The Conclusion of the BEIR VII Report Endorsing the Linear No-Threshold Model Is No Longer Valid Due to Advancement of Knowledge

TO THE EDITOR: I read with interest the Invited Perspective by Duncan et al. (*1*), which was in response to the article by Siegel et al. (*2*) criticizing the Biologic Effects of Ionizing Radiation (BEIR) VII report's endorsement of the linear no-threshold (LNT) model for radiation-induced cancer. Duncan et al. stated that the BEIR VII report provided a detailed case against a low-dose threshold, referring to the linearity of dose response in the atomic bomb survivor cancer data. However, the Ozasa et al. update (*3*) to the atomic bomb survivor cancer mortality data has shown significant curvature in the dose–response relationship in the 0–2 Gy range. This curvature is inconsistent with the LNT model but consistent with radiation hormesis (*4*). The Grant et al. update (*5*) to the cancer incidence data of the atomic bomb survivors has also shown significant curvature in the dose–response relationship that would not be consistent with the LNT model. Thus, the main epidemiologic evidence quoted in the BEIR VII report no longer supports the LNT model.

Duncan et al. also stated that a threshold dose could exist only if the repair mechanisms after exposure to low-dose radiation leave no cells harboring DNA mutations. In making such a statement, the authors did not consider the larger amount of DNA damage that occurs due to endogenous causes. Because low-dose radiation enhances defenses such as DNA repair enzymes, there would be reduced endogenous DNA damage in the period after exposure to low-dose radiation (*6*), and the ultimate result would be reduced overall DNA damage and mutations, as has been observed in mice, for example (*7*). Therefore, even though DNA repair mechanism is imperfect, there would be reduction of overall DNA damage after low radiation exposures.

In addition, Duncan et al. did not address the point raised by Siegel et al. (*2*) of the importance of the immune system deficiency as the cause of cancer. For example, with the suppression of the immune system, cancer mortality rate increased nearly 80-fold in young organ-transplant patients (*8*), and cancer incidence rate increased nearly 40-fold in young AIDS patients (*9*). Such data demonstrate the extreme importance of the immune system in preventing cancers. Therefore, low-dose radiation, which has an immune-enhancing effect, would reduce cancers (*10*).

In summary, the atomic bomb survivor data, with the updates, are inconsistent with the LNT model. The arguments presented by Duncan et al. (*1*) for the LNT model are invalid due to incomplete consideration of biologic response to low radiation exposures and the neglect of the importance of the immune system in preventing cancers.

REFERENCES

1. Duncan JR, Lieber MR, Adachi N, Wahl RL. Radiation dose does matter: mechanistic insights into DNA damage and repair support the linear no-threshold model of low-dose radiation health risks. *J Nucl Med.* 2018;59:1014–1016.
2. Siegel JA, Greenspan BS, Maurer AH, et al. The BEIR VII estimates of low-dose radiation health risks are based on faulty assumptions and data analyses: a call for reassessment. *J Nucl Med.* 2018;59:1017–1019.
3. Ozasa K, Shimizu Y, Suyama A, et al. Studies of the mortality of atomic bomb survivors, report 14, 1950–2003: an overview of cancer and noncancer diseases. *Radiat Res.* 2012;177:229–243.
4. Doss M. Linear no-threshold model vs. radiation hormesis. *Dose Response.* 2013; 11:480–497.
5. Grant EJ, Brenner A, Sugiyama H, et al. Solid cancer incidence among the life span study of atomic bomb survivors: 1958–2009. *Radiat Res.* 2017;187:513–537.
6. Pollycove M, Feinendegen LE. Radiation-induced versus endogenous DNA damage: possible effect of inducible protective responses in mitigating endogenous damage. *Hum Exp Toxicol.* 2003;22:290–306.
7. Osipov AN, Buleeva G, Arkhangelskaya E, Klokov D. In vivo gamma-irradiation low dose threshold for suppression of DNA double strand breaks below the spontaneous level in mouse blood and spleen cells. *Mutat Res.* 2013;756:141–145.
8. Acuna SA, Fernandes KA, Daly C, et al. Cancer mortality among recipients of solid-organ transplantation in Ontario, Canada. *JAMA Oncol.* 2016;2:463–469.
9. Biggar RJ, Frisch M, Goedert JJ. Risk of cancer in children with AIDS. AIDS-Cancer Match Registry Study Group. *JAMA.* 2000;284:205–209.
10. Liu SZ. On radiation hormesis expressed in the immune system. *Crit Rev Toxicol.* 2003;33:431–441.

