Considérations sur la linéarité sans seuil (LNT) à partir du rapport NCRP n°27

Laurier D

GT CIPR, Paris, 29 Nov 2018

Issues

History of Linearity

History of the LNT

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

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

1941: LNT Single-Hit biostatistical model (Zimmer)

1946: HJ Muller Nobel Prize in Biology and Medicine « The production of mutation »

1956: NAS BEAR I report (Science, « the genetic effects of atomic radiation »)

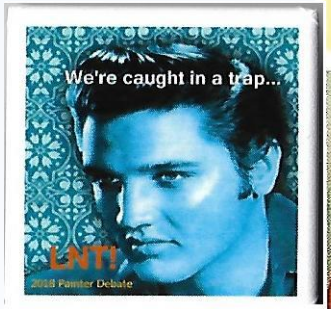
Still criticized

- EJ Calabrese 2016 « the LNTgate »
- C Tomasetti CRH 2018 « LNT is negation of 60 years of research on cancer », Tomasetti & Volgestein Science 2017)

Painter Debate: This house believes that the biological mechanisms that underlie cancer development are sufficient to dismiss linear-no-threshold (LNT) modeling of cancer risk

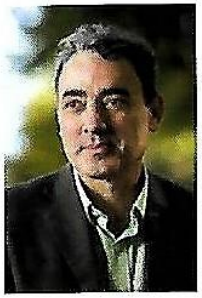
Moderator: Kathryn Held **Location:** Grand Ballroom **Time:** 12:30PM - 1:00PM

Box lunches will be located in the Grand Ballroom Foyer.
Grab your lunch on the way in and get ready for the debate of the year!



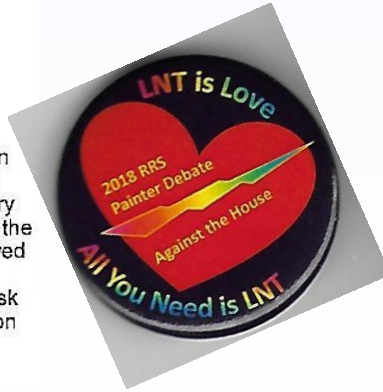
Mary Helen Barcellos-Hoff, PhD: FOR

Dr. Barcellos-Hoff received an undergraduate degree from the University of Chicago and earned a doctoral degree in experimental pathology from the University of California, San Francisco. She conducted postdoctoral research on extracellular matrix mediated functional differentiation at the Lawrence Berkeley National Laboratory (LBNL), which she joined as a staff scientist and rose to Senior Scientist and Associate Director of the Life Sciences Division before joining the Department of Radiation Oncology of New York University School of Medicine in 2008. In 2015, she joined UCSF as Professor and Vice Chair of Research i the Department of Radiation Oncology. The Barcellos-Hoff laboratory studies breast cancer, mammary biology radiation carcinogenesis, and mechanisms to biologically augment radiotherapy and is also interested in application of systems biology approaches to problems in radiation research.



Francis A. Cucinotta, PhD: AGAINST

Dr. Francis A. Cucinotta is a Professor of Health Physics at the University of Nevada, Las Vegas. Dr. Cucinotta received his Doctorate degree in nuclear physics from Old Dominion University in 1988. He worked at NASA Johnson Space Center from 1997-2013 as the Radiological Health Officer, Space Radiation Project Manager and Chief Scientist. He developed the astronaut exposure data base of organ doses and cancer risk estimates for all human missions from Mercury to the International Space Station (ISS). He was NASA's manager for construction and operations of the NASA Space Radiation Laboratory (NSRL) from 1999-2013. Dr. Cucinotta worked on radiation safety in NASA's Mission Control Center for the Space Shuttle and ISS programs in 1989-1990, and 2000-2006. He has published over 350 peer-reviewed journal articles in a broad range of topical areas, including nuclear and space physics, track structure, biophysics models of DNA damage repair and neuronal effects, biodosimetry, radiation cataracts, and risk assessment models for cancer and acute health effects. Dr. Cucinotta is a past President of the Radiation Research Society (2013-2014), and a Council Member of the National Council of Radiation Protection and Measurements (NCRP).



PLEASE NOTE: All areas of the meeting are being recorded and photographed. If you wish to opt-out of videos/photos, please visit the registration desk. You may also review all photographs and request removal at www.radres.org/photo.

Issues

Linearity in radiation protection

History of the LNT in the ICRP

[ICRP Publication 1, 1959]

(61) On the **assumption that the genetic effects are linearly related to the gonad dose** and **provided that no threshold dose exists**, it is possible to define a population dose average that is relevant to the assessment of genetic injury to the whole population. In the case of **somatic effects** no such dose can easily be defined although the annual per capita dose to certain tissues or to the whole body **may be relevant on the assumption of a non-threshold, linear dose-effect relation**.

History of the LNT in the ICRP

[ICRP Publication 9, 1966]

(7) **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. Also, 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 in the ICRP

[ICRP Publication 60, 1990]

(72) The simplest relationship between an increment in equivalent dose and the resulting increment in the probability of a defined stochastic effect is that of a **straight line through the origin**. The human epidemiological data are not sufficiently precise to confirm or exclude that relationship.

(74) …The Commission has decided to reduce by a factor of 2 the probability coefficients obtained directly from observations at high doses and high dose rates … The reduction factor is called by the Commission the **Dose and Dose Rate Effectiveness Factor,** DDREF. It has been included in the probability coefficients for all equivalent doses resulting from absorbed doses below 0.2 Gy and from higher absorbed doses when the dose rate is less than 0.1 Gy per hour.

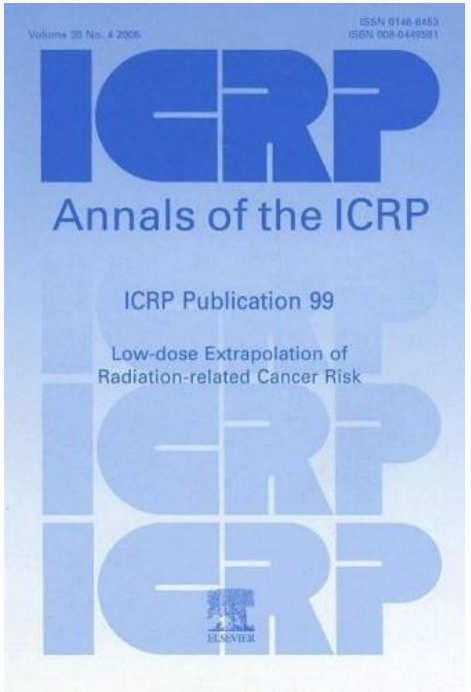
History of the LNT in the ICRP

[ICRP Publication 99, 2005]

Extrapolation of risk estimates based on epidemiological observations at moderate to high doses continues to be the primary basis for estimation of radiation-related risk at low doses and dose rates.

Although there are intrinsic **uncertainties** at low doses and low dose rates, direct epidemiological measures of radiation cancer risk necessarily reflect all mechanistic contributions including those from induced genomic instability, bystander effects, and, in some cases, adaptive responses, and therefore may provide insights about these contributions.

The report concludes that while existence of a low-dose threshold does not seem to be unlikely for radiation-related cancers of certain tissues, the **evidence does not favour the existence of a universal threshold**. The **LNT hypothesis, combined with an uncertain DDREF** for extrapolation from high doses, remains a prudent basis for radiation protection at low doses and low dose rates.



History of the LNT in the ICRP

[ICRP Publication 103, 2007]

(36) At radiation doses below around 100 mSv in a year, the increase in the incidence of stochastic effects is assumed by the Commission to occur with a small probability and in proportion to the increase in radiation dose over the background dose.

