National Cancer Institute

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Evidence for dose and dose-rate effects in human and animal radiation studies

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Outline of talk

- Introduction – extrapolating high dose to low dose, high dose-rate to low dose-rate – LDEF, DREF, DDREF
- What can human data tell us directly about low dose/low dose-rate risk?
  - Obstetric X-ray data
  - Background radiation studies
  - Computerised tomography (CT) studies
- Can we learn about DDREF, LDEF, DREF from animal data?
  - ICRP, BEIR VII
  - JANUS data (Haley *et al*, Tran and Little)(ICRP C1/TG91 work)
- Conclusions and further work

Curvature in dose response + low dose

- For many experimental + epidemiologic datasets cancer dose-response for acute dose of radiation D given by $F(D)=\alpha D+\beta D^2$ with $\alpha>0$, $\beta>0$
- Low dose extrapolation factor (LDEF) - ratio of slope obtained by fitting linear model over full dose range to limiting low dose slope of linear-quadratic model
- Pierce & Vaeth (*Radiat Res* 1991 **126** 36-42) and Little & Muirhead (*Int J Radiat Biol* 2000 **76** 939-53) in fits to LSS data estimated LDEF of ~1.1-1.5 for solid cancers, ~2.5 for leukaemia; at doses <0.1 Gy quadratic term contributes <1-3% for solid, 18% for leukaemia
- This suggests <0.1 Gy might be considered “low dose”, consideration supported by BEIR VII (2006)

Analysis of curvature in current LSS incidence and mortality data (ICRP C1/TG91 work)

- Analysis of LSS mortality data of Ozasa *et al* (*Radiat Res* 2012 **177** 229-43) and LSS incidence data of Grant *et al* (*Radiat Res* 2017 **187** 513-37)
- Analyze using linear-quadratic models adjusting for age, *a*, age at exposure, *e*, sex, *s*, with semi-parametric adjustment for background

$$PY_i\lambda_i\left[1+(\alpha D+\beta D^2)\exp[\gamma_1 e+\gamma_2\ln(a)+\gamma_3 1_{sex=female}]\right]$$

Results of re-analysis of LSS mortality data (Ozasa *et al Radiat Res* 2012 **177** 229-43) (ICRP C1/TG91 work) (Rühm *et al Annals ICRP* 2016 **45** (1 supp) 262-79)

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
All solid except breast, colon, liver, lung, stomach	0.257 (0.093, 0.480)	0.194 (0.026, 0.508)	0.163 (-0.173, 3.673)	1.320	0.501

Indications of LDEF ~1.2 overall, but some cancer sites much more (colon) and less (lung, breast) than this

Indications of larger curvature, LDEF~2, over lower dose range (0-2 Sv)

Results of re-analysis of LSS incidence data (Grant *et al Radiat Res* 2017 **187** 513-37) (ICRP C1/TG91 work)

	Linear model	Linear quadratic model			
	Linear ERR/Sv (+95% CI)	Linear ERR/Sv (+95% CI)	Quadratic/linear term (+95% CI)	Ratio linear / linear from linear-quadratic	*p*-value
Dose range	Unrestricted follow-up				
<1 Sv	0.478 (0.277, 0.704)	0.347 (0.127, 0.644)	0.643 (-0.196, 3.970)	1.378	0.186
<2 Sv	0.601 (0.452, 0.766)	0.404 (0.240, 0.603)	0.478 (0.100, 1.279)	1.489	0.006
unrestricted	0.585 (0.447, 0.736)	0.466 (0.309, 0.655)	0.206 (-0.009, 0.578)	1.256	0.063
	Follow-up < 2001				
<1 Sv	0.503 (0.273, 0.758)	0.408 (0.143, 0.772)	0.394 (-0.362, 3.531)	1.234	0.426
<2 Sv	0.638 (0.470, 0.823)	0.390 (0.204, 0.617)	0.613 (0.138, 1.834)	1.639	0.004
unrestricted	0.604 (0.450, 0.773)	0.460 (0.285, 0.675)	0.247 (-0.003, 0.726)	1.313	0.054
	Follow-up < 1991				
<1 Sv	0.698 (0.387, 1.052)	0.605 (0.219, 1.121)	0.273 (-0.437, 3.237)	1.154	0.579
<2 Sv	0.646 (0.437, 0.884)	0.513 (0.277, 0.825)	0.239 (-0.092, 0.993)	1.258	0.202
unrestricted	0.611 (0.420, 0.829)	0.590 (0.356, 0.891)	0.027 (-0.160, 0.373)	1.036	0.818