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Challenges to the Paper "Radiation Dose Does Matter: Mechanistic Insights into DNA Damage and Repair Support the Linear No-Threshold Model of Low-Dose Radiation Health Risks"

TO THE EDITOR: The recent article by Duncan et al. (*1*) challenges the contentions of Siegel et al. (*2*) regarding the validity of the Biologic Effects of Ionizing Radiation (BEIR) VII report (*3*) and its underlying linear no-threshold (LNT) assumption. Duncan et al. contend that Siegel et al. fail to appreciate the appropriateness of the BEIR VII report and its LNT basis. In particular, Duncan et al. conclude:

> However, the linear no-threshold model remains the best, and certainly the most conservative, means of estimating the risk of exposing humans to varied levels of ionizing radiation. When considering the risks at low levels of exposure, the BEIR VII report rightfully shifted from an epidemiologic to a mechanistic approach. The BEIR VII report also appropriately considered and rejected the possibility of a threshold.

Rather than repeating the DNA arguments of Duncan et al. and Siegel et al. (*1,2*), this letter provides commentary that adds additional support for challenging BEIR VII (*3*) in general, and its underlying LNT hypothesis in particular. The following 4 arguments support the Siegel et al. contentions and further challenge the commentary of Duncan et al. and BEIR VII:

1. BEIR VII includes only a portion of the relevant dosimetric data (i.e., high-dose and dose rate data from the atomic

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bomb survivors and high-dose therapy patients) and excludes relevant lower dose and dose rate data. These data include (a) the extensive dosimetric documentation from nuclear power reactor and military personnel, (b) lower dose imaging data, and (c) environmental data. The BEIR VII report notes that these types of studies were evaluated, but not incorporated into the analysis. Failure to include these lower dose data provides an inherent bias and overestimates the risk of low levels of ionizing radiation.

2. BEIR VII incorporates a dose and dose rate effectiveness factor (DDREF) for low linear energy transfer data. A range of DDREF values of 1.1 to 2.3 were considered, and a value of 1.5 was deemed to be appropriate (*3*). The DDREF value is applied for doses below 1 Sv, and a mathematic discontinuity in the *linear curve* is created by reducing the slope of the dose–response curve (effects vs. dose) by a factor of the reciprocal of the DDREF below 1 Sv (*3*). The use of the DDREF is a tacit admission of the fallacy of the LNT approach that is a fundamental underpinning of BEIR VII. There would be no need to create an artificial DDREF factor if the LNT model were correct. Other dose cutoff values can be defined that further serve to challenge the LNT approach. For example, Siegel, Pennington, and Sacks (*4*) credibly demonstrate the fallacy of the LNT hypothesis as applied to medical imaging. Siegel et al. (*4*) note that credible evidence of imaging-related carcinogenic risk at low absorbed dose (<100 mGy) is nonexistent. A 100 mGy, 1 Sv, or discontinuity at another value adds support to challenge the credibility of the LNT approach.
3. The most recent report of the Radiation Effects Research Foundation (RERF) (*5*) notes a definite curvature in the data that further serves to challenge the LNT approach. RERF report 14 (*5*) updated the RERF report 13 (*6*) results and noted that formal dose-threshold analysis indicated no threshold; that is, zero dose was the best estimate of the threshold. However, Ozasa et al. note that: "Although the linear model provided the best fit in the full dose range, statistically significant upward curvature was observed when the dose range was limited to 0–2 Gy ($\theta = 0.81$, $P = 0.02$) (Tables 6 and 7). The curvature over the 0–2-Gy range has become stronger over time, going from $\theta = 0.20$ for the period 1950–1985 to 0.81 for 1950–2003, and has become significant with longer observation (Table 7)." In the preceding quote, θ is the curvature of the fit, and P is the statistical significance (likelihood test). The reader should recall that RERF report 13 (*6*) was a significant basis for establishing the credibility of the LNT hypothesis in the BEIR VII report (*3*).
4. Although the evaluation of DNA and its robust repair mechanisms are important, risk is best formulated as the integrated challenge to an organism. The effects of adaptive response, human immune system repair and mitigation, apoptosis, and other inherent protective functions also influence the final risk. Focusing solely on DNA repair is only one aspect for formulating a risk estimation model.

