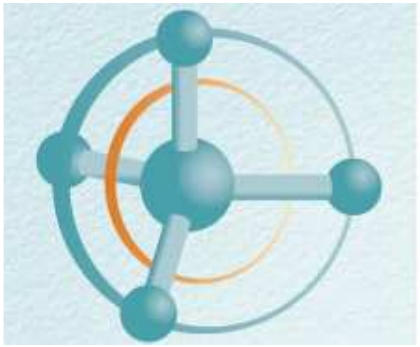

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Workshop summary

Kevin Prise and Laure Sabatier

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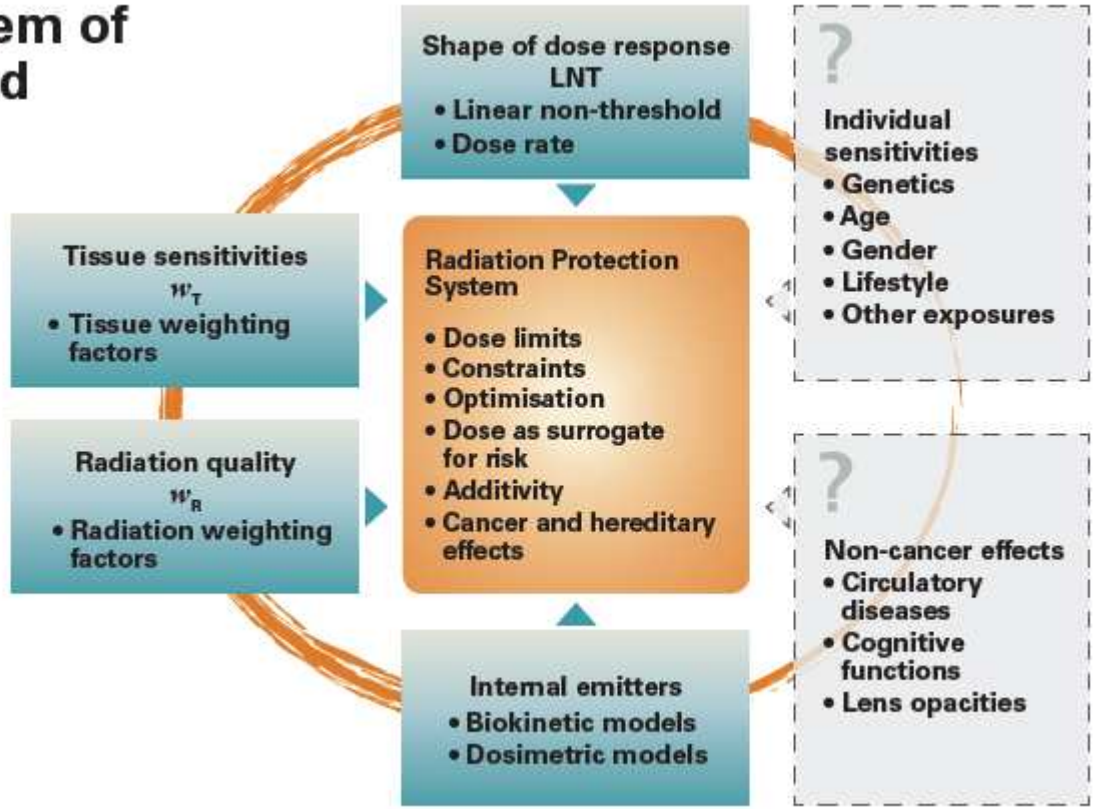
How robust is the system of radiation protection and risk assessment?

The current system of radiation protection makes judgements in several important areas: the four blue boxes indicate judgements that fall directly within the system of protection against the low dose radiation effects as recommended by ICRP, whereas the boxes on the right identify issues that are, at present, included only to a minor degree.



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Aim of MELODI

- Identifying research priorities in the low dose research
- Establishing and updating a Strategic Research Agenda (SRA) addressing low dose risk
- Sustaining education & training activities, maintaining infrastructures and disseminating results
- Promoting interdisciplinary collaboration
- Promoting regular interactions between the scientific community, international radiation protection bodies and stakeholders

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Third meeting

November 2-4, 2011

What we learnt?