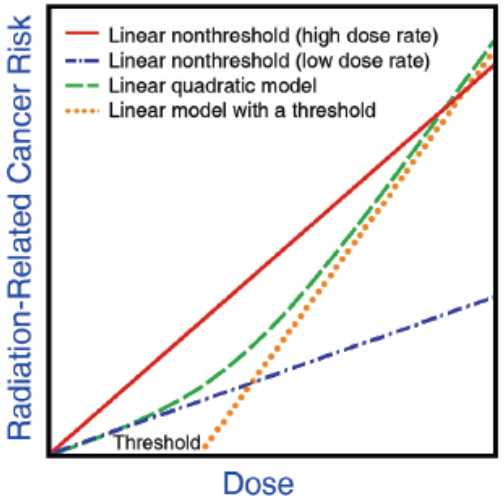
(65) …the practical system of radiological protection recommended by the Commission will continue to be based upon the assumption that at doses below about 100 mSv **a given increment in dose will produce a directly proportionate increment in the probability of incurring cancer** or heritable effects attributable to radiation. This dose-response model is generally known as 'linear-non-threshold' or **LNT**. …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

Linearity in epidemiology

NCRP COMMENTARY No. 27

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



National Council on Radiation Protection and Measurements

NCRP Commentary n°27 (April 2018)

NCRP Scientific Committee 1-25

Shore RE, Beck HL, Boice JD, Caffrey EA, Davis S, Grogan HA, Mettler FA, Preston RJ, Till JE, Wakeford R, Walsh L, Dauer LT.
Implications of recent epidemiologic studies for the linear nonthreshold model and radiation protection.
J Radiol Prot. 2018 Sep;38(3):1217-1233.

NCRP Commentary n°27: Experts

NCRP SC 1-25

R Shore, chair

L Dauer, co-chair

H Beck

E Caffrey

S Davis

R Hyer

F Mettler

J Preston

J Till

R Wakeford

L Walsh

NCRP Commentary n°27: Methodology

Selection of studies

- 29 recent (<10y) studies or group of studies: LSS + LD/LDR studies (occupational, medical, environmental)
- + studies of in utero exposure, specific cancer sites, non-cancer outcomes

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, consideration of non-linear alternatives…)

Overall evaluation of the support to LNT

- Composite of specific strengths and weaknesses identified in the epidemiologic, dosimetric and statistical critiques
- How supportive of the LNT model are the risk coefficient and the dose-response shape?

NCRP Commentary n°27: Results

	Studies (or groups of studies)
1	Life Span Study (LSS), Japan atomic bombs [Grant 2017]
2	INWORKS (UK, US, French combined cohorts) [Richardson 2015]
3	Tuberculosis fluoroscopic examinations and breast cancer [Little 2003]
4	Childhood Japan atomic bomb exposure [Preston 2008]
5	Childhood thyroid cancer studies [Lubin 2017]
6	Mayak nuclear workers [Sokolnikov 2015]
7	Chernobyl fallout, Ukraine and Belarus thyroid cancer [Brenner 2011]
8	Breast cancer studies, after childhood exposure [Eidemuller 2015]
9	In utero exposure, Japan atomic bombs [Preston 2008]
10	Techa River, nearby residents [Schonfeld 2013]
11	In utero exposure, medical [Wakeford 2008]
12	Japan nuclear workers [Akiba 2012]
13	Chernobyl cleanup workers, Russia [Kascheev 2015]
14	US radiologic technologists [Preston 2016]
15	Mound nuclear workers [Boice 2014]
16	Rocketdyne nuclear workers [Boice 2011]
17	French uranium processing workers [Zhivin 2016]
18	Medical x-ray workers, China [Sun 2016]
19	Taiwan radiocontaminated buildings, residents [Hsieh 2017]
20	Background radiation levels and childhood leukemia [Kendall 2013]
21	In utero exposures, Mayak and Techa [Akleyev 2016]
22	Hanford ^{131}I fallout study [Davis 2004]
23	Kerala, India, high natural background radiation area [Nair 2009]
24	Canadian worker study [Zablotska 2014]
25	US atomic veterans [Caldwell 2016]
26	Yangjiang, China, high natural background radiation area [Tao 2012]
27	CT examinations of young persons [Pearce 2012]
28	Childhood medical x rays and leukemia (aggregate of >10 studies) [Wakeford 2008]
29	Nuclear weapons test fallout studies (aggregate of eight studies) [Lyon 2006]

NCRP Commentary n°27: Results

	Studies (or groups of studies)	Epidemiology	Dosimetry	Statistics
1	Life Span Study (LSS), Japan atomic bombs [Grant 2017]	**3**	**3**	**3**
2	INWORKS (UK, US, French combined cohorts) [Richardson 2015]	**3**	**3**	**3**
3	Tuberculosis fluoroscopic examinations and breast cancer [Little 2003]	**3**	**3**	2
4	Childhood Japan atomic bomb exposure [Preston 2008]	**3**	**3**	**3**
5	Childhood thyroid cancer studies [Lubin 2017]	**3**	**3**	**3**
6	Mayak nuclear workers [Sokolnikov 2015]	2	2	**3**
7	Chernobyl fallout, Ukraine and Belarus thyroid cancer [Brenner 2011]	**3**	2	2
8	Breast cancer studies, after childhood exposure [Eidemuller 2015]	2	**3**	**3**
9	In utero exposure, Japan atomic bombs [Preston 2008]	2	**3**	**3**
10	Techa River, nearby residents [Schonfeld 2013]	2	2	2
11	In utero exposure, medical [Wakeford 2008]	1	2	2
12	Japan nuclear workers [Akiba 2012]	2.5	2	3
13	Chernobyl cleanup workers, Russia [Kascheev 2015]	1	1.5	2
14	US radiologic technologists [Preston 2016]	1	2	2
15	Mound nuclear workers [Boice 2014]	2	1.5	1.5
16	Rocketdyne nuclear workers [Boice 2011]	2	2	2
17	French uranium processing workers [Zhivin 2016]	2.5	**3**	1.5
18	Medical x-ray workers, China [Sun 2016]	1.5	1.5	2
19	Taiwan radiocontaminated buildings, residents [Hsieh 2017]	2	1.5	1.5
20	Background radiation levels and childhood leukemia [Kendall 2013]	1.5	2	2
21	In utero exposures, Mayak and Techa [Akleyev 2016]	1	1.5	2
22	Hanford ^{131}I fallout study [Davis 2004]	2	**3**	1.5
23	Kerala, India, high natural background radiation area [Nair 2009]	2	2	1.5
24	Canadian worker study [Zablotska 2014]	2.5	**3**	**3**
25	US atomic veterans [Caldwell 2016]	**3**	**3**	**3**
26	Yangjiang, China, high natural background radiation area [Tao 2012]	1.5	1	1
27	CT examinations of young persons [Pearce 2012]	1	1.5	1.5
28	Childhood medical x rays and leukemia (aggregate of >10 studies) [Wakeford 2008]	1	2	1.5
29	Nuclear weapons test fallout studies (aggregate of eight studies) [Lyon 2006]	1.5	1	1.5

