposure has been established or strongly suggested, such as childhood and adult leukaemia and adult brain tumours. I think citation of the Erren paper would have been useful.

3.2 Schernhammer & Hankinson (*Journal of the National Cancer Institute*, **97**, 1084-1108, 2005)

Comment on this paper (section 5.3) is confined to a conference abstract version. The peer-reviewed journal version was published in July 2005. This important paper reports that in a prospective study, higher melatonin levels, as measured in first morning urine, are associated with a lower risk of breast cancer.

3.3 Blask *et al*. (*Cancer Research*, **65**, 1-11, 2005).

A particularly important paper was published by Blask *et al.* in December 2005. While publication was too late for inclusion in the main body of the Report, account should have been taken of its findings in the press release.

Blask *et al.* transplanted MCF-7 human breast cancers into nude rats (rats with their immune system suppressed). Young women volunteers who slept in full darkness had blood samples taken in the early hours. This contained the normal nocturnal melatonin burden. When the blood was given to the rats, this prevented the growth of the human breast cancers. Blood samples were then taken from the same women at night, but after after they had been exposed to bright light which suppressed their nocturnal production of melatonin. When this blood was given to the rats the breast cancers continued to grow. Finally, this second blood sample was supplemented with melatonin at a level equivalent to those in the first blood samples. When given to the rats, this again prevented the growth of the human breast cancers.

This is the first demonstration, in a rat model, that normal levels of nocturnal plasma melatonin prevent the growth of human breast cancers. This is a key indicator that exposure to light-at-night, as in night shift workers, may increase the risk of breast cancer by suppressing nocturnal melatonin in the pineal gland.

The findings of this paper deserved mention in the press release accompanying publication of the AGNIR Melatonin Report.

4. Electric fields, magnetic fields and electric & magnetic fields

The Report discusses human experimental studies in which volunteers were exposed to magnetic fields in controlled laboratory conditions and the suppression and/or disruption of melatonin assessed from measurements of melatonin metabolite in urine. The results from these studies are generally equivocal, with some finding clear evidence of melatonin disruption while others find no detectable effect.

Paragraph 4.3, page 103 bottom and 104 top, provides an introduction to the human volunteer studies, discussing the work by Wever (1979). Page 103, 3 lines from the bottom states:

"*Wever (1979) provided the first indication that exposure to low frequency EMFs may also adjust the human biological clock.....He reported that a 10 Hz square wave electric field at 2.5 V/m could act as a zeitgeber* (literally 'timer') *with respect to free-*

running rhythms. The field was either continuous or switched on for half of each 'circadian day'....." (See now further description p104, lines 4 - 7).

Page 104, line 7 then reads: "*Nevertheless, there was consistent evidence that the field exposure (continuous or intermittent) could shorten free-running period* [of the circadian rhythm]*, reduce the variability between individuals in free-running period, and perhaps prevent 'internal desynchronisation' of the circadian system. Wever proposed that the circadian system provided a sensitive model with which to test the effects of low frequency fields on biology. This would manifest itself as a change in the timing of the melatonin rhythm if treatment were to occur at an appropriate phase*". (See now the remaining sentences in sect. 4.3).

It is noteworthy that Wever (1979) reported these effects with such low fields, 2.5 V m^{-1}.

So, we are given the impression that it was the work of Wever (1979) that led to the subsequent body of research with volunteers exposed to magnetic fields in laboratory-controlled conditions.

BUT, Wever (1979) is talking about ELECTRIC fields (EFs) and not MAGNETIC fields (MFs) and not 'electric and magnetic fields' (EMFs). So, the review that follows in sect 4.3.1 discusses a whole body of MF and not EF studies (the subsequent body of studies have apparently looked only at MFs!).

I have already indicated that Henshaw & Reiter (2005) agreed that the human volunteer studies provide equivocal evidence of melatonin disruption, but studies of populations exposed to 'neighbourhood' EMFs do find evidence of disruption which is more marked when magnetic field switching and/or exposure to electric fields is present.

So, where in the AGNIR Report is there insightful comment here? The Henshaw & Reiter findings tie in nicely with the work of Wever (1979) who, it appears, started the whole line of enquiry with volunteers exposure only to magnetic fields.

