Review of plausible interaction mechanisms of anthropogenic fields, with a focus on childhood leukemia

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University of Bristol
and
Children with Cancer UK
Epidemiological Studies show a doubling of **Childhood Leukaemia** risk associated with average 0.3/0.4 μT, 50/60 Hz magnetic field exposure – and links with other adverse health outcomes too...

**Is the magnetic field association with childhood leukaemia causal?**

- ELF Magnetic fields
- Primary physics detector
- Biological response
- Childhood Leukaemia
When the Earth was formed 4.5 billion years ago magnetic fields were already present, and had been since the Big Bang some 9 billion years earlier.

2 billion years ago aquatic magnetotactic bacteria evolved which contain a chain of magnetite particles enabling them to swim along the Earth’s magnetic field lines to find food.

Over 90 million years ago the avian magnetic compass developed, enabling pigeons to detect magnetic field changes around 0.02 muT, 20 nT, or even lower.

Some 6 million years ago, man evolved, some of whom appear sensitive to solar storm fluctuations in the geomagnetic field of around 0.1 muT or 100 nT.

So, by the time electrification was introduced in Nottingham on 4th November 1878, it was already the case that wide sections of the animal kingdom had evolved to detect and exploit magnetic fields at levels below those associated with this new invention, and with hindsight, a hint that there might be adverse health effects in humans.
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1894 with a regional electricity plant in Olten-Aarburg.

Notes only:
The species whose magnetic compass has been analyzed so far are not at all closely related. Chickens belong to an ancient line of birds, the Galloanseres, that separated from the remaining modern birds, the Neoaves, more than 90 million years ago in the beginning of the Late Cretaceous. Finding the same type of magnetic compass in species of all three groups suggests that this compass mechanism may have already been present in their common ancestor.
So, start by taking a quick look at Geomagnetic storms
K(p) index of 5 = 70-120 Minor storm G1/~2.4 days

Superimposed on the Earth’s static magnetic field of 46.7 μT in Monte Verita,
are small fluctuations caused by storms of charged particles emitted by the Sun

(GM field in Monte Verità is 46.7 μT on 10/8/12 changing by 13.6 nT/year)

They are categorised by their K-value, their maximum variation over a three hour period.

The storms of interest are those around 100 nT, there being about 4.6 such events per year.

**Acute health effects include**: increase in depressive illnesses, melatonin disruption, heart rate variability, blood pressure changes.

However, only 10-15% of the population seem affected

Much of this research was carried out as part of the US and Russian Space Programme
Here is a short list of some of the studies, the first two are reviews:

- Biomarker & Pharmacotherapy, 50:247-250x.
Now a common question that physicists ask is how can a field of 0.4 muT (at ELF frequency) make any difference alongside the existing DC field from the Earth?

The answer is that the physical detector need only detect the signal. It is the biological response that matters.

**Kenneth J. Lohmann**, Department of Biology, University of North Carolina, Chapel Hill, NC 27599


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“The magnetic map exists in turtles that have never migrated and thus appears to be inherited”
So, let’s now look at power frequency magnetic fields

The average exposure to power frequency magnetic fields in the home is only 0.05 μT (50 nT). However, close to certain appliances, levels can be tens of μT.

Under powerlines MFs can be several μT or evens tens of μT

Crucially a doubling of childhood Leukaemia risk is associated with average exposure of 0.3/0.4 μT
The literature includes four studies showing increased childhood leukaemia risk up to 600 metres from powerlines which is well beyond the range of the AC fields, although well within range of corona ion emission.

