Current views on low dose effects

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Member of Belgian delegation to UNSCEAR
R&D and Policy: a continuous loop

- Research: *production* of new data
- Follow up and evaluation of the data
- Implications of new data: regulation, guidance, policy, other R&D
- Residual uncertainties, research *needs* and priorities
Effects of ionizing radiation and Safety Standards: some major international players

• EU level: Article 31 Group of Experts (GoE)

• World level (scientific evaluation and/or recommendations RP)
  – ICRP
  – UNSCEAR
  – BEIR

• World level (requirements: International BSS): IAEA, FAO, ILO, NEA, WHO, PAHO
Rad.Research and Rad.Protection

There are in practice too few interactions between those performing research, and even those planning and financing research, and those interested in radiation protection (regulators, experts, practitioners, …).
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
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*
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 radiation induced circulatory diseases
- 2009: Childhood leukaemia – mechanisms and cause
- 2010: Issues with internal emitters
- 2011: Individual radiosensitivity
- 2012: Protection of the Environment
- 2013: Radiation induced long-term health effects after medical exposure
Proceedings of the EU RIHSS Seminars

Available on the web site of the EC:

Radiation Protection Serie

*Include a chapter highlighting potential implications*
UNITED NATIONS SCIENTIFIC COMMITTEE on the EFFECTS of ATOMIC RADIATIONS (UNSCEAR)

- 21 + 6 countries (incl. B)
- **Belgian delegation** (includes also Dutch scientists through a bilateral arrangement with the Netherlands):
  - H. Vanmarcke (Representative); P. Smeesters (Alternate)
  - F. Jamar; H. Bosmans; G. Eggermont; H. Engels; A. Wambersie; NL: H. Bijwaard, L. Mullenders

25/02/2014 Dr P. Smeesters
« Scientific cautiousness »: impact of mandate/objective

• The « cautiousness » of scientific world (UNSCEAR...): the main concern is to avoid concluding that a causal relationship exists before it is firmly proved.

• The « cautiousness » expected from groups like art 31 GoE: the main concern is to protect health; when there is scientific plausibility of the existence of a risk of serious and irreversible harm (even if there is still uncertainty), these groups should alert the policy-makers (precaution principle).
Low Dose Effects

• **Issues addressed:**
  – Cancer
  – Hereditary effects
  – In utero exposure
  – Cataracts
  – Circulatory diseases
Multistage model of tumorigenesis:

Mutational driving force
(UNSCEAR 2000)

- Damage to DNA
- Failure to correct DNA damage
- **Initiating mutation** (most tumours: *single* target stem-like cell)
- **Promotional growth** (clonal development of pre-neoplastic lesions: role of cellular environment)
- **Conversion to malignant phenotype** (driven by further mutations)
- **Progression: tumour spread** (driven by further mutations)
DNA-repair genes, cell-cycle regulation genes (U 2000)

- Many genes involved in the response to DNA-damage
- Puzzle not yet assembled
- Several pathways for DNA-repair: error-prone or « error-free » (homologous recombination)

« Error-free »?: uses template of parental copy but in heterozygotes can copy the bad allele!

Loss of heterozygosity!
Cancer-proneness

- **Human genetic disorders** affecting these genes (DNA-repair genes, cell-cycle regulations genes):
  - **High penetrance** disorders (strong expression): Rare individuals with *radiosensitivity* after acute exposure (radiotherapy, chromosome-damage tests) and **cancer-proneness** (in general and after irradiation);
  - **Low penetrance** disorders (subtle mutations or polymorphisms): frequent; *same potential risks*; current research with rodent models (ethical challenge in the future)

- Principal mechanism: **initiation** of mutations in critical target cells (mainly: gross deletions affecting TS genes): increases the general pool of tumor-initiated cells later subjected to age and environment (comforts relative risk projections)
- Principal damage: complex DNA double-strand lesions (« multiply damaged sites ») (difference with spontaneous lesions!), but no fingerprint!; possible with single tracks
- No expectation of wholly error-free repair of these lesions even at low doses and dose rates (particularly if genetic susceptibility)
- **Genetic instability**: Cell defenses can be bypassed by specific mutations
Radiation-induction of cancer: overall judgment (U 2000)

• On the basis of the current evidence:
  – **no threshold**;
  – cancer risk rising as a function of dose;
  – various patterns: \textit{L and LQ « the most scientifically defensible approximation »}
BEIR VII (2006) and current ICRP (103): position regarding LNT

Support U 2000 conclusions

BEIR VII conclusion: “The committee concludes that current scientific evidence is consistent with the hypothesis that there is a linear, no threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans.”
DDREF issue (DOSE AND DOSE RATE EFFECTIVENESS FACTOR)

- DDREF: reduction of risk coefficient at low dose and dose rate
- Human epidemiology: max 3-4 (UNSCEAR 2000)
- LSS: quasi-linear dose-response for solid cancers (means DDREF ~ 1)
- ICRP (current regulation + 103): DDREF: 2
- BEIR VII (central estimate): DDREF: 1.5 (LSS DDREF) (1.1 - 2.3)
- Art 31 GoE (Art 31 Sem. 2006): From a Radiation Protection point of view, a DDREF of 1.5 seems to be more justified
(from Preston et al., Radiat Res 2007; 168: 1-64)
UNSCEAR 2000 report:
Lifetime estimates of radiation-induced cancer risk

