Response to Calabrese and Selby "Mistakes discovered: Cancer risk assessment challenged"

Mark P Little Adjunct Professor Northwestern University, Evanston, IL, USA / Oxford Brookes University, Oxford, UK

Elizabeth Ainsbury Head of Radiation Effects Department Radiation Effects Department Radiation, Chemical, Climate and Environmental Hazards Directorate UK Health Security Agency, UK

Sally A Amundson Professor of Radiation Oncology Columbia University Irving Medical Center, Columbia University, New York, NY, USA

Jonine L Bernstein Attending Epidemiologist Memorial Sloan Kettering Cancer Center, New York, NY, USA

John D Boice Research Professor of Medicine Vanderbilt University Medical Center, Nashville, TN, USA

Simon D Bouffler Deputy Director of Radiation Radiation Effects Department, Radiation, Chemical, Climate and Environmental Hazards Directorate, UK Health Security Agency, UK

Francis A Cucinotta Professor University of Nevada Las Vegas, Las Vegas NV, USA

Won Jin Lee Professor Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea

Frank de Vocht Professor in Epidemiology and Public Health Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

Markus Eidemüller Scientist Federal Office for Radiation Protection, 85674 Oberschleissheim, Germany

Dale L Preston Principal Scientist Hirosoft International, LLC, CA, USA

Nobuyuki Hamada Senior Research Scientist Biology and Environmental Chemistry Division, Sustainable System Research Laboratory, Central Research Institute of Electric Power Industry (CRIEPI), Chiba, Japan

M Prakash Hande Associate Professor Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Tom K Hei Professor Soochow University, Suzhou, Jiangsu, China 215123

Werner Rühm Professor, Head of Department Federal Office for Radiation Protection, 85674 Oberschleissheim, Germany

Dominique Laurier Deputy Head Nuclear Safety and Radiation Protection Authority (ASNR), France

Andrzej Wojcik Professor MBW Department, Stockholm University, Stockholm, Sweden

Gayle E Woloschak Associate Director for Research, Department of Radiation Oncology Northwestern University, Evanston, IL, USA

Response to Calabrese and Selby "Mistakes discovered: Cancer risk assessment challenged"

Mark P Little Northwestern University, Evanston, IL, USA / Oxford Brookes University, Oxford, UK 1

Elizabeth Ainsbury Radiation Effects Department, Radiation, Chemical, Climate and Environmental Hazards Directorate, UK Health Security Agency, UK

Isaf Al-Nabulsi Retired scientist, Germantown, MD, USA

Sally A Amundson Columbia University Irving Medical Center, Columbia University, New York, NY, USA

Edouard I Azzam Department of Radiology, Rutgers New Jersey Medical School, Newark, NJ 07103, USA

Christophe Badie Radiation Effects Department, Radiation, Chemical, Climate and Environmental Hazards Directorate, UK Health Security Agency, UK

Oleg V Belyakov International Atomic Energy Agency, Vienna, Austria

Jonine L Bernstein Memorial Sloan Kettering Cancer Center, New York, NY, USA

John D Boice, Jr Vanderbilt University Medical Center, Nashville, TN, USA

Simon D Bouffler Radiation Effects Department, Radiation, Chemical, Climate and Environmental Hazards Directorate, UK Health Security Agency, UK

Francis A Cucinotta University of Nevada Las Vegas, Las Vegas NV, USA

Harry M Cullings Pittsburgh, PA, USA

Frank de Vocht Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

Markus Eidemüller Federal Office for Radiation Protection, 85674 Oberschleissheim, Germany

Eric J Grant Hirosoft International, LLC, CA, USA

Nobuyuki Hamada Biology and Environmental Chemistry Division, Sustainable System Research Laboratory, Central Research Institute of Electric Power Industry (CRIEPI), Chiba, Japan

M Prakash Hande Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Tom K Hei Soochow University, Suzhou, Jiangsu, China 215123

Kathryn D Held Mass General Brigham / Harvard Medical School, Cambridge, MA, USA

Munira Kadhim School of Biological and Medical Sciences, Faculty of Health, Science and Technology, Oxford Brookes University, Oxford, UK

J Christian Kaiser Federal Office for Radiation Protection, 85674 Oberschleissheim, Germany

Gerald M Kendall Nuffield Department of Population Health, University of Oxford, Old Road Campus, Oxford, UK

Amy Kronenberg USA

Dominique Laurier Nuclear Safety and Radiation Protection Authority (ASNR), France

