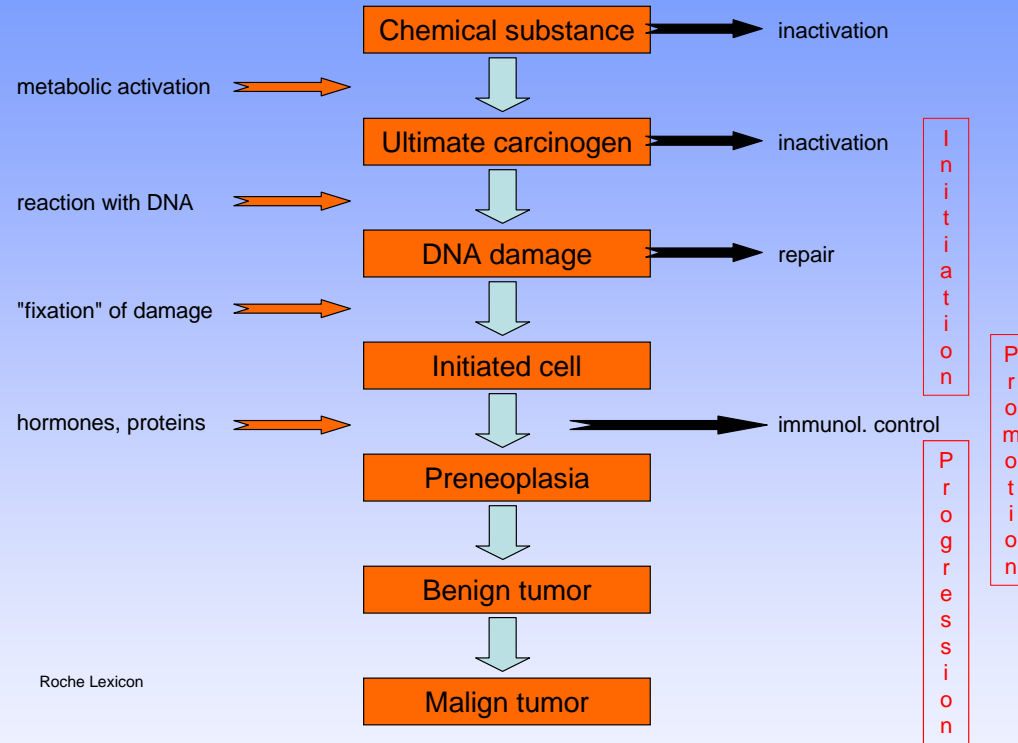

RF EMF cancer risk assessment: What do we know, what do we need to know? - Conclusions from animal studies

Jochen Buschmann



What we knew - before

Stages of Chemical Carcinogenesis



Animal Studies and RF EMF Cancer Risk Assessment

Examples: Carcinogenicity Literature 1

Author (year)	Field	Endpoint	Effect ?
Adey (1999)	NADC	spontaneous and induced CNS tumors	protection
Adey (2000)	NADC	spontaneous and induced CNS tumors	----- tumor type
Chagnaud (1999)	GSM	chemically induced tumors (2 weeks)	----- tumor type
Chou (1992)	2450	benign and malignant tumors	incr. malignant hist. contr. benigne reproducib. ?

Animal Studies and RF EMF Cancer Risk Assessment

Examples: Carcinogenicity Literature 2

Author (year)	Field	End point	Effect ?
Frei (1998)	2450	Mamma tumor devel. in susceptible strain	----- (2 x) tumor type
Higashikubo (1999)	FMCW CDMA	induced CNS tumors	----- tumor type
Imaida (1998)	TDMA	chemically induced liver tumors	----- tumor type

Examples: Carcinogenicity Literature 3

Author (year)	Field	Endpoint	Effect ?
Repacholi (1997)	900	Lymphomas in transgenic mice	increase methodology not reproduced
Salford (1993)	915	specifically induced brain tumor	----- tumor typ
Toler (1997)	435	total tumor rate !	-----

Summary of Previous Studies

Inconsistent data:

- equivocal results, different field types
- absence of "guideline studies"

Methodological problems:

- negative results in case of limited organ spectrum
- positive results: reproducibility

Human health risk (cancer):

