Radiation Epidemiology – Is There More to Learn?

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22 NOVEMBER 2018, Radiation Safety Standards Committee (RASSC), VIC, VIENNA
Is there more to learn?
YES!
New developments have recently, and will continue to, come from pooling either the results or the data from many similar epidemiological studies.

Important for low dose radiation risk inference are: e.g., Nuclear worker studies, CT studies, Environmental exposure studies.
Presentation Overview

1. First a few radiation epidemiology basics for non-radiation epidemiologists
   LNT, COHORT, ERR, EAR, DDREF (covered by W. Rühm), etc.

2. How individual study results have been pooled or brought together to
   synthesize knowledge bases useful for gaining information on quantities
   used in radiation protection (*LNT as an example described in detail*)

3. Is there more to learn? – New results expected in the short term
   – What can be expected in the long term?
Types of dose-response curves

a = Linear Non Threshold, LNT
Risk assessment: LNT controversy

A dose that stimulates one person may well be toxic to another

LNT and uncertainties in extrapolation at low doses

Hypersensitivity, Bystander effects Genomic instability

The risk at low doses might be greater than predicted by LNT

Adaptive response Hormesis (threshold)

The risk at low doses might be less than predicted by LNT
Cohort Studies (e.g., Japanese A-bomb survivors, various studies on nuclear workers, airline pilots)

A cohort was a 300-600-man unit in the Roman Army. 10 cohorts formed a legion (figure 1)

- A cohort is a group with something in common e.g., an exposure
- Start with disease-free “at-risk” population (susceptible to the disease of interest)
- Determine eligibility and exposure status
- Follow-up and count incident events (e.g., cancer incidence) or deaths from certain causes (the outcome)
- Analyse data statistically (since there are no general biomarkers of radiation induced cancer) to determine risks
**Excess Relative Risk (ERR) = Relative Risk - 1**

**e.g.,** ERR = 0.5
means that the spontaneous/baseline risk is increased by 50% by the radiation exposure

If this radiation exposure = 1 Sv

\[ \text{ERR} = \frac{A}{C} = \frac{B}{D} = 0.5 \]

---

**Hypothetical cancer rates - for illustration**

solid line = spontaneous risk
dashed line = total risk
ERR = A/C = B/D = 0.5

---

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If this radiation exposure = 1 Sv

\[ \text{ERR} = \frac{A}{C} = \frac{B}{D} = 0.5 \]
Excess Absolute Risk (EAR)

Hypothetical cancer rates - for illustration

solid line = spontaneous risk
dashed line = total risk
EAR = A = B = 0.002 deaths per PYR
What is low dose?

low absorbed doses (<100 mGy delivered acutely or accumulated over time) and/or
low absorbed dose rates (LD/LDR) (<5 mGy h\(^{-1}\) for any accumulated dose)
Is there a cancer risk at low doses?

INWORKS, Dose response for all cancers except leukemia, at low doses

<table>
<thead>
<tr>
<th>Range of Doses</th>
<th>Excess Relative Risk/Gy (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full dose range (0 - &lt;max. 1331.7 mGy - 90th percentile 53.4 mGy)</td>
<td>0.48 (0.20; 0.79)</td>
</tr>
<tr>
<td>0 – 150 mGy</td>
<td>0.69 (0.10; 1.30)</td>
</tr>
<tr>
<td>0 – 100 mGy</td>
<td>0.81 (0.01; 1.64)</td>
</tr>
</tbody>
</table>

(Richardson et al., Br Med J, 351: h5359, 2015)
Japanese A-bomb survivors Life Span Study (LSS) dose-response at 0-100 mGy for solid cancers, sexes combined

### Solid Cancer Incidence

<table>
<thead>
<tr>
<th>Dose Range</th>
<th>ERR Gy⁻¹ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full dose range</td>
<td>0.50 (0.42, 0.59)</td>
</tr>
<tr>
<td>&lt;4 Gy</td>
<td></td>
</tr>
<tr>
<td>0-100 mGy</td>
<td>0.49 (0.026, 1.01)</td>
</tr>
</tbody>
</table>

Risk estimates from:

