Current Work Programme of ICRP, Including Dose and Dose-Rate Effectiveness Factor

Topical Session

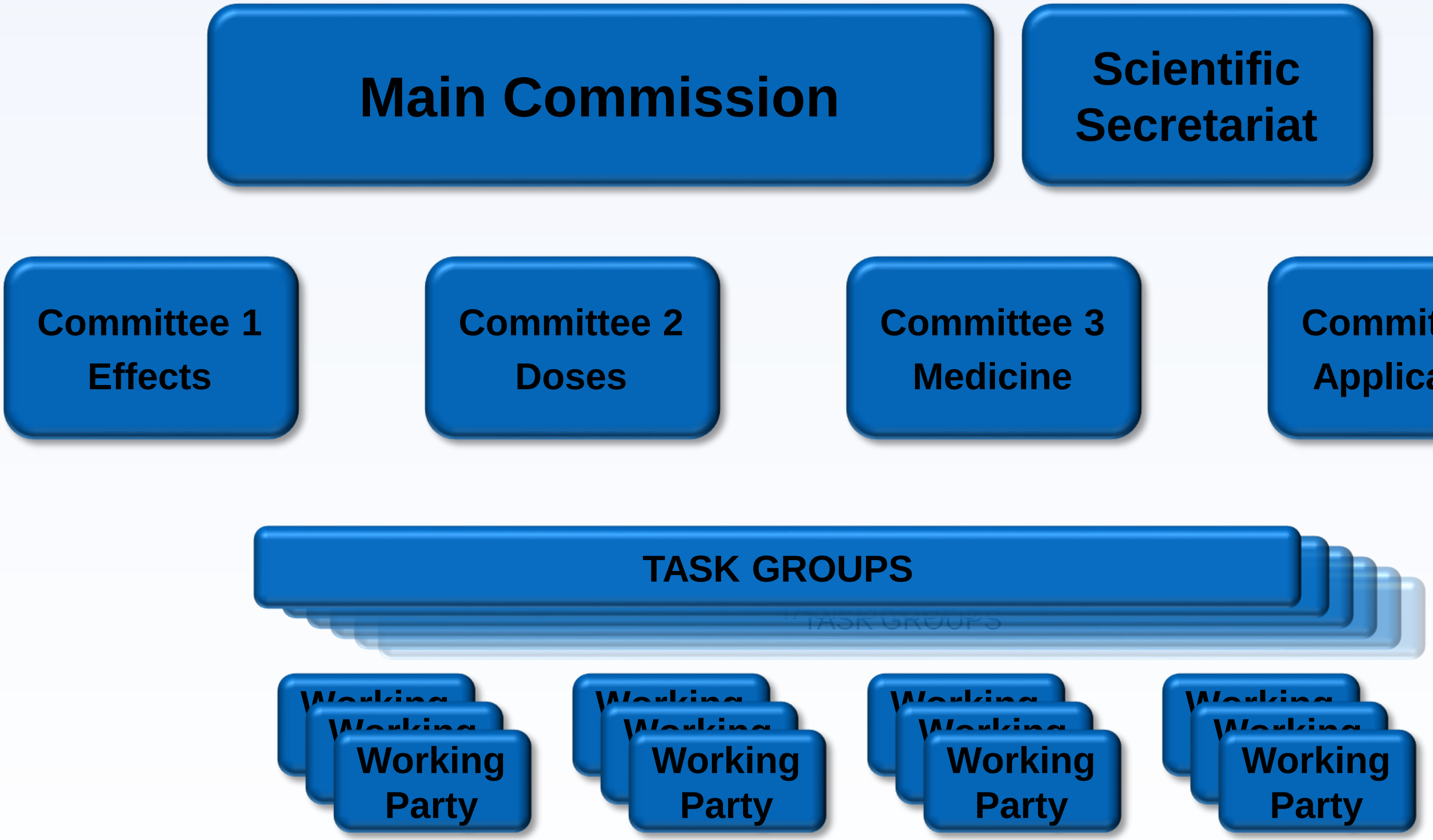
Radiation Safety Standards Committee (RASSC)

