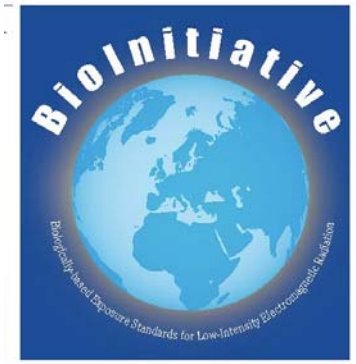

The BioInitiative Methodology

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BioInitiative Organizing Committee

Foundation of the BioInitiative

- At the Bioelectromagnetics Society meeting in Cancun, 2006, a symposium about EMF Research and the Precautionary Principle was organized by Martin Blank (Univ. Columbia) and Michael Kundi (Medical Univ. Vienna)
- At this occasion many participants voiced an urgent need for an independent and more balanced assessment of evidence and a precautionary approach for the derivation of guidelines
- Already in Cancun the organizing committee for the BioInitiative was established, consisting of:
  - Carl Blackman (US EPA, former president of BEMS)
  - Martin Blank (Univ. Columbia, former president of BEMS)
  - Michael Kundi (Medical Univ. Vienna)
  - Cindy Sage (Sage Assoc., California)

Assembling the BioInitiative

- The members of the organizing committee contacted scientists whether they are willing to join the initiative in fall 2006 (only 2 refused due to a possible conflict with their employer and one later cancelled his participation)
- The working principles were set up and discussed during Oct 2006 to Jan 2007 in several telephone conferences
- In Feb 2007 ~1000 articles of original research were sent out to all participants

Members of the BioInitiative Working-Group

- Carl Blackman (USA)
- Martin Blank (USA)
- David Carpenter (USA)
- Guangdi Chen (China)
- Zoreh Davanipur (USA)
- David Gee (Denmark)
- Kjell Hansson-Mild (Sweden)
- Lennart Hardell (Sweden)
- Olle Johansson (Sweden)
- Michael Kundi (Austria)
- Henry Lai (USA)
- Cindy Sage (USA)
- Eugene Sobel (USA)
- Zhengping Xu (China)

Procedure

- The topics were allocated to the different members of the BioInitiative working-group and all were asked to complete their chapters by July 2007
- Each author of a chapter takes responsibility for his/her text
- Although all authors should follow a certain procedure, there was no attempt made to reach consensus for all of the texts!

Procedure

Public health and risk management experts should evaluate the different chapters and arrive at a rational for a new biology-based exposure standard

- Assess whether or not the relevant literature has been considered by IEEE (2006) and WHO EHC (2007)
- Document key scientific findings indicating low-level effects which should be prohibited by new exposure guidelines
- Provide a scientific evaluation of the key findings with an attempt – if possible – to identify chains-of-evidence
- Indicate whether or not current international standards are protective with respect to the endpoints identified

"Data base" consisting of ~1000 articles of original research sent to all members and another ~1000 articles from the files of the authors

Risk Assessment

What constitutes a balanced risk assessment?

- Assess **all** the evidence laid down in the peer-reviewed literature
- Evaluate “positive” and “negative” studies with **equal scrutiny**
- In the case of possible bias indicate **direction of bias**
- For “negative” studies assess power and other **reasons for the failure** to detect an effect
- For “positive” studies indicate whether bias, confounding and **methodological limitations** can be made responsible for the finding

But be cautious!

- If in doubt (i.e. if results can be interpreted in several ways) **lean towards higher public safety**!

Unbalanced Risk Assessment

Reproductive outcomes. Two extensive studies on women treated with microwave diathermy to relieve the pain of uterine contractions during labor found no evidence for adverse effects on the fetus (Daels 1973, 1976). However, seven studies on pregnancy outcomes among workers occupationally exposed to microwave radiation and on birth defects among their offspring produced both positive and negative results. In some of the larger epidemiological studies of female plastic welders and physiotherapists working with shortwave diathermy devices, there were no statistically significant effects on rates of abortion or fetal malformation (Källen et al. 1982). By contrast, other studies on similar populations of female workers found an increased risk of miscarriage and birth defects (Larsen et al. 1991; Ouellet-Hellstrom and Stewart 1993). A study of male radar workers found no association between microwave exposure and the risk of Down's syndrome in their offspring (Cohen et al. 1977).

Overall, the studies on reproductive outcomes and microwave exposure suffer from very poor assessment of exposure and, in many cases, small numbers of subjects. Despite the generally negative results of these studies, it will be difficult to draw firm conclusions on reproductive risk without further epidemiological data on highly exposed individuals and more precise exposure assessment.

ICNIRP Guidelines 1998

Positive and negative studies are only counted and no attempt is made to assess them properly

Poor assessment of exposure would result more likely in an underestimation of risk

Although there are positive and negative results the conclusion is they are “generally negative”

Unbalanced Risk Assessment

ICNIRP Guidelines 1998

Some reports suggests that retina, iris, and corneal endothelium of the primate eye are sensitive to low levels of pulsed microwave radiation (Kues et al. 1985; UNEP/WHO/IRPA 1993). Degenerative changes in light-sensitive cells of the retina were reported for absorbed energy levels as low as 26 mJ kg^{-1}. After administration of timolol maleate, which is used in the treatment of glaucoma, the threshold for retinal damage by pulsed fields dropped to 2.6 mJ kg^{-1}. However, an attempt in an independent laboratory to partially replicate these findings for CW fields (i.e., not pulsed) was unsuccessful (Kamimura et al. 1994), and it is therefore impossible at present to assess the potential health implications of the initial findings of Kues et al. (1985).