Indications of LDEF ~1.3-1.4 overall

Indications of larger curvature, with LDEF~1.5 over lower dose range (0-2 Sv)

Curvature stronger in more recent time periods

Effect of dose rate – DREF and DDREF

- Even taking effect of radiation dose D into account (e.g. by $F(D)=\alpha D+\beta D^2$) there are independent effects of dose rate in *in vitro* and *in vivo* data
- This is plausible - saturation of repair mechanisms
- One could estimate dose rate effectiveness factor (DREF), measuring ratio of risk at given dose incurred at high dose rate to low dose rate
- In extrapolating high dose/high dose-rate cancer risks to low dose/low dose-rate risks ICRP (1990, 2007) used human +old radiobiological (*in vitro*+*in vivo*) data to recommend application of dose and dose-rate effectiveness factor (DDREF) of 2
- So DDREF combines LDEF and DREF

Assessment of DDREF

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Assessment of DDREF via meta-analysis

- Because directly evaluating DDREF in human data impossible (no cohorts with high+low-dose-rate exposure) alternative approach compares risks in high dose-rate (e.g., LSS) and low dose-rate data (e.g., nuclear workers)
- Approach adopted by Jacob *et al* (*Occup Environ Med* 2009 **66** 789-96) and Shore *et al* (*Int J Radiat Biol* 2017 **93** 1064-78) (ICRP C1/TG91 work)
- Controversially Jacob *et al* suggested DDREF≈1
- Shore *et al* suggested DDREF≈3 (≈1 excluding Mayak)
- Problem with method is that underlying cohorts different, e.g., LSS has mostly lower cancer rates than western populations (but some higher, e.g., stomach) – transfer of relative risks not necessarily correct (e.g., for breast absolute risks known to transfer better)

What can human data tell us directly about low dose/low dose rate risk?

Studies of childhood cancer in relation to obstetric (*in utero*) radiation exposure

Childhood leukaemia and other cancers in relation to obstetric radiation exposure

(Stewart *et al Lancet* 1956 **268** 447, Bithell & Stewart *Br J Cancer* 1975 **31** 271-87)

Oxford Survey of Childhood Cancers (OSCC)

Obstetric X-rays and risk of childhood cancer

Type of cancer	Odds ratio (+95% CI)
Lymphatic leukaemia	1.54 (1.34, 1.78)
Myeloid leukaemia	1.47 (1.20, 1.81)
All solid cancers	1.45 (1.30, 1.62)
All cancers	1.47 (1.34, 1.62)

Significant excess risks for most types of childhood cancer in relation to obstetric radiation exposure

