Article 31 RIHSS Report on Individual Radiosensitivity

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Effects of ionizing radiation and Safety Standards: major international players

- World level (scientific evaluation and/or recommendations RP)
  - **ICRP**
  - **UNSCEAR**
- World level (requirements: International BSS): **IAEA, FAO, ILO, NEA, WHO, PAHO**
- EU level (both): **Article 31 Group of Experts**
- World level (think tank): **CRPPH (NEA)**
- US level (scientific evaluation): **BEIR (NAS)**

The Article 31 group of experts

Article 31 Group of Experts: Group of independent scientific experts referred to in Article 31 of the Euratom Treaty, that assist the European Commission in the preparation of Basic Safety Standards

Scientific ?

Traditional concept of empirical science. Hypotheses are generated from observations and then **tested** by controlled experiments or observational studies.

Problem:

In the current world, **new** things (or situations) are introduced rapidly but with long term consequences, unknown by definition, asking for vigilance and responsiveness for early indications of health effects.

Potential observations may be only possible after a long time, generating hypotheses at a late stage, whose testing (if feasible) may again take a long time.

Informed **decision-making**

- Decisions frequently are to be made about these new introduced things (or situations), **while strong evidence or certainty is lacking.**
- Such decisions must be based on "**available "evidence"** (in the sense of "indications" or "**corpus of knowledge**").
- Decision-makers need then a sound basis for informed decision-making and are asking scientific experts (groups, committees …) for **science-based balanced information**.

Science-based balanced information

Involves avoiding unjustified causal associations **(false positives)**

as well as unjustified dismissal of real health effects **(false negatives)**.

The obsession of the false positives

By many scientists and in many scientific committees, too much importance is frequently given to the avoidance of false positives (by highlighting all possible bias for an association between effect and exposure) in comparison with the avoidance of false negatives,

while possible dismissal of real health effect of radiation is a major concern for

responsible decision-makers

A perfect illustration: UNSCEAR and the discussion on the Attributability report

There is

« no **compelling epidemiological** evidence »

of radiation-induction of health effects in a population under 100 mSv.

As a consequence no effect can be « attributed » (« **with certainty** ») to radiation under 100 Sv and even inference of risk for the future under this dose would be « non-scientific »

Precaution **within** Science: relevant!

Although frequently limited to the decision-making processes in situations of uncertainty, the **precautionary approach is also relevant and appropriate in science**.

As underlined in the COMEST report from UNESCO, the precaution approach in science includes:

- a systematic search for surprises ("**thinking the unthinkable**"), particularly for possible long term effects,
- a responsiveness to the first signals ("**early warnings**")
- and, last but not least, a **focus on risk plausibility rather than on hard evidence**.

Code of Ethics Art 31 GoE

"In fulfilling this function, the members of the group,

are independent experts and do not represent Member States or other bodies.

This means they take on, *as* *individuals*, high level responsibilities concerning *public health*, which requires appropriate ethical guidance. »

Code of Ethics Art 31 GoE

This code is conceived in a societal perspective and can be seen as an expert's deontology *ensuing from social expectations* regarding competence, neutrality and *objectivity*.

Code of Ethics Art 31 GoE

The experts shall take the necessary steps to update and to broaden their scientific knowledge, in relation with any major issue possibly affecting radiation protection. With this aim in view, they shall maintain *close contacts* with the scientific world in the relevant matters.

They shall use adequate means to take into account *all the available* scientific information and to avoid inappropriate selection of the sources.

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Code of Ethics Art 31 GoE

The experts shall respect all the points of view, *recognize the possible diversity of interpretation of the data* and favour interdisciplinary approaches, including disciplines belonging to human sciences.

The experts shall *avoid* creating *confusion between purely scientific judgements and value judgements* on ethical issues that are often deeply interwoven in the scientific evaluations and may not be directly apparent. They shall avoid trying to arbitrate ethical issues …and *make clear if there are uncertainties, value judgements or ethical issues*, what these are exactly and what is at stake.

The Art 31 RIHSS initiative

- RIHSS : Art 31 WP on Research Implications on the Health and Safety Standards
- ***Scientific RIHSS Seminars*** (yearly):
  - Leading experts summarize the **state of the art**
  - Invited experts act as ***peer reviewers***
  - **Discussion of the *potential regulatory implications***

Bridge RP/Research

Proceedings of the EU RIHSS Seminars

Available on the web site of the EC:

http://ec.europa.eu/energy/nuclear/radiation_protection/publications_en.htm

Radiation Protection Serie

Include a chapter highlighting potential implications

The RIHSS Seminars: often early warnings

- 1997: Radon
- 1998: Thyroid diseases and lessons from Chernobyl
- 1999: Genetic susceptibility
- 2000: Cancer risks at low dose
- **2001: In utero exposure in early phases of pregnancy**
- 2002: IR and breast cancer
- 2003: Medical overexposures
- 2004: Critical review ICRP draft 2005 recommendations
- 2005: Alpha-emitters: assessment of risk
- **2006: New insights in radiation risk and BSS *(incl: cataracts)***
- 2007: Tritium and low energy beta emitters
- **2008: Emerging evidence for rad. induced circulatory diseases**
- 2009: Childhood leukaemia – mechanisms and cause
- 2010: Issues with internal emitters
- **2011: Individual radiosensitivity**