Vienna International Center, Vienna, Austria,

November 22, 2018

Werner Rühm, Helmholtz Center Munich, Germany

Structure ICRP



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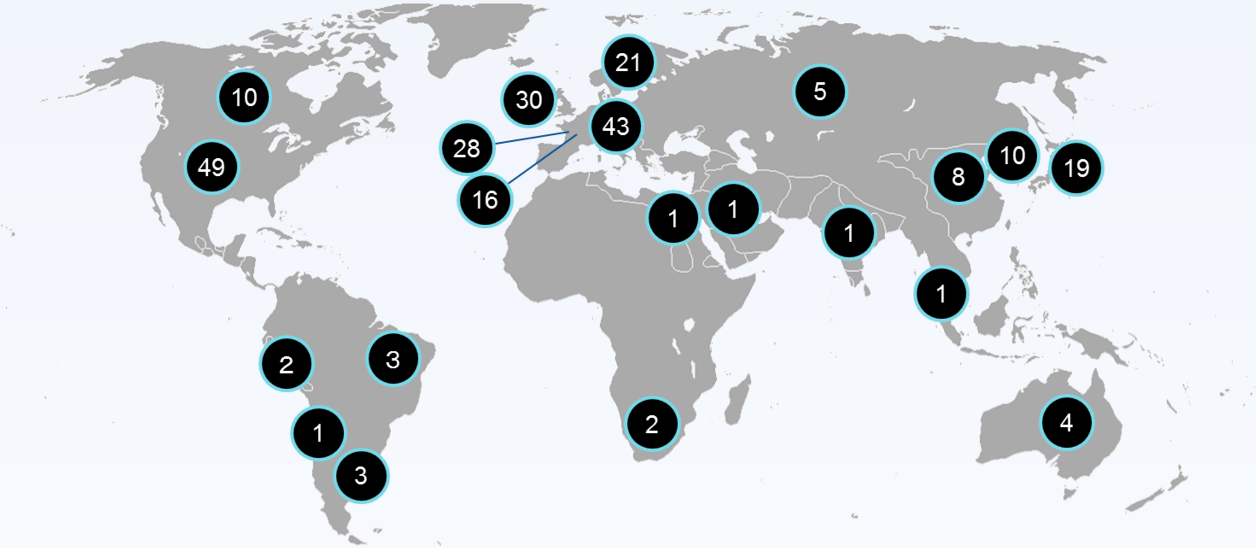

258 members from 36 countries

as of 2018 June 14, including liaison organization primary contacts

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ICRP Main Committees

- **Committee 1: Radiation Effects** (Chair: W Rühm; Vice chair: A Wojcik; Secr.: J Garnier-Laplace)

  Assesses knowledge on radiation risk relevant for radiological protection

- **Committee 2: Dosimetry** (Chair: J Harrison; Vice chair: F Paquet; Secr.: W Bolch)

  Develops reference models and data, including dose coefficients

- **Committee 3: Medical Exposures** (Chair: K Applegate; Vice chair: C Martin; Secr.: M Rehani)

  Develops recommendations to protect patients, staff, and the public

- **Committee 4: Application of Recommend.** (Chair: D Cool, Vice: KA Higley; Secr.: J Lecomte)

  Develops principles and recommendations on radiological protection

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ICRP Committee 1 (C1) on „Radiation Effects“

Members with expertise in biology, genetics, human and veterinary medicine, mathematics and statistics, physics and dosimetry, epidemiology, and radioecology

Werner Rühm (Chair), Germany
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Ranajit Chakraborty (deceased), USA
Michael Hauptmann, Netherlands
Preetha Rajaraman, India
Sisko Salomaa, Finland
Dan Stram, USA
Richard Wakeford, UK

***) new since 07/2017**

ICRP Committee 1: General Topics

The focus of C1 work is on

- Risk of induction of **cancer and heritable disease (stochastic effects)**, and the underlying mechanisms of radiation action.
- Risks, severity, and mechanisms of induction of **tissue/organ damage and developmental defects (tissue effects)**.
- Endpoints considered manifest on various organisation levels such as sub-cellular systems (e.g., DNA), cells, tissues, animals, humans, **and populations.**

The Committee also addresses issues such as high background radiation areas, CT in children, radiation sensitivity and individual susceptibility, sequencing and omics technologies, and the impact of epigenetics on radiological protection.

