The Linear No-Threshold (LNT) risk model and Radiological Protection: major issues to understand for a better risk communication

Dominique Laurier

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Paris, October 24, 2019
History of LNT
Issues about LNT
Epidemiology and LNT
Conclusions and perspectives
History of LNT
History of the LNT

1927: HJ Muller « The artificial transmutation of genes »
X-Rays can induce transgenerational phenotypic changes in Drosophila, and the mutation rate is linear with dose (Science)

1928-1940: confirmation of the mutagenicity of X-Rays by different authors in plants and different species – X-Rays also induce somatic mutations
mutation is a single hit process with no threshold

1941: LNT Single-Hit biostatistical model (Zimmer)

1946: HJ Muller Nobel Prize in Biology and Medicine « The production of mutation »
History of the LNT at the ICRP

[ICRP Publication 9, 1966]

The mechanism of the induction by radiation of leukaemia and other types of malignancy is not known. Such induction has so far been clearly established after doses of more than 100 rads, but it is unknown whether a threshold dose exists below which no malignancy is produced. If such a threshold dose did exist, there would be no risk of the induction of malignancy, as long as the threshold was not exceeded. As the existence of a threshold dose is unknown, it has been assumed that even the smallest doses involve a proportionately small risk of induction of malignancies.

Because of the lack of knowledge of the nature of the dose-effect relationship in the induction of malignancies in man -- particularly at those dose levels which are relevant in radiological protection -- the Commission sees no practical alternative, for the purposes of radiological protection, to assuming a linear relationship between dose and effect, and that doses act cumulatively.

The Commission is aware that the assumptions of no threshold and of complete additivity of all doses may be incorrect, but is satisfied that they are unlikely to lead to the underestimation of risks. Information is not available at the present time which would lead to any alternative hypothesis.
History of the LNT at the ICRP

[ICRP Publication 60, 1990]
[ICRP Publication 99, 2005]

[ICRP Publication 103, 2007]
The practical system of radiological protection recommended by the Commission will continue to be based upon the assumption that at doses below about 100 mSv a given increment in dose will produce a directly proportionate increment in the probability of incurring cancer or heritable effects attributable to radiation.

The Commission considers that the adoption of the LNT model combined with a judged value of a dose and dose rate effectiveness factor (DDREF) provides a prudent basis for the practical purposes of radiological protection, i.e., the management of risks from low-dose radiation exposure.
Issues about LNT
Critics of the LNT

LNTgate: The ideological history of cancer risk assessment

Edward J Calabrese

Variation in cancer risk among tissues can be explained by the number of stem cell divisions

Cristian Tomasetti\textsuperscript{1,*} and Bert Vogelstein\textsuperscript{2,*}

« LNT is negation of 60 years of research on cancer »

(C Tomasetti CRH 2018)
Biological effects at low doses

The Lowest Radiation Dose Having Molecular Changes in the Living Body

Noriko Shimura¹ and Shuji Kojima²

Abstract
We herein attempted to identify the lowest radiation dose causing molecular changes in the living body. We investigated the effects of radiation in human cells, animals, and humans. DNA double-strand breaks (DSBs) formed in cells at γ or X-ray irradiation doses between 1 mGy and 0.5 Gy; however, the extent of DSB formation differed depending on the cell species. The formation of micronuclei (MNs) and nucleoplasmic bridges (NPBs) was noted at radiation doses between 0.1 and 0.2 Gy. Stress responsive genes were upregulated by lower radiation doses than those that induced DNA DSBs or MN and NPBs. These γ or X-ray radiation doses ranged between approximately 10 and 50 mGy. In animals, chromosomal aberrations were detected between 50 mGy and 0.1 Gy of low linear energy transfer radiation, 0.1 Gy of metal ion beams, and 9 mGy of fast neutrons. In humans, DNA damage has been observed in children who underwent computed tomography scans with an estimated blood radiation dose as low as 0.15 mGy shortly after examination. The frequencies of chromosomal translocations were lower in residents of high background areas than in those of control areas. In humans, systemic adaptive responses may have been prominently expressed at these radiation doses.
Biological effects at low doses