- currently not deducible with sufficient certainty
- majority of studies is not supportive of cancer risk
- null hypothesis is not provable

Carcinogenesis

- Carcinogenesis is a multi-step process
- Currently no alternative to lifetime bioassay
- Whole tumor spectrum vs. selected tumors
- ... this was what we expected from PERFORM A
- **"In vivo Research on Possible Health Effects of the Use of Mobile Telephones and Base Stations (Carcinogenicity Studies in Rats and Mice)"**
- **www.item.fhg.de/PERFORMA.pdf**

PERFORM A: General Information

Lack of appropriate in vivo data from lifetime exposure studies

Critical points of previous studies:

- relatively small no. of animals (group size, sex, controls)

- focus on selected tumour types

- only one exposure "dose" (no dose-response relationship)

- problematic exposure conditions and dosimetry data

- disputable data analysis

PERFORM A: General Information

Title: "In vivo Research on Possible Health Effects Related to Mobile Telephones and Base Stations (Carcinogenicity Studies in Rodents)"

Period: 1999 - 2006

- Total Costs: 8 Mio € (EU: 2 Mio €)
 - Blind studies, GLP, WHO/IARC terminology
 - 2 (4) "NTP-like" Carcinogenicity studies (tumour initiation in mice and rats)
 - 2 Co-Carcinogenicity studies ("tumour promotion", DMBA in rats, transgenic mice)
(each including 3 RF "doses" + 1 Sham exposure group)
-

What we know - now

PERFORM A

PERFORM-A1: A Combined Chronic Toxicity / Carcinogenicity Study of 900 MHz GSM & 1800 MHz DCS Wireless Communication Signals In B6C3F1 Mice (Fraunhofer ITEM, Hannover, Germany).

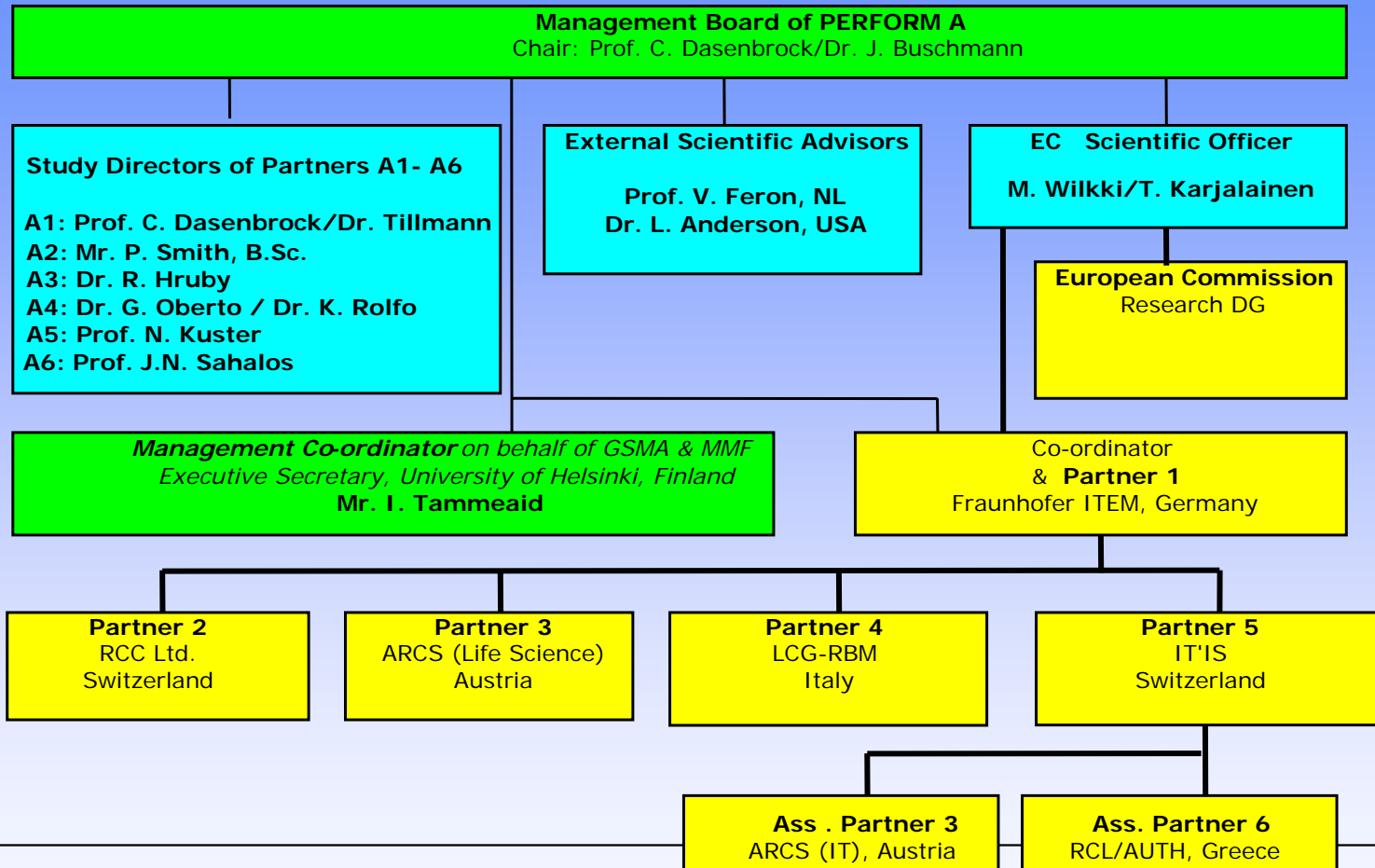
PERFORM-A2: A Combined Chronic Toxicity / Carcinogenicity Study of 900 MHz GSM & 1800 MHz DCS Wireless Communication Signals In WISTAR Rats (RCC Ltd, Switzerland).