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- **Task Group TG64**

  "Alpha Emitters": TG Chairs - Margot Tirmarche (former), Richard Wakeford, Eric Blanchardon (C2)

- **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"

  TG Chair: Werner Rühm

- **Task Group TG99**

  "Reference Animals and Plants Monographs" - TG Chair: Jacqueline Garnier-Laplace

- **Task Group TG102 (together with C4)**

  "Detriment Calculation Methodology": TG Chair - Nobuhiko Ban

- **Task Group TG111 (together with C3)**

  "Individual Response of Humans to Ionising Radiation": TG Chair - Simon Bouffler

C1 Working Parties

"Cardiovascular Diseases"
Wolfgang Dörr, Tamara Azizova

"Hereditary and Transgenerational Effects"
Sisko Salomaa, Jacqueline Garnier-Laplace

"Parameters of Detriment not Related to Radiation"
Michael Hauptmann

"Cancer Risk Models to Calculate Detriment"
Richard Wakeford

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) (Germany),
T Azizova (Russia),
S Bouffler (UK), M Little (USA)
R Shore (USA), **L Walsh** (Switzerland)
G Woloschak (USA)

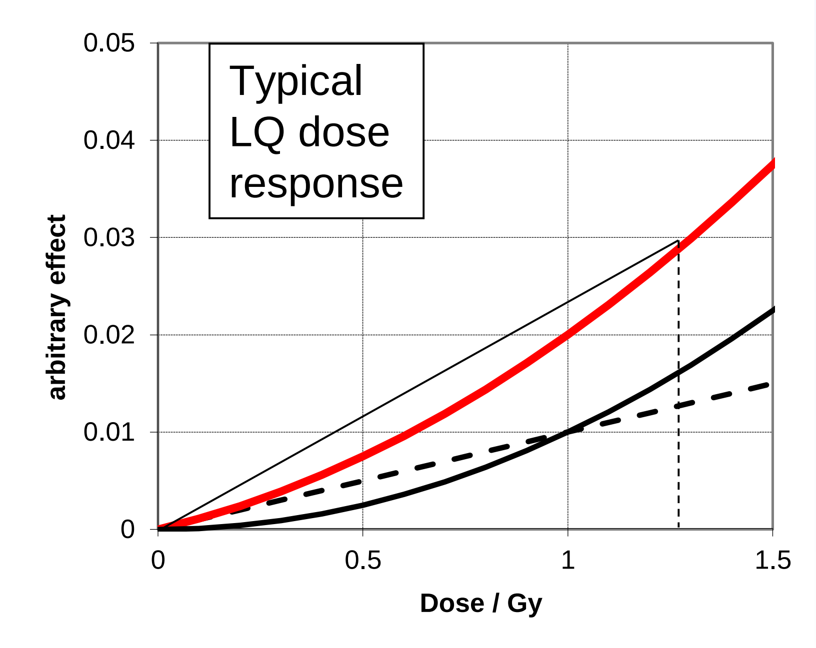
Corresponding Members

B Grosche (Germany), M Kai (Japan),
K Ozasa (Japan), K Sakai (Japan),
Q Sun (China), A Gonzales (Argentina, consultant)

Dose Rate Effectiveness Factor (DREF): Comparison of effects at low vs. high dose rates (at similar dose)

Low Dose Effectiveness Factor (LDEF):

Measure of deviation from linear dose response



Reminder (UNSCEAR definitions): low dose rate: < 6,000 µGy/h; low dose: < 100 mGy

History – Governed by Advances in Science

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 human populations**

… long story … long story …

ICRP 1991 (approach confirmed in 2007)

- 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 2006 (approach confirmed recently in 2017)

- 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 (US)

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

WHO 2013 (Fukushima Report)

- Did not use a DDREF

SSK 2014 (Germany)

- Suggested a DDREF of one

SENES Report 2017 (To be used in the US for compensation claims)

- Suggests 1.3 (50%) and a range of values of 0.47 – 3.46 (5% – 95%)

Review done ✓

In Rühm, W., Woloschak, G. E., Shore, et al. (2015) Dose and dose-rate effects of ionizing radiation: a discussion in the light of radiological protection. Radiat Environ Biophys 54: 379-401

(see also A. Gonzalez, Medical Radiology and Radiation Safety, 2017)

Review of typical dose rates and doses in radiobiological and epidemiological studies - Examples

- **Human cohorts – examples**

General Population:	0.3 (0.1 – 1) µSv/h
Air crew:	2 (< 6) µSv/h
Astronauts:	~18 µGy/h
Mayak workers:	<150 µGy/h
Chernobyl clean-up:	320 µGy/h (first year)