Melodi SRA
12 conferences (3+9)
DOREMI up to date

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- Strategic Research Agenda
  - Dietrich Averbeck (Chairman)
  - David LLOYD, Peter Oneill

  - Tool, living process, living document

  - Melodi www.melodi-online.eu
  - SRA is on line : OPEN to discussion

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What Radiation Protection Can Request from Radiation Research P. Smeesters

Most of the money we obtain for radiation research come from radiation protection

basic research versus Consequence on radiation protection

Radiation protection policies : regulation, guidance,

RR versus RP too few interactions,

RR and Society : even fewer interactions

stake holders involvement is frequently a façade

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What Radiation Protection Can Request from Radiation Research P. Smeesters

Science : “club spirit”

Focus on risk plausibility rather than on hard evidence : precaution

Missed early warnings

lens opacity, cardiovascular effects

Irradiation in utero needs more research

Hereditary effects Increase from unscear 1993 (U93) to U200

Lack of human (health) effects does not mean evidence of lack of effect Dutrillaux view : recessive mutations due to small deletions: several generations are needed to observe an effect

Chernobyl : report published : birth defects, children’s mobidity Pb publication in russian, : why not take them into account : for at least verification

- Need for epi studies on non cancer effects on diagnostic and interventional imaging particularly in children
- Need for user friendly indicators
- True independence, thinking the unthinkable* => scientist need to look out of the box

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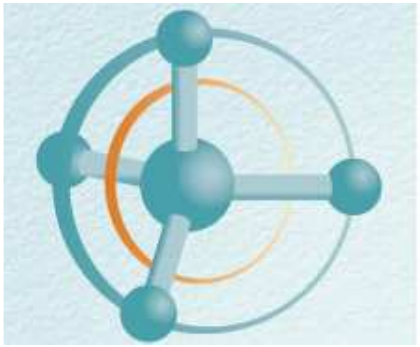
- Strategic Research Agenda
  - Open and integrative SRA
    - To guide coherent integration national progrmme on low dose
    - EC topics/programmes calls
    - TRA of doremi
  - **scientific vision**
  - **research priorities**
  - **List of uncertainties**
  - **Current consensus**
  - Close association of epi with experimental mechanistic studies
    - 3 priorities
    - **Shape of dose reponse**
    - **Noncancer**
    - **Individual susceptibility**

What is not in SRA



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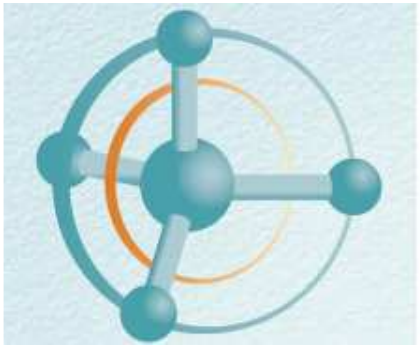
- Strategic Research Agenda
  - Suitable prospective cohortes/lifespan cohortes
  - Combined animal studies and epi
  - **Cross cutting issues**
    - Radiation qualiy
    - Tissue sensitivity
    - Research on internal emitters
  - Upgrading and establishment of suitable infrastructures
  - Training
- Roadmap is on going end 2011
- Establishment of melodi scientific committee



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– Epidemiology of ionizing radiation

SRA : Epidemiological and fundamental mechanistic studies should be undertaken in order to determine the dose-effect relationships (absence or presence of thresholds) for the induction of cancer, cardiovascular, and neurological (cognitive) impairments.

For this, suitable cohorts (some retrospective already existing cohorts, most prospective) with sound dosimetry and medical control have to be identified and/or set up.