Don Jones originally asked me to talk about our corona ion hypothesis, but I am grateful to the ARR committee for agreeing to let me talk about where I think we are with the general issue of understanding the mechanisms of ELF MF interactions which may lead to adverse health effects.
Here is what various review bodies have said about Magnetic Field and adverse health effects

IARC 2002 must have had a bad day because their own listing of studies shows strong evidence of association (See O’Carroll & Henshaw 2008 and also Kheifets et al 2008). In fact the MF link with adult leukaemia is, if anything, even stronger than the link with childhood leukaemia

Representative results from 33 independent adult leukemia 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.
Some MF effects *in vitro*

1. At high fields - 1 mT 50 Hz:


Enhance cell proliferation and DNA damage in HL-60 human leukaemia cells ([Wolf et al. 2005 Biochim Biophys Acta 1743 :120-9](#))

2. At environmentally relevant fields:

Stress response induced in HL-60 cells ([10 µT, 50 Hz: Tokalov & Gutzeit 2004, Environ. Res. 94:145–51](#))

A gene–environment analysis in 123 childhood ALL patients revealed an association between DNA repair enzymes and average MF exposure of 0.18 µT.

- [Yang et al. 2008 Leuk Lymphoma 49:2344–50 – Shanghai School of Medicine](#)
Magnetic sensitivity is widespread throughout the animal kingdom, and these are some of the animals which possess biogenic magnetite or other iron-mineral particles used for navigation.

Notes:

Lohmann: magnetic sensitivity is phylogenetically widespread; it exists in all major groups of vertebrate animals, as well as in some molluscs, crustaceans and insects. The list includes groups such as flies, chickens and mole rats, none of which migrate.
Magnetite can readily transduce a 0.4 μT 50 Hz field

Single domain permanent magnets, particles >50 nm where the whole particle physically rotates in an MF

And

Superparamagnetic particles which remains stationary but the MF vector quantum flips

Flessner et al 2007 Goethe-Universität, Frankfurt
Treiber et al 2012 Institute of Molecular Pathology, Dr Bohr-Gasse, 1030 Vienna, Austria

Eder & Michael Winklhofer Ludwig-Maximilians-University Munich

Notes:

Magnetic particles in human brain and ferritin

(Kirschvink et al. (1992) PNAS 89:7683-7 and Allen et al. 2000 Biochimica et Biophysica Acta 1500:186-196)

1. Human brain: Kirschvink et al. characterised magnetite biomineralisation in adult human brain:

- Sizes 10 – 70 nm & 90 – 200 nm, some 600 nm. 5 million single-domain crystals/g for most brain tissues, >100 million crystals/g for pia and dura.
- Particles in clumps of between 50 and 100 particles; \( U/kT \) values between 20 and 150.
- The larger particles could respond to a 50 Hz field at 0.4 \( \mu \)T - putting mechanical stress on neighbouring cells

2. Ferritin:

- has a natural ferricydrite nano-particle, ~5 nm, superparamagnetic, SP at room temperature.
- 1 – 200 mT fields in their vicinity, ~1 mT at 50 nm away
- SP particle would effectively “amplify” a 0.4 \( \mu \)T 50 Hz field by induced magnetisation - Binhi 2008 IJRB 84:569-579

Notes:

Binhi 2008 IJRB 84:569-579

In horse spleen ferritin, up to 30% of the core exhibits magnetite/maghemite structure (Brem et al 2006)

See also, magnetite in the brain of Alzheimer’s patients and human heart, liver and spleen


Allen et al. 2000. Low-frequency low-field magnetic susceptibility of ferritin and Hemosiderin Biochimica et Biophysica Acta 1500:186-196
A second mechanism of low level MF detection

- Low intensity MFs can increase the lifetime of free radical pairs making them potentially more available to cause biological damage

They do so by altering the spin states of radical pairs
- Increasing the rate of transition from the short-lived singlet (S) to the longer-lived triplet (T) state

Radical pairs created by - created by light absorption, excitation and electron transfer

Typical timescale of ~1 μs

This is known as the Radical Pair Mechanism, RPM
The RPM may act due to the MF around magnetite particles - increasing the lifetime of free radicals


1 μm Magnetite particles encapsulated in polystyrene dramatically decreased the time for 50% haemolysis of UV irradiated human erythrocytes.

