Current ICRP Stance on DDREF

The University of Tokyo
Tokyo, Japan
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ICRP Committee 1, Task Group TG91

"Radiation Risk Inference at Low-dose and Low-dose Rate Exposure for Radiological Protection Purposes: Use of Dose and Dose Rate Effectiveness Factors"

Full Members

W Rühm (Chair) (C1, Germany)
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S Bouffler (C1, UK)
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Corresponding Members

B Grosche (Germany)
M Kai (C4, Japan)
K Ozasa (Japan)
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Q Sun (C1; China)
M Little (USA)
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Abel Gonzales (Argentina, consultant)

Working programme

- Reviews current literature to come up with a recommendation on the use of DDREF
- Discusses cellular data (gene expression, DSBs, chromosome aberrations)
- Reviews animal data and performs pooled analyses
- Performs meta-analysis on available epidemiological studies
- Reviews biologically-based mechanistic models to describe epidemiological data

Recent TG91 Activities

TG91 ICRP Kick-off Meeting

Dec 10 – 11, 2013
Helmholtz Center Munich, Germany

TG91 Ad-hoc Meeting

July 22, 2014
During UNSCEAR session, Vienna, Austria

ICRP C1 Meeting 2014

September 7 - 10, 2014
Beijing, China

TG91 Meeting with Jap. Experts

May 22, 2015
Kyoto, Japan

TG91 Meeting

May 25, 2015
Kyoto University, Japan

ICRP MC Meeting 2015

October 18, 2015, Status Report
Seoul, Korea

International Space Agencies

October 27, 2015, Status Report
HMGU, Germany

TG91 Meeting

October 6-7, 2015, Status Report
RERF, Hiroshima, Japan

DDREF - Dose and Dose Rate Effectiveness Factor

Terminology confusing

- Low-dose effectiveness factor (LDEF)
- Dose-rate effectiveness factor (DREF)
- Linear extrapolation overestimation factor
- Linear risk overestimation factor
- Low-dose extrapolation factor
- Risk ratio …

Experimental approaches

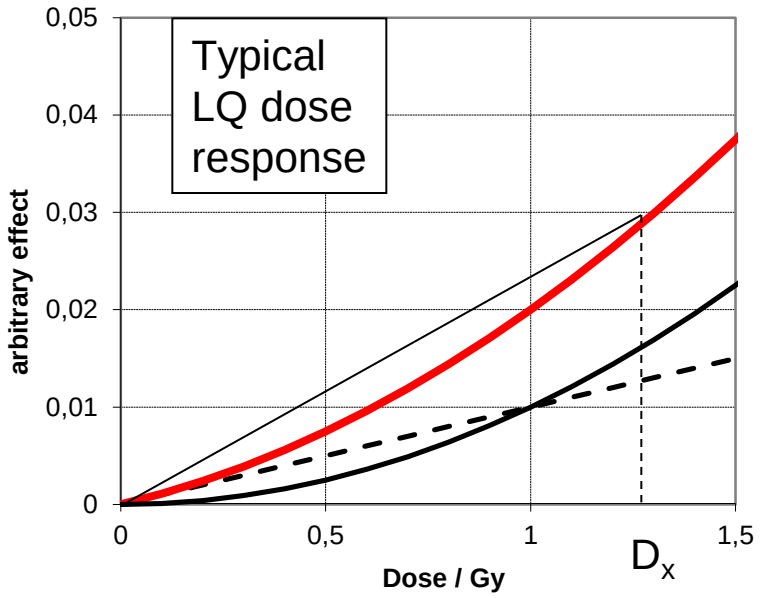
- Exposure to various doses of acute exposure + analysis of curvature of dose response

  >> Low-dose effectiveness factor (**LDEF**)

- Comparison of exposures with high and low dose rate (for similar dose)