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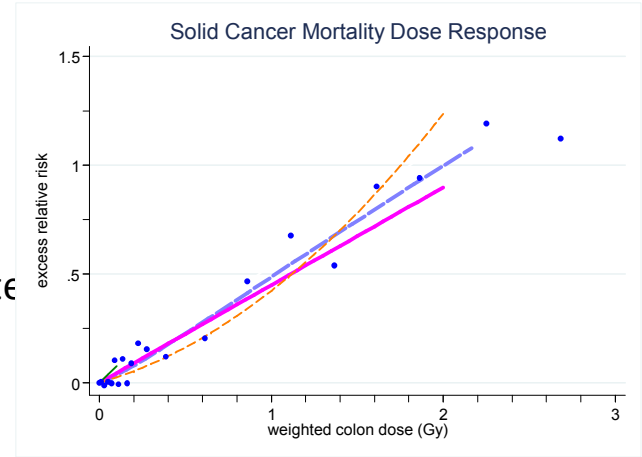
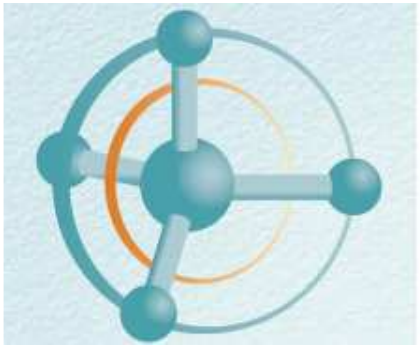
• From Epidemiology to Risk Factors

- DDREF : light and shadows : Dale Preston
  - Overview of DDREF estimation over the years (mostly atomic bomb survivors)
    - DDREF is the « Dose and Dose-Rate Effectiveness Factor
    - Used to reduce dose response slope to allow a presume reduction of risk at low dose low dose rate (1,5-2)

DDREF TODAY

- More LSS data
  - LSS often described as high dose studies has in fact a lot of information below 100mGy
  - Risk estimates are described with more detail and precision
- Other epi studies provide relevant risk estimates
  - Mayak and Techa River
  - UK nuclear workers (NRRW), IARC 15-country worker study, …
  - Chernobyl liquidators
- Evolving efforts to more fully characterize uncertainty in risk estimate
  - Dose errors, model uncertainty, …
- "New" radiobiology





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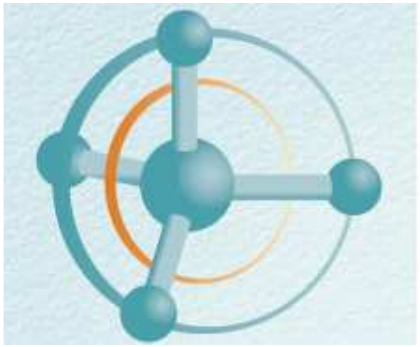
• From Epidemiology to Risk Factors (D. Preston)

- Cancer (and possible non-cancer) dose response is highly uncertain at low doses and low-dose rates
- Epi studies are extremely unlikely to resolve issue at doses / dose-rates of primary interest to radiation protection (e.g. < 10 mGy)

- Relevance of experimental radiobiology unclear (and will remain so)
- **There is no compelling evidence against the LNT as a description of radiation effects on cancer risks**
- Despite limitations the Epi data are the most relevant to radiation protection
- Little reason to use DDREF for radiation protection at this time



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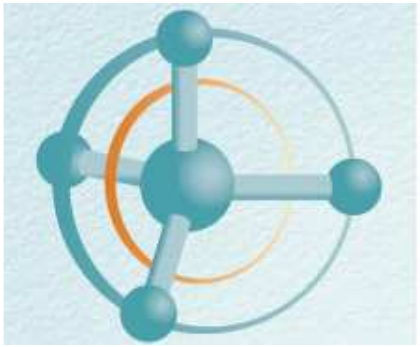
Epidemiology of ionizing radiation

- **Childhood leukemia and ionizing radiation Richard Wakeford**
  - first paper1931
- LSS : Clear and pronounced excess risk of leukaemia in the atomic bomb survivors.
  - Excess Relative Risk (ERR) at 1 Sv of leukaemia mortality in both sexes and all ages during 1950-2000 4.02 (90% CI: 3.02, 5.26)
  - Age effect++++ (nothing after 30y at irradiation)
  - High relative risk of childhood leukemia following radiation
- Recent risk models for radiation-induced leukaemia suggest that ~15% of cases of childhood (<15 years of age) leukaemia in Great Britain may be caused by natural background radiation.(red bone marrow dose ~1.3 mSv per annum)
  - Epidemiological studies have been unable to reliably demonstrate this source of risk (probably have insufficient statistical power)
- Controversies about leukemia and nuclear sites
- Role of infection
- chernobyl not mentioned : Data problematics?