### Solid Cancer Mortality

Non-CLL leukemia risks in studies with low-dose/low dose-rate exposures and ≥20 cases

<table>
<thead>
<tr>
<th>Study</th>
<th>ERR/Gy (90% CI)</th>
<th>ERR/Gy (90% CI)</th>
<th>Mean Dose (mGy) / No. Leukemias</th>
</tr>
</thead>
<tbody>
<tr>
<td>US NPPs nuc (Howe’04) A</td>
<td>5.7 (-1.2, 26)</td>
<td></td>
<td>26 / 26</td>
</tr>
<tr>
<td>Kerala, high background radiat (Akiba’13)[I] B</td>
<td>3.7 (-276, 283)</td>
<td></td>
<td>161 / 20</td>
</tr>
<tr>
<td>US Fernald U-processing nuc (Silver’13)</td>
<td>3.3 (-1.7, 24)</td>
<td></td>
<td>24 / 28</td>
</tr>
<tr>
<td>INWORKS (UK,US,Fr) nuc (Leuraud’15)</td>
<td>3.0 (1.2, 5.2)</td>
<td></td>
<td>16 / 531</td>
</tr>
<tr>
<td>Chernobyl clean-up, Ukr. (Zablotska’13) [I]</td>
<td>2.2 (0.4, 6.7)</td>
<td></td>
<td>82 / 52</td>
</tr>
<tr>
<td>Techa River, residents (Krestinina’13) [I]</td>
<td>2.2 (1.0, 4.9)</td>
<td></td>
<td>420 / 72</td>
</tr>
<tr>
<td>German U miners (Kreuzer’17)</td>
<td>0.9 (-3.1, 4.9)</td>
<td></td>
<td>48 / 120</td>
</tr>
<tr>
<td>US Rocketdyne nuc (Boice’11)</td>
<td>0.6 (-4.1, 10)</td>
<td></td>
<td>14 / 25</td>
</tr>
<tr>
<td>Chernobyl clean-up, Russ. (Ivanov’12) [I]</td>
<td>0.4 (-1.7, 2.6)</td>
<td></td>
<td>108 / 111</td>
</tr>
<tr>
<td>US Mound nuc (Boice’14)</td>
<td>0.4 (-3.0, 6.0)</td>
<td></td>
<td>26 / 26</td>
</tr>
<tr>
<td>Mayak nuc (Preston’17)</td>
<td>0.1 (-0.2, 0.5)</td>
<td></td>
<td>120 / 90</td>
</tr>
<tr>
<td>Japan nuc (Akiba’12)</td>
<td>-1.9 (-5.5, 6.9)</td>
<td></td>
<td>12 / 80</td>
</tr>
<tr>
<td>US atomic veterans (Caldwell’16)</td>
<td>-50 (-125, 26)</td>
<td></td>
<td>3.2 / 27</td>
</tr>
<tr>
<td>A-bomb LSS (exposed ages 20-39) (Hsu’13)[I]</td>
<td>3.9 (2.3, 6.1)</td>
<td></td>
<td>230 / 122</td>
</tr>
</tbody>
</table>

A “nuc” = nuclear workers;  B [I] = incidence; otherwise mortality.  
(Compilation by R. Shore for ICRP TG-91 Report in preparation)
All Solid Cancer (*mortality or incidence*): Excess Relative Risk (ERR) Gy\(^{-1}\) in the 12 Largest LD/LDR Studies (>
250 cases)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Solid Cancers</th>
<th>Mean Dose (mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayak nuc (Sokolnikov-15) (^{A})</td>
<td>1,825</td>
<td>354</td>
</tr>
<tr>
<td>China, med x-ray (Sun-16) (^{II})</td>
<td>1,643</td>
<td>40.6</td>
</tr>
<tr>
<td>INWORKS (UK,US,Fr.) nuc (Richardson-15)</td>
<td>17,957</td>
<td>20.9</td>
</tr>
<tr>
<td>Techa River (Schonfeld-13)</td>
<td>2,303</td>
<td>35</td>
</tr>
<tr>
<td>Kerala HBRA (Nair-09) (^{II}) (^{B})</td>
<td>1,349</td>
<td>161</td>
</tr>
<tr>
<td>Chernobyl clean-up (Kashcheev-15)</td>
<td>2,442</td>
<td>132</td>
</tr>
<tr>
<td>Japan nuc (Akiba-12)</td>
<td>2,636</td>
<td>12.2</td>
</tr>
<tr>
<td>Yangjiang HBRA (Tao-12)</td>
<td>941</td>
<td>63.2</td>
</tr>
<tr>
<td>US NPPs (Howe-04)</td>
<td>368</td>
<td>25.7</td>
</tr>
<tr>
<td>Rocketdyne (Boice-11)</td>
<td>651</td>
<td>13.5</td>
</tr>
<tr>
<td>German U millers (Kreuzer-15)</td>
<td>434</td>
<td>26</td>
</tr>
<tr>
<td>Canada nuc (Zablotska-13)</td>
<td>324</td>
<td>21.64</td>
</tr>
</tbody>
</table>