PERFORM-A3: Evaluation of 900 MHz GSM Wireless Communication Signals on DMBA-Induced Mammary Tumours in Sprague Dawley Rats (ARC Research GmbH, Austria).

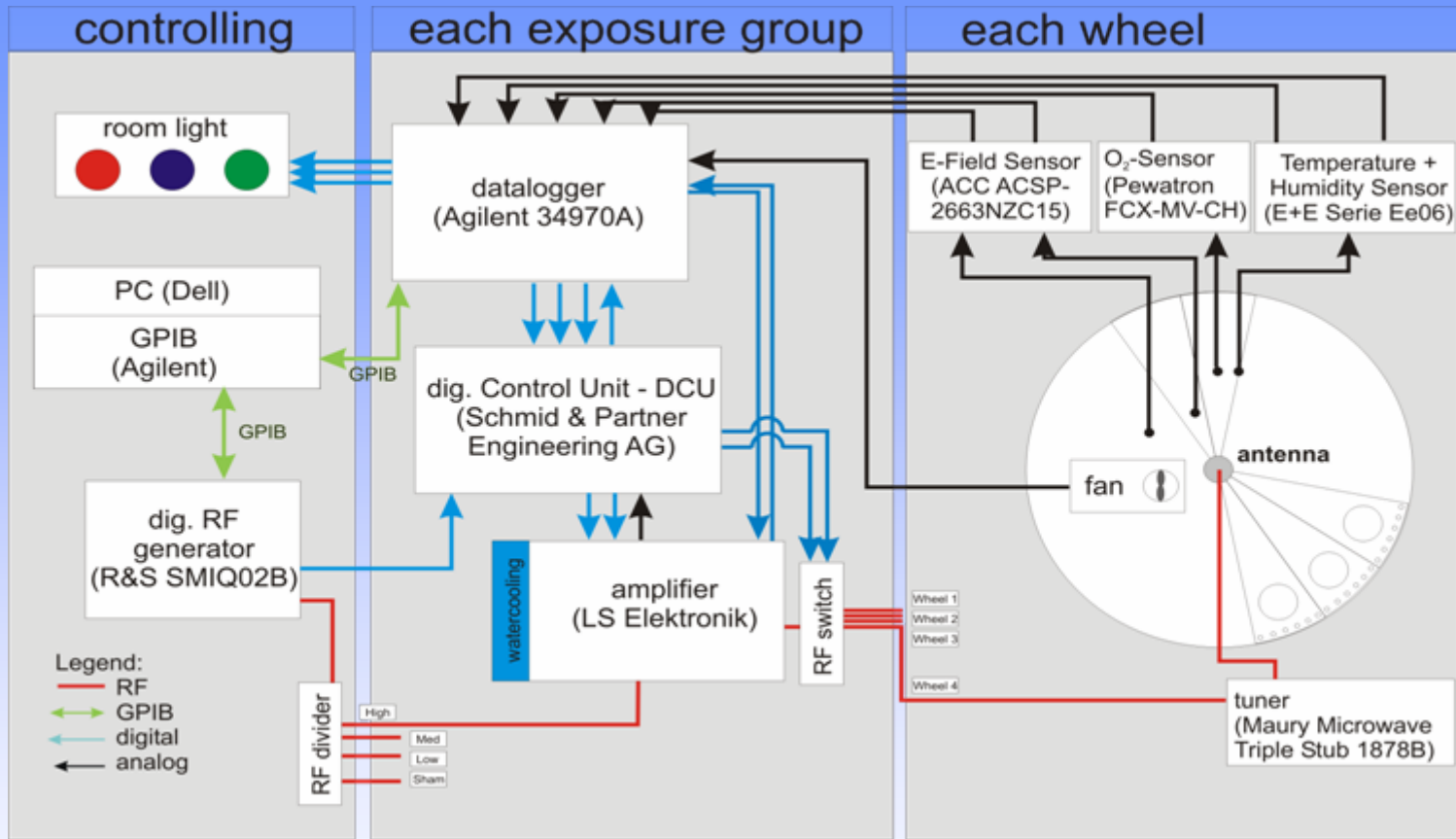
PERFORM-A4: Evaluation of 900 MHz GSM Wireless Communication Signals on Lymphoma Induction in E μ -Pim 1 Transgenic Mice (Istituto di Ricerche Biomediche "A. Marxer" (RBM), Italy).