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- **Experimental Models**
  - SRA

The identification and the nature and number of 'target' cells at risk for specific cancers in humans are important questions (for example: thyroid cancer). (…) The target cells are likely to be **stem cells** or at least relatively early progenitor (little differentiated) cells.

What is the implication of irradiation of **stem cells** in carcinogenesis?

The long-term priorities include the following areas: (1) for radiation-induced cancers and non cancer diseases Continuing development of suitable whole animal as well as human cellular models (including **somatic stem cells**) for radiation carcinogenesis and non- cancer diseases which bear clear relationships to human diseases.

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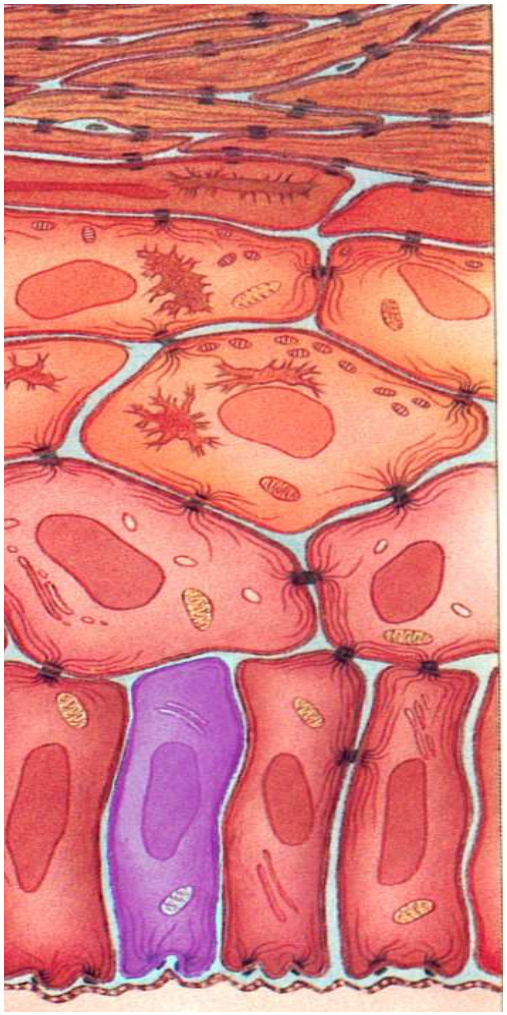
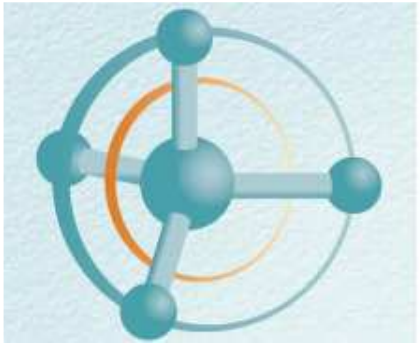
- **Experimental models**

- **Sensing Radiation Effects on Stem Cells of Human Skin**
  M.T. Martin
  - Epidermis renewal each 28 days
  - Basal layer proliferation and renewal : contains stem cells
  - Dormant, high growth potential, asymmetric division : stem cell + progenitors
  - Radiation can induce all type of carcinoma





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- **Experimental models**

- **Sensing Radiation Effects on Stem Cells of Human Skin** M.T. Martin
  - Radiosenitivity ? Keyplayer genes,?
    - 2 Gy vesus 10mGy : differenciated keratinocytes are resistant (cel survival) gene expression :
    - 10mGy : 5% of the probes and kinetics are modified (mostly repressed genes
    - after 2Gy it was mainly induced genes
    - GATA3 orchestrates protection at low doses If KO : induced increased radiosensitivity at 10mGy
  - Isolation of stem cells : flow cytometry
    - Stem cells, progenitors, differentiated cells
  - 2GY : stem cell radio resistant (cell survival, colonies) progeneitors are more radiosensitiv
  - Test cell signaling : cytokines and growth factors are activated : blocking FGF2 inhibit repa
    - Prorepair factor ; a new way to protect human skin
  - What about long term consequences

    Follow up of progenitor clones tree gave rise to established clones
    - Genomic instability, amplifications cmyc
  - Human model could be Gorlin patients mutations in PTCH1 gene
  - No big differences between stem cells from different donors in term of short term radisoensitivity

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Cardio-vascular and lens opacity research SRA

Compared with cancer much less information is available on effects of low and medium dose radiation exposures in producing long term consequences such as **cardiovascular dysfunction**, neurological alterations, **lens opacities**, or effects on other physiological functions.