– principal basis: Life Span Study
– risk of exposure-induced death
– projection models unavoidable (most survivors LSS still alive)
– global estimate (all ages, both sexes, all cancers)
Lifetime estimates of radiation-induced cancer risk (leukaemia included)

• UNSCEAR 1994:
  – time-constant absolute risk m. abandon.
  – **time-constant relative risk model**: 12 % Sv\(^{-1}\)
  – RR ↓ toward 0: 8.6 % Sv\(^{-1}\)
  – RR ↓ toward RR 50 y age-at-exposure: 10.3 % Sv\(^{-1}\)

• UNSCEAR 2000:
  – **age-at-exposure model** (time-constant relative risk): 12.1 % Sv\(^{-1}\)
  – **attained age model** (age at death by cancer): 8.3 % Sv\(^{-1}\)
  – concl.: **about 12% Sv\(^{-1}\)** (unc: f.2 ↓or↑)
Lifetime cancer risk estimates
ICRP 60 (1990; current regulation)

High dose/high dose rate:
about 10% Sv\(^{-1}\)

Low dose/low dose rate:
about 5% Sv\(^{-1}\)
UNSCEAR 2006 report: 
Lifetime estimates of radiation-induced cancer risk: mortality

For all solid cancers together:

At 0.1 Sv:   UK: 3.3 - 5.4 % Sv$^{-1}$
            US: 3.0 - 5.0 % Sv$^{-1}$ (BEIR VII: 7.4 % Sv$^{-1}$)
At 1 Sv:    4.3 – 7.2 % Sv$^{-1}$ (U 2000: around 10 % Sv$^{-1}$)

For leukaemia:
1 Sv: 0.6 – 1.0% Sv$^{-1}$
0.1 Sv: 0.3 – 0.5% Sv$^{-1}$

Lower than U 2000 and BEIR VII, particularly solid cancers at 1 Sv
UNSCEAR 2006 report:
Lifetime estimates of radiation-induced cancer risk: mortality

- risk estimates lower than those previously published, particularly at 1 Sv
- reduction of about 10% due to the new atomic bombings dosimetry
- small reduction of 3-7% due to increased follow-up.
- large reduction of 35 - 40% due to the different risk projection and transfer models used.
- DRREF included: the estimates for 0.1 Sv implicitly adjust for extrapolation to low doses, so that no extra adjustment for chronic exposure (i.e. application of a DDREF) is needed.
UNSCEAR 2006 report: Lifetime estimates of radiation-induced cancer risk: incidence

For all solid cancers together:

At 1 Sv:   
  UK: 10.8 – 23.1 % Sv\(^{-1}\)  \(\textit{(U 2000: 17 – 19.3 % Sv}^{-1}\))  
  US: 10.6 – 37 % Sv\(^{-1}\)

At 0.1 Sv:  
  UK: 11.7 - 16.8 % Sv\(^{-1}\)  
  US: \textbf{11.6 - 24.1 % Sv}^{-1}  \(\textit{(BEIR VII: 16.9 - 18.6 % Sv}^{-1}\))

Very similar to U 2000 and BEIR VII; practically linear
Variations in risks

- Age-at-exposure: lifetime cancer risk $\times 2-3$ for those exposed as children
- Woman: $+30$ to $60\%$ (all solid cancers)
- Incidence v/mortality: about $\times 2$
- Changes from neutron doses (LSS: DS02): max - $10\%$ decrease of the slope of the dose-response
EU Scientific Seminar 2006
Luxembourg, 17 October 2006

New Insights in Radiation Risk and BSS
EU Scientific Seminar 2006: important issues discussed

• Age at exposure
  – Children are not young adults!
  – Need to do something more to take this factor into account?
  – Organ dose limits/constraints, where necessary (thyroid, ..) would be an easy way

• Gender
  – Cancer risk women clearly higher v/men (BEIR VII)
  – The use of gender specific Wt is proposed by some, disputed by others
  – The question is whether such a decision should be made by ICRP or by the regulators (societal judgement)
Non-Targeted Effects: conclusions
UNSCEAR Report 2007

• NTE: Bystander effects, radiation-induced genomic instability, …

• Are in fact included in epidemiological observations

• Could result in over- or under- estimation of health effects of IR at low dose

• More research is needed
γ-H2AX foci in T-lymphocytes

Control sample

0.5 Gy in vitro
Comparison of γ-H2AX foci induced in vivo in pediatric patients versus in vitro irradiation

Dashed line: LNT extrapolation from in vitro 0.5 Gy
Recent studies:  
Joint European analysis on indoor radon risk

• 7 000 cases of lung cancers; 14 000 controls
• **Clear linear** DR relationship between radon in houses and lung cancer risk
• RR = 1.08 for 100 Bq/m3 CI 95% = [1.03 – 1.16]
• **significant relationship even if limited to those exposed to ≤ 200 Bq/m3**
• also a significant increase in the non-smokers population
Other recent low dose studies
E. Cardis (Art 31 Sem. 2006)

• Nuclear Industry Workers (15-country study): low dose protracted exposures (most $\leq 100$ mSv cumulative dose); results **statistically consistent** with A-bomb data (ERR higher! But smoking issue)

• Techa River Cohort (protracted exposures ext/int): results **statistically consistent** with A-bomb data (ERR higher! But dosimetric issues)
New data: Pearce 2012 (Lancet)

Radiation exposure from CT scans in childhood and risk of leukaemia and brain tumours:

- Retrospective study (based on NHS UK): 180,000 patients < 22 y with CT (1985-2002); cancers 1985-2008
- Relative risk of leukaemia for patients who received a cumulative dose of about 50 mGy: 3.18 (95% CI 1.46–6.94)
- Relative risk of brain cancer for cumulative dose of about 60 mGy: 2.82 (1.33 - 6.03)

Linear dose–response; supports LSS extrapolations
New data: Kendall 2013 (Leukemia)

A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980–2006:

- 28 000 cases
- 12% ERR (95% CI 3, 22) of childhood leukaemia per mSv of cumulative red-bone-marrow dose from gamma-radiation

• supports the extrapolation of high dose-rate risk models to protracted exposures at natural background exposure levels.
Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (Pijpe 2012 GENE-RAD-RISK)

In this large European study among carriers of BRCA1/2 mutations,

“any exposure to diagnostic radiation before the age of 30 was associated with an increased risk of breast cancer.”
Low Dose Effects

• Issues addressed:
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  – Cataracts
  – Circulatory diseases
Radiation-induced genetic risk
UNSCEAR 2001 - BEIR VII - ICRP

• Genetic studies of A-bomb survivors: no measurable adverse effects in children
• Risks estimated indirectly using mouse data with the ‘doubling dose method’
• New concept introduced: congenital abnormalities caused by large deletions (analogy with human microdeletion syndromes: multi-system developmental abnormalities)
Equilibrium theory

Mutation-selection balance

Mutation

Selection
Doubling dose method
(based on equilibrium theory)

- **Risk per unit dose** = \( P \times \frac{1}{DD} \times MC \times PRCF \), where:
  - \( P \) = Baseline frequency of genetic disease class (\( \times \) cases / million life born)
  - \( DD \): Doubling dose; \( \frac{1}{DD} \): relative mutation risk
  - \( MC \) = mutation component (0-1) (expected increase in disease frequency as a result of increase in mutation rate)
  - \( PRCF \): Potential Recoverability Correction Factor
UNSCEAR (2001) estimates of genetic risks from continuing exposure to low LET, low-dose or chronic irradiation. Assumed doubling dose = 1 Gy

<table>
<thead>
<tr>
<th>Disease class</th>
<th>Baseline frequency (per million live births)</th>
<th>Risk per Gy per million progeny</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; generation</td>
</tr>
<tr>
<td>Mendelian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant&amp; X-linked</td>
<td>16,500</td>
<td>~ 750 to 1,500</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>7,500</td>
<td>0</td>
</tr>
<tr>
<td>Chromosomal</td>
<td>4,000</td>
<td>a</td>
</tr>
<tr>
<td>Multifactorial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>650,000</td>
<td>~ 250 to 1,200</td>
</tr>
<tr>
<td>Congenital abn.</td>
<td>60,000</td>
<td>~ 2,000</td>
</tr>
<tr>
<td>Total</td>
<td>738,000</td>
<td>~ 3,000 to 4,700</td>
</tr>
<tr>
<td>Total per Gy</td>
<td></td>
<td>~ 0.3 to 0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(U93: 0.18)</em></td>
</tr>
</tbody>
</table>

*a: included under autosomal dominants & congenital abn.*
Genetic risk: concerns regarding international evolution:

• “New genetic risk coefficients recommended by ICRP consider exposure and genetic risk for two generations only - the equilibrium value used in ICRP 60 is judged to be of questionable scientific validity because of the unsupported assumptions necessary on selection coefficients, mutation component and population changes over hundreds of years.”

• “As a result, the risk associated with gonadal dose is now estimated to be around 20 cases per 10,000 people/Sv, rather than around 100 cases in ICRP 60”
Genetic risk: concerns

• There are 3 fundamental issues:
  – is the total genetic risk lower than we thought in 1990?
  – Is the genetic risk limited to the two first generations?
  – Do we know enough to draw final conclusions?
Genetic risk first generation
(one-shot or continuous irradiation)
(low dose-low LET)
U2001 / U93

- Number of cases per Gray per million progeny: 3000-4700 (U93:1740)
  - 750-1500 mal. dom./sex-link. (U93:1500)
  - 250-1200 mal. multif. chron. (U93:ne)
  - 2000 anom. cong. (U93: 240 chrom.)

- $= 0.3-0.47 \% \text{ Sv}^{-1}$ (U93: 0.18 \% \text{ Sv}^{-1})
Genetic risk **equilibrium**

(*continuous irradiation low dose-low LET*)

U2001 / U93

- **U93**: 1.2% par Gy (sans les aff. multifactorielles et les anomalies congénitales)
- **U2001** (mais avec bcp de prudence): en % par Gy
  - Aff. dominantes et X-linked: 
    \[ P \times 1/\text{DD} \times \text{MC} \times \text{PRCF} = 0.25 \text{ à } 0.5 \]
  - Aff. Récessives: = 0.11 à 0.22
  - Aff. Multifact.: = 1.3 à 5.8
  - Aff. Congén.: ?
  - Total: **1.65 à 6.5% par Gy**
Genetic risk:
Some radiobiological issues

– The question of the minisatellite mutations:
  • increased germline mutagenesis detected in various populations exposed to ionizing radiation, by genotyping minisatellites
  • Sometimes « associated » with diseases like neuropathies (then possibly not pure markers without health significance)

– The complexity of the genome machinery:
  • new data regarding transgenerational mutagenesis: the appearance of mutations in the second generation offspring of irradiated parents (mouse)
  • The possible differences in genetic changes between external and (chronic) internal exposures

« Lack of human (health) evidence does not mean evidence of lack of effect »
Dutrillaux views
(Art 31 Seminar 2004)

• According to him, the main problem is the radiation induction of small deletions leading to recessive mutations and diseases of which the phenotypes might frequently not be recognized by the physicians. Such cumulative small genetic disorders may propagate in the future generations with the risk of leading to more important pathological consequences.