There is a suspicion that the authors of the Report may not understand the distinction between EFs, MFs, and EMFs (and not *electromagnetic* fields – see below).

Notwithstanding the suggested importance of electric fields *per se*, Henshaw & Reiter (2005) suggest reasons why the human volunteer experiments have provided equivocal evidence of melatonin disruption:

Page S90 right-hand column paragraph 3 of our paper 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 be a factor in melatonin disruption."

Table 4.6 of the AGNIR Report lists the various human volunteer experiments with MF exposures. The studies by Crasson *et al.* (2001), Hong *et al.* (2000), Griefahn *et al.* (2001) and Kurokawa *et al.* (2003) are listed as finding '*no effect*' of melatonin disruption. In fact, all of these studies do see effects but below statistical significance at the 95% confidence level. For example, Crasson *et al.* (2001) finds effects with p-values of 0.07 and 0.08, and in the reported '*no effect*' results of Kurokawa *et al.* (2003), of the 10 volunteers, one has a highly anomalous melatonin response which if removed from the analysis would suggest an effect of melatonin disruption in the remainder. The point here is that '*absence of evidence*' does not constitute '*evidence of absence*' - the '*no effect*' studies have not proved a negative. It is fine to be strict with the statistics for individual studies but for the pooled data the overall pattern in the studies should be brought out.

I discuss the results of Warman *et al.* (2003a) separately below.

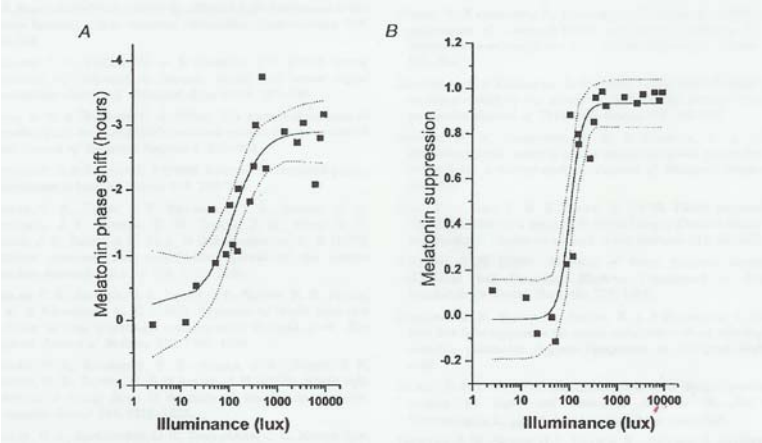
5. Dose response effects.

I first point out that for populations exposed to neighbourhood electric and magnetic fields, Henshaw & Reiter (2005) found evidence of melatonin suppression with time-weighted average (TWA) magnetic fields as low as 0.2 microtesla (μT), and two studies of fluctuations in geomagnetic fields found effects (i) in the <30 vs >30 nT region (Burch *et al.* 1999) and (ii) in the 30 -70 nanotesla region (Weydahl *et al.* 2001). In addition, Table 1 of Henshaw & Reiter (2005) contains two examples of volunteer studies where the exposures were non-acute, over a period of days or weeks, and these do reveal evidence of melatonin disruption (Wilson *et al.* 1990; Wood *et al.* 1998).

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



The adverse health effects associated with power frequency MFs, including the evidence of melatonin suppression in those chronically exposed, occurs in the approximate range 0.2 - 1.5 μT. Could it be that this constitutes the linear region of the dose response for magnetic fields, meaning that exposure to much higher fields is no more effective? Put another way, is the response to MFs a 'switch' effect similar to that for visible light? If so, this would go some way to explain why those volunteer studies with high MF exposures showed no effects of melatonin disruption.

I raise these questions because there is a question concerning the level of control fields in the body of volunteer studies. If the control fields are themselves around 0.2 or 0.4 μT, then these could be in a region where they themselves result in melatonin disruption. This could apply to the results of Warman *et al.* (2003a) cited in figure 4.1, page 105 of the Report.

In summary therefore, we do not know what form of dose response to expect from MF exposures, and we have no *a priori* reason for assuming a linear response up to 100s of microtesla.

The above considerations were fully explained to the AGNIR Sub-committee on the 27th April 2005 but I do not see any reference to dose-response issues in the Report.

