Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Uses of Isotopes (ACMUI)

Final Report on the Hormesis/Linear No-Threshold Petitions

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Subcommittee Members
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Charge
To consider the requests in the recent petitions to the NRC related to radiation hormesis and the linear no-threshold dose-response model of radiation carcinogenesis and to suggest recommendations the ACMUI should make to the Commission.

Recommendation
The "correct" dose-response model for radiation carcinogenesis remains an unsettled scientific question. There is a large, and growing, body of scientific literature as well as mechanistic considerations which suggest that 1) the LNT model may overstate the carcinogenic risk of radiation at diagnostic medical, occupational, and environmental doses and 2) such low doses may, in fact, exert a hormetic (ie a beneficial or protective) effect. However, in the absence of definitive refutation of the LNT model and while strongly encouraging continued investigation critically comparing alternative models, regulatory authorities should exercise prudent (though not excessive) conservatism in formulating radiation protection standards. The ACMUI therefore recommends that, for the time being and subject to reconsideration as additional scientific evidence becomes available, the NRC continue to base the formulation of radiation protection standards on the LNT model.

Discussion
Linear no-threshold versus alternative dose-response models
The linear no-threshold (LNT) dose-response model posits that there is no "safe" dose of radiation below which there is no increased risk of cancer. Since the LNT model has not been scientifically validated in the low-dose range[1], dose-effect data at high doses (eg the A-bomb survivor lifespan study) have been extrapolated linearly down to zero dose. Some have argued that the data supporting the LNT model are equivocal and are refuted by epidemiologic and experimental studies. The validity, applicability, and utility of the LNT model are questioned and subject to contentious debate (1-3). There is, in fact, mounting evidence that the risk of radiation carcinogenesis at doses below 100 mSv is overestimated by the LNT model and there is some evidence that such low doses actually exert a hormetic effect. The phenomenon of radiation hormesis posits that individuals exposed to such low radiation doses actually have a *lower* subsequent risk of cancer than unexposed individuals, presumably as a result of radiogenic upregulation of cellular repair mechanisms or other adaptive response(s) (1-3).

No prospective epidemiologic studies with appropriate non-irradiated controls have definitely demonstrated either the adverse or the beneficial effects of radiation doses less than 100 mSv in man, and current estimates of the risks of low-dose radiation suggest that very large-scale

[1] While there is no rigorous distinction between "low"- and "high"-dose radiation, the former are generally consistent with radiation doses encountered in diagnostic medical, occupational, and environmental contexts – of the order of 100 mSv or less when delivered acutely and perhaps somewhat greater when delivered over a protracted period of time.

epidemiological studies with long-term follow-up would be needed to actually quantify any such risks or benefits; such studies may be logistically and financially prohibitive. As a result, a mathematical extrapolation model remains the only practical approach to estimating the presumed excess cancer risk from low-dose radiation, and the dose-response data derived from epidemiological studies of human cohorts, such as the A-bomb survivors, exposed to high-dose radiation are largely consistent with an LNT model. The LNT model has thus been endorsed by a number of authoritative scientific organizations including the National Council on Radiation Protection and Measurements (NCRP) and the International Commission on Radiological Protection (ICRP) as a prudently conservative model (4). Regulatory bodies such as the NRC formulate radiation protection standards based on the recommendations of organizations such as the NCRP and ICRP and thus have adopted, at least indirectly, the LNT model.

The literature on radiation carcinogenesis and on radiation hormesis is vast and continues to grow, and even a cursory review of this literature is beyond the scope of this Report. However, in order to provide some context for this ongoing controversy, several notable studies are summarized below[2].

Atomic bomb survivors

The Radiation Effects Research Foundation (RERF) published its 14th report (1950-2003) on mortality in the Life Span Study (LSS) group. The LSS group is composed of ~120,000 subjects who were either atomic bomb survivors and residents of Hiroshima and Nagasaki or were not in either city at the time of the bombing (7). The last report provided six years of additional follow-up, and showed: 1) the risk of death from all causes, especially solid tumors, increases with radiation dose, with a linear dose-response relationship; 2) the sex-averaged excess relative risk (ERR)[3] increased by ~29% (95% CI 17%, 41%) per decade decrease at exposure; and 3) the estimated lowest dose range with a significantly increased ERR for solid cancers was 0 to 0.2 Gy with no non-zero dose threshold apparent. The study did show that a concave (linear quadratic) curve was the best fit for data restricted to doses less than 2 Gy, as the risk estimates for doses up to ~0.5 Gy were lower than those predicted by the linear model. Using a nonparametric statistical procedure, reanalysis of the LSS cohort of atomic bomb survivors has exhibited a low dose threshold (<0.2 Sv or 200 mSv) with negative ERR, suggesting a radiation hormesis model (8).