Evidence for Non-linear responses in radiobiology at low doses from in vitro or in vivo experimental data

Sub-linear responses or threshold
- adaptive responses (triggered defence mechanisms)
- stimulated DNA repair

Supra-linear responses
- induced genomic instability (damages in the progeny of irradiated cells)
- bystander effects (damages in cells neighbouring irradiated cells)
- threshold for DNA repair activation

Complex contribution of many biological mechanisms to cancer
Lack of global understanding of cancer development
Difficult to use to consolidate the system of radiological protection
Plausible dose-response relationships for the risk of cancer in the ranges of very low, low and moderate doses

Doses are in addition to the total background exposure to natural sources of radiation.

The data points and confidence intervals represent observations of increased frequency of occurrence of a specific cancer type in populations exposed to moderate doses.

The various lines represent the following plausible dose-response relationships for inferred risks of cancer for exposures in the range of low and very low doses: (a) supralinear; (b) linear non-threshold (LNT); (c) linear-quadratic; (d) threshold and (e) hormetic.
Epidemiology and LNT
NCRP Commentary n°27 (April 2018)
Implications of recent epidemiologic studies for the linear-nonthreshold model and radiation protection

Critical review of recent studies (10y)
• 29 studies (occupational, medical, environmental)

Systematic application of quality criteria
• Epidemiology (design, follow-up, outcome ascertainment, confounding…)
• Dosimetry (quality of input data, dose reconstruction, consideration of dose uncertainties…)
• Modelling (appropriateness of analytic method, adjustment, non-linear alternatives…)

Overall evaluation of the support to LNT
• Composite score of specific strengths and weaknesses
• How supportive of the LNT model are the risk coefficient and the dose-response shape?
Is the LNT Model Appropriate for Assessing Cancer Risk for Purposes of Radiation Protection?

- Study-size constraints, dose uncertainties and epidemiological weaknesses of low dose-rate studies limit the statistical power and precision of risk estimates, especially for data below 100 mGy.

- Preponderance of low dose-rate studies showing reasonable consistency with LNT for total solid cancer and for leukemia. Some studies not precise enough to statistically exclude models with a dose-response threshold or strong upward curvature. Only a few studies with evidence of no risk after low dose-rate exposures.

- Thus much of the quantitative low dose-rate epidemiological data broadly support a LNT model for total solid cancer and leukemia.

- **NCRP committee concluded that the LNT model, perhaps with a DREF >1, is prudent and practical for radiation protection purposes.**
A-Bomb survivors: Solid cancer excess relative risk

**Mortality**
Follow-up 1950-2003

Excess Relative Risk

**Solid cancer**

- Linear: $\beta=0.42$
- Linear-Quadratic $<2$Gy: $\beta=0.22$, $\beta^2=0.18$

[Ozasa et al, Rad Res 2012]
A-Bomb survivors: Solid cancer excess relative risk on the 0-500 mGy dose range

[Ncrp 2018, Based on Ozasa et al, Rad Res 2012]

LSS Solid Cancer Mortality 1950-2003

Linear and Nonparametric Curves at doses of 0 to 0.5 Gy
INWORKS: Relative Risk per Gy for cancer excluding leukemia

[from Richardson et al, BMJ 2015]

Note: The number of cancers in the lowest dose category (10,433 deaths) has not been annotated on this figure for reasons of legibility.

ERR per Gy = 0.48 ; 90%CI [0.20 – 0.79]

No indication of non linearity

308 297 workers in the nuclear industry from France, the UK, and the US
Mortality study
Follow-up 1944-2005
19,064 cancer deaths

Note: The number of cancers in the lowest dose category (10,433 deaths) has not been annotated on this figure for reasons of legibility.
INWORKS: Relative risk of cancer excluding leukemia over restricted dose ranges

[from Richardson et al. BMJ 2015]

Linear trend still borderline significant when cumulative doses above 100 mSv were excluded
Pooled analysis of cancer risk after childhood exposure