Surrounding MF

surface: ~200 mT
1 mm away: ~0.5 mT
5 mm away: ~3 μT

Erythrocytes
(7 mm dia)

1 μm magnetite particles
(1 per 4 erythrocytes)

Binhi 2008 (JRB 84:569-79): - Hypothesised childhood leukaemia arose from SP magnetite particles in blood which transduced/amplified 50 Hz fields, creating free radicals by the RPM
The adverse health effects associated with ELF MF exposure could all potentially be explained by circadian rhythm disruption.

Melatonin is a broad-spectrum, ubiquitously-acting antioxidant and anti-cancer agent. Which also reduces growth of human myeloid leukemia cells and whose disruption by light-at-night is associated with increased cancer risk.

Richard G. Stevens 2012 Hypothesis: Does electric light stimulate cancer development in children?
Cancer Epidemiology Biomarkers & Prevention, doi:10.1158/1055-9965.EPI-12-0015
Magnetic field disruption of melatonin, pineal cells, cryptochromes and circadian rhythms

- in humans
  - Not revealed in volunteer short exposures to pure AC MFs
  - Seen in populations exposed to “real” EMFs¹ – down to 0.2 μT

- in animals
  - Most effects observed with non-smooth AC MFs
  - Strong findings in cows and sheep with “real” EMFs²

- on pineal cells
  - Small but detailed literature – action in synthesising melatonin disrupted. Some animals have MF compass in the pineal gland

Clock genes and cryptochrome:

- the gene Cry1 codes the Cryptochrome³ protein molecule, CRY1, in the eye, which in turn is involved in the regulation of circadian rhythms.

Cryptochrome acts as the magnetic compass in animals

¹Henshaw & Reiter 2005 BEMS Suppl 7:S86-S97
³Evolved ~2.5 bn years (Gu 1997 Mol Biol Evol 14:861-866)


So what about magnetic field effects on melatonin, pineal cells, cryptochromes and circadian rhythms?

Melatonin disruption in humans is really seen in populations exposed to “real” fields – down to 0.2 μT

Similarly in animals, effects are seen in “real” fields, both in the laboratory and outdoors

There’s a small but detailed literature - that MFs interfere with the action of pineal cells in synthesising melatonin.

The human light-detection threshold is sensitive to MF exposure

But most importantly, cryptochrome, expressed by the CRY genes controls the mammalian circadian clock and acts as the magnetic compass in animals.

And I will be saying more about that later.
Now let's look at a second mechanism of MF detection in animals
– a chemical compass in the eye based on the RPM*

*Note that in salamanders the MF compass is housed in the pineal gland. The gland is also involved in the light-dependent compass in frogs, lizards and some fish

These species all have a light-dependent compass with evidence that it is based on the RPM. Notice that in some cases, this is in addition to magnetite. Notice also the involvement of the pineal gland in some species.

From Lohmann 2010: Figure 1 | Animal magnetism. Diverse species have magnetic compasses, including (clockwise from top left) the European robin, the loggerhead sea turtle, the brown bat, the Caribbean spiny lobster and the red-spotted newt. A few, including turtles, lobsters and newts, also have magnetic maps.
Ritz et al 2000 proposed that the avian compass was based on cryptochrome molecules in the eye and that as an experimental test, this might be interfered with by application of an appropriate RF field.

RP lifetimes up to 20 ms – five orders of magnitude higher than 1 mS required have been observed: Liedvogel et al. 2007, Chemical magnetoreception: bird cryptochrome 1a is excited by blue light and forms long-lived radical-pairs" PLoS One 2(10): e1106; and

Cry1a located in UV/V-cones in robins and chickens, in ordered bands along the membrane discs (Niessner et al. 2011 PLoS ONE 6(5): e20091)

FAD = flavin-adenine dinucleotide
Here I talk through how RP mixing occurs, using the precession model.
Continued:

The field vector, $B$ has two components: (i) due to high-abundance magnetic nuclei e.g. $^1$H $^14$N, and (ii) due to the Earth’s field.