Low-dose protracted or intermittent radiation exposure

A study from the International Nuclear WORKers Study (INWORKS) followed 308,297 monitored radiation workers from the United Kingdom, France and United States, who were employed for at least one year, to determine deaths caused by multiple myeloma, lymphoma, and leukemia (9). Although the estimated red bone marrow absorbed dose was very low (mean $\pm$ standard deviation (SD): 1.1 $\pm$ 2.6 mGy/year), the ERR for leukemia excluding chronic lymphocytic leukemia (CLL) was 2.96 per Gy (90% confidence interval (CI): 1.17-5.21) with a 2-year latency period). A simple linear function of cumulative dose described the trend in ERR of leukemia excluding CLL with dose. The ERR of leukemia excluding CLL persisted even for doses less than 300 mGy and less than 100 mGy, although the 90% CI were much wider for these respective dose ranges.

Radiation exposure from CT scans in childhood

[2] For additional references and critical, though reasonably succinct, reviews of the LNT model and alternative dose-response models (including hormesis), the reader is referred to references (5) and (6).
[3] The excess relative risk is the fractional increase in the cancer incidence per unit dose.

A retrospective cohort of over 176,000 children and young adults (younger than 22 years of age at exposure and without an antecedent history of cancer) was analyzed by the National Health Services Central Registry from 1985 to 2008 to assess excess risk for leukemia and brain tumors after CT scans (10). The absorbed dose to the brain and red bone marrow doses per CT scan in mGy were estimated using Poisson relative risk models. For example, a 10-year-old child had an estimated dose to the brain and red bone marrow of 35 and 6 mGy, respectively. The ERR per mGy was 0.036 (95% CI: 0.005-0.120; p=0.0097) for leukemia and 0.023 (95% CI: 0.010-0.049; p<0.0001) for brain tumors. The analysis showed little evidence for non-linearity of the dose-response.

Biological Effects of Ionizing Radiation (BEIR) VII

For six decades, the US National Academy of Sciences has commissioned a series of reports, the Biological Effects of Ionizing Radiation (BEIR) reports, to study the health effects from low levels of ionizing radiation. The most recent such report, BEIR VII, places the greatest emphasis on RERF data, which may not be applicable to the US and other Western populations. The Report concluded that, ‘‘…current scientific evidence is consistent with the hypothesis that there is a linear, no-threshold dose-response relationship between exposure to ionizing radiation and the development of radiation-induced solid cancers in humans” (11). The BEIR VII Report did acknowledge the significant limitations and uncertainties of its risk estimates.

Mechanistic considerations and epidemiologic studies of background radiation and of nuclear accidents

Mechanistic studies and epidemiologic studies of background radiation and recent nuclear accidents (Fukushima and Chernobyl) suggest that LNT may not be the correct model. From a biologic standpoint, the frequency of foci of DNA damage low radiation doses is much lower than that associated with spontaneous mutation, suggesting that molecular repair mechanisms are very efficient at eliminating DNA damage and mitigating the impact of such damage at low radiation doses. There are some recent data that suggest an increased risk of cancer after CT scans. Opponents of LNT, however, contend that the dosimetry was not individualized and suggest that preexisting medical conditions may have led to higher cancer risks (12). Although areas such as Yangjiang, China and Kerala, India have high natural background levels of radiation (eg up to an order of magnitude higher than the mean natural background radiation doses per capita in the United States), the incidence of cancer in such areas does not appear to be increased (13,14). Finally, data from nuclear accidents suggest that low-dose radiation does not increase the cancer risk among exposed residents.

Endorsement

This report was presented and discussed with the full Committee on October 28, 2015. During the public teleconference, the Committee unanimously endorsed the report.

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