Dose Rate Effects in Radiation Biology and Radiation Protection

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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

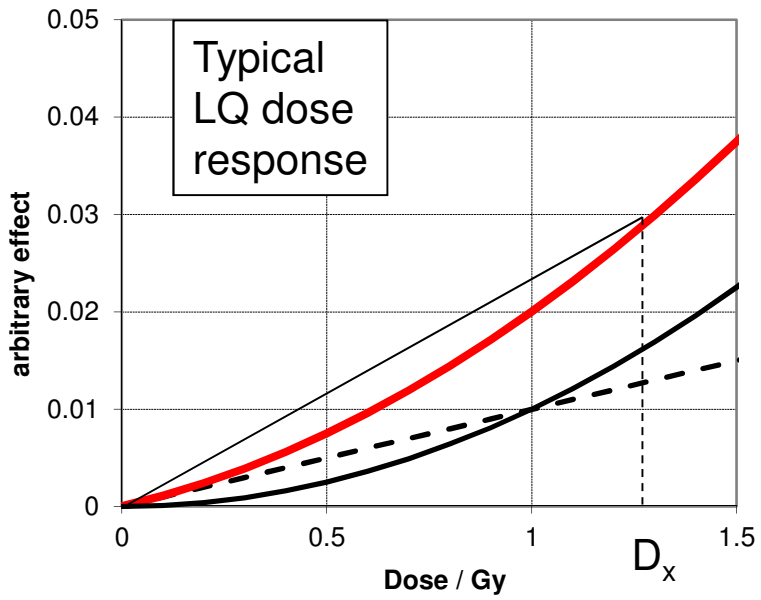
- Exposure to various doses of acute exposure + analysis of curvature of dose response

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

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

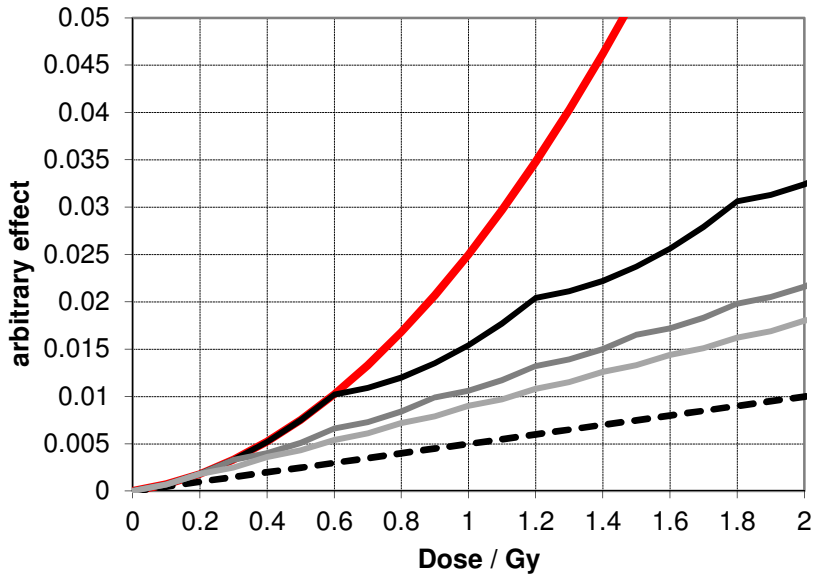
  >> dose-rate effectiveness factor (**DREF**)