PERFORM-A5: Exposure System Design, Construction & Dosimetry (IT'IS, Switzerland).

Animal Studies and RF EMF Cancer Risk Assessment



Animal Studies and RF EMF Cancer Risk Assessment

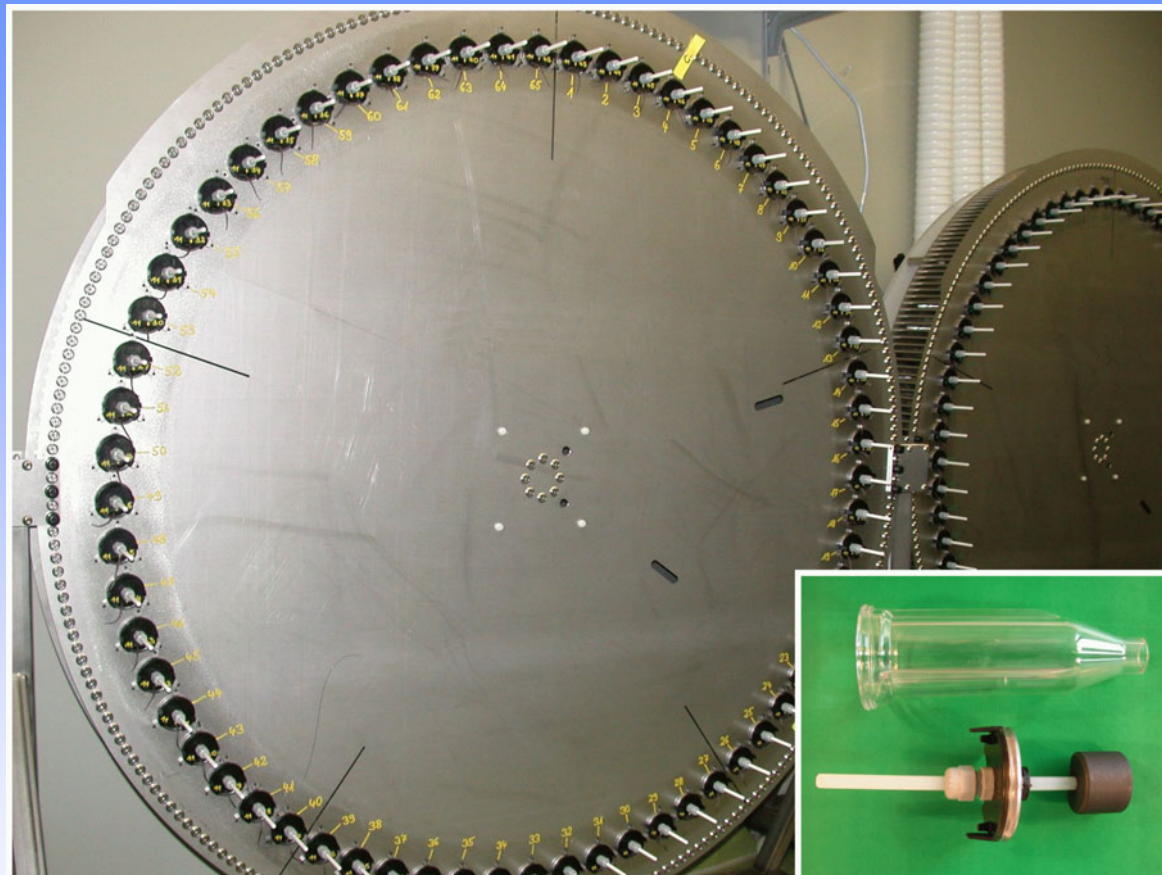


Animal Studies and RF EMF Cancer Risk Assessment



Exposure setup
in the animal
rooms

Animal Studies and RF EMF Cancer Risk Assessment



Setup detail and exposure tube

PERFORM A

- Blind studies
- Restrained animals
- NTP type studies
- Good Laboratory Practice
- SAR between 0.4 and 4 W/kg
- Full histopathology

PERFORM A1: Chronic / Carcinogenicity Study in Mice

PERFORM-A1 produced no evidence that the exposure of male and female B6C3F1 mice to electromagnetic fields (EMF) of GSM and DCS at an absorption rate of up to 4.0 W/kg for two hours per day, 5 days per week, over a period up to 24 months had any adverse health effect or any influence on the incidence or severity of the background non-neoplastic and neoplastic lesions. The study thus **did not provide any evidence of RF possessing a carcinogenic potential.**

PERFORM A2: Chronic / Carcinogenicity Study in Rats

PERFORM-A2, using Wistar rats exposed to 902 MHz GSM wireless communication signals at SAR levels of up to 0, 0.44, 1.33 or 4.0 W/kg or 1747 MHz DCS wireless communication signals at SAR levels of 0.41, 1.23 or 3.7 W/kg for 2 hours/day and 5 days/week over a period of up to 24 months produced no evidence of any adverse health effect or any influence on the incidence or severity of the background non-neoplastic and neoplastic lesions. The study thus **did not provide any evidence of RF possessing a carcinogenic potential.**