EU RIHSS Scientific Seminar 2011

Luxembourg, 22 November 2011

Individual radiosensitivity

Highlights of the seminar

Radiation Protection No 171

- Radiation Sensitivity: an Introduction *Mike Atkinson*
- Genetic tools to address individual radiosensitivity and their limitations. *Christian Nicolaj Andreassen*
- Genetic pathways for the prediction of the effects of ionizing radiation. *Peter O'Neill*
- Genetic predisposition and radiation sensitivity: the potential of genome sequencing. *Paul D.P.Pharoah*
- Identification of candidate susceptibility genes in human radiation-associated thyroid tumors. *Sylvie Chevillard*
- Ethical aspects of testing for individual radiosensitivity. *Sven Ove Hansson*
- *Summary, discussions and conclusions*

Radiosensitivity?

- Important to clearly define the term:
  - enhanced sensitivity towards development of *side effects during radiotherapy*
  - susceptibility to *development of cancer* after radiation exposure at doses relevant in diagnosis, at workplaces or in everyday life
- Because:
  - other *implications*
  - differences in *molecular pathways* involved
  - very likely different sensitivity *profiles* .

Enhanced?

- Assuming a *Gaussian distribution* of sensitivity towards development of side effects in *radiotherapy*, one could define the *tails* of the distribution as being *hypersensitive* or, on the other side, *hyper-resistant*.
- Rare true outliers, for example patients that suffer from certain severe syndromes (e.g. Ataxia teleangiectasia, Nijmegen breakage Syndrome, Bloom's Syndrome): easily identified and specific treatment regimens
- In addition to the genetic profile, *many factors play a role*, such as treatment modalities, age, co-morbidities, smoking habits, diet, …

Dilemna in radiotherapy

- *therapeutic window:* defined by:
  - dose-effect curve for tumour control
  - dose-effect curve for induction of side effects
- *steepness of these curves*: to increase the probability of tumour control, the dose to the treatment volume should be as large as possible, but the probability of side effects is also increasing….
- *trade-off necessary*: conventionally, doses applied so high that only a small proportion (*5%) of the patients develops side effects.*

Underlying issue

If the most sensitive 5% could with high accuracy be identified:

- treatment doses could be increased for the other 95%,
- *But:* will the lower tolerated doses be sufficient for the 5% group of sensitive patients? *danger of under-treatment*

Identification in radiotherapy?

Functional testing

- Predictive functional assays :
  - Suppose identification of *relevant* end-point (DNA-repair, misrepair products, ….): identical for all side effects? (fibrosis,…)
- In operation in several hospitals
- But no generally accepted procedure (problem of large-scale validation)

Identification in radiotherapy?
Genetic testing

- genetic variants associated with enhanced sensitivity
- So far mainly *candidate gene* driven association studies.
  - many statistically significant associations in patient groups of limited size
  - *general lack of reproducibility*
- Modern *high-throughput methods* *(genome-wide associations* or radiation-induced alterations in *gene expression* patterns):
  - not limited to preconceived pathways.
  - up to several 100 000 markers tested at the same time, thus *very large cohorts*, and data validation in independent cohorts are necessary
  - large-scale *international cooperation's* have been set up to fulfill these criteria.

Cancer susceptibility

- Identification of persons carrying genetic variants that make them more susceptible for radiation-induced tumours is even more difficult
- Few cohorts with cancers clearly or very likely due to radiation
- Some preliminary data suggest that certain gene expression patterns may be used to differentiate radiation-induced from spontaneous tumours; validation of these data has not yet been obtained.

Ethical questions discussed

In ICRP Publication 103

calculation of *effective doses* for the purpose of radiation protection

does not account for age- or sex-specific differences

(tissue weighting factors averaged):

protection sufficient?

Ethical questions discussed

Issue of enhanced risk for women

not unequivocally clarified:

estimated relative risks for women higher , but

(due to lower spontaneous tumour incidence),

absolute risks comparable :

But does this imply the protection can be comparable?

Ethical questions discussed

- Other issues of **protection of sensitive or critical parts of the population**:
  - *children and pregnancy (in nuclear accidents*),
  - predictive testing for *emergency workers?* ,
  - breast cancer families (mammography strategy),
  - elderly persons?
- All future **epidemiological studies** on radiation-induced cancer (and *also non cancer* diseases) *should carefully investigate* risk coefficients after sex- and age-specific stratification.

Art 31 RIHSS added value

Keeping scientifically up to date its radiation protection advices

Taking into account all the available scientific information

Open discussion on the potential implications