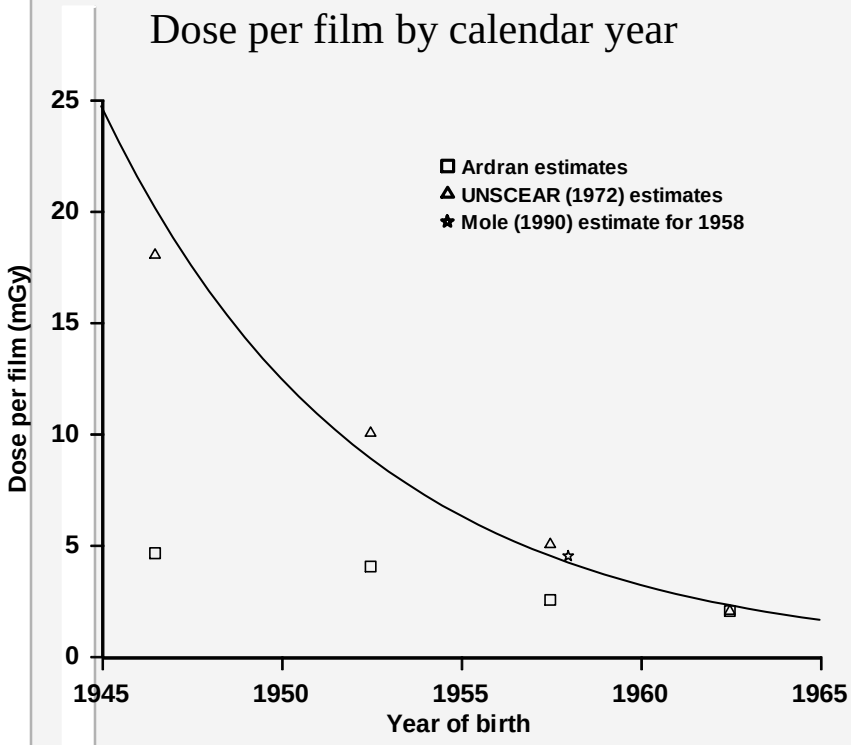
Childhood leukaemia case-control studies in relation to obstetric radiation exposure

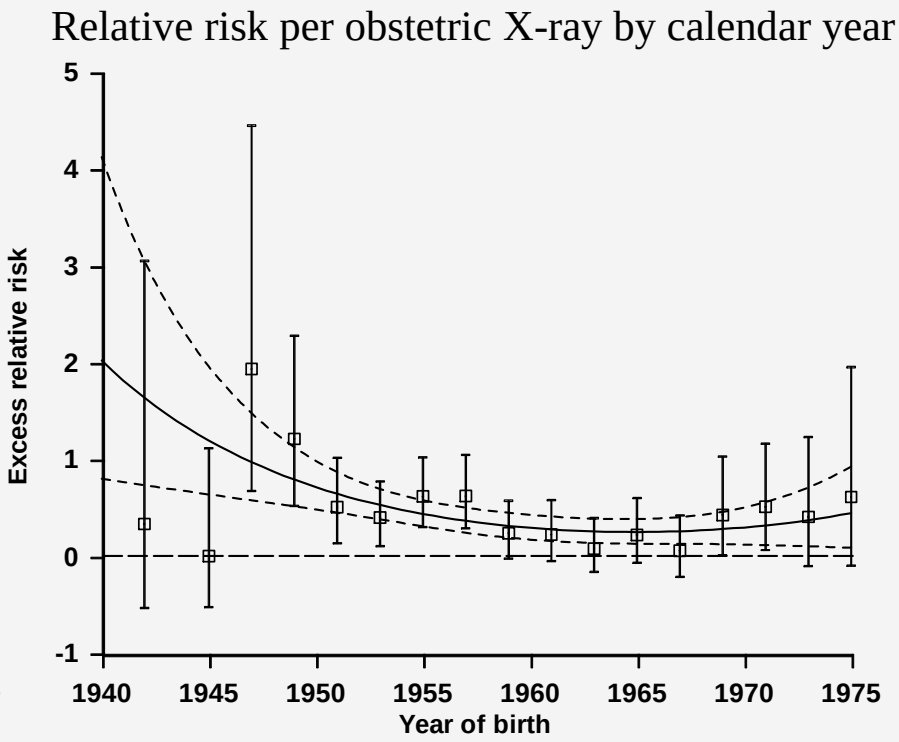
(Wakeford *Radiat Prot Dosim* 2008 **132** 166-74)

Period	Study	Relative risk (95% CI)
1947-1960	Monson & MacMahon (1984)	1.48 (1.18, 1.85)
1950-1957	Polhemus & Koch (1959)	1.23 (0.82, 1.85)
1953-1967	Bithell & Stewart (1975) [OSCC]	1.49 (1.33, 1.67)
1955-1956	Kaplan (1958)	1.60 (1.00, 2.57)
1960-1969	Robinette & Jablon (1976)	1.08 (0.80, 1.46)
1969-1977	Hirayama (1979)	1.60 (1.42, 1.79)
1973-1979	Van Steensel-Moll *et al* (1985)	2.22 (1.27, 3.88)
1980-1983	Hopton *et al* (1985)	1.35 (0.86, 2.11)
1980-1998	Infante-Rivard (2003)	0.85 (0.56, 1.30)
1989-1993	Shu *et al* (2002)	1.16 (0.79, 1.71)
1992-1996	Roman *et al* (2005)	1.05 (0.73, 1.52)