PERFORM A3: DMBA Model in Rats (1)

- less animals with benign neoplasms in all EMF-exposed groups,
 - more animals with malignant neoplasms in the high EMF-dose group,
 - more adenocarcinoma in the low EMF-dose group,
 - more malignant neoplasms in the low and the high EMF-dose group,
 - more animals with adenocarcinoma in the high EMF-dose group,
 - less animals with fibroadenoma in the low and the mid EMF-dose group.
-

PERFORM A3: DMBA Model in Rats (2)

In the mammary glands and their neoplastic lesions there were some significant differences between one or more of the EMF-exposed groups and the sham exposed groups, especially:

- more palpable tissue masses,
- more animals with malignant neoplasms,
- less animals with benign neoplasms.

PERFORM A3: DMBA Model in Rats (3)

Consequently, for study PERFORM-A3 it is concluded, that this study produced a **borderline evidence** of long term repeated exposure to 902 MHz GSM signals affecting the DMBA-induced mammary tumour response in rats with an equivocal biological relevance.

PERFORM A4: Lymphoma Induction in Transgenic Mice

In PERFORM-A4, exposure of *Pim 1* transgenic mice to a pulsed 900 MHz electromagnetic field (EMF) at an absorption rate of 0.5, 1.4 or 4.0 W/kg, daily for one hour, over a period of not less than 18 months produced **no evidence** that exposure had any effect on the incidence or severity of any neoplastic or non-neoplastic condition.