• Data on atomic bombing survivors and patient progeny have thus a major flaw: several generations are necessary for the passage to homozygoty of induced recessive mutations. There is not a sufficient delay to observe their expression today.
Angulo’s views
(Art 31 Seminar 2006)

• Mutagenesis of Repeated DNA regions:
  – mutation rate increases linearly with radiation dose
  – similar number of germline mutations are induced by acute and chronic exposures
  – the detected increase is similar when comparing the coding and noncoding regions of the genome (NTE!)
  – germline mutagenesis depend on the integrity of DNA repair systems

• Conclusions: “possibility that small DNA modifications induced by IR destabilise replication and produce a “cascade effect” leading to a general enhanced mutagenesis”
Evidence relevant to untargeted and transgenerational effects in the offspring of irradiated parents
A review by Little et al 2013

• Observed in animal studies after high dose irradiation of males
• Effects mainly if conception short times after exposure
• Clinical health effects not identified in human studies (but some evidence of cellular effects)
Types of transgenerational effects reviewed (1)

- Chromosome damage: animal + 1 human study (Aghajajanyan, 2011) but method. issues; need to deepen by further studies
- ESTR mutations: only animal studies, important differences with human minisatellites
- Germline DNA changes in humans: no robust evidence but few studies and little power to detect risk
- Somatic gene mutations in the offspring: mouse studies, no human data
- Minisatellites mutations in humans: not seen after acute high dose paternal exposures; but evidence in groups with internal or mixed exposure from environmental contamination (Chernobyl, Kazakhstan, Techa-River); further studies needed
Types of transgenerational effects reviewed (2)

- Induced radiosensitivity; not seen in radiotherapy; 1 report in Chernobyl (Aghajanyan 2009)
- Cell proliferation defects: in mice; persistant gene expression changes (multigenerational); studies needed for still birth, untoward pregnancy outcomes, proliferative deficits
- Transgenerational induction of cancer: seen mainly with chemical carcinogens
- Congenital malformations: yes but transgenerational?
- Epidemiological evidence of health effects: little evidence but few studies
Transgenerational effects: too early to conclude!

- **Minisatellite** DNA mutations in children: seen in populations of areas contaminated with **internal** emitters (Ukraine and Belarus, Techa river,….) but not in those exposed to **external** radiation sources: **role of internal and/or protracted exposures to be deepened** (also in relation with children’s morbidity)

- **Lack of human studies:** for example: studies suggesting trangenerational induced sensitivity or chromosomal damage in children of liquidators (Aghajanyan): although methodological limitations, should be deepened or verified instead of rejected

- **Further research** is needed, including in the offspring of persons exposed after Chernobyl, as underlined in the ARCH strategic long term research agenda. (2011 EC Radiation Protection 170; similar recommendation in Little 2013)
Current reassuring messages regarding in utero irradiation and transgenerational effects are based on a relative lack of «hard evidence» about effects on «human» health,

but:

«Lack of human (health) evidence does not mean evidence of lack of effect»
Such messages are misleading for decision-makers as they fail to draw the attention on the large epistemic and aleatory uncertainties and on some challenging data that could be « early warnings ». Such unbalanced information affects judgments about policy implications.
Low Dose Effects

- **Issues addressed:**
  - Cancer
  - Hereditary effects
  - In utero exposure
  - Cataracts
  - Circulatory diseases
Irradiation in utero: current views and statements: the 100 mSv break-point

- **Pre-implantation** period: all or nothing: possible death of embryo above 0.1 Gy; if not killed the embryo develops normally; no congenital malformation

- **Early organogenesis**: no congen. malf. under 0.1 Gy
  - ICRP 103: “there is a true dose threshold of around 100 mGy”
  - 100 mSv frequently presented as the “official” break-point criterion in situations like emergency planning, or post-accidental decisions

- **8 -25 weeks post-conception:**
  - Severe mental retardation above threshold dose (lower confidence limit A-bomb study: 0.3 Gy)
  - Lower IQ: ICRP 103: “Under 100 mGy, any effect on IQ would be of no practical significance “(ICRP 103)”
100 mGy? ICRP 90: more nuances

• **Pre-implantation** period: no congenital malformation, but exceptions mentioned (“due to genetic predispositions”)

• **Early organogenesis**: dose range of 0.05-0.25 Gy

• **8 - 25 weeks post-conception**: Lower IQ:
  • 8-15 w: Linear radiation dose response (21 IQ points/Gy)
  • 16-25 w: LQ dose response (13 IQ points/Gy)
  • a threshold dose is not apparent
Irradiation in utero in early phases: challenging data (Jacquet, ....)

- **Pre-implantation period**: Irradiation in animals during the pre-implantation period *can* induce congenital malformations (sometimes non lethal) or genomic instability, *with or without genetic factors of predisposition*; *thresholds uncertain particularly in zygote stage*; similar observations with chemicals.