\(^{A}\) Nuc = nuclear workers

\(^{B}\) HBRA = high background radiation area

\(^{II}\) = incidence data

DREF from a meta-analysis comparing 22 LD/LDR studies to the Life Span Study

<table>
<thead>
<tr>
<th>LD/LDR Studies in the Comparison</th>
<th>DREF (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 22 LD/LDR studies (19 mort + 3 inci)</td>
<td>3.0 (1.9; 7.7)</td>
</tr>
<tr>
<td>All studies, except Mayak workers</td>
<td>1.9 (1.0; 11)</td>
</tr>
<tr>
<td>All mortality studies, except Mayak workers</td>
<td>0.9 (0.5; 2.5)</td>
</tr>
<tr>
<td>All studies, but including only the Mayak workers without potential plutonium exposure</td>
<td>2.0 (1.2; 6.2)</td>
</tr>
<tr>
<td>Hoel et al 2018, analysis of 12 LD/LDR studies</td>
<td>2.6 (1.6; 7.1)</td>
</tr>
</tbody>
</table>

A Comparisons used statistical modeling to match the LSS to individual LD/LDR studies on sex, mean age at initial exposure, mean final attained age and dose conversion factors.


LNT?
Published in April, 2018

Prepared by Scientific Committee 1-25
included experts with a broad purview of the recent radiation epidemiology literature

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NCRP COMMENTARY No. 27

IMPLICATIONS OF RECENT EPIDEMIOLOGIC STUDIES FOR THE LINEAR-NONTHRESHOLD MODEL AND RADIATION PROTECTION

National Council on Radiation Protection and Measurements
Two associated publications (1 Memorandum, 1 Summary) in international journals:

Memorandum

Implications of recent epidemiologic studies for the linear nonthreshold model and radiation protection

R E Shore$^{1,2,15}$, H L Beck$^{3,15}$, J D Boice$^{4,5}$, E A Caffrey$^6$, S Davis$^7$, H A Grogan$^8$, F A Mettler$^9$, R J Preston$^{10}$, J E Till$^{11}$, R Wakeford$^{12}$, L Walsh$^{13}$ and L T Dauer$^{14,16}$

Submitted to Health Physics:
Recent Epidemiologic Studies and the Linear Nonthreshold Model for Radiation Protection – A Summary of NCRP Commentary No. 27 – with the same author list
AIM:

To determine if recent epidemiological studies of low-LET radiation, particularly those at low absorbed doses and/or low absorbed dose rates (LD/LDR): 

EITHER broadly support the LNT model of carcinogenic risk 

OR demonstrate sufficient evidence that the LNT model is not appropriate for RP
WHY:
Last reviews, by BEIR VII phase 2 report 2008 and UNSCEAR 2006 report ~10 years ago, included a large fraction of studies based on acute exposures to moderate and high doses. Since then a considerable number of results for updated or new cohorts, many of them with LD/LDR exposures, have been published

STUDY SELECTION:
In accordance with a recent comprehensive meta-analysis of such studies (ICRP TG 91) (Shore, Walsh, Azizova, Rühm, Int J Radiat Biol, 93:1064-78, 2017) By consensus of the Committee
TYPES OF STUDY:
1) large cohorts
2) with individual dosimetry
3) with radiation risk to dose-response analyses and risk coefficients for total solid cancer, individual cancers or non-CLL leukemia.