- **For comparison – LSS Hiroshima**

Kerma rates and kerma fia, various sources, at 1,000 m distance

prompt sec. γ:	**6.9 Gy/s**	**1.38 Gy**
delayed γ:	**0.3 Gy/s**	**2.77 Gy**

- **Cellular studies**

1,000 – 60,000 µGy/h

- **Animal studies**

780 µGy/h – 22.6 Gy/h	(US database)
1,350 µGy/h – 240 Gy/h	(EC database)
2, 42, 830 µGy/h	(IES, Japan)

Review done ✓

In Rühm., W., Azizova, T., Bouffler, S., Cullings, H., Grosche, B., Little, M.P., Shore, R., Walsh, L., Woloschak, G. (2018) Typical Doses and Dose Rates in Studies Pertinent to Radiation Risk Inference at Low Doses and Low Dose Rates. J. Radiat Res 59 (S2): ii1-ii10

Review of Molecular and Cellular Studies (S. Bouffler)

What sort of information to be used (preliminary)?

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

Provisional conclusions (still to be discussed…)

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

but …

- Much time between induction of those changes and clinical presentation of cancer
- Many processes could have a significant influence on the magnitude of DDREF.

S. Bouffler in Rühm, W., Woloschak, G. E., Shore, et al. (2015) Dose and dose-rate effects of ionizing radiation: a discussion in the light of radiological protection. Radiat Environ Biophys 54: 379-401

Paper published ✓

See also talk by Gayle Woloschak today!

Evidence from animal studies

- BEIR VII report based much on the Oak Ridge animal data set

- **Now: Use of large animal data sets for the first time ever possible including US JANUS and EU ERA databases**

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, 10(12): e0140989

Paper published ✓

- **Pooled analysis, linear model, life-shortening (Woloschak et al., prelim.)**

Data	$DREF_{LSS}$ estimate	Effect of age at exposure per 13% increase in age
Primary analysis 0 – 4 Sv	2.1 (1.7, 2.7)	0.80 (0.55, 1.01)
Sensitivity analysis 0 – 3 Sv	2.6 (1.8, 4.4)	0.78 (0.29, 1.13)

Paper in preparation

TG91: Animal LDEF, DREF (Tran & Little, 2017)

- Study based on animal mortality, among Janus mice
- Various endpoints considered (including cancer and non-cancer mortality)
- Photon and neutron exposures investigated
- Dose and dose rate effects considered

Gamma-Radiation, all tumors combined

LDEF: 0.86 (0.65; 1.24) **– 1.06** (0.99 – 1.14) depending on dose rate

DREF: 1.19 (0.86 – 1.72)

Paper published ✓

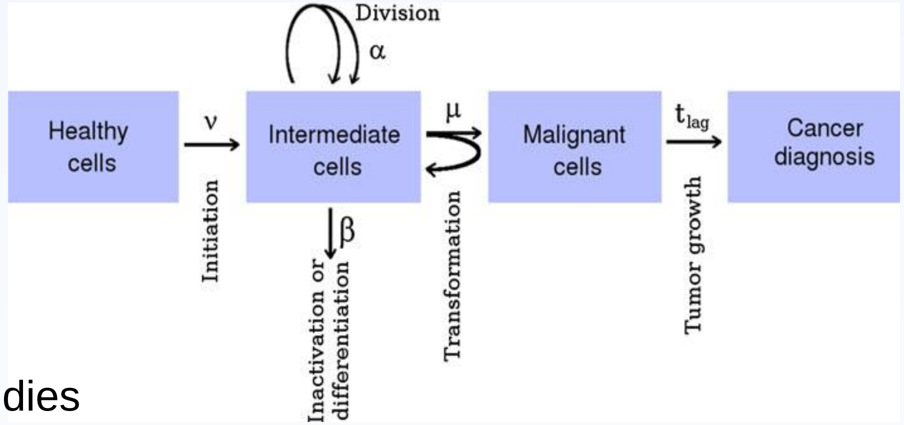
Tran., V., Little, M.P. (2017) Dose and dose rate extrapolation factors for malignant and non-malignant health endpoints after exposure to gamma and neutron radiation. Radiat Environ Biophys 56, 299-328

See talk by Gayle Woloschak today!

Biologically-Based Mechanistic Models to Describe Epidemiological Data

Example: The Two-Stage Clonal Expansion Model

- Based on two-stage theory of carcinogenesis developed by (Armitage & Doll 1957).