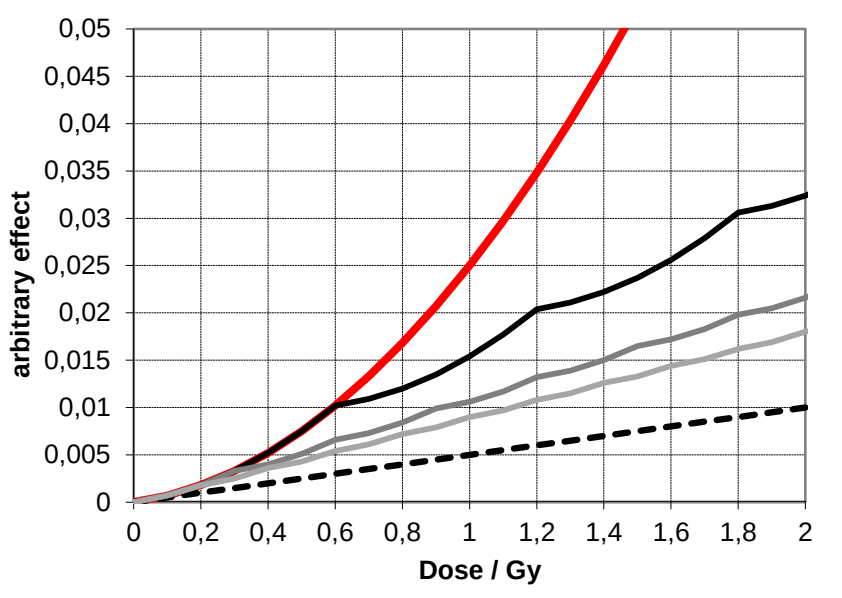
  >> dose-rate effectiveness factor (**DREF**)

Low Dose Effectiveness Factor (LDEF) – Definition



- Effect as a function of dose: E(D)
- LQ-curve: $E(D) = \alpha D + \beta D^2$
- Slope of linear extrapolation from D_x: $(\alpha D_x + \beta D_x^2) / D_x$
- Slope of linear component: α (dashed)
- **LDEF: ratio of both slopes**

Dose Rate Effectiveness Factor (DREF) – Definition



- Red curve: acute
- Black curve: 3 fractions
- Dashed curve: chronic, αD

>> For chronic exposures: DREF ~ LDEF

>> ICRP: combined both, introduced DDREF=2

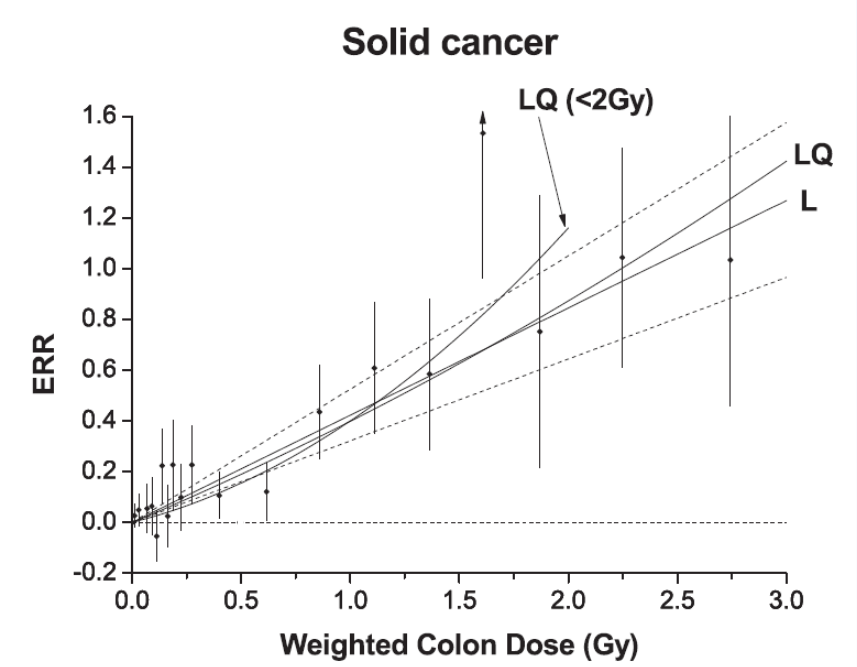
>> If α-term does not depend on dose rate