- **Early organogenesis**: new data: more congenital malformations in *genetically susceptible mice* (alteration of genes involved in DNA-damage response).

- **Mechanism**: persistence of *un_* or misrepaired DNA-damaged cells ("teratogenically damaged cells").
Precautionary lecture
(2001 RIHSS Scientific Seminar; 2011 SCK/FANC Symposium)

In humans, the same genetic susceptibilities probably exist.

If the mechanisms are similar (persistence of mis-repaired DNA-damaged cells), it is plausible that human genotypes leading to cancer-proneness are also associated with a genetic susceptibility to the radiation-induction of congenital abnormalities (or more subtle tissue dysfunctions).

The thresholds could be different, or …..absent at day 1.
Effects of prenatal exposure: still major open questions (cfr ICRP 90)

- « Data from human studies with protracted exposures are almost nil »
- « High-LET radiation and incorporation of radioactive substances: virtually no data available from human studies »
- « Prenatal exposures and chronic mental deficiencies: completely open field that should be studied »
(Low dose) irradiation in utero: concerns

There are still many uncertainties (genetic susceptibilities, long term effects due to modification of gene expression, internal chronic exposures, subtle effects or long term effects of NCS irradiation….)

But: Few research! Few labs! ; lack of budget; statistical limitations (small numbers of animals; cost of KO animals)
Whole pregnancy: cancer induction

- Embryo and fetus more sensitive
- Cancers appear in first 10 y or later
- No threshold dose!
- Risk dose-related (fatal cancers): LNT
  - 10 mSv (IV. Urogr.): 1-2/1000
  - 100 mSv (some CT exams): 1-2/100
I don’t know!!…
euh…no

Not pregnant?
NET ZWANGER?
MIJD STRALING

Veel zwangere vrouwen weten niet dat een onderzoek waarbij X-stralen te pas komen, schadelijk kan zijn voor haar ongeboren kind. Zelfs in het allervroegste stadium kan dit een risico zijn.

Uw arts zal u informeren, maar denk er zelf ook aan. Een gewaarschuwd mene telt immers voor twee!

Voor meer info: www.fanc.fgov.be/netzwanger.mijdstraling
Low Dose Effects

• Issues addressed:
  – Cancer
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Cataracts
(Art 31 Seminar 2006: N. Kleiman)

- New data from animal models and from exposed human populations (Chernobyl liquidators, A-bomb) suggests that lens opacities occur at doses far lower than those generally assumed to be cataractogenic

- Some observations are consistent with the possible absence of a dose threshold (genetic susceptibilities: Atm, Brca1 and Rad9 heterozygotes)
**Cataracts** among Chernobyl clean-up workers: implications regarding permissible eye exposures.

**Worgul BV, Kundiyev YI, Sergiyenko NM, Chumak VV, Vitte PM, Medvedovsky C, Bakhanova EV, Junk AK, Kyrychenko OY, Musijachenko NV, Shylo SA, Vitte OP, Xu S, Xue X, Shore RE.**

Eye Radiation and Environmental Research Laboratory, Columbia University, New York, New York 10032, USA.

The eyes of a prospective cohort of 8,607 Chernobyl clean-up workers (liquidators) were assessed for cataract at 12 and 14 years after exposure. The prevalence of strictly age-related cataracts was low, as expected (only 3.9% had nuclear cataracts at either examination), since 90% of the cohort was younger than 55 years of age at first examination. However, posterior subcapsular or cortical cataracts characteristic of radiation exposure were present in 25% of the subjects. The data for Stage 1 cataracts, and specifically for posterior subcapsular cataracts, revealed a significant dose response. When various cataract end points were analyzed for dose thresholds, the confidence intervals all excluded values greater than 700 mGy. Linear-quadratic dose-response models yielded mostly linear associations, with weak evidence of upward curvature. The findings do not support the ICRP 60 risk guideline assumption of a 5-Gy threshold for "detectable opacities" from protracted exposures but rather point to a dose-effect threshold of under 1 Gy. Thus, given that cataract is the dose-limiting ocular pathology in current eye risk guidelines, revision of the allowable exposure of the human visual system to ionizing radiation should be considered. *Radiat Res. 2007 Feb* ;167(2):233-43.
Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold.


Department of Clinical Studies (Hiroshima), Radiation Effects Research Foundation, Japan. Neriishi@rerf.or.jp

Recent evidence argues against a high threshold dose for vision-impairing radiation-induced cataractogenesis. We conducted logistic regression analysis to estimate the dose response and used a likelihood profile procedure to determine the best-fitting threshold model among 3761 A-bomb survivors who underwent medical examinations during 2000-2002 for whom radiation dose estimates were available, including 479 postoperative cataract cases. The analyses indicated a statistically significant dose-response increase in the prevalence of postoperative cataracts [odds ratio (OR), 1.39; 95% confidence interval (CI), 1.24-1.55] at 1 Gy, with no indication of upward curvature in the dose response. The dose response was suggestive when the restricted dose range of 0 to 1 Gy was examined. A nonsignificant dose threshold of 0.1 Gy (95% CI, <0-0.8) was found. The prevalence of postoperative cataracts in A-bomb survivors increased significantly with A-bomb radiation dose.