In order to tackle these important aspects, there is an urgent need for multidisciplinary approaches bringing together radiation biosciences with disciplines such as cardiology, ophthalmology and neurology that to date have had little or no involvement with ionising radiation research.

Most urgent issues to resolve are the possible induction of cardiovascular, lens opacities and neurological (cognitive) impairments by low/medium dose ionising radiation. Feasibility studies carried out in the DoReMi project and elsewhere in EC programmes are likely to orient the different lines of future research in these areas.

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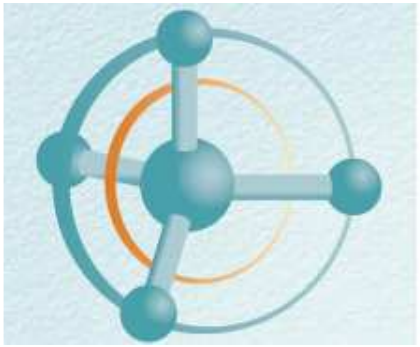
Experimental models

- **Radiation-Induced Cardiovascular and Cerebrovascular Disease** F. A. Stewart Netherlands cancer institute
- Incresed risk of vascular disease mortality bomb A survivior: 1984!!
  - (heart disease, stoke)
- Metaanalysis controversy : suggestive more that persuasive for moderate or low doses
- Pb : multifactorial disease : counfonding effects

- Modele ApoE–mice
- Data below 2Gy espected from Cardio risk
- No disease does not mean no effect



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Experimental models

- **Radiation-Induced Cardiovascular and Cerebrovascular Disease** F. A. Stewart Netherlands cancer institute

- the etiology of radiation-induced atherosclerosis is not the same as age-related atherosclerosis
- YES there an interaction between elevated cholesterol and radiation in development of atherosclerosis
- Both coronary artery disease (atherosclerosis) AND microvascular damage ar important in radiation induced cardiac damage.
- We still don't know if mean heart dose is the most relevant parameter or if it is dose distribution to major arteries

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- **Experimental models**
- **Animal Models and the Analysis of the Mechanisms Determining Individual Sensitivity to Radiation**

M. Atkinson

Jean-René Jourdain

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Experimental models

- Radiation-Induced Lens Opacities — Jean-René Jourdain
- Epidemiology of Radiation-Induced Cataracts
  - A-Bomb survivors
  - Chernobyl accident clean-up workers
  - Children living in ^{60}Co-contaminated buildings in Taiwan
  - Airline pilots and astronauts
  - Patients exposed to ionizing radiation
  - Health professionals exposed to ionizing radiation
- The O'CLOC Study
- **O**ccupational **C**ataracts and **L**ens **O**pacities in Interventional **C**ardiologists
  - Objective: to test the existence of an increased risk of lens opacities among interventional cardiologists compared to a non-exposed control group comprising non-exposed cardiologists
    - there is a significant risk of posterior subcapsular lens opacities in the population of French interventional cardiologists compared with unexposed workers
    - Range of doses from 25 mSv to 1600 mSv: CICs AND electrophysiologists
    - "Dose-response" relationship with duration of work

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Experimental models

Radiation-Induced Lens Opacities Jean-René Jourdain

- Mechanistic hypothesis
  - Molecular and Cell Biology
  - Genetic Susceptibility
  - Oxidative Stress
- Objectives of future researches
  - Establishment of over-life dose-response curves at low doses in animal models
  - Design of more appropriate experimental models (in vivo, in vitro, ex vivo)
  - Identification of the suitable cohorts for epidemiological and clinical studies
  - Collection of quantitative data on lens opacities
  - Increase understanding of the role played by factors affecting cataract development, including genetic background, gender, strain, age at exposure
  - Identification of early predictive markers and clinical endpoints