Risks in later studies tend to be lower, probably because of lower obstetric radiation doses used

Oxford Survey of Childhood Cancer (OSCC) childhood cancer obstetric radiation risk and dose by birth year (Wakeford & Little *IJRB* 2003 **79** 293-309)





General reduction in childhood cancer risk per film in Oxford Survey of Childhood Cancer (OSCC) over time, paralleling reduction in dose per film over this period

Possible problems and their resolution in causal interpretation of obstetric case-control studies

- **Differences between *in utero* risks and risks after birth:** known biological differences between *in utero* irradiation and period shortly after birth (animal studies)(UNSCEAR 1986)
- **Differences between cohort studies and case-control studies:** cohort studies have insufficient cases/deaths (lack statistical power), and in some cases subject to bias (e.g., selection bias in Court Brown *et al* (*BMJ* 1960 **2** 1539-45) study)
- **Lack of excess risk in LSS:** excess relative risk (ERR) per Sv in Japanese *in utero* study is compatible with OSCC (Wakeford & Little *IJRB* 2003 **79** 293-309)
  - Japanese leukaemia ERR/Sv <0 (95% CI <0, 50)
  - Japanese solid cancer ERR/Sv 22 (95% CI 0, 78)
  - OSCC all cancer ERR/Sv 51 (95% CI 28, 76)
- Doll & Wakeford (*Br J Radiol* 1997 **70** 130-9) concluded "on the balance of evidence … irradiation of the fetus *in utero* [by doses of the order of 10 mGy] increases the risk of childhood cancer"

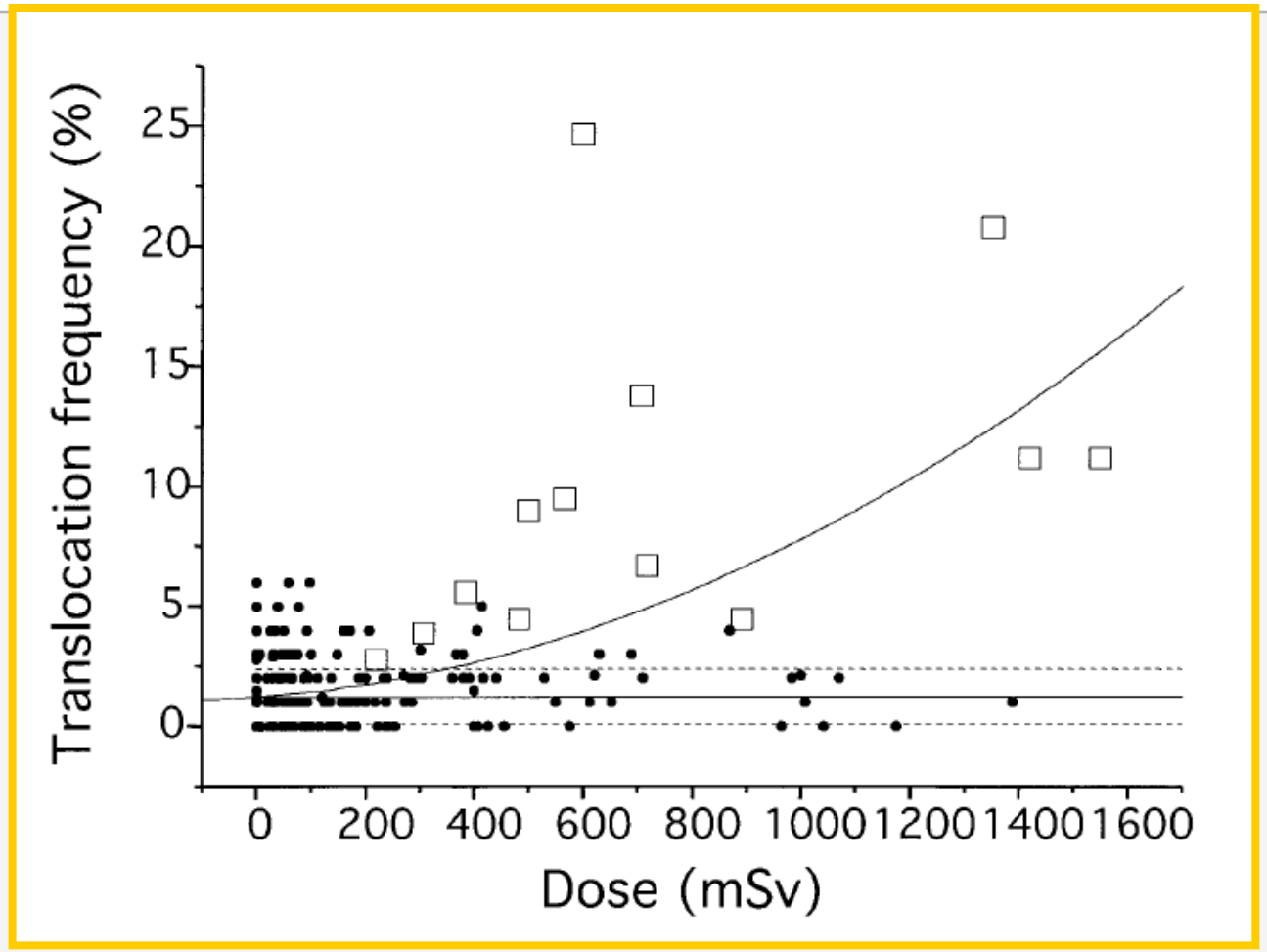
Solid cancer after *in utero* and childhood exposure in Japanese atomic bomb survivors