For a compass, maximum sensitivity occurs when the Earth’s field has little influence on precession on radical 1, but is the only influence on radical 2.

The precession is governed by hyperfine interaction with the proton in the nucleus, consisting of an isotropic S-wave, or S-orbital interaction, and an anisotropic dipole interaction.
Ritz et al. 2004
Nature 429:177-180

Birds: European robins, Erithacus rubecula: 12 individually tested in spring migration season.

MF exposure: Local GMF 46 μT, inclination 66° and 565 nm light (control) plus: (i) broadband 0.1–10 MHz, 0.085 μT, (ii) single frequency 7 MHz, 0.47 μT, all parallel, 24° or 48° to GMF vector.

Results:
- RF magnetic fields disrupt the magnetic orientation behaviour of migratory birds.
- Robins were disoriented when exposed to a vertically aligned broadband (0.1–10 MHz) or a single-frequency (7-MHz) field in addition to the geomagnetic field.
- In the 7-MHz oscillating field, effect depended on the angle between the oscillating and the geomagnetic fields.
- Birds exhibited seasonally appropriate migratory orientation with no applied RF or when the RF field was parallel to the geomagnetic field, but were disoriented when it was presented at an angle of 24° or 40° at 0.085 μT.

Conclusion:
These results are consistent with a resonance effect on singlet-triplet transitions and suggest a magnetic compass based on a radical pair mechanism.

These findings have been replicated in robins and seen in chickens, zebra finches and American cockroaches.

Ritz et al 2000 reported…..

FAD = flavin-adenine dinucleotide
### Effects of animal magnetic compass orientation with RF and ELF EMF exposures (GMF = geomagnetic field)

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<tr>
<th>Study</th>
<th>MF and light exposure</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritz et al. 2004: European robins, Zorobravine pellidina</td>
<td>Local GMF 48 μT, inclusions 60° and 55° on light (control) plus 60° and 55° on dark (experimental).</td>
<td>Birds exhibited seasonal appropriate migratory orientation with no applied RF or when the RF field was parallel to the geomagnetic field, but were disrupted when it was presented at an angle of 24° or 48° of 0.003 μT.</td>
</tr>
<tr>
<td>Thalau et al. 2005: As in Ritz et al. 2004 using 12 robins in spring and 18 robins in autumn.</td>
<td>As in Ritz et al. 2004, but applying RF at the local Larmor frequency of 45.3 MHz at 0.003 μT, parallel and at 24° to GMF vector.</td>
<td>Birds exhibited seasonal appropriate migratory orientation in both spring and autumn with no applied RF or when the RF field was parallel to the geomagnetic field, but were disrupted when applied at 24° or 48° of 0.003 μT.</td>
</tr>
<tr>
<td>Wiltschko et al. 2007: Domestic chickens, Gallus gallus, in total, between 12 and 22 days old.</td>
<td>Local GMF 35 μT, inclusions (i) vertically oriented East as control and West, 45° max light or 65° max light (ii) local Larmor frequency 1.3 MHz at 0.003 μT, vertical (iii) 0° from GMF vector, (iv) 45° weaker and stronger, 27° μT and 83.1 μT, and 30° weaker and stronger 41.9 μT and 69.9 μT.</td>
<td>1. Chickens orientated well to control field, but not to the weaker and stronger fields, suggesting a functional window around the GMF. 2. Tendency to orientate westwards, blue light, but not red, results not statistically significant. 3. Exposure to 1.36 MHz led to disorientation suggestive of an underlying radical pair mechanism.</td>
</tr>
<tr>
<td>Stapp et al. 2008: European robins, Zorobravine pellidina, 12-16 per nest.</td>
<td>Local GMF 48 μT, inclusions 60° and 55° on green light or total darkness, alone (control) plus 1.15 MHz at 0.48 μT, parallel and at 24° to GMF vector.</td>
<td>Normal seasonal migratory orientation under 550 μT, in total darkness, birds orientated NNE, not the migratory direction, and were not disrupted by 1.15 MHz fields, although were disrupted by absence of the upper bank. Findings suggestive of two magnetic compass systems: (i) an orientation compass based on radical-pair processes allowing orientation in the migratory direction and (ii) an in-built pattern that, aside from providing “map” information, can affect orientation in “used directions” in the absence of light, but is normally dominant when the radial-pair mechanism is operating.</td>
</tr>
<tr>
<td>Keary et al. 2009: Zebra finches, Taeniopygia guttata, 10 for MF orientation, 7 for visual perception.</td>
<td>Local GMF 43 μT, inclusions 67° day/night. Local Larmor frequency 1.16 MHz at 0.47 μT, horizontal component of GMF shifted 90° clockwise (control), RF added in same vector direction. Separately, birds were trained to associate with respect to visual cues.</td>
<td>Birds exhibited migratory orientation in the 90° shifted control field, but this was disrupted when the RF field was added. Birds trained for visually guided orientation were unaffected by either the static or RF fields.</td>
</tr>
</tbody>
</table>