1 Weak
2 Moderate
3 Strong

NCRP Commentary n°27: Results

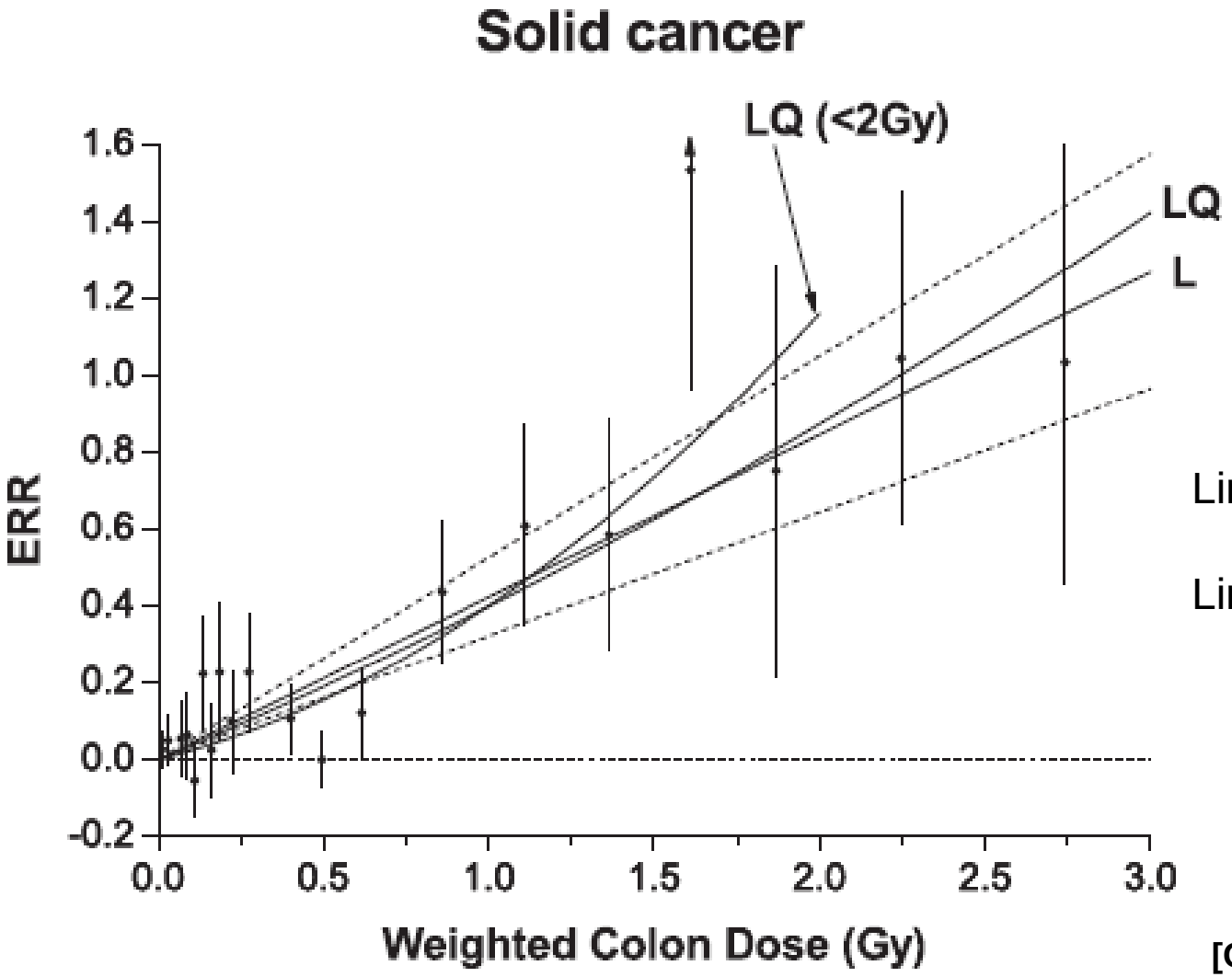
Quality evaluation

- 20 (69 %) of the studies had no component on which they were scored as weak.
- 14 (48 %) of the studies were scored moderate to strong on all three components of evaluation.

NCRP Commentary n°27: Results

	Studies (or groups of studies)	Epidemiology	Dosimetry	Statistics	Support for LNT model
1	Life Span Study (LSS), Japan atomic bombs [Grant 2017]	**3**	**3**	**3**	**Strong**
2	INWORKS (UK, US, French combined cohorts) [Richardson 2015]	**3**	**3**	**3**	**Strong**
3	Tuberculosis fluoroscopic examinations and breast cancer [Little 2003]	**3**	**3**	2	**Strong**
4	Childhood Japan atomic bomb exposure [Preston 2008]	**3**	**3**	**3**	**Strong**
5	Childhood thyroid cancer studies [Lubin 2017]	**3**	**3**	**3**	**Strong**
6	Mayak nuclear workers [Sokolnikov 2015]	2	2	**3**	**Moderate**
7	Chernobyl fallout, Ukraine and Belarus thyroid cancer [Brenner 2011]	**3**	2	2	**Moderate**
8	Breast cancer studies, after childhood exposure [Eidemuller 2015]	2	**3**	**3**	**Moderate**
9	In utero exposure, Japan atomic bombs [Preston 2008]	2	**3**	**3**	**Moderate**
10	Techa River, nearby residents [Schonfeld 2013]	2	2	2	**Moderate**
11	In utero exposure, medical [Wakeford 2008]	1	2	2	**Moderate**
12	Japan nuclear workers [Akiba 2012]	2.5	2	3	**Weak-to-moderate**
13	Chernobyl cleanup workers, Russia [Kascheev 2015]	1	1.5	2	**Weak-to-moderate**
14	US radiologic technologists [Preston 2016]	1	2	2	**Weak-to-moderate**
15	Mound nuclear workers [Boice 2014]	2	1.5	1.5	**Weak-to-moderate**
16	Rocketdyne nuclear workers [Boice 2011]	2	2	2	**Weak-to-moderate**
17	French uranium processing workers [Zhivin 2016]	2.5	**3**	1.5	**Weak-to-moderate**
18	Medical x-ray workers, China [Sun 2016]	1.5	1.5	2	**Weak-to-moderate**
19	Taiwan radiocontaminated buildings, residents [Hsieh 2017]	2	1.5	1.5	**Weak-to-moderate**
20	Background radiation levels and childhood leukemia [Kendall 2013]	1.5	2	2	**Weak-to-moderate**
21	In utero exposures, Mayak and Techa [Akleyev 2016]	1	1.5	2	No support
22	Hanford ^{131}I fallout study [Davis 2004]	2	**3**	1.5	No support
23	Kerala, India, high natural background radiation area [Nair 2009]	2	2	1.5	No support
24	Canadian worker study [Zablotska 2014]	2.5	**3**	**3**	No support
25	US atomic veterans [Caldwell 2016]	**3**	**3**	**3**	No support
26	Yangjiang, China, high natural background radiation area [Tao 2012]	1.5	1	1	Inconclusive
27	CT examinations of young persons [Pearce 2012]	1	1.5	1.5	Inconclusive
28	Childhood medical x rays and leukemia (aggregate of >10 studies) [Wakeford 2008]	1	2	1.5	Inconclusive
29	Nuclear weapons test fallout studies (aggregate of eight studies) [Lyon 2006]	1.5	1	1.5	Inconclusive