What is a “low dose rate”? – Basics

- Occupational exposures: for 2,000 working hours per year and 20 mSv maximum: 2×10^{-4} mSv / min
- Dose rate of natural exposures: ~ mSv / y, corresponds to ~ 2×10^{-6} mSv / min
- UNSCEAR 2012: low dose rate: < 0.1 mGy / min averaged over 1 hour

What is a “low dose”? – Basics

- Atomic bomb survivors (based on Ozasa et al. 2012): at 0 – 0.2 Gy first significant ERR per dose
- UNSCEAR 2012: < 100 mGy



Meeting between ICRP TG members and Japanese experts

22 May 2015, Kyoto, Japan
Chair: Nobuhiko Ban

Session 1 – Information from ICRP

(Chair: B. Grosche, BfS, Germany)

Current discussions on DDREF – activities initiated by ICRP and other institutions (W Rühm)

DDREF determination based on large-scale animal studies (G Woloschak)

Preliminary epidemiologic Results regarding solid cancer risks and DDREF (R Shore)

Results of epidemiological studies of the Mayak Worker and Techa River cohorts" (T Azizova)

Session 2 – Information from Japanese Scientists

(Chair: M. Kai, C4, Japan)

Does DDREF correctly predict DREF? (O Niwa)

Cancer risk among residents in NBR areas (S Akiba)

Biological effects of chronic low dose-rate irradiation in mice: A summary of the studies performed in IES (T Ono)

DNA damage and tissue reaction in tissues/organs exposed to low-dose and low-dose-rate γ-radiation in mice (K Suzuki)

The intestinal stem cell turnover (T Iwasaki)

Session 3: Scientific Questions Raised and Discussed at the Meeting

- **Should DREF and LDEF be separated or combined as DDREF?**
  - With an LQ model, LDEF and DREF are similar
  - This does not hold if the alpha-term is dose-rate dependent
  - Note that in the end the radiological protection framework should be practicable!

- **Should a DREF also be applied to leukemia?**
  - Leukemia incidence can be described by an LQ model
  - This implies an LDEF, so is there still the need to apply a DREF?
  - Note that the LQ model is driven by the incidence of AML among LSS
  - Animal data on leukemia could be helpful and should be evaluated
  - Low-dose and low-dose-rate studies (natural exposures, workers) could be helpful
  - Note again that in the end the radiological protection framework should be practicable!

- **How robust are the scientific results obtained from human epidemiological studies at low doses and low dose rates?**
  - Pooling several epidemiologcial cohorts using individual data may be beneficial
  - Even without individual data, meta-analyses can be performed
  - Robustness can be tested by systematically leaving out single studies
  - However, care must be taken when confounding factors are not adequately known

- **Animal studies: How variable are other factors besides radiation?**
  - BEIR VII used Oak Ridge animal data only
  - Nowadays, the US Janus Tissue Archives and the European Radiobiology Archives are available
  - A large animal experiment is currently being performed in Japan at IES
  - There is a historical chance now to analyse a much larger data set
  - Better statistics, various endpoints, differences in species

- **Are animal data applicable to humans?**
  - Critical question since decades
  - Again, the new data bases and archives offer new possibilities
  - In particular, analyses of same endpoints among different species (mice, dogs) might help to study inter-species variability
- **Which endpoints are relevant in radiobiological studies?**
  - DNA damage considered important
  - No clear endpoint identified specific for carcinogenesis
  - Role of ethnicity, immune system, microenvironment etc. needs further research
  - However, care must be taken when confounding factors are not adequately known

Rühm, W., Woloschak, G.E., Shore, R.E., Azizova, T.V., Grosche, B., Niwa, O., Akiba, S., Ono, T., Suzuki, K., Iwasaki, T., Ban, N., Kai, M., Clement, C.H., Bouffler, S., Toma, H., Hamada, N. (2015) Dose and Dose Rate Effects of Ionizing Radiation – A Discussion in the Light of Radiological Protection. Radiat Environ Biophys 54: 379-401

Review of Molecular and Cellular Studies (S. Bouffler)

- **Critical to define the processes** that contribute to the diseases of interest
- Current evidence (eg UNSCEAR 2010, 2012) places **greatest emphasis on gene and chromosomal mutations** arising following DNA damage

What sort of information to be used?