6. Section 4.4, Epidemiology - studies of populations chronically exposed to EMFs.

Section 4.4, from pages 110 - 112, discusses essentially the same population studies with chronic EMF exposures as discussed in Henshaw & Reiter (2005). In the Report, however, each study is discussed separately and the reasons for doubting the positive findings are given. The problem with this approach is that the overall trend of melatonin/suppression disruption in these studies is not brought out, especially that this occurs with fields as low as

0.2 μT and that the presence of magnetic fields switching and/or electric fields appears to be important. I do feel that the authors should have assembled these studies in a table as was done in Henshaw & Reiter (2005).

7. Section 7: Conclusions

7.1 Page 159, Section 7.3, "Epidemiology"

The press release accompanying the issue of this Report states in the final sentence of the headline paragraph: "*In addition, EMFs do not appear to affect the production or biological action of the hormone melatonin.*" This is not correct. Whatever one may think of these data, the trend towards melatonin disruption in those chronically exposed to EMFs is clear. Indeed, despite the caveats given, this observational fact is acknowledged in this section of the Report. The press release is factually wrong in what is actually said in the Report.

7.2 Page 160, Section 7.4 under "Epidemiology: breast cancer risk in relation to light exposure"

Line 3 states "*...there is no direct evidence that the associations* [between breast cancer risk and light exposure] *involve melatonin.*"

The paper by Blask *et al.* (*Mut Res*, 65 (23): 1-11, 2005 – also mentioned above in 3.3) was published too late for the Report but not too late to be of value for the press release. I circulated this paper last December. Dr Blask and his colleagues showed that blood taken from women containing normal nocturnal levels of melatonin halted the growth of MCF-7 human breast tumours in nude rats. This is an explicit demonstration that "physiological concentrations" of nocturnal melatonin *per se* suppresses human breast cancer growth.

8. Section 8: Research Recommendations

I would like to repeat here, that I really sense that the authors fail to appreciate the distinction between electric fields (EFs), magnetic fields (MFs) and electric and magnetic fields (EMFs). In the Research Recommendations on page 163, line 2, the term "*electromagnetic fields (EMFs)*" is used. Physicists and engineers will be aware that at 50 Hz the wavelength is 6,000 km. Near powerlines we are in the "near field" situation and the electric and magnetic fields should be considered separately and the term EMFs has a different meaning to that at radio frequencies.

I presume that the whole section on Research Recommendations refers to magnetic field studies and (despite the pioneering work of Wever 1979) nowhere is there any recommendation to look at electric fields *per se* or the combined effects of electric and magnetic fields.

Here are some particular comments on the recommendations:

8.1 Human experimental studies.

It was gratifying to see the statement that longer-term (rather than the current acute) controlled studies are required.

8.2 Epidemiology

I do not agree with the statement: "*The existing literature does not suggest that further epidemiological study of the possible relation between EMFs and melatonin should be a priority...".* I understand the difficulty with uncontrolled studies, especially in relation to exposure to light-at-night, nevertheless the existing studies have revealed features that have not been understood by this Sub-committee and further epidemiological studies would I think be useful.

8.3 Epidemiology: breast cancer risk in relation to light exposure

I welcome the statements made. At the same time, I am again wondering why the important prospective study by Schernhammer & Hankinson (2005) is cited only from a conference abstract when the peer-reviewed paper was published in July 2005 in the *Journal of the National Cancer Institute*.

9. Geomagnetic fields and melatonin disruption

There is a sizeable literature on reported adverse health effects arising from fluctuations in the Earth's geomagnetic (GM) field. This field is widely described as static, when in fact it is a dynamic field, with variations taking place on timescales from hours to hundreds of years. Nanotesla-level variations occur on a timescale of hours arising from geomagnetic storms, from bursts of electrically charged particles emitted from the Sun and arriving at the surface of the Earth.

The literature on adverse health effects from short-term variations in the GM field includes at least two papers reporting melatonin disruption ((Burch *et al.* 1999; Weydahl *et al.* 2001 – see sect. 5 above).

Clearly the AGNIR Sub-committee had to draw a line somewhere, but inclusion of a discussion of these studies with GM fields would have added useful and insightful comment on melatonin suppression by magnetic fields.