The estimate (0.1 Gy) and upper bound (0.8 Gy) of the dose threshold for operative cataract prevalence was much lower than the threshold of 2-5 Gy usually assumed by the radiation protection community and was statistically compatible with no threshold at all. (Radiat. Res. 2007 Oct; 168(4): 404-408)
ICRP Seoul April 2011: agrees; lower dose limits (20 mSv/y)!
Low Dose Effects

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  – Circulatory diseases
Cardiovascular disease following radiation exposure: U 2006

• There is an increased risk of cardiovascular disease associated with high radiation doses to the heart, which may be incurred during radiotherapy,

• To date, the evidence for an association between fatal cardiovascular disease and radiation exposure at doses in the range of less than about 1-2 Gy comes only from the analysis of the data on the Japanese atomic bombings survivors.

• Other studies provide no clear or consistent evidence of a risk of cardiovascular diseases for radiation doses of less than about 1-2 Gy.
Emerging evidence for radiation induced circulatory diseases

Overview and conclusions of the seminar
Epidemiological evidence for radiation-induced circulatory diseases – A-bomb survivors

*R. Wakeford and M.P. Little*

- Cohorts: LSS (~ 87,000; mortality); AHS (~ 20,000; morbidity)
- Confounding factors: healthy survivor effect; no data prior to 1950
- First indications: Jablon & Kato, 1972 (only women); Wong, 1993 (↑ RR myocardial infarction incidence for < 40y ATB; > 2 Gy)
- Shimizu, 1999; Preston, 2003: ERR v/dose is L for heart disease and stroke mortality; 165 deaths v/ 421 for cancer!; Yamada, 2004: quadratic dose resp for incidence
- Tatsukawa, 2008: significant effect for cardiovascular disease among childhood exposed
- **Conclusion:** clear increased risk even < 2 Gy; consistent with LNT or with threshold of ~ 0.5 Gy; significant proportion of radiation-associated mortality
Radiation-induced circulatory diseases (EU Seminar 2008)

  - Mayak workers: 12 000 men and 3500 women; mortality/morbid.
  - Very good info on confounding factors (incl. smoking and alcohol)
  - ERR for ischemic heart disease and cerebrovascular disease
  - Evidence from 0.5 Gy (recent publication: Azizova nov 2011: also 0.2-0.5: mainly women)
  - Protracted doses!
ERR/Gy & 95% CI for analyses of external dose
IHD (morbidity)
ERR/Gy = 0.109 (0.049-0.168)
ERR/Gy & 95% CI for analyses of external dose

CVD (morbidity)

ERR/Gy = 0.464 (0.360-0.567)
Evidence for radiation-induced circulatory diseases among patients treated with radiotherapy

K.R. Trott

- Known for a long time but increased concern
- Hodgkin; head and neck cancer; breast c. (carotid arteries; coronary arteries);
- Key issue: critical anatomical structures (on going EU studies);
- Other issues: dose threshold? Latency related to dose? Mechanisms? Age at exposure?
Biological mechanisms of radiation-induced circulatory diseases

G. Hildebrandt and S. Schultz-Hector

• Ongoing studies (NOTE; CARDIORISK)

• Mechanisms unknown: inflammatory hypothesis so far supported

• R&D is ongoing but good animal models are lacking (disease absent in wild type rodents!)
Radiation-induced circulatory diseases (EU Seminar 2008)

• Although a lot of confounding factors have to be taken into account, epidemiological evidence is accumulating in favour of an increased risk of circulatory disease (ischemic heart disease and cerebrovascular disease) for doses higher than 0.5 Gy, including after protracted exposures (Mayak workers).

• Significant proportion of radiation-associated mortality
• Growing concern in radiotherapy: critical target in heart?
• Mechanisms unknown: R&D is ongoing
• ICRP Seoul April 2011: agrees; optimisation of organ doses
Current EU BSS

Introduces Organ and Heart dose constraints

New Art 31 WP to elaborate guidance
Some issues from discussions

• Relevancy for high dose diagnostic exposure
• Age/gender differences (cfr Mayak studies: ERR/Gy for CVD)
• Deterministic/stochastic paradigm strictly applicable?
• Quid other organs (also blood vessels)?
Developments in Radiation Protection Standards

- **Scientific Research**: incl. EU FP
- **Evaluation** of the scientific data +
  Implications: 3 pitfalls
  - Value judgments even in scientific evaluation
  - Mandates
  - Weight of dominant paradigms
- **Interest of having various think tanks**
« Scientific cautiousness »

• The « cautiousness » of scientific world (UNSCEAR...): the main concern is to avoid concluding that a causal relationship exists before it is firmly proved.

• The « cautiousness » expected from national regulators, art 31 GoE, ICRP, ....: the main concern is to protect health; when there is scientific plausibility of the existence of a risk of serious and irreversible harm (even if there is still uncertainty), these groups should alert the policy-makers (precaution principle).