PERFORM A: General Summary

As an overall conclusion, three out of four studies produced no evidence that exposure had any adverse health effect or any influence on the incidence, severity or time of appearance of any neoplastic or non-neoplastic condition. The only effect observed is a borderline one found in the DMBA rat mammary tumour model assay.

PERFORM A vs. Chemicals

For chemicals, two lifetime studies in rats and mice are necessary for a risk assessment on carcinogenicity.

These were negative in PERFORM A ...

but:

Chemicals are subject to **regulation**

EMF are subject to **research** ...

Chemicals and Carcinogenesis

Even in a regulated field, it is not always like black and white:

IARC – International Agency for Research on Cancer (Lyon)

Classification Phrases:

- sufficient evidence
- limited evidence
- inadequate evidence
- evidence suggesting lack of effects

EMF and Toxicity Guidelines

Main Problem:

Overdosing as an important paradigm in toxicity studies

But: adding quantity of EMF exposure leads to a different quality (thermal effects)

We will end up in a vicious circle, unless we agree on some points

dosimetry, exposure scenarios, relevance of thermal effects, study designs, relevance of different frequencies

What we need to know – ASAP ...

Dosimetry

Safety factor (100) in toxicity studies to take into account inter- and intraspecies differences in susceptibility

even in types of endpoints with no threshold (like carcinogenicity)
part of the variability is due to toxicokinetics

(absorption, distribution, metabolism, excretion)

"geometrical" differences in the case of EMF

Dosimetry data could reveal a "build-in" safety factor of animal models compared to humans

We need detailed comparative data !

Exposure Scenarios in Humans

"Hazard" versus "Risk"

What is the worst case under practical conditions for users, workers ... ?

In connection with dosimetry in humans, where are we in relation to retrospective animal studies, what should be the target for future ones?

Decide on necessary energy flow densities in animal studies

Even in toxicology – trend away from overdosing towards realistic exposures (SOT, Seattle, March 2008)

Relevance of Thermal Effects

When performing animal studies on potential adverse effects of EMF, energy is added to biological systems. As a consequence of this, any addition leads to thermal reactions in animals, and there is no real "athermal" range.

Attempts were made to introduce such a threshold at the energy flow density that leads to an increase in rectal body temperature of 1 °C, but this appears to be rather artificial.

Can we solve this gordian knot approaching the problem differently ?

Relevance of Thermal Effects

Pragmatic approach:

Check required energy flow density in appropriate animal models

rectal temperature

temperature drop immediately after exposure

If there is no indication of thermal effects – go ahead !

Negative results – no problem

Effects – check whether they are of thermal origin ...

Thermal vs. athermal effects are an interesting academic issue

But: what counts is – can it happen in humans !

Relevance of Different Frequency Ranges

Different frequency ranges (within reasonable limits) should be handled like different compounds

have to be tested again

"binning" (grouping, read-across) based on structure analogues possible, but:

lack of a (compound) class effect does not automatically mean that each single compound does not exert this effect

Relevance of Additional Information

Genotoxicity

Mechanism of Action

important for the interpretation of data and mainly for existence of threshold values

But:

Lack of an obvious/explainable mechanism for an observed (adverse) effect does not mean to disregard the effect (if reproducible)

Preneoplastic lesions

Epidemiological data

Possible Role of "Omics" Studies

Screening of different frequency ranges

- set priorities in terms of frequencies for future investigations

- link effects to gene expression patterns

Once effects were determined – investigate possible underlying mechanism

Part of a regulatory strategy ?

Next Steps

There is an urgent need to move away from (descriptive) **research** towards **regulation** !

Cooperation between

authorities (governmental, non-governmental, international)

industries (cell phone producers, network suppliers)

research (academia, CRO)

Set up a guideline network **beforehand** !

REACH: Registration, Evaluation, Authorisation and Restriction of Chemical substances.

Important Bases

PARACELSUS: The dose makes the poison !

Put another way: nothing is without risk

Absence of effects is not provable

Agree on acceptable risks

Somebody has to take the lead ...

- Create a set of guidelines

- Communication to the public

- Stimulate dialogue between basic and applied researchers

Thanks for Listening !