Thyroid cancer  Lubin J et al JCEM, 2017
- Pooled analysis of 9 cohorts of children with low-dose radiation exposure (< 200 mGy)
- 107,594 people, mean follow-up 41y, mean thyroid dose 30 mGy, 394 thyroid cancer cases
  Significant association when excluding doses above 100 mGy
  No indication of departure from linearity

Leukemia (excluding CLL)  Little M et al. Lancet Haematol, 2018
- Pooled analysis of 9 cohorts of children with low-dose radiation exposure (< 100 mSv)
- 262,573 people, mean follow-up 20y, mean ABM dose 20 mSv, 221 leukaemia cases
  Significant association when excluding doses above 50 mSv
  Few indications of departure from linearity

“These findings support an increased risk of leukaemia associated with low-dose exposure to radiation and imply that the current system of radiological protection is prudent and not overly protective.”
Quantifying the dose-risk relationship at low dose
Quantifying the dose-risk relationship at low dose
Conclusions and perspectives
Conclusions and perspectives: Epidemiological evidence

- Reinforcement in the last decade of the epidemiological evidence of some excess risk of some cancers after low dose radiation exposure
- No reliable evidence in favour of a deviation from linearity, no evidence of a threshold.
- Still uncertainties and lacks of knowledge (internal exposures, modifying effect of sex, age and time since exposure, variation between cancer sites…)
- Additional results to come in the near future (LSS, Inworks, MWS, Epi-CT, NCI review on sources of bias…)

→ Recent results support non-threshold linearity as the most plausible dose-response model at low doses
Conclusions and perspectives: interpretation of risks at low dose

Calculation of the attributable fraction

Among 1000 workers*
216 deaths
Of which 64 by cancer or leukaemia
Of which 1 attributable to exposure to ionizing radiation

* based on results from the INWORKS cohort: 308297 workers - mean dose 24 mSv - follow-up 27 years – age at end of follow-up 58 years
Conclusions and perspectives: integrating biology and epidemiology

- The LNT dose-response model is not able to reflect the complete mechanism of cancer

- Molecular epidemiology: collection of biological material in epidemiological cohorts

- Adverse Outcome Pathways (AOP): multilevel integration of existing biological knowledge
Conclusion and perspectives: LNT and radiological protection

- The LNT dose-response model is the most parsimonious description of the available scientific evidence
- The LNT dose-response model provides a practicable basis for the system of radiological protection
- The LNT dose-response model is not overly protective at low doses

- LNT is also used outside of the radiation field: a no-threshold relationship is considered for assessing risk for many carcinogens (chemicals, diesel exhausts, heavy metals, alcohol….) [U.S. EPA. 2005]
Conclusion and perspectives: communicating on low dose risks

- Implication of the LNT: low dose – low risks
- Improving communication on risks and on uncertainties
- Better separation of what is science-based and what is expert judgement
- Acceptability of risk: tolerability and reasonableness
- Establishing dialogue with the public: the example of local information commissions in the vicinity of nuclear power plants in France
Thank you for your attention

"Which line do you like best?"

Warm thanks to R Shore, R Wakeford, D Klokov and MA Tabocchini for sharing slides and to L Vaillant for his help in reconstructing the history of the LNT.
Bands of radiation dose

<table>
<thead>
<tr>
<th>Terminology for dose bands</th>
<th>Range of absorbed dose for low-LET radiation</th>
<th>Scenarios</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Greater than about 1 Gy</td>
<td>Typical dose (whole or partial body) to individuals after severe radiation accidents or from radiotherapy</td>
</tr>
<tr>
<td>Moderate</td>
<td>About 100 mGy to about 1 Gy</td>
<td>Doses to about 100,000 of the recovery operation workers after the Chernobyl accident (annex D [U14])</td>
</tr>
<tr>
<td>Low</td>
<td>About 10 to about 100 mGy</td>
<td>Dose to an individual from multiple whole-body computerized tomography (CT) scans</td>
</tr>
<tr>
<td>Very low</td>
<td>Less than about 10 mGy</td>
<td>Dose to an individual dose from conventional radiology (i.e. without CT or fluoroscopy)</td>
</tr>
</tbody>
</table>