Earlier reports containing redundant data were eliminated.

Analyses of the Japanese Life Span Study of atomic bomb survivors and LD/LDR studies of exposed groups or tumour sites of special interest (fallout, in utero and early childhood exposures; breast cancer, thyroid cancer) were also included.

Twenty-nine major studies were critically reviewed.
Review of A-bomb papers and LD/LDR Epidemiological Studies

- Life Span Study (LSS) of Japanese Atomic Bomb Survivors
- INWORKS (International Nuclear Workers Study)
- Mayak workers
- Million Person Study – Rocketdyne, Mound, U.S. atomic veterans, industrial radiographers, U.S. nuclear power plant workers, etc.
- Techa River cohort
- High natural background areas – Kerala, India; Yangjiang, China
Review of A-bomb papers and LD/LDR Epidemiological Studies

- Life Span Study (LSS) of Japanese Atomic Bomb Survivors
- INWORKS (International Nuclear Workers Study)
- Mayak workers
- Million Person Study – Rocketdyne, Mound, U.S. atomic veterans, industrial radiographers, U.S. nuclear power plant workers, etc.
- Techa River cohort
- High natural background areas – Kerala, India; Yangjiang, China
- Japanese nuclear workers
- Canadian nuclear workers
- Chernobyl clean-up workers
- Other worker studies – Chinese X-ray workers, U.S. radiological technologists, French uranium processing workers
- Taiwan residents of radiocontaminated buildings
- Chernobyl and other radiation fallout studies
- Pooled studies of external irradiation and thyroid cancer
- Medical studies: Pediatric CT scans, TB multiple fluoroscopic exams

(Slide courtesy of R. Shore)
Critical Review of Individual Epidemiological Studies in NCRP
Commentary No. 27

- **Epidemiological data & methodology** – size of study; soundness of methods; potential for bias; epidemiological uncertainties considered?
- **Dosimetry** – data quality; methods; dose uncertainties examined?
- **Statistical methods & results** – appropriate; statistical precision; evaluation of shape of dose-response?
- **Study strengths and limitations**?
- **Implications for LNT and radiation protection**?

(Slide courtesy of R. Shore)
Evaluations of consistency with the LNT model

- **Strong support** – 5 studies (17%)
  - INWORKS: US, UK and French combined cohorts (Richardson 2015; Leuraud 2015)

- **Moderate support** – 6 studies (21%)
  - Mayak nuclear workers (Sokolnikov 2015, 2017)

- **Limited-to-moderate support** – 9 studies (31%)
  - Chernobyl clean-up workers, Russia (Kashcheev 2015)

- **No support** – 5 studies (17%)
  - Kerala, India – high natural background radiation area (Nair 2009)

- **Inconclusive** – 4 studies (14%)
  - CT examinations of young people, Australia (Mathews 2013)
  - Nuclear weapons test fallout studies (e.g., Marshall Islands)

Nearly 70% provided some support for LNT, ranging from fairly-weak to strong.

(Slide courtesy of R. Shore)
Various studies of radiation and total solid cancer showed risk at low doses or low dose rates.

Dose uncertainties & epidemiological shortcomings exist and risk estimates below 100 mGy have large uncertainties.

Current data are not precise enough to definitively exclude other models.

The majority of the quantitative epidemiological LD/LDR results broadly support the LNT model for total solid cancer and leukemia

Very weak to no evidence of a dose-response threshold or of strong upward curvature.

(Adapted from NCRP Commentary No. 27)
Based on current epidemiological data, no notably different alternative to the LNT model appears more practical and prudent for radiation protection purposes.