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**

DREF – Definition



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

>> For chronic exposures: DREF ~ LDEF

>> ICRP: combined both, introduced DDREF

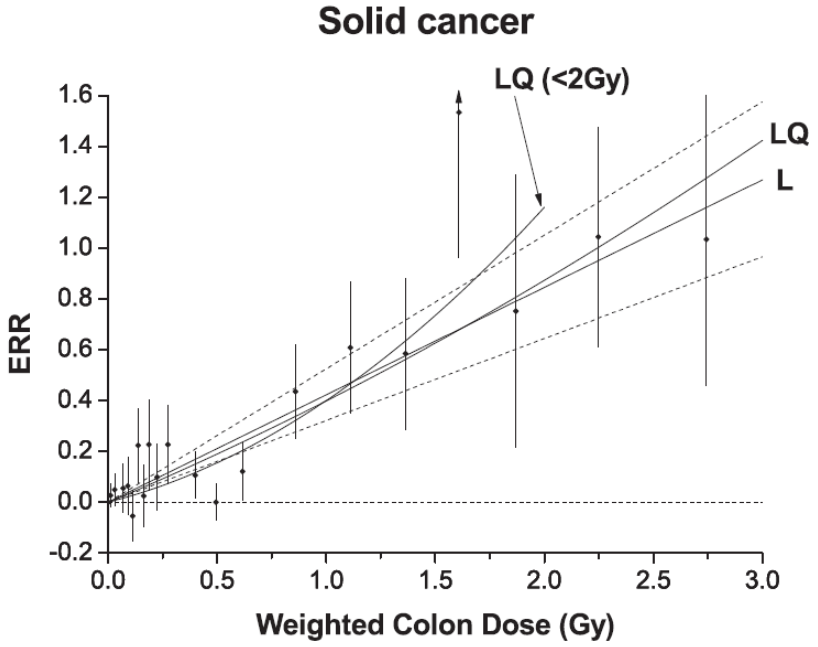
>> If α-term does not depend on dose rate

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



Knowledge on DDREF - Changes with Time

UNSCEAR 1958

Mentions the distribution of ionizing radiation in time as important physical factor

"Opinions as to the possible effects of low radiation levels ***must be based only on extrapolations from experience with high doses and dose rates****."*

UNSCEAR 1962

- Information from the atomic bomb survivors was still limited
- Animal experiments were considered important. However, their usefulness was judged limited *"by the* ***difficulty of making valid extrapolations … to man from animals …****"*.

UNSCEAR 1969

- "*Incidence of chromosome aberrations and that of tumours both increase with increasing dose, but the* ***relationship between the two effects is complex****."*

UNSCEAR 1977

- From animal data, reduction **factors between 2 and 20 were reported**
- Estimates of harmful effects in man should use data from exposed human populations

NCRP 1980

- Introduced the “dose-rate effectiveness factor (DREF)”
- For a variety of endpoints **in animal models values between 2 and 10 were observed**

UNSCEAR 1988

- *“… such a factor certainly **varies very widely with individual** **(human) tumour type** and with dose rate range. However, an appropriate range to be applied … should lie between 2 and 10”*

ICRP 1991

- Introduced the “Dose and Doserate Effectiveness Factor (DDREF)” **with a value of 2**
- Acknowledged that the chosen **value of 2 might be somewhat arbitrary**, and it was felt that **it may be conservative**.

UNSCEAR 1993

- **Suggested a value of about 2 for DDREF**, based on radiobiological information, animal data, and human data from epidemiological studies
- **Substantial uncertainties with this value were acknowledged**

UNSCEAR 2006

- Fitted the LSS data using a dose-response curve that included a quadratic component
- In this way, an LDEF was implicitly taken into account
- *Values of DDREF of about 2 consistent with this approach*

BEIR VII, 2006

- Bayes analysis yielded a range of values: 1.1 – 2.3 with a point estimate of 1.5

ICRP 2007

- A DDREF of 2 as recommended by ICRP in 1991 should be retained

WHO 2013 (Fukushima Report)

- Used a DDREF of one

UNSCEAR 2013 (Comment on WHO report)

- *"**This is not incompatible with the Committee's estimates of cancer risks** … and with (Ozasa et al. 2012), …*

SSK 2014 (Dedicated report on DDREF)

Discussion of scientific principles

- Radiobiological studies on molecular and cellular systems,
- Radiobiological studies on animals,
- Epidemiological studies
- Mechanistic radiobiological models

Discussion of operational implementation criteria

- Influence of uncertainties
- Implementation in real-life radiation protection
- International involvement
- Consequences for stipulating limits
- Risk communication

- **The SSK therefore recommends abolishing the DDREF or adjusting it to bring it into line with more recent findings.**
- **All of the other parameters pertaining to the detriment should be adapted to the latest scientific findings.**
- **An international agreement in these issues is urgently necessary.**

The International System of Radiological Protection has been developed by ICRP based on

(i) The current understanding of the science of radiation exposures and effects

(ii) Value judgements

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

Werner Rühm (Chair) (C1; HMGU, Germany)
Tamara Azizova (C1; SUBI, Russia)
Simon Bouffler (C1; PHE, UK)
Roy Shore (former RERF, Japan)
Gayle Woloschak (Northwestern University, USA)