A-Bomb survivors: Solid cancer excess relative risk



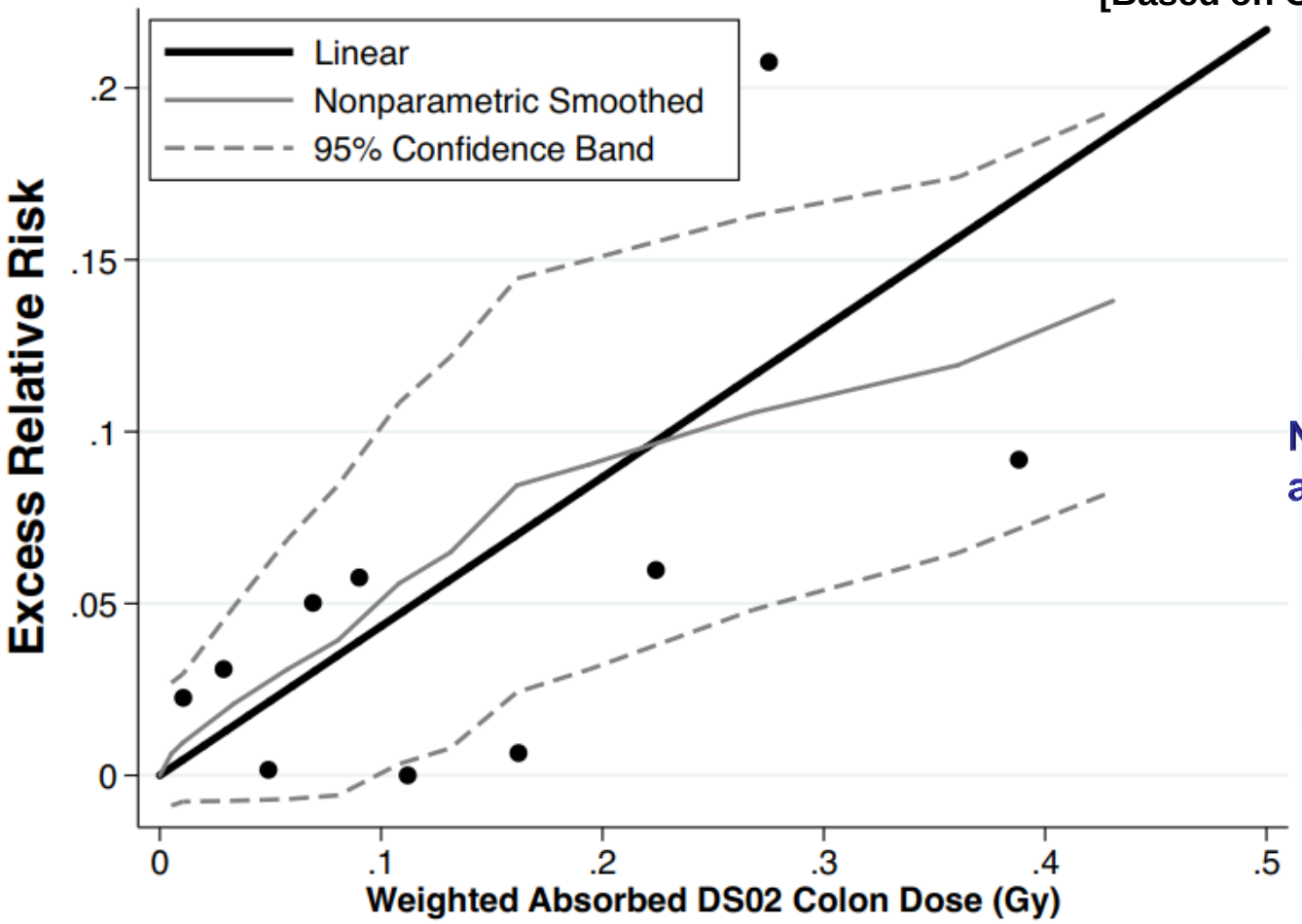
Linear: β=0.42

Linear-Quadratic <2Gy:
β=0.22
β^2=0.18

[Ozasa et al, Rad Res 2012]

A-Bomb survivors: Solid cancer excess relative risk on the 0-500 mGy dose range

[Based on Ozasa et al, Rad Res 2012]



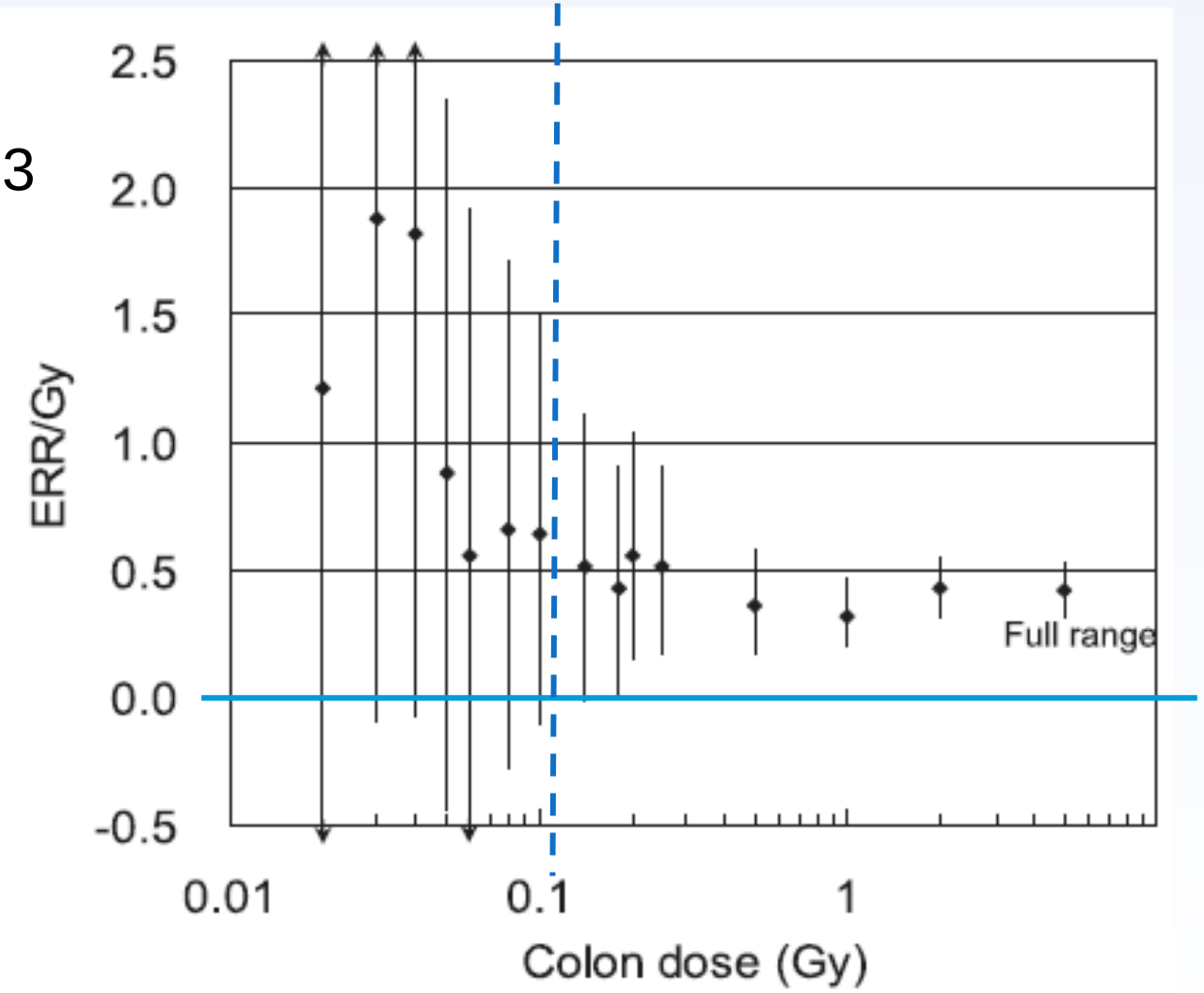
LSS Solid Cancer Mortality 1950-2003

Linear and Nonparametric Curves at Doses of 0 to 0.5 Gy

A-Bomb survivors: Solid cancer excess relative risk on restricted dose range

Mortality
Follow-up 1950-2003

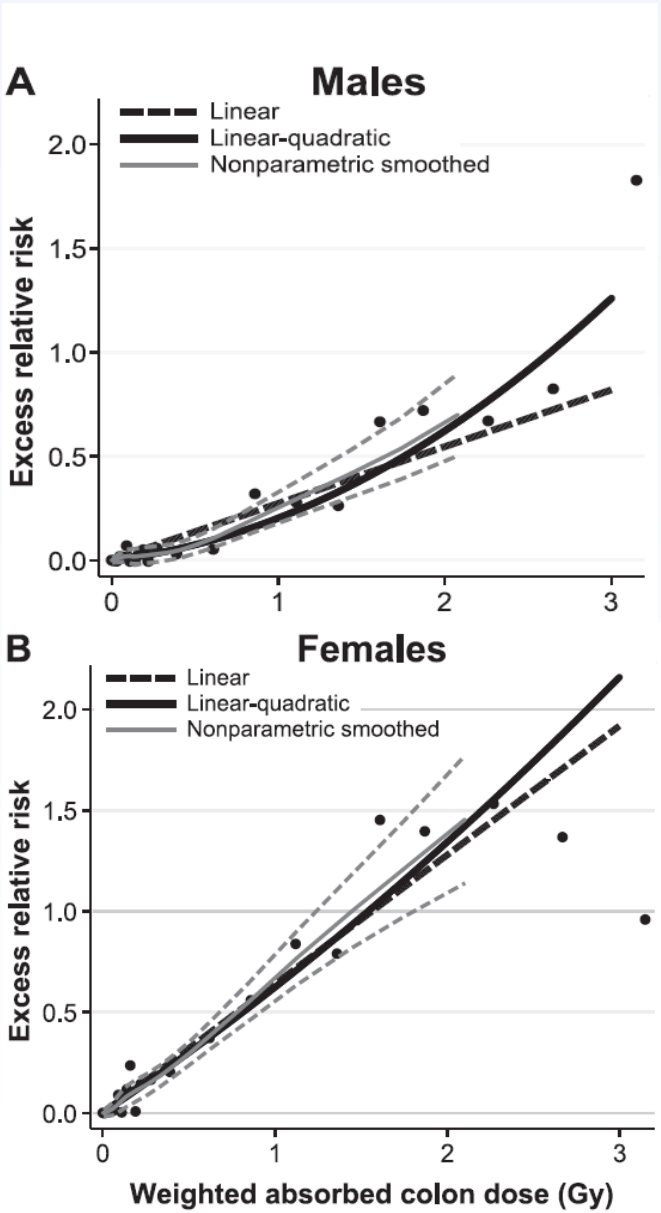
Linear ERR model on restricted dose range