Modest doubt is called the beacon of the wise.
William Shakespeare
Evidence for non-cancer effects at low doses

15-country study of nuclear industry workers (Vrijheid et al. Int J. Epi. 2007, TABLE 5):
All CIs for 15-Country study outcomes investigated included zero.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>N</th>
<th>ERR/Sv (95% CI)</th>
<th>N</th>
<th>ERR/Sv (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cancer diseases</td>
<td>11 255</td>
<td>0.24 (−0.23, 0.78)</td>
<td>4563</td>
<td>0.12 (0.01, 0.24)</td>
</tr>
<tr>
<td>Circulatory diseases</td>
<td>8412</td>
<td>0.09 (−0.43, 0.70)</td>
<td>2571</td>
<td>0.16 (0.02, 0.32)</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>792</td>
<td>1.16 (−0.53, 3.84)</td>
<td>911</td>
<td>0.04 (−0.17, 0.30)</td>
</tr>
<tr>
<td>Digestive diseases</td>
<td>620</td>
<td>0.96 (&lt;0, 4.52)</td>
<td>370</td>
<td>−0.03 (−0.35, 0.40)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>263</td>
<td>1.54 (&lt;0, 9.67)</td>
<td>167</td>
<td>0.02 (&lt;0, 0.73)</td>
</tr>
</tbody>
</table>
A variety of non-malignant effects (other than cataract and CVD) have been observed after moderate/low dose exposure in various groups (respiratory and digestive disease and central nervous system, neuro-cognitive damage).

However these associations must be treated with caution because generally these outcomes are only observed in isolated groups, or the evidence is very heterogeneous (see M. Little REB 2013)

### INWORKS (Gillies et al Rad Res 2017) :-

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ERR/Sv; 90% CIs</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>all non-cancer death</td>
<td>0.19; 0.07, 0.30</td>
<td>46,029</td>
</tr>
<tr>
<td>circulatory diseases</td>
<td>0.22; 0.08, 0.37</td>
<td>27,848</td>
</tr>
<tr>
<td>cerebrovascular disease</td>
<td>0.50; 0.12, 0.94</td>
<td>4,444</td>
</tr>
<tr>
<td>ischemic heart disease</td>
<td>0.18; 0.004, 0.36</td>
<td>17,463</td>
</tr>
<tr>
<td>nonmalignant respiratory disease</td>
<td>0.13; -0.17, 0.47</td>
<td>5,291</td>
</tr>
<tr>
<td>digestive disease</td>
<td>0.11; -0.36, 0.69</td>
<td>2,180</td>
</tr>
</tbody>
</table>

Caratact (see Little REB 2013)
Doses of 1 Gy or more associated with increased risk of posterior subcapsular cataract.
Evidence from e.g., LSS, Chernobyl liquidators and USA astronauts suggests cortical cataracts may also be associated with ionizing radiation but a threshold cannot be ruled out.

A variety of non-malignant effects (other than cataract and CVD) have been observed after moderate/low dose exposure in various groups (respiratory and digestive disease and central nervous system, neuro-cognitive damage).
Is there more to learn? – New results expected in the short term

EPI-CT pooled results

**EXPECTED SOON:**

Approx. 1.2 million patients:
- France
- Germany
- UK
- Denmark
- Belgium
- Netherlands
- Norway
- Sweden
- Spain
Mayak:-
In preparation: a paper on lung cancer risk in Mayak workers (incorporating shared/unshared dosimetry error)

LSS:-
Statisticians are working on dosimetry issues and trying to figure out more about the dose response curvature at low doses.
Updated comparisons of the LSS, Techa & Mayak risk estimates for solid cancer and leukemia are in preparation for publication.

USA. Million Worker Study:-
Expected series of papers in Int. J. Radiation Biol. next year
Some new LDR studies of **non-CLL Leukemia** mortality by cumulative dose

**US nuclear power plant workers, n=333 non-CLL leukemia deaths.**
(Boice et al, NCRP Commentary No. 27, 2018; Fig. 4.5, p 74, Preliminary data, dashed line = LQ)

**Industrial radiographers, n=177 non-CLL leukemia deaths.**
(Boice et al, NCRP Commentary No. 27, 2018; Fig 4.6, p75, Preliminary data, lower line = LQ)
“Leukaemia and myeloid malignancy among people exposed to low doses (<100 mSv) of ionising radiation during childhood: a pooled analysis of nine historical cohort studies”

9 cohorts (from Canada, France, Japan, Sweden, the UK, and the USA)
Not treated for malignant disease
Enrolled between 1915 and 2004
Exposures < 21 years of age
262,573 persons
Mean follow-up 19.6 years, mean bone marrow dose 19.6 mSv
EAR at 100 mSv range 0.1 to 0.4 cases or deaths per 10,000 person-years

Results imply that the current system of radiological protection is prudent and not overly protective.
AML + Myelodysplastic disease, n=87

AML, n=79

CML, n=36

ALL, n=40

95% CIs shown

Relative risk (95% CI)

Bone marrow dose (mSv)
Is there more to learn – what can be expected in the long term?