*This corresponds to the Larmor frequency for the free electron in the local GMF.


This and the next slide:

The findings of Ritz et al 2000 have now been repeated in robins and also in chickens, zebra finches and American cockroaches.

The table is very busy but I just want to point out the very low level of RF fields that disturb the compass and at frequencies corresponding to the Larmor precessional frequency of the free electron.


I point also to the findings of Begall et al. 2008 and Burda et al. 2009.

The ICNIRP Exposure Limit is:

0.92 µT at 1 MHz
0.092 µT between 10 – 400 MHz
0.2 µT at 2 GHz

Note that RF disruption of the animal compass occurs at levels below the ICNIRP limit.


**Test of an RPM action in the animal compass**

- Interference of animal magnetic compass be radio frequency EMFs

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Frequency (MHz)</th>
<th>Field level for compass disruption (μT)</th>
</tr>
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<tbody>
<tr>
<td>Ritz et al. 2004</td>
<td>European robins</td>
<td>0.1 - 10</td>
<td>0.085</td>
</tr>
<tr>
<td>Thalau et al. 2005</td>
<td>European robins</td>
<td>1.315</td>
<td>0.488</td>
</tr>
<tr>
<td>Wiltschko et al. 2007</td>
<td>Domestic Chickens</td>
<td>1.566</td>
<td>0.048</td>
</tr>
<tr>
<td>Stapput et al. 2008</td>
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<td>1.315</td>
<td>0.48</td>
</tr>
<tr>
<td>Keary et al. 2009</td>
<td>Zebra finches</td>
<td>1.156</td>
<td>0.47</td>
</tr>
<tr>
<td>Vacha et al. 2009</td>
<td>American cockroach</td>
<td>1.2</td>
<td>12 - 18 nT</td>
</tr>
<tr>
<td>Ritz et al. 2009</td>
<td>European robins</td>
<td>1.315</td>
<td>15 nT</td>
</tr>
</tbody>
</table>
Here I talk through the significance that cryptochromes control circadian rhythm

doi:10.1371/journal.pbio.1000086

FAD = flavin-adenine dinucleotide
Are human cryptochromes magnetosensitive?

Foley, Geogear & Reppert 2011 Nature Comm ncomms1364:

"Human cryptochrome exhibits light-dependent magnetosensitivity"

- **Study:** Magnetic behavioural response of CRY-deficient and hCRY2 Drosophila melanogaster (10 – 12 groups of 100-150 individual flies per test), under control of tim-GAL4 driver.

- **Methods:** Flies exposed between 10 – 500 μT with full spectrum and blocked (>500 & >400 nm) light

- **Findings:** (i) CRY-deficient flies showed no MF response; (ii) Human CRY-rescued flies showed light-dependent magnetosensitivity; positive responses under full spectrum light was blocked at >500 nm but partially restored at >400 nm.