(Preston *et al J Natl Cancer Inst* 2008 **100** 428-36)

Risk at age 50	In utero exposure	Early childhood exposure	Heterogeneity *p*-value
Excess relative risk / Sv	0.42 (0.00, 2.0)	1.7 (1.1, 2.5)	>0.10
Excess absolute risk /10^4 PY Sv	6.8 (0.002, 48)	56 (36, 79)	0.04

- Non-significant (p>0.10) difference between excess relative risk (ERR) estimates for *in utero* and childhood exposure
- Borderline significant (p=0.04) differences in excess absolute risk (EAR) between *in utero* and childhood exposure

Chromosome translocation frequencies in peripheral blood lymphocytes from A-bomb survivors exposed *in utero* (●) and some of their mothers (□) (Ohtaki *et al Radiat Res* 2004 **161** 373-9)



Indications of low dose hypersensitivity among *in utero* exposed, but not their mothers – possible explanation of lack of *in utero* leukemias

Studies of childhood leukaemia and other cancers in relation to natural background radiation

UK NRCT case-control study of childhood cancer in relation to natural background (air γ) radiation

Kendall *et al Leukemia* 2013 **27** 3-9

Excess relative risk per cumulative gamma air dose (Gy)

Endpoint	Excess relative risk per Gy (γ) (95% CI)	p-value
Lymphoid leukaemia	100 (20,190)	0.01
All leukaemia	90 (20, 170)	<0.01
Lymphoid leukaemia + non-Hodgkin lymphoma	90 (20, 160)	0.02
Total leukaemia + non-Hodgkin lymphoma	80 (20, 150)	0.01
All lymphoma	10 (-70, 90)	0.86
Brain/CNS	20 (-40, 90)	0.49
All cancer	30 (0, 70)	0.04

Highly significant ($p<0.01$) excess risk for all leukemia
No excess risk for other cancers

Summary of studies of childhood cancer in relation to natural background radiation

Excess relative risk per cumulative gamma dose (Sv) (+95% CI)