[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

β=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)

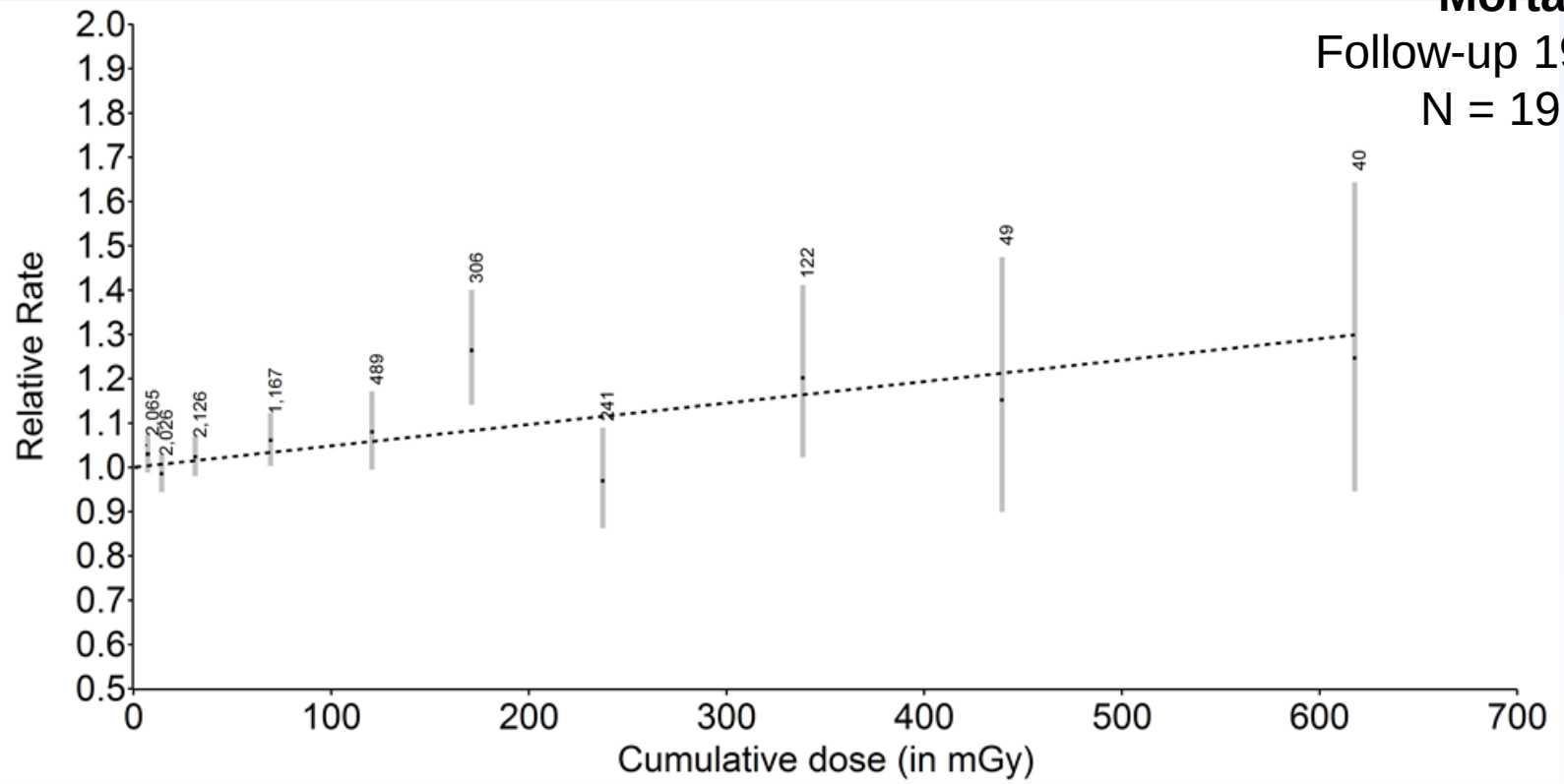
males (P = 0.49; estimate 750 mGy; upper 800 mGy).

ERR/Gy at attained age of 70 years after exposure at age 30 years, adjusted for smoking

INWORKS: Relative Risk per Gy for cancer excluding leukemia

[Richardson et al, BMJ 2015]

Mortality
Follow-up 1944-2005
N = 19,064



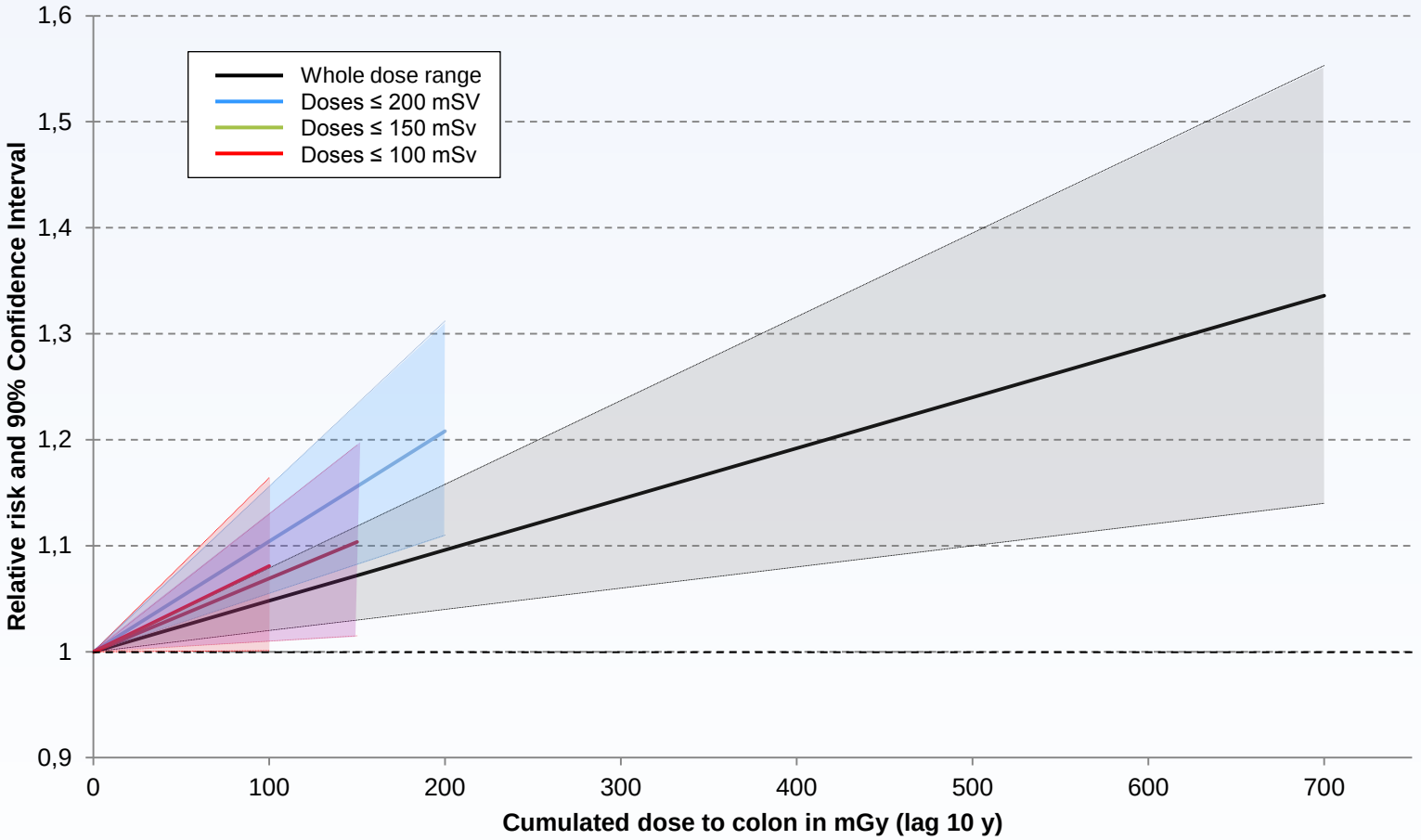
ERR per Gy = 0.48 ; 90%CI [0.20 – 0.79]