10. Melatonin and cancer treatment

Melatonin, in conjunction with other drugs, is being used in a number of trials internationally to treat both breast and other cancers. While this is discussed in the Report, in view of this potential use of melatonin (it is inexpensive and readily available), I feel that more should have been said about this.

I will conclude this critique by commenting that the e-mail comments I have received from outside the UK on the AGNIR Report are all negative in their comments and particularly critical of the negative tone adopted in the Report.

References

BADR, F. M., EL HABIT, O. H. M. and HARRAZ, M. M., 1999. Radioprotective effect of melatonin assessed by measuring chromosomal damage in mitotic and meiotic cells. *Mutation Research*, **444**, 367-372.

BARLOW-WALDEN, L. R., REITER, R. J., ABE, M., PABLOS, M., MENENDEZ-PELAEZ, A., CHEN, L-D. and POEGGELER, B., 1995. Melatonin stimulates brain glutathione peroxidase activity. *Neurochem Int*, **26** (5), 497-502.

BLASK, D. E., BRAINARD, G. C., DAUCHY, R. T., HANIFIN, J. P., DAVIDSON, L. K., KRAUSE, J. A., SAUER, L. A., RIVERA-BERMUDEZ, M. A., DUBOCOVICH, M. L., JASSER, S. A., LYNCH, D. T., ROLLAG, M. D. and ZALATAN, F., 2005. Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Research*, **65**, 1-11.

CARRILLO-VICO, A., CALVO, J. R., ABREU, P., LARDONE, P. J., GARCIA-MAURIÑO, S., REITER, R. J. and GUERRERO, J. M., 2004. Evidence of melatonin synthesis by human lymphocytes and its physiological significance: possible role as intracrine, autocrine, and/or paracrine substance. The FASEB Journal (express article), 10.1096/fj.03-0694fje. (Published online 08.01.04),

CARRILLO-VICO, A., LARDONE, P. J., FERNÁNDEZ-SANTOS, J. M., MARTÍN-LACAVE, I., CALVO, J. R., KARASEK, M. and GUERRERO, J. M., 2005. Human lymphocyte-synthesized melatonin is involved in the regulation of the Interleukin-2/Interleukin-2 receptor system. *The Journal of Clinical Endocrinology & Metabolism*, **90**, 992-1000.

CRASSON, M., BECKERS, V., PEQUEUX, CH., CLAUSTRAT, B. and LEGROS, J. J., 2001. Daytime 50 Hz magnetic field exposure and plasma melatonin and urinary 6-sulfatoxymelatonin concentration profiles in humans. *Journal of Pineal Research*, **31**, 234-241.

ERREN, T. C., 2001. A meta-analysis of epidemiologic studies of electric and magnetic fields and breat cancer in women and men. *Bioelectromagnetics,* Supplement **5**, S105-S119.

GRIEFAHN, B., KÜNEMUND, C., BLASZKEWICZ, M., GOLKA, K., MEHNERT, P. and DEGEN, G., 2001. Experiments on the effects of a continuous 16.7 Hz magnetic field on melatonin secretion, core body termperature, and heart rates in humans. *Bioelectromagnetics*, **22,** 581-588**.**

Hardeland R.,2005. Endocrine; 27: 119-130

HENSHAW, D. L. and REITER, R. J., 2005. Do magnetic fields cause increased risk of childhood leukaemia via melatonin disruption? *Bioelectromagnetics* Supplement 7, S86-S97.

HONG, S. C., KUROKAWA, Y., KABUTO, M. and OHTSUKA, R., 2001. Chronic exposure to ELF magnetic fields during night sleep with electric sheet: Effects of diurnal melatonin rhythms in men. *Biolectromagnetics*, **22**, 138-143.

KUROKAWA, Y., NITTA, H., IMAI, H. and KABUTO, M., 2003. Acute exposure to 50 Hz magnetic fields with harmonics and transient components: Lack of effects on nighttime hormonal secretion in men. *Bioelectromagnetics*, **24**, 12-20.

LEÓN, J., ACUÑA-CASTROVIEJO, D., ESCAMES, G., TAN, D-X. and REITER, R. J., 2005. Minireview: Melatonin mitigates mitochondrial malfunction. *Journal of Pineal Research*, **38**, 1-9.