Corresponding Members

Bernd Grosche (Germany)
Michiaki Kai (liaison, C4, Japan)
Mark Little (NCI, USA)
Kotaro Ozasa (RERF, Japan)
Kazuo Sakai (liasion, C5; Japan)
Quanfu Sun (C1; China)
Linda Walsh (BfS, Germany)
Abel Gonzales (Argentina, consultant)

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 Jap. 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 g-radiation in mice (K Suzuki)

The intestinal stem cell turnover (T Iwasaki)

Session 3. Discussion (Chair: Nobuhiko Ban, C1, Japan)

- **Should DREF and LDEF be separated or combined as DDREF?**
  - With an LQ model, LDEF and DREF are simliar
  - This does not hold if the alpha-term is dose-rate dependent
  - This is a scientific question
  - It was noted, 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
  - Although this implies an LDEF, there might still be 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
  - It is noted, 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 is 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, DOI 10.1007/s00411-015-0613-6

Review of Molecular and Cellular Studies (S. Bouffler)

What sort of information is available?

- DNA dsb 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** at low doses.
- Chromosomal studies indicating values of around 4
- There is of course **much time that elapses between induction of gene and chromosomal mutations and clinical presentation of cancer**. Many processes are likely to modulate this and while poorly defined **could together have a significant influence on the magnitude of DDREF**.

Further steps

- Evaluation of radiobiological evidence for treating dose and dose rate effects separately (decided after Kyoto workshop)

Evidence from animal studies (G. Woloschack, US)

Review on animal data

- 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)

First preliminary results

- For dose rates 0.001 – 4 Gy/min; doses up to 4 Gy; low-LET radiation
- Studies with both acute and chronic exposures, or chronic exposure with different dose rates
- Indications that dose-response (for life shortening) is linear
- Indications that DREF may be larger than one, in the investigated data set

Status and further steps

- Use of large animal data sets possible (use of contemporary tissue banks and data bases!)

> 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

- Studies should include tumor incidence (instead of life shortening)

Major cohorts for epidemiologic LDLDR studies (R. Shore, US)

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

- Pubmed literature survey carried out in August 2015
- Studies covering period January 1980 – June 2015
- 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)

- 22 studies that can be compared to the LSS
- 960,000 individuals, 17 Mio Person-years, 36,000 Person-Sv, 33,000 solid cancer deaths
- 18 studies with mean doses < 50 mSv
- 13 studies, with at least 250 solid cancer deaths
- 11 out of these with positive risk coefficients (4 statistically significant)

Further steps

- Include results from INWORKS study (combined nuclear workers in US, UK, France)

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

Strategy

- 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 "matching" cancer risks in sub-cohorts of the atomic bomb survivors 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

Status and further steps

- Analysis already done, but final analysis should include INWORKS data
- Similar study on leukemia planned (decided after Kyoto workshop)

Analysis of dose response among the atomic bomb surivors to deduce LDEF values (M.P. Little, NCI, US)

- Use latest LSS mortality study (Ozasa et al. 2012)
- Individual data were not available, so analyses used the publicly available stratified data
- Parameters included are time since exposure, age at exposure, attained age, city, sex, ground distance category, and (measurement-error adjusted) dose
- Curvature analysed depending on cut-off dose (so far 4 Gy, 2 Gy)
- Use of different models

Status and further steps

- Analysis to be done for additional dose cut-offs
- Various models to be tested (including linear-exponential)
- Disucssions with RERF (K. Ozasa) planned
- Bayesian analysis similar to UNSCEAR 2006

Summary and Outlook

- **DDREF has always been a moving target**

TG91 is currently …

- … scrutinizing biolgocial studies at molecular and cellular level
- … evaluating the radiobiological evidence for treating dose and dose rate effects separately
- … going beyond BEIR VII and including a more detailed analysis of more animal data
- … performing a meta analysis on total solid cancers, selected cancer sites incl. leukemia (incl. sensitivity analyses and comparison with adjusted LSS data)
- … performing an analysis of dose response curves (L vs. LQ models)
- … discussing further (e.g., methodological) aspects

THANK YOU!