The BEIR VII report and Duncan et al. do not consider the aforementioned 4 factors that serve to challenge the LNT approach. As such, this letter supports the contentions of Siegel et al. (*2*) and encourages future BEIR reports to incorporate the challenges offered by these authors to improve future reports. In addition, the updated RERF report 14 data and low-dose and dose rate data should be incorporated into future BEIR reports to provide the best scientific assessment of the risk of ionizing radiation.

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I acknowledge Dr. Ozasa, who kindly supplied raw data from RERF report 14 (*5*) that were used to independently verify curvature in the dose–response curve noted in argument 3 above.

REFERENCES

1. Duncan JR, Lieber MR, Adachi N, Wahl RL. Radiation dose does matter: mechanistic insights into DNA damage and repair support the linear no-threshold model of low-dose radiation health risks. *J Nucl Med.* 2018;59:1014–1016.
2. Siegel JA, Greenspan BS, Maurer AH, et al. The BEIR VII estimates of low-dose radiation health risks are based on faulty assumptions and data analyses: a call for reassessment. *J Nucl Med.* 2018;59:1017–1019.
3. National Research Council of the National Academies. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2*. Washington, DC: The National Academies Press; 2006.
4. Siegel JA, Pennington CW, Sacks B. Subjecting radiologic imaging to the linear no-threshold hypothesis: a non sequitur of non-trivial proportion. *J Nucl Med.* 2017; 58:1–6.
5. Ozasa K, Shimizu Y, Suyama A, et al. Studies of the mortality of atomic bomb survivors, report 14, 1950–2003: an overview of cancer and noncancer diseases. *Radiat Res.* 2012;177:229–243.
6. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: solid cancer and noncancer disease mortality—1950–1997. *Radiat Res.* 2003;160:381–407.

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Mechanistic Insights Into Why Radiation Dose Matters? It Matters Most Because of Adaptive Responses at Low Radiation Doses

TO THE EDITOR: In their Invited Perspective, Duncan et al. (*1*) continue a defense of the linear no-threshold (LNT) model for low-dose radiation (LDR) but do not respond to Siegel et al. (*2*) regarding important issues within the Biologic Effects of Ionizing Radiation (BEIR) VII report. This usually means that the authors concur with those contents, or do not find them objectionable. Here are 2 concerns:

1. Both Siegel et al. (*2*) and the National Research Council (*3*) agree that at low doses in the range of 0−100mSv, there are no data supporting the LNT model. BEIR VII uses data to support the LNT model (*4,5*) down to about 20 mSv, but Siegel et al. demonstrate the BEIR VII effort shows the failure of the LNT model in the 0- to 100-mSv range. Duncan et al.'s (*1*) nonresponse to Siegel et al. (*2*) seems a tacit admission of BEIR VII's failure to make a valid claim for linearity in the "low-dose range" of 0–100 mSv.
2. Siegel et al. (*2*) emphasize "at relatively low doses, there is still uncertainty as to whether there is an association between radiation and disease, and if there is an association, there is uncertainty about whether it is causal or not" (*3*). Duncan et al. (*1*) ignore this observation, which is key to their claims about the risks of low-dose CT scans.