• « Lack of (human health) evidence does not mean evidence of lack of effect »
Art 31 GoE Meeting
June 8-9 2011

Recent scientific findings and publications on the Health effects of Chernobyl:
Summary report

Dr Patrick Smeesters
Chairman of RIHSS WP
Sources

• The UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) 2008 Report (UNSCEAR 2011) concerning the “Health effects due to radiation from the Chernobyl accident”.
• This report has been discussed and approved in mid-2008 and the coverage of literature practically finishes at that time.
• EC scientific seminar on “Issues with internal emitters” (November 2010): updating on radiation induced thyroid cancers by D. Williams
• Recent scientific findings and publications, mainly from 2008, reviewed by Art 31 RIHSS WG
Warning

Unfortunately not possible to take due account of the **large number of non translated publications** by Ukrainian, Russian and Byelorussian researchers. By the way, it is surprising that the competent international organizations did not give more interest in translating these multiple publications, particularly those on children’s morbidity. This will be a real challenge in the future if we really want to cover correctly the situation.
Most exposed population groups

1. Workers (liquidators, or emergency and recovery operations workers): 600 000
2. Inhabitants who were evacuated or relocated: first 116 000, later 220 000 more
3. Inhabitants of contaminated areas who were not evacuated. About 5 million people continue to live in areas of Belarus, Ukraine and Russia that were contaminated by the accident (by convention, contaminated areas were defined as areas where the average deposition density of $^{137}\text{Cs}$ exceeded 37 kBq/m$^2$).
Radiation doses

Liquidators:

• average effective dose: about 120 mSv.
• range: from less than 10 to more than 1,000 mGy
• 85% in the range 20–500 mGy
• uncertainties from < 50% to up to a factor of 5
• average thyroid dose: ?
Radiation doses

Inhabitants of contaminated areas:
• mean effective dose up to 2005: about 50 mSv
• range: from a few mSv to some hundred mSv
• Thyroid doses (Drozdovitch 2010):
  • Median: 0.37 in Belarus and 0.034 Gy in Russia
  • Highest individual thyroid doses: 10.2 Gy in Belarus and 5.3 Gy in Russia
  • doses from short-lived radioiodines and radiotelluriums: up to 0.53 Gy.
  • uncertainty of the reconstructed individual thyroid doses: from 1.7 to 4.0
Maybe the major think to underline regarding radiation doses to the exposed population is their \textit{huge variabili}ty, largely due to the consumption of wild foods, especially mushrooms, and locally produced foods, by a large part of the local population.

This has a major influence on any attempt to interpret or predict the effects of the accident on the health of (subsets of) the population.
Radiation induced thyroid cancers

• Papillary carcinomas in children: the main recognized direct consequence of exposure to fallout of Chernobyl

• Causal relation: no more doubt
Radiation induced thyroid cancers: Size of the increase

- **6848 cases** reported between 1991 and 2005 in the three affected republics (the whole of Belarus and Ukraine and the four most affected regions of the Russian Federation) amongst those **under age 18 years in 1986**; substantial fraction attributable

- **No signs of diminishing**

- **Previsions:** variable but if **ERR constant** (as shown in previous studies: *Adams 2010*) then currently only **top of the iceberg**
Radiation induced thyroid cancers: ERR

Estimation of the ERR

– Review of Chernobyl studies: from 2.15 to 50/Gy
– Case-control and cohort studies: about 7/Gy (=RX)

NB: LSS: mortality solid tumors: < 1/Gy
Radiation induced thyroid cancers: modifying risk factors

1. Age at exposure:
   - **first 3 years** v/ 15-20 y: ERR x 10
     (idem 2d cancers post-Rxth: *Ronckers 2006*)
   - **Adults:** lower (*Fuzik 2010; Richardson 2009: women A-bomb 0.7/Gy*); screening issue

2. Iodine deficiency (Cardis 2005)

3. Genetic susceptibility
Radiation induced thyroid cancers: **Clinical aspects**

- **Agressive** in small children (invasive, metastases)
- Lifetime treatment; chirurgical risks
- With increasing latency, smaller in size and less agressive

- *Signature?: debated; recent EU results (Sc Sem 2011!)*
Radiation induced thyroid diseases other than thyroid cancers

- increased risk of thyroid adenomas and nodules (Ron 2010)
- chronic autoimmune thyroiditis (Hashimoto):
  - conflicting results
  - autoimmune reactions initially observed in several studies (6 to 8 years after the accident: Belarus) still present but with lower levels of thyroid autoantibodies; thyroid function remains normal: future? (Agate 2008)
  - Hashimoto = long term effect in Nevada cohort (age at exposure less than 7 year, time since exposure 24-35 years) (Lyon 2006)
Radiation induction of cancers other than thyroid cancers: *Leukaemia’s*

- **Liquidators** (Romanenko 2008; Kesminiene 2008; RADRUE dose reconstruction method): significantly increased ERR, with a linear dose-response

- **Childhood leukaemia’s**: *debated* (methodology) but significantly increased ERR in Ukraine (Davis 2006; Noshchenko 2010)
Radiation induction of cancers other than thyroid cancers: **Breast cancer**

- Belarus and Ukraine: significant 2-fold increase (1997-2001), in the most contaminated districts (average estimated cumulative dose of 40 mSv or more) compared with the least contaminated districts (Pukkala 2006)

- Unlikely due to increased diagnostic activity
Radiation induction of cancers

• Many of the cancer consequences of exposure to atomic bomb radiation were not observed until decades after the event
• There are major uncertainties over the individual doses from the Chernobyl accident
• It is certainly wrong to consider that we are “at the end of the story”
• It will be necessary to continue for a long time the follow up of these populations.
Hereditary effects

- Exposed families from rural areas of Ukraine and Belarus: increases in the rate of minisatellite DNA mutations in children born to exposed parents after Chernobyl (Dubrova)
- Role of minisatellites? (“associations” with diseases)
- Studies in families of Chernobyl cleanup workers globally failed to show increases
- Birth defects could also be due to germline mutations

Further studies are essential to address the currently somewhat neglected issue of hereditary effects (ARCH 2011)
Birth defects