MARTIN, M., MACÍAS, M., ESCAMES, G., LEÓN, J. and ACUNA-CASTROVIEJO, D., 2000. Melatonin but not vitamins C and E maintains glutathione homeostasis in t-butyl hydroperoxide-induced mitochrondrial oxidative stress. *The FASEB Journal*, **14**, 1677-1679.

PIERI, C., MARRA, M., MORONI, F., RECCHIONI, R. and MARCHESELLI, F., 1994. Melatonin: A peroxyl radical scavenger more effective then vitamin E. *Life Sciences*, **55** 271-276.

QI, W., REITER, R. J., TAN, D-X., GARCIA, J. J., MANCHESTER, L. C., KARBOWNIK, M., and CALVO, J. R., 2000. Chromium (III)-induced 8-hydroxydeoxyguanosine in DNA and its reduction by antioxidants: Comparative effects of melatonin, ascorbate, and vitamin E. *Environmental Health Perspectives*, **108**, 399-402.

REITER, R., J. and TAN, D., 2003. Editorial note: What constitutes a physiological concentraion of melatonin? *J. Pineal res.*, **34**, 79-80

RODRIGUEZ, C., MAYO, J. C., SAINZ, R. M., ANTOLIN, I., HERRERA, F., MARTIN, V. and REITER, J. R. 2004. Minireview. Regulation of antioxidant enzymes: a significant role for melatonin. *J Pineal Res,* **36**, 1-9.

SCHERNHAMMER, E. S. and HANKINSON, S. E., 2005. Urinary melatonin levels and breast cancer risk. *Journal of the National Cancer Institute*, **97**, 1084-1087.

Tan DX et al, Endocrine J 1993; 1: 57-60

VIJAYALAXMI., REITER, R. J., HERMAN, T. S. and MELTZ, M. L. 1996. Melatonin and radioprotection from genetic damage: In vivo/in vitro studies with human volunteers. *Mutation Research*, **371**, 221 -228.

VIJAYALAXMI., REITER, R. J., HERMAN, T. S. AND MELTZ, M. L. 1998a. Melatonin reduces gamma radiation-induced primary DNA damage in human blood lymphocytes. *Mutation Research*, **397**, 203 -208.

VIJAYALAXMI., REITER, R. J., MELTZ, M. L. AND HERMAN, T. S., 1998b. Melatonin: possible mechanisms involved in its 'radioprotective' effect. *Mutation Research*, **404**, 187-189.

VIJAYALAXMI., MELTZ, M. L., REITER, R. J., HERMAN, T. S. and SREE, K. K., 1999. Melatonin and protection from whole-body irradiation: survival studies in mice. *Mutation Research*, **425**, 21-27.

WARMAN, G. R., TRIPP, H., WARMAN, V. L. and ARENDT, J., 2003. Acute exposure to circularly polarized 50-Hz magnetic fields of 200-300 μT does not affect the pattern of melatonin secretion in young men. *The Journal of Clinical Endocrinology & Metabolism*, **88**, 5668-5673.

WARMAN, G. R., TRIPP, H., WARMAN, V. L. and ARENDT, J., 2003. Circadian neuroendocrine physiology and electromagnetic field studies: precautions and complexities. *Radiat Protect. Dosim.,* **106(4):**369-373

WEVER, R. A., 1979. The circadian system of man. Results of experiments under temporal isolation. Ed: K E Schaefer. Pub: Springer-Verlag, New York.

WILSON, B.W., WRIGHT, C.W., MORRIS, J.E., BUSCHBOM, R.L., BROWN, D.P., MILLER, D.L., SOMMERS-FLANNIGAN, R. and ANDERSON, L.E., 1990. Evidence for an Effect of ELF Electromagnetic Fields on Human Pineal Gland Function. *Journal of Pineal Research,* **9**, 259-269.

WOOD, A. W., ARMSTRONG, S. M., SAIT, M. L., DEVINE, L. and MARTIN, M. J., 1998. Changes in human plasma melatonin profiles in response to 50 Hz magnetic field exposure. *Journal of Pineal Research*, **25**, 116-127.

ZEITZER, J. M., DIJK, D-J., KRONAUER, R. E., BROWN, E. N and CZEISLER, C. A., 2000. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol.,* **526:**695-702.