No indication of non linearity

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 Richarson et al. BMJ 2015]



Linear trend still borderline significant when cumulative doses above 100 mSv were excluded

NCRP Commentary n°27: Results

Evaluations of Consistency with the LNT Model

- Strong support – 5 (17%) (LSS, INWORKS, TB fluroscopy)
- Moderate support – 6 (21%) (Mayak, Chernobyl thyroid K, Techa)
- Weak-to-Moderate support – 9 (31%) (Chernobyl clean-up workers, Taiwan buildings)
- No support – 5 (17%) (Kerala)
- Inconclusive – 4 (14%) (childhood CT-scan, Yangjiang, nuclear test fallout)

- Most of the larger, stronger studies broadly supported an LNT model.
- The 9 studies (31 %) that provided no support for the LNT model either had a totally null dose response (*i.e.*, the slope was negative or close to zero) or had data considered unreliable and inconclusive.

NCRP Commentary n°27: Conclusions

Is the LNT Model Appropriate for Assessing Cancer Risk for Purposes of Radiation Protection?

- LDR study-size constraints, dose uncertainties and epidemiological weaknesses limit the statistical power and precision of risk estimates, especially for data below 100 mGy.
- Preponderance of LDR studies showed reasonable consistency with LNT for total solid cancer and evidence of risk for leukemia, but some individual 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 LDR 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.**

(Courteously provided by R Shore)

NCRP Commentary n°27: Future improvements

- Examine the generality of the LNT model across tumor sites
- Extend cohorts follow-up
- Update information on cancer risk among those exposed *in utero* or in early childhood
- Improve dose reconstruction and consider uncertainties
- Control for possible confounding by lifestyles
- Use banks of blood and tissue samples to identify bioindicators of adverse outcome pathways (AOPs) that mediate between radiation and disease development

NCRP Commentary n°27: Strengths and Limitations

Strengths

- Comprehensive review
- Systematic evaluation criteria

Limitations

- Limited to external exposure
- Criteria for selection of the studies
  - Could have merit more detailed justification
  - Some studies considered as a group (childhood CT-scans, fallout studies…)
- Mix of different characteristics in the same table (in utero exposure, specific outcome…)
- Overestimation of the importance of potential biases

Since the NCRP report

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

Mark P Little, Richard Wakeford, David Borrego, Benjamin French, Lydia B Zablotska, M Jacob Adams, Rodrigue Allodji, Florent de Vathaire, Choonsik Lee, Alina V Brenner, Jeremy S Miller, David Campbell, Mark S Pearce, Michele M Doody, Erik Holmberg, Marie Lundell, Siegal Sadetzki, Martha S Linet*, Amy Berrington de González*

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 excl 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."**

Since the NCRP report

Cancer mortality and incidence following external occupational radiation exposure: an update of the 3rd analysis of the UK national registry for radiation workers

Richard G. E. Haylock[1], Michael Gillies[1], Nezahat Hunter[1], Wei Zhang[1] and Mary Phillipson[1]

BJC British Journal of Cancer

BJC, August 2018

- 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 excl leukemia

Since the NCRP report

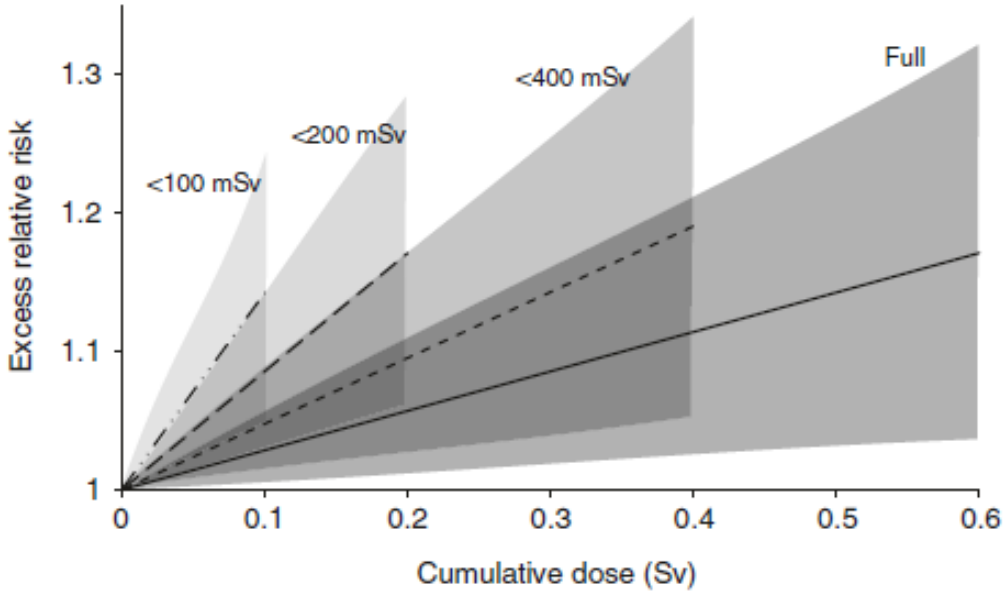
Cancer mortality and incidence following external occupational radiation exposure: an update of the 3rd analysis of the UK national registry for radiation workers

Richard G. E. Haylock[1], Michael Gillies[1], Nezahat Hunter[1], Wei Zhang[1] and Mary Phillipson[1]

BJC British Journal of Cancer

BJC, August 2018

- 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"

In preparation

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

EPI-CT

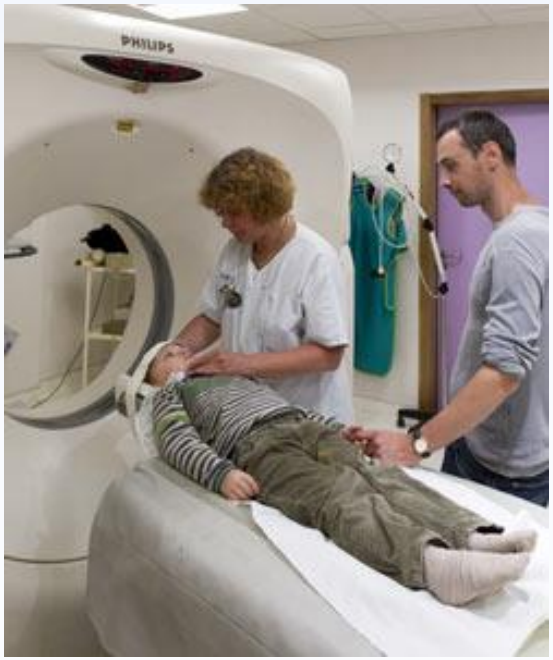
the International Pediatric CT-scan study