All leukemia	Leukemia	Solid cancers	CNS	Lymphoma
UK-NRCT study (Kendall *et al Leukemia* 2013 **27** 3-9)	90 (20, 170) (*n*=9058)	20 (-20, 60) (*n*=18,389)	20 (-40, 90) (*n*=6585)	10 (-70, 90) (*n*=2319)
Swiss study (Spycher *et al Environ Health Perspect* 2015 **123** 622-8)	46 (-1, 96) (*n*=530)	-	60 (15, 106) (*n*=423)	22 (-27, 73) (*n*=328)
Finnish study (Nikkila *et al Int J Cancer* 2016 **139** 1975-82)	-30 (-110, 60) (*n*=937)	-	-	-
French study (Demoury *et al Environ Health Perspect* 2017 **125** 714-20)	0 (-10, 10) (*n*=9056)	-	-	-

Significant excess risk for all leukemia for UK and nearly so for Swiss study

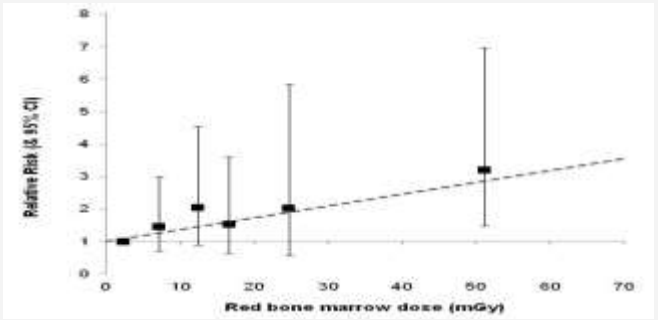
Apart from CNS risk in Swiss study, generally no excess risk for other cancers and other studies

Problem with French study? CI may be too narrow given that numbers of cases and dose distribution same as UK

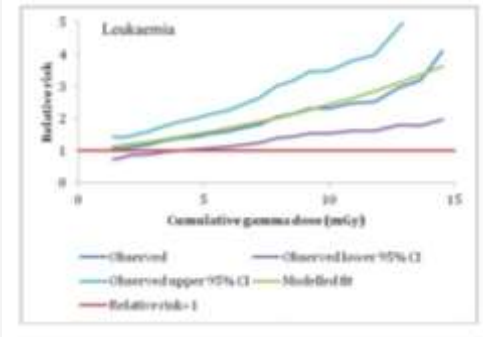
UK-NCI CT *vs* childhood-exposed LSS leukemia+brain *vs* UK NRCT risks (ERR / Sv + 95% CI)

	Leukemia ERR /Gy	Brain/CNS ERR/Gy
UK-NCI CT cohort (Pearce *et al. Lancet* 2012 **380** 499-505)	36 (5, 120)	23 (10, 49)
LSS age at exposure < 20, follow-up < 20 years after exposure	37.08 (14.22, 127.2)	6.14 (0.12, 63.93)
UK NRCT study (Kendall *et al. Leukemia* 2013 **27** 3-9)	90 (20, 170)	20 (-40, 90)

UK-NCI CT leukemia



UK-NRCT leukemia



Both for solid cancer and brain cancer risks in UK-NCI CT and UK-NRCT studies are compatible with those in Japanese A-bomb survivors (but possible problems with brain cancer findings in UK-NCI CT study)

Can we learn about DDREF, LDEF, DREF from animal data?

Estimates of DDREF from animal data

- ICRP (1990, 2007) estimated DDREF of 2 taking into account curvature in LSS dose response and older *in vivo* and *in vitro* radiobiological data
- BEIR VII (2006) estimated 'LSS DDREF' to be 1.5 (95% CI: 1.1, 2.3), on the basis of estimates of curvature from older Oak Ridge BALB/c +RFM murine data and from current (1958-1998) LSS solid cancer incidence data
- Animal data used by ICRP and BEIR VII was simply summary data (which is all that now exists for many older datasets), and may not have been properly analyzed (e.g. using life shortening, not taking account of intercurrent mortality) etc

Estimates of DDREF (mostly from JANUS data)(ICRP C1/TG91 work)(1)