• not dealt with in UNSCEAR 2011…..
  – Reason: prevalence at birth of the malformations recorded in the registry in Belarus: similar positive trend in areas of low and high contamination

• Eurocat workshop Budapest 2007:
  – From oblasts to districts
  – Clear excess of the congenital anomalies under study in the highly contaminated districts during the three first years (mainly polydactyly, reduction defects of limbs, multiple congenital malformations)
Prevalence at birth of 9 mandatory registered congenital anomalies in the areas contrasting by radionuclide contamination

1. Anencephaly *
2. Spina bifida
3. Cleft lip and (or) palate
4. Polydactyly *
5. Reduction defects of limbs *
6. Oesophageal atresia (stenosis)
7. Rectal atresia (stenosis)
8. Down’s syndrome
9. Multiple congenital malformations *

12,167 cases in 4 oblasts
2,189 cases in 47 rayons

25/02/2014
Dr P. Smeesters
Birth defects: recent observations

• Wertelecki 2010 (University of South Alabama)
  – Ukraine oblast of Rivne: one of the populations most exposed to chronic low-dose radiation from Chernobyl
  – births between 2000 and 2006: overall rate of neural tube defects (including spina bifida) among the highest in Europe
  – limitations of this study: lack of data regarding levels of low-dose radiation, diet, possible folate deficiency, prenatal alcohol exposure.

• Dancause 2010: exposure routes in Rivne
  – Alcohol intake was low
  – Wild foods, especially mushrooms and berries, and locally produced foods, especially milk related, were major radiation exposure routes
Children’s morbidity

- **Many claims** concerning the health of children in the contaminated territories around Chernobyl, which seem to suffer from multiple diseases and co-morbidities with repeated manifestations (compilation in Yablokov 2009)
- **Reports from international organizations did not give until now much interest:** “psycho-social”
- **But** most studies not available in English and not translated!

Although many studies do not meet the scientific and editorial criteria generally required in the Western peer reviewed literature, scientists cannot refuse to take the available information into account or at least to verify it!
Children’s morbidity: recent initiatives (1/2)

• Series of IRSN studies:
  – Rats exposed to $^{137}$Caesium contamination during several months through drinking water (150 Bq/day/animal: comparable with a typical low intake in the contaminated territories (Handl’s: 100 Bq/day but with variations from 20 up to 2000 as when excess consumption of mushrooms)
  – Although the animals tested in these studies did not show induced clinical diseases, a number of unexpected biological effects were observed on various systems: increase of CK and CK-MG, decrease of mean blood pressure and disappearance of its circadian rhythm; EEG modifications, perturbations of the sleep-wake cycle, neuro-inflammatory response, particularly in the hippocampus, etc
  – currently IRSN clinical research (EPICE) on children in the area of Bryansk, particularly on cardiac rhythm and ECG perturbations. First results would be available in 2013
Children’s morbidity: recent studies (2/2)

• Series of longitudinal studies initiated recently in Ukraine in conjunction with the US University of South Carolina:
  – Stepanova 2008: 1993 to 1998: significant reduction in red and white blood cell counts, platelet counts and haemoglobin with increasing residential soil contamination (cfr Techa River)
  – Svendsen 2010: 1993 to 1998: spirometry: statistically significant evidence of both airway obstruction and restriction with increasing soil contamination (immune mechanism?)

• “The optimism of the UN reports may be based on too few studies published in English, conducted too soon after the event to be conclusive”.
Morbidity of liquidators, particularly heart diseases

• Numerous studies have been published concerning non cancer diseases in liquidators, many of them also not published in English, and often being controversial: same issue ……

• Risk of ischemic heart disease and cerebrovascular diseases seems increased (soon results from EU FP7 CARDIORISK project)

• Ukrainian American Chernobyl Ocular Study (UACOS): significant lowering of the supposed cataract “threshold” radiation dose (Worgul 2007): the evidence points to a dose threshold no greater than 700 mGy.
Follow up and research needs

Many of the cancer and non-cancer consequences of exposure to atomic bomb radiation were not observed until decades after the event, so that other thyroid and non-thyroid effects will probably occur in the future in those exposed to fallout, particularly as there are major uncertainties over the individual doses from the Chernobyl accident. It is therefore necessary to continue the follow up of these populations, through well-designed studies, while really taking into account all of the available evidence.

FP7: strategic Agenda for Research on Chernobyl Health (ARCH); Chernobyl RERF?

25/02/2014

Dr P. Smeesters
Precaution in 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.
Missed early warnings

Recent developments regarding the late recognized radiation effects of low to moderate doses on the lens of the eye and on the circulatory system are good illustrations of a lack of vigilance and responsiveness regarding early warnings that were described many years ago.
Children’s morbidity and internal exposures: thinking the unthinkable

We need further good quality research on morbidity in children living in contaminated territories (ARCH). This may have major influence on our evaluation of the radiotoxicity, particularly for children and infants, of major radioisotopes susceptible to cause chronic internal exposures of the population.

A major underlying issue is the adequacy of the effective dose as risk indicator.
“La physique, la chimie et la biologie essayent de “redécouvrir”, pas à pas, ce que nos atomes, nos molécules et nos cellules “savent”, à leur façon. Que savent-elles encore que nous ne suspectons même pas qu’elles savent”

“What else do they know that we even don’t suspect they know?” (Hubert Reeves)