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ELF Animal Studies, Mechanisms of Action

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OUTLINE

- ELF EMF and development
- ELF EMF and cancer
- Mechanisms of action
Development

• **Review by Juutilainen, 2005**
  – “The only finding that shows some consistency is an increase in minor skeleton alterations in several studies”
  – “Taken as a whole, the results **do not show robust adverse effects** of ELF fields on development”

• **EMF-NET project, 2008**
  Skeleton anomalies: not confirmed
  Other developmental effects in mammals: weak evidence
Cancer related to children

• Brain tumours
  gliomas
  medulloblastomas

• Hematopoietic tumours
  lymphomas
  leukaemias
• Possibly carcinogenic to humans

• *Childhood leukaemia*

• Based on an association in epidemiology and lack of experimental support (biology and mechanism)
Cancer: hematopoietic tumours

  – Review in animals

### Cancer: hematopoietic tumours (1)

**Brain et al (2003)**

- 5 studies, 1 – 5000 µT

<table>
<thead>
<tr>
<th>Species</th>
<th>Group size</th>
<th>Exposure</th>
<th>Percent incidence of hematopoietic neoplasia</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats (F344)</td>
<td>100/both sexes/exposure group</td>
<td>Sham control 10 G (continuous) 10 G (intermittent; 1 hr on/off) 2 G (continuous) 0.02 G (continuous) 60 Hz; 18.5 hr/day</td>
<td>Leukemia: male 50 50 36* 47 44</td>
<td>Leukemia: female 20 25 22 24 18</td>
</tr>
<tr>
<td>Rats (F344)</td>
<td>46/both sexes/exposure group</td>
<td>Sham control 50 G 5 G</td>
<td>Leukemia: male 10 8</td>
<td>Leukemia: female 16 14 12</td>
</tr>
<tr>
<td>Rats (F344)</td>
<td>56 female/exposure group</td>
<td>Sham control 20 G 2 G 0.2 G 0.02 G 60 Hz; 22.6 hr/day</td>
<td>Leukemia 10 10 6 18 8</td>
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</tr>
<tr>
<td>Mice (B6C3F1)</td>
<td>100/both sexes/exposure group</td>
<td>Sham control 10 G (continuous) 10 G (intermittent) 2 G (continuous) 0.02 G (continuous) 60 Hz; 20 hr/day</td>
<td>Lymphoma: male 6 7 6 4 7</td>
<td>Lymphoma: female 32 26 20* 22 31</td>
</tr>
<tr>
<td>Mice (C57BL/6)</td>
<td>150 or 380 female/exposure group</td>
<td>Sham control 14 G (circularly polarized) Sham control 14 G (circularly polarized) 60 Hz; 18 hr/day</td>
<td>Total hematopoietic neoplasms 56 59 35</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05 versus sham control.*
Cancer: hematopoietic tumours


- 3 studies, 1 – 1000 µT
- *Pim-1, TSG-p53* mouse models

<table>
<thead>
<tr>
<th>Species</th>
<th>Group size</th>
<th>Exposure</th>
<th>Percent incidence of lymphoma</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>30/both sexes/ exposure group</td>
<td>Sham control</td>
<td>Male 49, Female 47</td>
<td>McCormick et al. (1998)</td>
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<tr>
<td>(pim-1)</td>
<td></td>
<td>10 G (continuous)</td>
<td>23*, 47</td>
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<td></td>
<td></td>
<td>10 G (intermittent)</td>
<td>57, 53</td>
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<td></td>
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<td>2 G (continuous)</td>
<td>43, 45</td>
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<td></td>
<td></td>
<td>0.02 G (continuous)</td>
<td>47, 45</td>
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<td></td>
<td></td>
<td>60 Hz, 18.5 hr/day, for 26 weeks</td>
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<tr>
<td>Mice</td>
<td>100 female/ exposure group</td>
<td>Sham control</td>
<td>T-cell 5, B-cell 23</td>
<td>Harris et al. (1998)</td>
</tr>
<tr>
<td>(pim-1)</td>
<td></td>
<td>10 G (continuous)</td>
<td>8, 22</td>
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<td></td>
<td></td>
<td>10 G (intermittent)</td>
<td>7, 28</td>
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<td>1 G (continuous)</td>
<td>8, 18</td>
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<td>0.01 G (continuous)</td>
<td>4, 25</td>
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<td>50 Hz, 20 hr/day, up to 18 months</td>
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<tr>
<td>Mice</td>
<td>30/both sexes/ exposure group</td>
<td>Sham control</td>
<td>Male 3, Female 3</td>
<td>McCormick et al. (1998)</td>
</tr>
<tr>
<td>(TSG-p53)</td>
<td></td>
<td>10 G (continuous)</td>
<td>0, 7</td>
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<td></td>
<td></td>
<td>60 Hz, 18.5 hr/day, for 26 weeks</td>
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*p < 0.05 versus sham control.*
Cancer: hematopoietic tumours