Won Jin Lee Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea

Harald Paganetti Massachusetts General Hospital & Harvard Medical School, Cambridge, MA, USA

David Pawel CA, USA

Dale Preston Hirosoft International, LLC, CA, USA

James C Root Memorial Sloan Kettering Cancer Center, Professor of Psychology in Psychiatry, Weill Cornell Medical College, NY, USA

Werner Rühm Federal Office for Radiation Protection, 85674 Oberschleissheim, Germany

Dorthe Schaue David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA

Roy E Shore New York University Grossman School of Medicine, New York, NY, USA

Graham Smith Clemson University, Clemson, SC, USA

Brock Sishc Mayo Clinic at Florida, Jacksonville, FL, USA

Samantha Y A Terry School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK

Robert L Ullrich Columbia University Irving Medical Center, Columbia University, New York, NY, USA

Ludovic Vaillant CEPN, Fontenay-aux-Roses, France

Richard Wakeford University of Manchester, Manchester, UK

Jacqueline P Williams University of Rochester, NY, USA

Andrzej Wojcik MBW Department, Stockholm University, Stockholm, Sweden

Lydia Zablotska Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco (UCSF), San Francisco, CA, USA

Gayle E Woloschak Northwestern University, Evanston, IL, USA

1to whom all correspondence should be addressed, via email: mark.little.icl@gmail.com, tel +44 77 257 22992

We read with considerable concern the letter of Calabrese and Selby (1). They incorrectly claim that the data of W. L. Russell (2) submitted to the BEAR Genetics Committee (3) forms the basis of the linear-no threshold (LNT) model currently used for radiation protection. In fact, the LNT model is not based on hereditary genetic analyses but primarily informed by human epidemiologic data (4) supported by radiobiological evidence (5), in addition to societal considerations (as further outlined below). There is a solid body of biological and epidemiological data supporting the current radiation protection assumption of linearity for all solid cancers combined in a population exposed at low doses or low dose rates, as summarized in recent reviews (4, 6-10). In particular there is direct evidence of excess risk of leukemia and thyroid cancer following exposure to doses less than 100 mGy in childhood (11, 12), and for solid cancers in the dose range from 0-100 mGy in the Japanese atomic bomb survivors (13) and in groups of nuclear workers (14, 15). These findings are consistent with risks that have been extrapolated from higher dose epidemiological data. While there are epidemiological data suggesting a moderate degree of curvature in the dose response for solid cancer at relatively low doses (6, 13, 16), there is little or no evidence for a threshold dose. A review by UNSCEAR on biological mechanisms found that the dose response of important carcinogenic processes such as mutations and micronuclei are linear in form in the low dose range down to at least 50 and 10 mGy acute doses of sparsely ionizing radiation, respectively (5). UNSCEAR further concluded that an overall threshold for cancer induction is unlikely, and that the mutational mechanism would imply a dose-risk relationship without a threshold (5).

However, it is also important to appreciate that the LNT model was never intended to define the exact biological response to radiation. While it was broadly consistent with much of the data, the LNT model is also based on ethical considerations of prudence (17, 18), to be used for the purpose of radiation protection, i.e., to protect persons exposed to radiation as well as reasonably achievable (19, 20). LNT is a practical way to make use of current scientific evidence to support the safe use of ionizing radiation in society (21). Its origin can be traced back to ICRP Publications 9 (22) and 6 (23). ICRP Publication 9 (the 1965 Recommendations) states: "As the existence of a threshold dose is unknown, it has been assumed that even the smallest doses involve a proportionally 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 [ICRP] sees no practical alternative, to assuming a linear relationship between the dose and effect, and that doses act cumulatively. The Commission [ICRP] is aware that the assumption 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" (22). We judge that, 60 years later, this assessment remains valid. In summary, the LNT model is intended as a prudent approximation for stochastic responses to low doses and/or low dose rates of radiation. While these responses may contain some small or moderate curvature below LNT that cannot be quantified with present scientific methods and data (6, 16), LNT remains the most appropriate model for radiation protection purposes (24).

ACKNOWLEDGMENTS

Author contributions: All authors contributed to the development of the concept and writing of the manuscript. The views expressed in this letter do not necessarily reflect those of the authors' professional affiliations and any committees on which they serve.

Competing interests: The authors declare that they have no competing interests.