International Agency Research on Cancer

World Health Organization

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

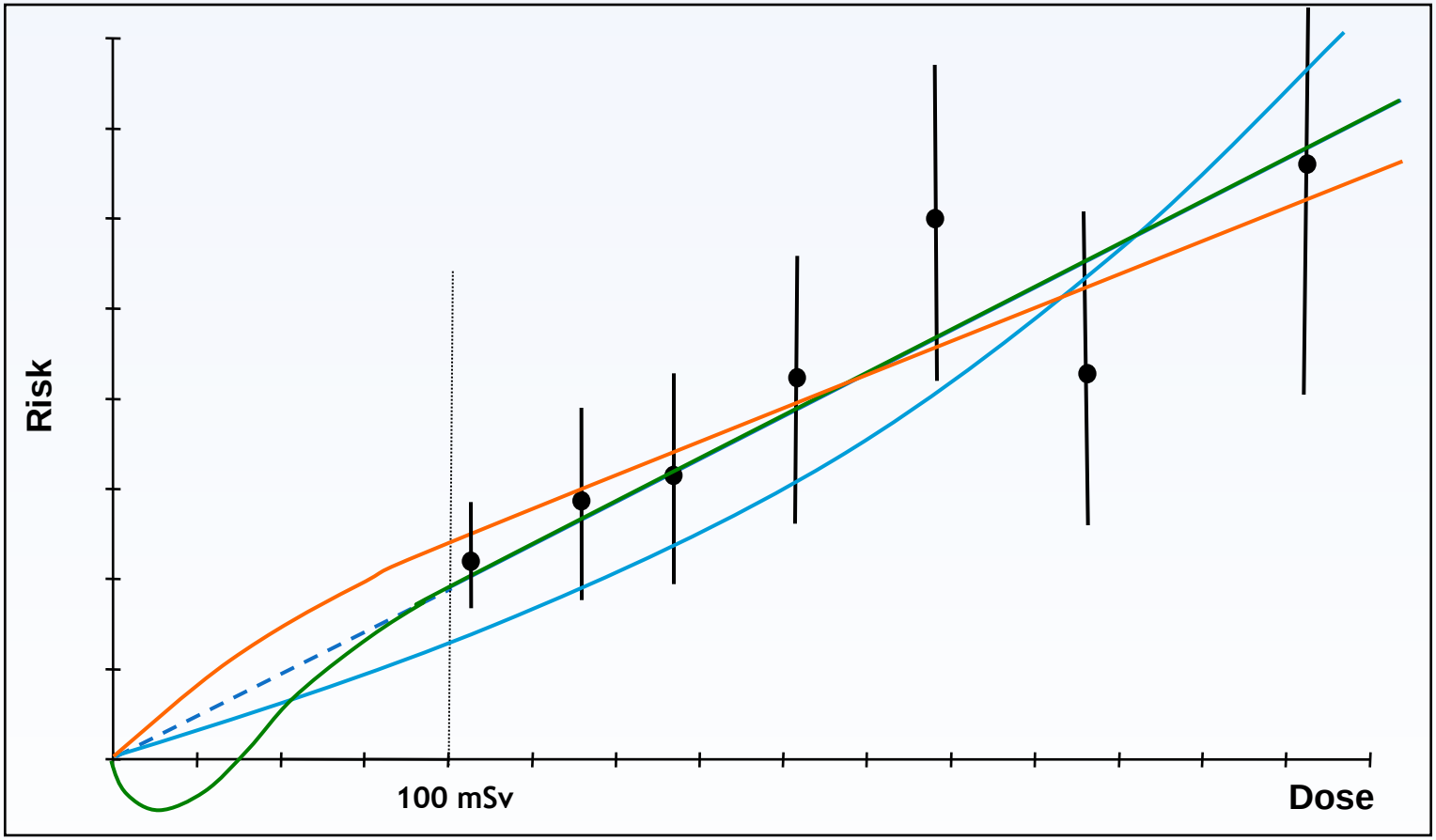
- Cohort profile [Bernier et al. Int J Epidemiol 2018]
- Analysis of the risk of leukemia and solid cancers in association with repeated doses delivered by CT-scan examinations in childhood – **publication in 2019**

Conclusion and perspectives: Epidemiological evidence

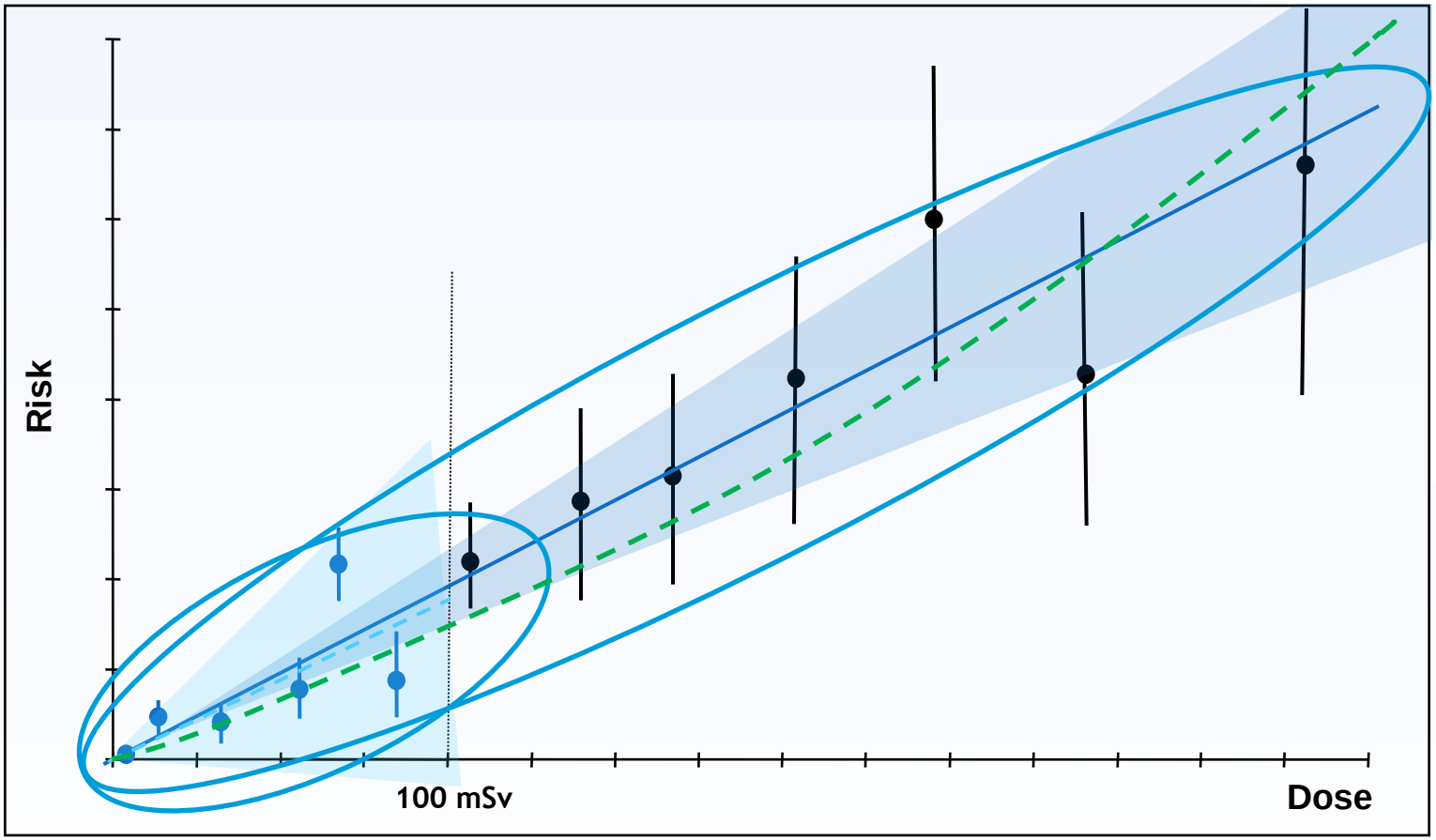
- Strong reinforcement of the epidemiological evidence of a risk of cancer related to dose at low levels of exposure in the last decade
- Questions on the linearity, but no evidence of a threshold
- Still some limitations (external exposure, modifying effect of sex, age and time since exposure, variation between cancer sites…)
- Additional results to come in the near future (LSS, Inworks, MWS, Epi-CT, NCI review on sources of bias)

- Does not solve the controversies between biology and epidemiology

Quantifying the dose-risk relationship at low dose



Quantifying the dose-risk relationship at low dose



Issues

Linearity and risk assessment

Cancer risk assessment outside of the radiation field

[U.S. EPA.. Guidelines for Carcinogen Risk Assessment. 2005]

The procedures used to extrapolate from high to low levels of exposure are different for assessment of carcinogenic effects and non-carcinogenic effects

- Noncarcinogenic effects (e.g. neurotoxicity) are considered to have dose thresholds below which the effect does not occur. The lowest dose with an effect in animal or human studies is divided by Safety Factors to provide a margin of safety.
- **Carcinogenic effects are not considered to have a threshold** and mathematical models are generally used to provide estimates of carcinogenic risk at very low dose levels.