- Grahn *et al* conducted a large number of animal experiments using JANUS reactor at Argonne National Lab in 1970-1992
- >50,000 mice (mostly *Mus musculus*, some *Peromyscus leucopus*) were treated with mixture of gamma, neutrons at varying doses/dose rates
- Haley *et al* (PLoS ONE 2015 **10(12)** e0140989) recently estimated from JANUS and ERA data what they termed $DDREF_{LSS}$ (because of derivation from A-bomb survivor Life Span Study data)
- Haley *et al* (PLoS ONE 2015 **10(12)** e0140989) modeled mean lifespan, mostly using linear regression with simple lin-quad model recommended by BEIR VII (2006)

Estimates of DDREF (mostly from JANUS data) (ICRP C1/TG91 work)(2)

- Haley *et al* (PLoS ONE 2015 **10(12)** e0140989) found that BEIR VII recommended lin-quad model did not fit mouse lifespan data well
- Haley *et al* (PLoS ONE 2015 **10(12)** e0140989) derived central estimates of $DDREF_{LSS}$ of $0.9 - \infty$
- However, there are statistical problems with linear model fitted by Haley *et al* (PLoS ONE 2015 **10(12)** e0140989), which does not have correct (Normal) error structure, and introduces non-linearities in model fitting

Fits to JANUS mouse data (ICRP C1/TG91 work) (Tran & Little *Radiat Environ Biophys* 2017 in press)

- JANUS multi-experiment mouse data performed 1970-1992 by Grahn and others
- 13 experiments with 50,110 individual mice exposed to gamma and neutrons
- Most experiments performed on *Mus musculus* (common house mouse), one experiment performed on *Peromyscus leucopus* (white-footed deer mouse)
- Previously analyzed by Haley *et al* (*PLoS ONE* 2015 10(12) e0140989)

Models fitted (ICRP C1/TG91 work) (Tran & Little *Radiat Environ Biophys* 2017 in press)

- Cox model, age as timescale, stratified by sex+experiment, lagged dose, scaling mean age at death/censoring [~900 days] x latent period for most endpoints in man in proportion to lifespan [5/80] = 900 x (5/80) ~ 60 days.
- Optimal model adjusted for linear/quadratic terms in lagged dose D, sex s, age at entry e, k fractions, dose rate (mGy/h) DR

$$RR[D, DR, k, s, e \mid (\alpha_i)] = \exp\left[\begin{array}{l} \alpha_1 D + \alpha_2 D^2 + \alpha_3 D^2 / k \\ +\alpha_4 D 1_{DR<5mGy/h} + \alpha_5 D^2 1_{DR<5mGy/h} \\ +\alpha_6 [e - e_0] + \alpha_7 D[e - e_0] + \alpha_8 D 1_{s=male} \end{array}\right]$$

- Assess LDEF and DREF, latter using <5mGy/h threshold suggested by ICRP

Differences of Tran & Little (*Radiat Environ Biophys* 2017 in press) from Haley *et al* (*PLoS ONE* 2015 10(12) e0140989)

- Haley *et al*: ERA+JANUS *vs* Tran & Little: JANUS
- Haley *et al*: unlagged dose, <1.5 Sv *vs* Tran & Little: lagged dose, <5 Gy (<0.1 Gy neutrons) + without restriction
- Haley *et al*: mixture of models, some using lifespan as endpoint (statistically improper?) *vs* Tran and Little: Cox model only
- Haley *et al*: formula for LDEF employed by BEIR VII, derived from Pierce & Vaeth (*Radiat Res* 1991 126 36-42) *vs* Tran & Little: bootstrap methods to derive LDEF, DREF (perhaps better takes account of uncertainty?)