- 2 studies, 1000 and 1400 μT
- Initiators: X rays, dimethylbenz[a]anthracene

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<thead>
<tr>
<th>Species</th>
<th>Group size</th>
<th>Exposure</th>
<th>Percent incidence of lymphoma</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice (C57BL/6)</td>
<td>380 female/exposure group</td>
<td>X-ray:</td>
<td>3.0 Gy</td>
<td>Babbitt et al. (2000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sham control</td>
<td>41</td>
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<tr>
<td></td>
<td></td>
<td>14 G (circular) 60 Hz, 18 hr/day, lifetime</td>
<td>34</td>
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<td>41</td>
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<td>47</td>
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</tr>
<tr>
<td>Mice (Swiss Webster)</td>
<td>155–165/ exposure group</td>
<td>Dimethylbenz[a]anthracene:</td>
<td>24</td>
<td>Shen et al. (1997)</td>
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<td></td>
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<td>Sham control</td>
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<tr>
<td></td>
<td></td>
<td>10 G</td>
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<td></td>
<td>50 Hz, 3 hr/day, 5 days/week, for 16 weeks</td>
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</tbody>
</table>

No evidence of effect
Cancer: hematopoietic tumours (2)


- AKR/J mouse model of lymphoma
- 1, 100, and 1000 µT
- 24 h/d or night-time, 7 d/w, 32-38 weeks

No evidence of effect
Cancer: hematopoietic tumours (3)
- WKAH/Hkm rat model of leukemia (B-ALL)
- 100 µT ± harmonics:
  150 Hz (5 µT), 250 Hz (6 µT), 350 Hz (5 µT)
- 18 h/d, 7 d/w, 13 months

No evidence of effect
Cancer:

Conclusions on hematopoietic tumours

- 13 studies investigated hematopoietic tumours
  - 1 to 5000 µT
  - 16 weeks to lifetime
  - 3 to 22.6 h/d

- 4/13 investigated leukaemia
- 1/13 investigated B-ALL

Globally, no evidence of effect

... only one study relevant to children leukaemia
ELF EMF and childhood leukaemia

Conception

Birth

1

2

3

4

Preleukemic clone

2nd event

ALL

Any track to go further?
To go further: track 1

  - MLL-AF9 mouse model (Stubbs et al, 2008)
  - TEL-AML1 mouse model (Ford et al, 2009; Schindler et al, 2009)
  - Double- p19Arf/Rag1 knockout mouse model (Hauer et al)
  - WKAH/Hkm rat model: not included

- Escribano et al, IJRB (1997)
  1 Gy X-rays during gestation affects the developing murine hematopoiesis.

Track 1: Use available B-ALL animal models as a starting point
To go further: track 2

Environmental Factor: ELF EMF

1st event

2nd event

Preleukemic clone

Conception  →  Birth  →  1 →  2 →  3 →  4

Age [years]

ALL

Track 2: Expose animals starting *in utero* and/or genitors
To go further: track 3

Gene silencing by DNA methylation in haematological malignancies

Jacqueline Boulwood and James S. Wainscoat

MicroRNA expression signatures accurately discriminate acute lymphoblastic leukemia from acute myeloid leukemia

Shuangli Mi†, Jun Lu§, Miao Sun†, Zejuan Li†, Hao Zhang†, Mary Beth Neilly†, Yungui Wang§, Zhijian Qian†, Jie Jin§, Yanming Zhang†, Stefan K. Bohlander†, Michelle M. Le Beau†, Richard A. Larson†, Todd R. Golub§§‡‡‡, Janet D. Rowley‡‡‡, and Jianjun Chen‡‡‡

Track 3: Test the capability of ELF EMF to induce epigenetic changes
Mechanisms:
Internal electric fields

• *Induction of E fields and currents* by exposure to ELF EMF is the currently accepted mechanism

• Target: Excitable tissues (muscle and nerve)
• Exposure limits to prevent such phenomenon
• Exposure limit recommendation for public: 200 µT

➤ Cannot explain the epi data
Mechanisms:
The radical pair mechanism (RPM)

• Magnetic fields have an effect on radical pairs and thus on biochemistry *in vivo*
• Best evidence comes from bird navigation
• Could this have an effect on the leukemic cells and/or their microenvironment?
Mechanisms:
The radical pair mechanism (RPM)

- **Example: cryptochrome (CRY)**

- Plausible candidate for bird navigation
- The radical pair is formed following blue light absorption by CRY
- CRY involved in circadian rhythms in the whole organism and all cells
Conclusion

• Since the 2002 IARC classification
  – B-ALL mouse models available
  – Better knowledge gained on childhood leukaemia
  – RPM testable due to the ubiquitous presence of CRY

• FP7 project: ELF magnetic fields and childhood leukaemia
  – To begin soon
  – Will close the debate?
Thank you