Although the original study was about retinal damage caused by PW and the “replication” about CW, the combined evidence is considered inconclusive!

Unbalanced Risk Assessment

Epidemiology of Health Effects of Radiofrequency Exposure

ICNIRP (International Commission for Non-Ionizing Radiation Protection) Standing Committee on Epidemiology: Anders Ahlbom,[1,2] Adele Green,[3] Leeka Kheifets,[4] David Savitz,[5] and Anthony Swerdlow[6]

Incorrect for several reasons:

1. Garland found in fact also an increased risk for “electrician’s mate”
2. Groves study was about radar exposure and Garland’s about occupational categories with no special focus on radar or other RF exposures

Possible misclassification would rather lead to an underestimation of risk

Incorrect: these ‘historical reports’ were only used to validate the job-exposure matrix!

Considering study size, design, and likely quality of RF assessment, the most informative studies (Groves et al. 2002; Milham 1988; Morgan et al. 2000) provide little evidence of an association with either brain tumors or leukemia. The one possible exception was an increased risk of nonlymphocytic leukemia in radar-exposed navy veterans (Groves et al. 2002) restricted to only one of three highly exposed occupations (aviation electronics technicians), but this finding was divergent from that of an earlier study of U.S. naval personnel (Garland et al. 1990). Two U.S. case–control studies of brain tumor etiology have shown elevated odds ratios (ORs) of around 1.5 in relation to jobs believed to have RF exposure. However, the study by Thomas et al. (1987) was based on interviews with relatives of dead cases and hence was unable to identify exposure with much certainty. The other study (Grayson 1996) assessed exposures by a job–exposure matrix based on historical reports of incidents of exposure above permissible limits (10 mW/cm^2). No clear or consistent trend was found in risk of brain tumor in relation to exposure score.

Example: Attributable Fraction for Childhood Leukaemia & Residential Exposure to Power Frequency EMF

WHO EHC 238

- Assumption: Threshold at 0.3 or 0.4 µT
- Point estimate used instead of upper confidence limit
- Also Attributable Fraction assessed at the point estimate
- The average magnetic flux density is the correct metric

Although a causal relationship between magnetic field exposure and childhood leukaemia has not been established, the possible public health impact has been calculated assuming causality in order to provide a potentially useful input into policy. However, these calculations are highly dependent on the exposure distributions and other assumptions, and are therefore very imprecise. Assuming that the association is causal, the number of cases of childhood leukaemia worldwide that might be attributable to exposure can be estimated to range from 100 to 2400 cases per year. However, this represents 0.2 to 4.9% of the total annual incidence of leukaemia cases, estimated to be 49 000 worldwide in 2000. Thus, in a global context, the impact on public health, if any, would be limited and uncertain.

Example: Attributable Fraction for Childhood Leukaemia & Residential Exposure to Power Frequency EMF

BioInitiative

The results are equally likely for models with and without threshold

Is there an indication of a threshold?

Ahlbom et al. 2000		Greenland et al. 2000	
< 0.1 µT	1.00	< 0.1 µT	1.00
0.1-0.2 µT	1.08 [0.89-1.31]	0.1-0.2 µT	1.01 [0.84-1.21]
0.2-0.4 µT	1.11 [0.89-1.49]	0.2-0.3 µT	1.06 [0.78-1.44]
>0.4 µT	2.00 [1.27-3.13]	>0.3 µT	1.68 [1.24-2.31]

Under the rule in case of equally possible alternatives to lean in the direction of higher public safety → assume no threshold!

Example: Attributable Fraction for Childhood Leukaemia & Residential Exposure to Power Frequency EMF

BioInitiative

The upper confidence limit for the AF is highest in the Bayesian analyses

What is the range of attributable fractions?

Estimation Base	Classical	Bayesian Analysis
Case-Control Studies		
Europe	1.0 [0.5-2.3]	1.7 [-0.2-20.0]
US	3.2 [2.3-4.7]	4.4 [-1.0-28.0]
Surveys		
Europe	3.0 [1.2-6.0]	3.8 [0.0-30.0]
US	3.8 [1.7-7.0]	4.4 [0.0-36.9]

Up to ~30% of cases of childhood leukaemia could be due to exposure

Example: Attributable Fraction for Childhood Leukaemia & Residential Exposure to Power Frequency EMF

- The analyses so far assumed that 24-hour averages of magnetic flux densities are the correct metric. But if it is not? Is there a possibility that another metric results in even higher attributable fractions?
  - Assume z is the metric actually associated with the risk and x is the 24 hour average
  - Two criteria must be met:
    - $E(z|x)=a+b*x$
    - $\sigma^2(z|x)$ decreases with increasing x
  - Under these assumptions the results of the pooled analyses can be reconstructed but the metric z is associated with a manifold higher risk as compared to x

These assumptions (although arbitrary) are perfectly compatible with the epidemiological evidence and result in an attributable fraction of up to 80%

Summary

- Previous risk assessments were essentially defensive assuming results indicating a health risk of low-level long-term exposure are due to some unknown source of bias and evidence was assessed in such a way as to result in the lowest margin of safety
- The BioInitiative tried to give a balanced assessment of all evidence applying a cautious procedure: Whenever the evidence can be interpreted in different ways the interpretation resulting in the highest margin of safety was chosen

Epilogue

"All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."

Sir Austin Bradford Hill 1965. The environment and disease: association or causation? Proc R Soc Med 58:295–300.