Bands (approximate ranges) of total absorbed dose (to the whole body or to a specific organ or tissue of an individual) received in addition to the total from normal background exposure to natural sources of radiation. The bands of radiation dose do not account for the rate at which the dose is delivered.
<table>
<thead>
<tr>
<th>Studies (or groups of studies)</th>
<th>Epidemiology</th>
<th>Dosimetry</th>
<th>Statistics</th>
<th>Support for LNT model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Life Span Study (LSS), Japan atomic bombs [Grant 2017]</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>Strong</td>
</tr>
<tr>
<td>2. INWORKS (UK, US, French combined cohorts) [Richardson 2015]</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>Strong</td>
</tr>
<tr>
<td>3. Tuberculosis fluoroscopic examinations and breast cancer [Little 2003]</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>Strong</td>
</tr>
<tr>
<td>4. Childhood Japan atomic bomb exposure [Preston 2008]</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>Strong</td>
</tr>
<tr>
<td>5. Childhood thyroid cancer studies [Lubin 2017]</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>Strong</td>
</tr>
<tr>
<td>6. Mayak nuclear workers [Sokolnikov 2015]</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>7. Chernobyl fallout, Ukraine and Belarus thyroid cancer [Brenner 2011]</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>9. In utero exposure, Japan atomic bombs [Preston 2008]</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>10. Techa River, nearby residents [Schonfeld 2013]</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>11. In utero exposure, medical [Wakeford 2008]</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>12. Japan nuclear workers [Akiba 2012]</td>
<td>2.5</td>
<td>2</td>
<td>3</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>13. Chernobyl cleanup workers, Russia [Kascheev 2015]</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>15. Mound nuclear workers [Boice 2014]</td>
<td>2</td>
<td>1.5</td>
<td>1.5</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>17. French uranium processing workers [Zhivin 2016]</td>
<td>2.5</td>
<td>3</td>
<td>1.5</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>18. Medical x-ray workers, China [Sun 2016]</td>
<td>1.5</td>
<td>1.5</td>
<td>2</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>19. Taiwan radiocontaminated buildings, residents [Hsieh 2017]</td>
<td>2</td>
<td>1.5</td>
<td>1.5</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>20. Background radiation levels and childhood leukemia [Kendall 2013]</td>
<td>1.5</td>
<td>2</td>
<td>2</td>
<td>Weak-to-moderate</td>
</tr>
<tr>
<td>21. In utero exposures, Mayak and Techa [Akleyev 2016]</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>No support</td>
</tr>
<tr>
<td>22. Hanford 131I fallout study [Davis 2004]</td>
<td>2</td>
<td>3</td>
<td>1.5</td>
<td>No support</td>
</tr>
<tr>
<td>23. Kerala, India, high natural background radiation area [Nair 2009]</td>
<td>2</td>
<td>2</td>
<td>1.5</td>
<td>No support</td>
</tr>
<tr>
<td>24. Canadian worker study [Zablotska 2014]</td>
<td>2.5</td>
<td>3</td>
<td>3</td>
<td>No support</td>
</tr>
<tr>
<td>25. US atomic veterans [Caldwell 2016]</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>No support</td>
</tr>
<tr>
<td>26. Yangjiang, China, high natural background radiation area [Tao 2012]</td>
<td>1.5</td>
<td>1</td>
<td>1</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>27. CT examinations of young persons [Pearce 2012]</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>28. Childhood medical x rays and leukemia (aggregate of &gt;10 studies) [Wakeford 2008]</td>
<td>1</td>
<td>2</td>
<td>1.5</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>29. Nuclear weapons test fallout studies (aggregate of eight studies) [Lyon 2006]</td>
<td>1.5</td>
<td>1</td>
<td>1.5</td>
<td>Inconclusive</td>
</tr>
</tbody>
</table>
A-Bomb survivors: Solid cancer excess relative risk on restricted dose range

Mortality
Follow-up 1950-2003

Linear ERR model on restricted dose range

[Ozasa et al, Rad Res 2012]
A-Bomb survivors: Solid cancer excess relative risk

[Grant et al, Rad Res 2017]

**Incidence**
Follow-up 1958-2009
N = 22,538

On full dose range

Males: Linear-Quadratic
ERR=0.20 at 1 Gy / ERR=0.01 at 100 mGy

Females: Linear
\( \beta=0.64 \) CI95% [0.52 ; 0.77 ]

Significant on range 0-100 mGy
(Sex average model)

No evidence against a threshold of zero
females (P = 0.18; estimate 80 mGy; upper 200 mGy)
males (P = 0.49; estimate 750 mGy; upper 800 mGy).