Cancer risk assessment outside of the radiation field

[U.S. EPA.. Guidelines for Carcinogen Risk Assessment. 2005]

- Under the guidelines, linear extrapolation is appropriate when the evidence supports the mode of action of gene mutation due to direct DNA reactivity or another mode of action that is thought to be linear in the low dose region.
- A linear mode of action will also be the approach when available evidence is not sufficient to support a nonlinear extrapolation procedure, even in the absence of evidence of DNA reactivity.
- Nonlinear methods are to be used if there is sufficient evidence to support a nonlinear mode of action.

A linear no-threshold relationship is considered for most carcinogens
(many chemicals, diesel exhausts, heavy metals, alcohol…)

Health Risk Assessment: underlying hypotheses

Transposition: the relationship is valid in another population than the source population

(sex, lifetime risk, transfer weights)

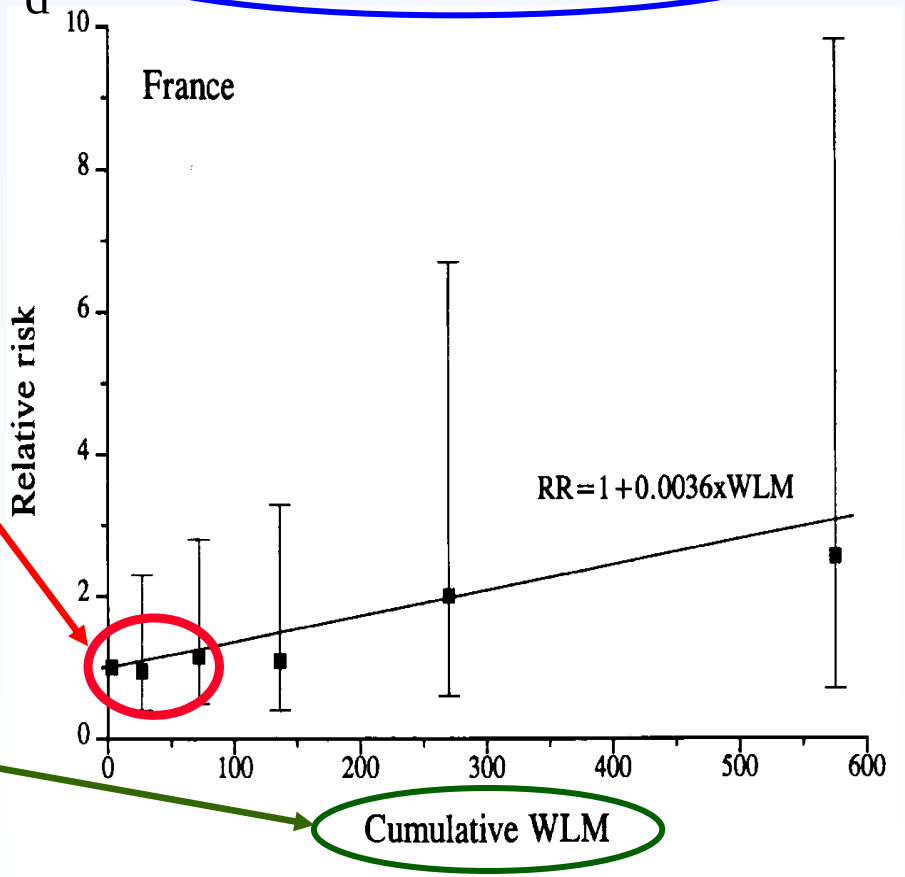
Extrapolation: the relationship is valid outside of the range of exposure of the source population

(LNT, LDEF)

Analogy: the relationship is valid for other type/pattern of exposure than that of the source population

(DREF, additivity, W_R, W_T)

French Uranium miner cohort



Conclusion and perspectives: Use in risk assessment / protection

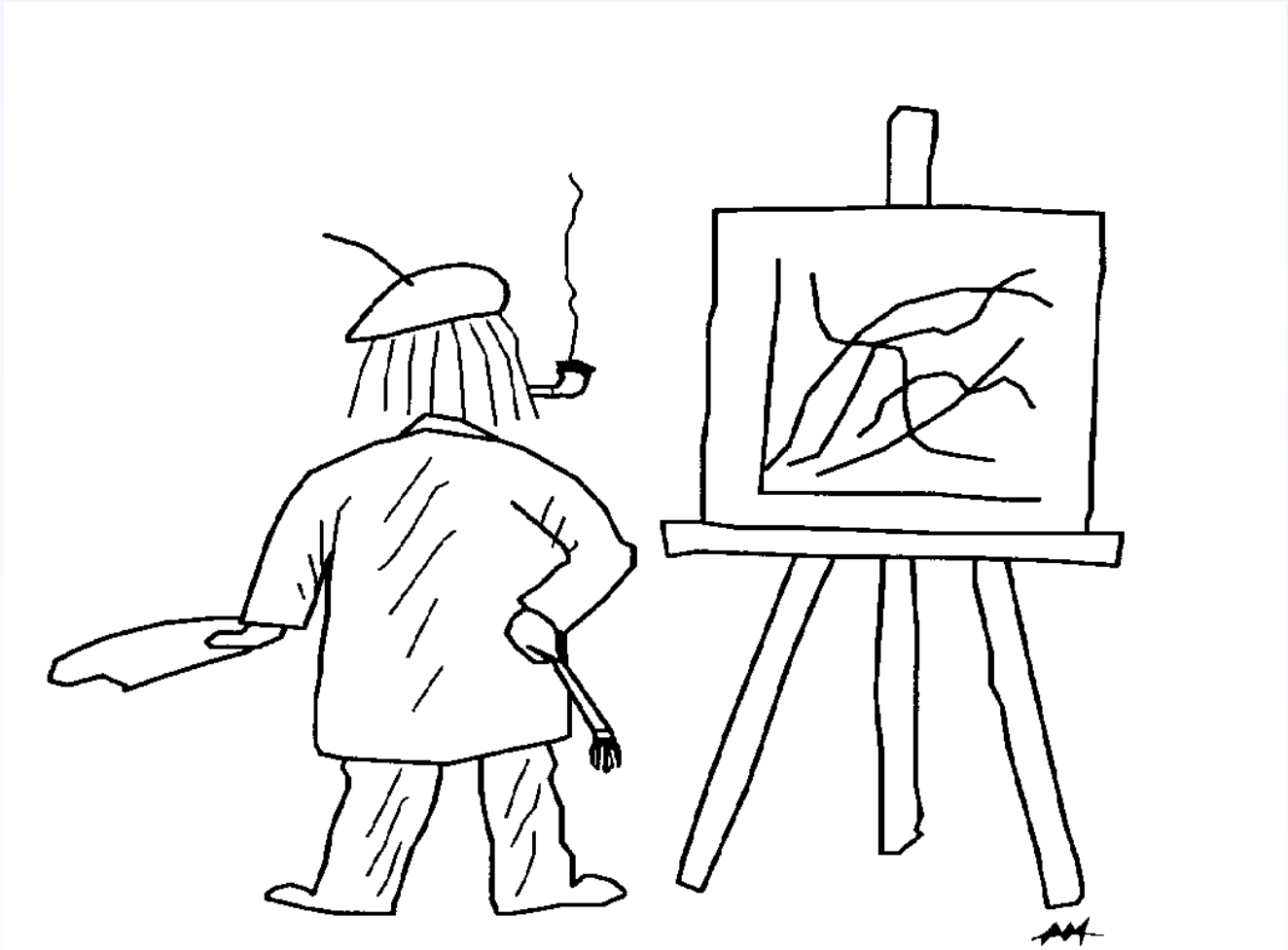
- **The LNT hypothesis is not a specificity of the radiation field**
- **LNT is one of the major hypothesis underlying the calculation of Detriment (but not the only one)**
- **Is it a prudent or a realistic hypothesis ?**

Acknowledgements

- **R Shore for kindly providing me a copy of his slides on the NCRP report**

- **L Vaillant for his help in the reconstruction of the history of the LNT**

"Which line do you like best ?"



“All models are wrong but some are useful"

(Box GEP, 1979)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