From the Epidemiology:-
Further follow-ups of major studies e.g., INWORKS, LSS, Million Worker Study, including information on internal exposure and other potential confounders (lifestyle factors) will be instructive.

More pooling – “pooling of results studies“ (meta-analyses) are planned e.g., Leukaemia, Breast cancer, by ICRP- TG91

– “pooling of data studies“ are in progress e.g., Uranium miner cohort pooling

From interdisciplinary work:-
Further work on elucidating the biological mechanisms that might cause cancer/non-cancer effects at low doses

Analysis of epidemiological data including Biomarkers – so that we do not just need to rely on purely statistical ascertainment i.e., Biomarkers will help identify which cases actually belong to excess and baseline?
Only a few very specific ones know already (e.g., 2014, CLIP2, for thyroid cancer).
New: H. Zitzelsberger (HZM) team, based on experimental data from radiation exposed breast cancer collectives (Chernobyl clean-up workers and Mayak workers), found molecular markers for radiation associated breast cancer.

Mechanistic models – can integrate radiobiological mechanisms into epidemiological data analysis
Thank you to all colleagues involved in the LNT and DREF work

<table>
<thead>
<tr>
<th>NCRP SC 1-25 – LNT</th>
<th>ICRP Task Group 91 - DREF</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Shore, Chair</td>
<td>W Rühm, Chair</td>
</tr>
<tr>
<td>L Dauer, co-chair</td>
<td>R Shore</td>
</tr>
<tr>
<td>H Beck</td>
<td>T Azizova</td>
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<tr>
<td>J Boice</td>
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<td>E Caffrey</td>
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<td>S Davis</td>
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<td>H Grogan</td>
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<td>F Mettler</td>
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<td>J Preston</td>
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<td>J Till</td>
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<tr>
<td>R Wakeford</td>
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</tbody>
</table>
Spare slides from here on – potentially to support any discussions or if there is more time.
Models of risk
Life Span Study (LSS) of Japanese Atomic Bomb Survivors


Comparison of Linear and LQ ERR Models (detail)

* Note:
  * Close agreement for female response for L and LQ models
  * Male smoothed response and LQ match well (but below linear response)

LSS solid cancer mortality, 1950-2003: linear and nonparametric curves for colon doses ranging from 0 to 0.5 Gy.

[Based on mortality data, both sexes, available online at http://www.refr.jp; from LSS Report 14 (Ozasa, Radiat Res, 177:229-, 2012)]
Examples of dose-response analyses of low-dose or low dose-rate (LD/LDR):
Data for ‘Solid Cancer’ or closest surrogates
INWORKS and LSS, mortality from all cancer except leukemia by colon dose

Error bars show 90% confidence intervals.

ERR/Gy = 0.48 (90% CI 0.20, 0.79)

(Slide, courtesy of Richard Wakeford) (Richardson et al., BMJ 2015; 351:h5359)
Mayak Workers – external radiation and mortality from solid cancer (excluding lung, liver & bone – main plutonium deposition sites)

Full Dose Range

Dose Range 0 – 1.5 Gy

ERR/Gy = 0.12 (95% CI 0.03, 0.21)*

* Risk estimate adjusted for estimated plutonium deposition.