ERR/Gy at attained age of 70 years after exposure at age 30 years, adjusted for smoking
Cancer mortality and incidence in UK radiation workers

Cancer mortality and incidence in relation to external radiation exposure
- Cohort of 167,003 workers (UK National Registry for Radiation Workers)
- Mean Follow-up 32 y (+10y) with 3.7 M person-years, mean dose 25 mSv
- 11,329 death from all neoplasms excluding leukemia

Significant association with both cancer mortality and incidence
- Narrower confidence bounds
- Linear trend still significant when cumulative doses above 100 mSv were excluded

“This study provides direct evidence of cancer risk from low dose and dose rate occupational external radiation exposures”
“Overall results consistent with the risk estimates from the LSS and those adopted in the current ICRP recommendations”
Pooled analysis of thyroid cancer risk after childhood exposure

Lubin J et al JCEM, July 2017

- Pooled analysis the risk of thyroid cancer associated with low-dose radiation exposure (< 200 mGy) in childhood (age at exposure <19 years).
- 9 cohorts: 8 medical (childhood cancer survivors; children treated for benign diseases (hemangioma, tinea capitis, thymus); + LSS (Jp)
- 107 594 people. Mean follow-up 41y, mean thyroid dose 30 mGy
- 394 thyroid cancer cases

- Significant association between dose and risk, even when restricting to doses below 100 mGy
- No indication of departure from linearity
- Estimates of threshold dose between 0.0 to 0.03 Gy (up. 95%CI of 0.04 Gy)
- Dose–response trend persisting >45 years after exposure, greater at younger age at exposure and younger attained age, similar by sex

“Our analyses reaffirmed linearity of the dose response as the most plausible relationship for “as low as reasonably achievable” assessments for pediatric low-dose radiation-associated thyroid cancer risk.”
Pooled analysis of leukemia risk after childhood exposure

Little M et al. Lancet Haematol, July 2018

- Pooled analysis the risk of leukaemia associated with low-dose radiation exposure (< 100 mSv) in childhood (age at exposure <21 years).
- 9 cohorts: 8 medical (tuberculosis (US, Can), haemangioma (Fr, Sw), thymus enlargement (US), spinal Curvature (US), CT-scan (UK)) + LSS (Jp)
- 262,573 people. Mean follow-up 20y, mean cumulative ABM dose 20 mSv
- 221 leukaemias excluding CLL (79 AML, 8 MDS, 36 CML, 40 ALL)

- Significant association for AML and ALL (even below 50 mSv)
- Few indications of between-cohort heterogeneity or departure from linearity

“These findings support an increased risk of leukaemia associated with low-dose exposure to radiation and imply that the current system of radiological protection is prudent and not overly protective.”
Monograph on Epidemiological Studies of the Low-dose Ionizing Radiation and Cancer

Eligible studies

- Published since the BEIR VII report in 2006
- Individualized dose estimates, predominantly, low-LET radiation exposure.
- Mean dose < 100 mSv
- Provides risk estimates and confidence intervals for the dose-response for cumulative radiation dose

Conducting a formal assessment of the potential impact of biases

- Confounding and selection bias
- Sources of dose errors
- Study power, lost of follow-up and outcome uncertainty
- Model misspecification

Publication at the beginning of 2019
In preparation

the International Pediatric CT-scan study

Protocol
- Coordination IARC
- 9 European countries
- ≈ 950,000 patients included
- mean number of CT scans per patient: 1.5
- mean age at first examination: 10 y
- 8.7 million person-years of incidence

Results
- Analysis of the risk of leukemia and solid cancers in association with repeated doses delivered by CT-scan examinations in childhood – publication in 2019