- DNA double strand break induction and repair
- Gene mutation studies
- Chromosomal aberration studies
- Thresholds for cell cycle checkpoint activation & apoptosis

Provisional conclusions

- **Cellular data tend to support the application of a DDREF** to estimate risk at low doses.
- Chromosomal studies indicate DDREF values around 4

But …

- M**uch time between induction of those mutations and clinical presentation of cancer**
- Many processes **could have a significant influence on the magnitude of DDREF**.

Further steps discussed this week at RERF, Hiroshima

- Evaluation of the radiobiological evidence for treating LDEF and DREF separately
- Include recent review by Brooks et al. 2016

Evidence from animal studies (G. Woloschak, US)

- BEIR VII report based much on the Oak Ridge animal data set
- Now: study based on 28,000 mice can be performed (16 individual studies)
- Use of large animal data sets possible including US Janus and EU ERA databases
- Pooled analysis already performed based on life-shortening
- **Mean DREF values of about 2, depending on dose cut-off used (preliminary)**

Haley, B., Paunesku, T., Grdina, D.J., Woloschak, G.E. (2015)
Animal Mortality Risk Increase Following Low-LET Radiation Exposure is not Linear-Quadratic with Dose. PLOS One, DOI 10.1371/journal.pone.0140989

Further steps discussed this week at RERF, Hiroshima

- Study of tumor mortality
- Study of other species (dogs)
- Study of influencing factors (e.g., dose cut-off)
- Comparison with NCI study (M. Little)
- Comparison with results Japanese studies

Metastudy of LDLDR Epidemiological Studies (R. Shore, L. Walsh, WR)

Review on solid tumor risk (total, breast, lung, colon, stomach, liver)

- Pubmed literature survey carried out until May 2016
- Studies covering period January 1980 – May 2016
- Cohort or nested case-control studies in environmental, occupational, emergency settings
- Avoiding overlapping data, and using most recent follow-up data of a study

Results (detailed tables available)

- 21 studies that can be compared to the LSS
- 900,000 individuals, 16.4 Mio Person-years, 45,300 Person-Gy, 32,000 solid cancer deaths
- 16 studies with mean doses < 50 mGy
- 11 studies, with at least 250 solid cancer deaths
- 9 out of 11 with positive risk coefficients (4 statistically significant)

Methodology for meta-analyses to deduce DREF (L. Walsh, Germany)

- Use of studies identified in Pubmed literature survey
- Parameters used:
  - dose reported (e.g., colon dose, skin dose, etc.),
  - type of risk measure reported (usually *ERR* per unit dose)
  - proportion of males, length of follow-up,
  - age at first exposure, age at end of follow-up.
- Compute corresponding LSS cancer risks with matching distributions according to sex, age at exposure, grouping of cancer types and follow-up time
- Calculate ratio of the *ERR* per unit dose from an individual study to the corresponding *ERR* from the atomic bomb survivors
- Calculate weighted overall ratio from the individual ratios
- Leave studies out one-by-one
- **Mean DREF values consistent with current understanding (preliminary)**

Further steps disussed this week at RERF, Hirosima

- Summarize results on cancer sites
- Similar study on leukemia already initiated
- Analysis of curvature in LSS data (LDEF!)

Review of Biologically-Based Mechanistic Models to Describe Epidemiolgical Data (W Rühm, JC Kaiser, M Eidemüller)

Question to be answered by this review

- On which cohorts have those models already been applied?
- Can they account for non-linear radiobiological low-dose effects such as bystander effects, genomic instability, adaptive response, low-dose hypersensitivity, etc.?
- ***Which implications do these models have on the dose-response at low doses and dose rates of ionizing radiation?***

Conclusions

- Those models can be simple, offer to test various options of radiation action, and allow indeed to account for a number of nonlinear processes
- Only few papers investigate the implications of such models on the dose-response curve
- Uncertainties involved are still considerable
- **Current assumptions in radiation protection (including the LNT model) are not in contradiction to what is presently known on the process of cancer development**

Current ICRP stance on DDREF …

… we are still working on it!

THANK YOU!