LDEF, DREF for gamma (ICRP C1/TG91 work) (Tran & Little *Radiat Environ Biophys* 2017 in press)

Disease endpoint	$LDEF_{high}$ (95% CI)	$LDEF_{low}$ (95% CI)	DREF (95% CI)
All tumour	1.056(0.992,1.139)	0.857(0.648,1.239)	1.190(0.861,1.723)
Lymphoreticular	1.159(1.062,1.313)	0.906(0.563,2.217)	1.371(0.802,3.681)
Respiratory	0.758(0.667,0.874)	0.982(0.637,2.392)	1.403(0.878,3.843)
Vascular	0.701(0.574,0.854)	0.645(0.339,1.487)	1.193(0.675,3.129)
Kidney & urinary bladder	0.638(0.450,0.864)	2.035(-8.704,11.173)	2.336(-10.778,13.506)
All non-tumour[a]	1.630(1.429,1.995)	0.601(0.346,1.287)	0.608(0.365,1.393)
Pulmonary[a]	1.695(1.166,2.755)	0.336(0.154,0.600)	0.275(0.119,0.769)
Renal[a]	-3.503(-28.172,32.319)	-0.472(-1.667,0.863)	-0.205(-1.207,0.555)
Cardiovascular[a]	0.983(-2.397,3.540)	0.021(-0.756,0.735)	0.169(-0.238,0.815)
Other non-tumour diseases[a]	1.473(1.290,1.822)	0.800(0.426,2.362)	0.783(0.399,2.809)

[a]non-tumour disease

$LDEF_{high}$ = 1.06 for all tumour

$LDEF_{high}$ = 1.63 for all non-tumour disease

For many malignant endpoints $LDEF_{high}$ 0.2-0.8 (some significantly)

Most malignant DREF~1.2-2.3 [all tumour =1.19] (but most not significantly different from 1)

LDEF, DREF for neutrons (ICRP C1/TG91 work) (Tran & Little *Radiat Environ Biophys* 2017 in press)

Disease endpoint	$LDEF_{high}$ (95% CI)	$LDEF_{low}$ (95% CI)	DREF (95% CI)
All tumour	0.490(0.450,0.526)	0.073(-0.166,0.304)	-0.182(-0.695,-0.105)
Lymphoreticular	0.571(0.470,0.691)	0.148(-0.890,0.971)	-0.133(-0.843,1.363)
Respiratory	0.507(0.439,0.584)	0.004(-0.358,0.305)	-0.095(-0.379,-0.051)
Vascular	0.413(0.305,0.544)	0.539(-3.440,4.360)	-0.214(-1.940,1.661)
Kidney & urinary bladder	0.351(0.255,0.458)	-0.408(-4.389,3.745)	-0.187(-1.460,1.301)
All non-tumour[a]	0.791(0.660,0.942)	-0.090(-2.361,3.458)	0.226(-1.938,1.135)
Pulmonary[a]	0.808(0.618,1.120)	0.259(-3.185,3.248)	0.207(-1.044,1.368)
Renal[a]	-0.072(-1.663,0.251)	0.048(-4.113,2.807)	0.084(-0.383,0.248)
Cardiovascular[a]	0.530(0.183,1.138)	0.153(-1.978,4.204)	-0.081(-0.530,0.379)
Other non-tumour diseases[a]	0.902(0.737,1.124)	-0.492(-4.240,3.415)	0.202(-0.750,1.337)

[a]non-tumour disease

For most endpoints $LDEF_{high}$ =0.1-0.9 [all tumour=0.49](most significantly<1) – a challenging finding!

Most DREF~0.0-0.2 [all tumour <0] (many significantly<1) – a challenging finding!

[DREF < 0 generally means conventional (sparing) dose rate effect]

Conclusions

- LDEF measures dose extrapolation, DREF measures dose rate extrapolation, DDREF combines two
- Some evidence of low dose/low dose rate risk in obstetric and background radiation studies
- DDREF for ICRP (=2) and BEIR VII (=1.5) based on older animal data, LSS curvature: former may be flawed
- JANUS data analyses (ICRP C1/TG91 work)
  - After gamma for many malignant endpoints $LDEF_{high}$ 0.2-0.8 (some significantly)
  - After gamma most malignant DREF~1.2-2.3 [all tumour =1.19] (but most not significantly different from 1)
  - After neutron for most endpoints $LDEF_{high}$ =0.1-0.9 [all tumour=0.49](most significantly<1) – a challenging finding!
  - After neutron most DREF~0.0-0.2 [all tumour <0] (many significantly<1) – a challenging finding!