- Review initiated by TG91
  - 14 low-LET studies, 14 high-LET studies
  - 5 low-LET cohorts, 12 high-LET cohorts
  - Mainly TSCE, but recently also more sophisticated models

Conclusions - On the Use of Mechanistic Models

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Long story

- Uncertainties involved are still considerable, probably because carcinogenesis is often too complicated to be described just by simple mathematical approaches

Current assumptions in radiation protection (including the LNT model) are not in contradiction to what is presently known on the process of cancer development.

Rühm, W., Eidemüller, M., Kaiser, J.C. (2017) Application of Biologically-Based Models of Radiation-Induced Carcinogenesis to Epidemiological Data. Int J Radiat Biol 93, 1093-1117

Paper published ✓

New US NCRP Committee SC1-26

"Approaches for Integrating Biology and Epidemi-ology for Enhancing Low Dose Risk Assessment"

Chair: J Preston; Co-chair: W. Rühm

Kick-off meeting: Nov 29-30, 2017

Last meeting: July 25 – 26, 2018

TG91 members

Update of Meta-Analysis of Low-Dose-Rate Epidemiological Studies on Solid Cancer

- Update of Jacob et al. 2009 study (most epi studies included until 2007)
- 22 low-dose-rate 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

- 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

- **All cohorts together (mort + incidence): DREF consistent with 2 to 3**
- **If Mayak is left out: DREF ~ 0.9 for mortality; ~ 1.3 for mortality + incidence**

Shore, R., Walsh, L., Azizova, T., Rühm, W. (2017) Risk of Solid Cancer in Low-dose and Low Dose-Rate Radiation Epidemiological Studies and the Dose Rate Effectiveness Factor. Int J Radiat Biol 93, 1064-1078

(Results confirmed recently by D. Hoel, IJRB, 2018)

Paper published ✓

See talk by Linda Walsh today!

Analysis of dose response curvature in LSS mortality data (M. Little) Ozasa *et al* 2012

Solid cancer endpoint	Linear model	Linear-quadratic model			
	ERR/Sv (α) (+95% CI)	Linear ERR/Sv (α) (+95% CI)	Quadratic/linear term (β/α) ERR/Sv (+95% CI)	Ratio linear / linear from linear-quadratic	p-value[a]
All solid	0.277 (0.183, 0.385)	0.233 (0.121, 0.380)	0.105 (-0.087, 0.544)	1.190	0.362
Female breast	0.897 (0.294, 1.778)	1.155 (0.355, 2.425)	-0.102 (-0.256, 0.200)	0.777	0.330
Colon	0.337 (0.068, 0.741)	0.055 (-0.254, 0.364)	1.787 (-10.536, 14.107)	6.130	0.024
Liver	0.304 (0.044, 0.593)	0.380 (-0.066, 0.987)	-0.093 (-0.462, 0.275)	0.801	0.721
Lung	0.379 (0.148, 0.651)	0.474 (0.155, 0.941)	-0.099 (-0.312, 0.376)	0.800	0.480
Stomach	0.140 (-0.024, 0.324)	0.121 (-0.064, 0.374)	0.081 (-0.223, 3.957)	1.153	0.749

- **LDEF ~1.2 overall, some cancer sites more (colon) and less (lung, breast)**
- **Indications of larger curvature over lower dose range (0-2 Sv)**

In Rühm, W., Azizova, T. V., Bouffler, S. D., Little, M. P., Shore, R. E., Walsh, L., & Woloschak, G. E. (2016). Dose-rate effects in radiation biology and radiation protection. Ann ICRP 45(1S), 262-279

Paper published ✓

Summary and Conclusions

- **Required reviews done**
  - History
  - Dose and dose rates
  - Biological models
- **Molecular and Cellular data**
  - DREF ~ 4
- **Animal data, Janus, cancer mortality**
  - LDEF ~ 0.9 – 1.1
  - DREF ~ 1.2
- **Animal data, Janus + ERA, life short.**
  - DREF ~ 2.1 – 2.6
- **Meta analysis epidemiological cohorts**
  - DREF ~ 2-3 (all cohorts together)
  - DREF ~ 0.9 – 1.3 (Mayak left out)
- **Curvature LSS Mortality data**
  - LDEF ~ 1.2

TG91 work includes

- Reviews
- Own scientific analyses
- Publications in open literature
- Presentations at various occasions
- Preparation of TG report

But …

- Considerable uncertainties involved in any single estimate
- Much remains to be done

And … the story continues!

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