References

1. E. J. Calabrese, P. B. Selby, Mistakes discovered: Cancer risk assessment challenged. Science, (eLetter).

2. W. L. Russell, X-ray-induced mutations in mice. Cold Spring Harb Symp Quant Biol 16, 327–336 (1951).

3. W. Weaver et al., Genetic Effects of Atomic Radiation. Science 123, 1157–1164 (1956).

4. National Council on Radiation Protection and Measurements (NCRP), Implications of recent epidemiologic studies for the linear-nonthreshold model and radiation protection. NCRP Commentary no 27., (National Council on Radiation Protection and Measurements (NCRP), Bethesda, MD, USA, 2018), vol. SC 1-27, pp. i–ix + 1–199.

5. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), UNSCEAR 2020/2021 Report. Volume III. Annex C. Biological mechanisms relevant for the inference of cancer risks from low-dose and low-dose-rate radiation. (United Nations, New York, 2021), pp. 1–238.

6. M. P. Little, R. Wakeford, E. J. Tawn, S. D. Bouffler, A. Berrington de Gonzalez, Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do. Radiology 251, 6–12 (2009).

7. A. Berrington de Gonzalez et al., Epidemiological studies of low-dose ionizing radiation and cancer: rationale and framework for the monograph and overview of eligible studies. J. Natl Cancer Inst. Monogr. 2020, 97–113 (2020).

8. M. Hauptmann et al., Epidemiological studies of low-dose ionizing radiation and cancer: summary bias assessment and meta-analysis. J. Natl Cancer Inst. Monogr. 2020, 188–200 (2020).

9. D. Laurier, Y. Billarand, D. Klokov, K. Leuraud, The scientific basis for the use of the linear no-threshold (LNT) model at low doses and dose rates in radiological protection. Journal of Radiological Protection 43, 024003 (2023).

10. W. Rühm, D. Laurier, R. Wakeford, Cancer risk following low doses of ionising radiation – Current epidemiological evidence and implications for radiological protection. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 873, 503436 (2022).

11. J. H. Lubin et al., Thyroid cancer following childhood low-dose radiation exposure: a pooled analysis of nine cohorts. J. Clin. Endocrinol. Metab. 102, 2575–2583 (2017).

12. M. P. Little et al., 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. Lancet Haematol 5, e346–e358 (2018).

13. E. J. Grant et al., Solid cancer incidence among the Life Span Study of atomic bomb survivors: 1958-2009. Radiat. Res. 187, 513–537 (2017).

14. D. B. Richardson et al., Cancer mortality after low dose exposure to ionising radiation in workers in France, the United Kingdom, and the United States (INWORKS): cohort study. BMJ 382, e074520 (2023).

15. J. D. Boice, Jr. et al., Mortality from leukemia, cancer and heart disease among U.S. nuclear power plant workers, 1957-2011. Int J Radiat Biol 98, 657–678 (2022).

16. M. P. Little, N. Hamada, H. M. Cullings, Analysis of Departures from Linearity in the Dose Response for Japanese Atomic Bomb Survivor Solid Cancer Mortality and Cancer Incidence Data and Assessment of Low-Dose Extrapolation Factors. Radiat Res 203, 115–127 (2025).

17. International Commission on Radiological Protection (ICRP), ICRP Publication 138. Ethical foundations of the system of radiological protection. Ann. ICRP 47, 1–65 (2018).

18. A. Wojcik, F. Zölzer, The scientific nature of the linear no-threshold (LNT) model used in the system of radiological protection. Radiat Environ Biophys 63, 483–489 (2024).

19. National Council on Radiation Protection and Measurements (NCRP), NCRP Report No. 136. Evaluation of the linear-nonthreshold dose-response model for ionizing radiation., (National Council on Radiation Protection and Measurements (NCRP). Bethesda, MD, 2001).

20. International Commission on Radiological Protection (ICRP), Low-dose extrapolation of radiation-related cancer risk. ICRP Publication 99. Ann. ICRP 35, 1–140 (2006).

21. M. Schnelzer et al., The linear no-threshold model in radiation protection—the view of the German Federal Office for radiation protection. Journal of Radiological Protection 45, 033001 (2025).

22. International Commission on Radiological Protection (ICRP), ICRP Publication 9. Recommendations of the International Commission on Radiological .Protection Ann. ICRP, i–iv+1–27 (1966).

23. International Commission on Radiological Protection (ICRP), ICRP Publication 6. Recommendations of the International Commission on Radiological .Protection Ann. ICRP, i–v+1–35 (1964).

24. W. Rühm et al., Essentials of the system of radiological protection. Journal of Radiological Protection 45, 033002 (2025).