(Sokolnikov, PLoS One, 2015;e0117784)
Dose response for solid cancer incidence, Techa River cohort

Data adjusted for smoking.  (Davis et al, Radiat Res, 2015; 184:56-65)
Relative Risk for Incidence of all cancer except leukemia by cumulative dose – high natural background radiation area in Kerala, India


(Slide courtesy of John Boice, Jr.)
UK Study of Leukemia Incidence after CT Examinations at Ages 0-21

(ERR/Gy = 36 (95% CI 5, 120))

<table>
<thead>
<tr>
<th>Studies (or groups of studies) and representative publications</th>
<th>Support for LNT model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Span Study (LSS), Japan atomic bombs [9]</td>
<td>Strong</td>
</tr>
<tr>
<td>INWORKS (UK, US, French combined cohorts) [13]</td>
<td>Strong</td>
</tr>
<tr>
<td>Tuberculosis fluorescent examinations and breast cancer [67]</td>
<td>Strong</td>
</tr>
<tr>
<td>Childhood Japan atomic bomb exposure [63]</td>
<td>Strong</td>
</tr>
<tr>
<td>Childhood thyroid cancer studies [48]</td>
<td>Strong</td>
</tr>
<tr>
<td>Mayak nuclear workers [25]</td>
<td>Strong</td>
</tr>
<tr>
<td>Chemobyl fallout, Ukraine and Belarus thyroid cancer [46]</td>
<td>Moderate</td>
</tr>
<tr>
<td>Breast cancer studies, after childhood exposure [68]</td>
<td>Moderate</td>
</tr>
<tr>
<td><em>In utero</em> exposure, Japan atomic bombs [63]</td>
<td>Moderate</td>
</tr>
<tr>
<td>Techa River, nearby residents [43]</td>
<td>Moderate</td>
</tr>
<tr>
<td><em>In utero</em> exposure, medical [61]</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Japan nuclear workers [28]</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Chemobyl cleanup workers, Russia [32]</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>US radiologic technologists [33, 69]</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Rocketdyne nuclear workers [31]</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>French uranium processing workers [34]</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Medical x-ray workers, China [35]</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Taiwan radiocontaminated buildings, residents [70]</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>Background radiation levels and childhood leukemia [71]</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td><em>In utero</em> exposures, Mayak and Techa [72]</td>
<td>No support</td>
</tr>
<tr>
<td>Hanford $^{131}I$ fallout study [73]</td>
<td>No support</td>
</tr>
<tr>
<td>Kerala, India, high natural background radiation area [51]</td>
<td>No support</td>
</tr>
<tr>
<td>Canadian worker study [29]</td>
<td>No support</td>
</tr>
<tr>
<td>US atomic veterans [36]</td>
<td>Inconclusive$^e$</td>
</tr>
<tr>
<td>Yangjiang, China, high natural background radiation area [52]</td>
<td>Inconclusive$^e$</td>
</tr>
<tr>
<td>CT examinations of young persons [54]</td>
<td>Inconclusive$^e$</td>
</tr>
<tr>
<td>Childhood medical x rays and leukemia (aggregate of &gt;10 studies) [61, 74]</td>
<td>Inconclusive$^e$</td>
</tr>
<tr>
<td>Nuclear weapons test fallout studies (aggregate of eight studies) [75]</td>
<td>Inconclusive$^e$</td>
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</tbody>
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<th>Notes:</th>
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<tbody>
<tr>
<td>$^a$ Study ratings were based on reported solid cancer (or close surrogates) risk unless noted otherwise.</td>
</tr>
<tr>
<td>$^b$ A representative recent publication is listed for each study or study group. Others are found in the NCRP commentary text.</td>
</tr>
<tr>
<td>$^c$ A number of studies were excluded for various reasons, including but are not limited to: ecological studies of residents around nuclear power plant facilities, studies of hereditary effects, studies of tissue reaction (or 'deterministic') effects, and the 15-Country study and other studies that overlap with the more recent INWORKS study.</td>
</tr>
<tr>
<td>$^d$ Considered borderline between 'Moderate' and 'Weak-to-Moderate' support for the LNT model.</td>
</tr>
<tr>
<td>$^e$ Considered 'weak' support or 'inconclusive' primarily because of weaknesses in epidemiology, dosimetry or statistical risk modelling. The studies listed as 'No support' had reasonable methodologies but provided little or no support for the LNT model because their risk coefficients were essentially zero or negative.</td>
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</tbody>
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