Figure 1b
Light, cryptochrome expression and reduced plasma melatonin


- Jaundiced neonates treated by blue light exposure with the eyes covered*

- Expression of circadian genes: Bmal1 and Cry1 in peripheral blood mononuclear cells and reduction in plasma melatonin

- Reduction in plasma melatonin usually interpreted as reduced production in the pineal gland

- Could indicate increased consumption in quenching free radicals in the bloodstream

- Could it be that the blue light also creates radical pairs in the cryptochromes, so that plasma melatonin was consumed in quenching these radicals?

- If so, could environmental MFs exacerbate this effect – resulting in increased radical damage to blood cells?

*Zhejiang Children’s Hospital. 24 h exposure to 5,500 – 7,200 lux from 12 x 20 W fluorescent light bulbs.
Summary

ELF Magnetic fields → Primary physics detector → Biological response → Childhood Leukaemia

(i) Magnetic particles: Mechanical stress or free radical damage via the RPM

(ii) Cryptochromes (in the eye): Circadian rhythm disruption

(iii) Cryptochromes (in peripheral blood cells): Free radical damage by the RPM
Acknowledgements

Illia Solov'yov (Illinois)
Jonathan Woodward (Tokyo)
Mike O’Carroll

and

Children with Cancer UK.

Fuller version: www.electric-fields.bris.ac.uk
I’ve slipped this slide in here to point out models of the actual RP pathways in cryptochrome.

FAD = flavin-adenine dinucleotide
As an introduction to the RPM this slide goes back to basics.

On the left we see the familiar Zeeman effect. If you put an electron in a static magnetic field, it will align its spin vector either up or down with respect to the field direction.

This energy difference between these states may be represented by a photon of energy $h\nu$ where $h$ is Planck’s Constant and $\nu$ is the photon frequency. A spectroscopic transition can be induced between these energy states by applying radiation at the correct frequency. At 50 $\mu$T, $\nu = 1.4$ MHz.

I am showing this to point out that the energy difference is $\sim 10^-7$ of the thermal energy $kT$. i.e. the phenomenon is not only well below $kT$, but is has nothing to do with classical energies, rather we are talking about the quantum-mechanical interaction of the magnetic field with the electron spin.

On the right is the classical physics model of this, taken from NMR & MRI, that the electron is precessing about the magnetic field at frequency $\nu$, 1.4 MHz, the so-called Larmor frequency. I will be using this model in a moment.
Low fields open up new S-T mixing pathways increasing the rate of S-T conversion

**Examples of RPM in chemical systems:**

Scaiano et al 1997: Photoreduction of benzophenone by 1,4-cyclohexadiene;
Mohtat et al 1998: Radical pair derived from hydrogen abstraction of triplet benzophenone;
Streiner & Ulrich 1989: Table 6 (Molecular crystals): e.g. Naphthalene, 1,4-dibromonaphthalen, anthracene; Table 5: e.g.s of photochemical reactions in the gas phase
Brocklehurst & McLauchlan 1996: benzaldehyde (PhCHO, Ph = C6H5) in tetrachloromethane; RPs created from UV irradiation of the condensed ring aromatic hydrocarbon pyrene (Py) in solution with 1,3-dicyanobenzene (DCB)
Vink & Woodward (2004): Radical recombination reaction occurring after the photodecomposition of 2-hydroxy-4¢-(2-hydroxyethoxy)-2-methylpropophenone (R-HP)
Woodward et al 2002: Pyrene with isomers of dicyanobenzene

**References:**

Brocklehurst R, McLauchlan KA 1996. Free radical mechanism for the effects of environmental electromagnetic fields on biological systems. International Journal
Spare slide: showing that RF disruption of the animal compass occurs at levels below the ICNIRP limit