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General Comment

See attached file(s)

Attachments

NCI comments for NRC rule making

National Cancer Institute
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Contribution to Nuclear Regulatory Commission (NRC) comments on petitions on linear no-threshold model and standards for protection against radiation

The Radiation Epidemiology Branch (REB) of the National Cancer Institute conducts epidemiologic research on the effects of exposure to ionizing radiation on the risk of cancer and other diseases, including risk from lower radiation doses. Thus, our comments focus on evidence from epidemiologic studies, particularly those that include persons exposed to relatively low radiation doses (generally <100 mGy). We also briefly touch on biological issues. Our review of the relevant current scientific literature leads us to support the use of the linear no-threshold (LNT) hypothesis for developing the risk estimates that form the basis of radiation protection.

The petitions also touch on biological issues, which we address towards the end of the document.

Epidemiological issues

Direct study of persons exposed at low doses poses challenges, and results must be interpreted cautiously. Cancer risks predicted by the LNT model are likely to be small at low doses; so small as to be difficult to detect in the presence of large numbers of cancers resulting from other causes. For example, exposure to 0.1 Gy is predicted to increase solid cancer risks by less than 5% (1, 2). This means that most studies of persons exposed at low doses will not have sufficient statistical power for detecting risks, and that estimates of risks at low doses are uncertain (3). In addition, because epidemiologic studies are observational and not controlled experiments, differences in risks in exposed and unexposed may reflect differences in life style factors such as smoking and may not necessarily result from radiation exposure. Large studies with individual dose estimates to evaluate evidence for a dose-response are, therefore, the most informative and their results should be given more weight when considering the evidence.

None of the three petitions under consideration by NRC take account of the limitations of the epidemiologic studies cited. In addition, the petitions are selective in citing studies that appear to support hormesis (or a threshold) and omitting mention of the many studies that provide evidence of a dose-response at low doses. In some cases, analyses published many years ago are cited, when more recent analyses based on current follow-up of the same populations, often with improved dose estimates, do not support their claims. The examples below illustrate these points (page numbers refer to the letter from Dr. Marcus, which we judge to be the most substantial of the three petitions, although very similar points are made by the other two petitions).

- Japanese atomic bomb survivors (p.3, last paragraph). The low risks in the 0.3 to 0.7 Gy range are cited as evidence of hormesis. As discussed by the authors of the cited atomic bomb survivor paper, this may suggest departure from linearity. However, two of the three estimated excess relative risks (ERRs) cited in the 0.3-0.7 Gy range are positive (with lower confidence bounds >0), and one is zero, whereas evidence of hormesis would require negative ERRs. The generally elevated ERRs at doses lower

than 0.3 Gy, which were higher than the linear prediction, are not mentioned. The observed pattern is not clearly consistent with hormesis.

- Nuclear workers (p.4 paragraph 1). The fact that cancer rates among nuclear workers are lower than those of the general population is cited as evidence of hormesis with criticism of the "healthy worker effect (HWE)" as an explanation. Many worker studies other than those in the nuclear industry have demonstrated lower cancer rates than the general population, giving credibility to the HWE explanation (4-6). More importantly, the paper of Cardis et al. that is cited (7) does not include comparisons with the general population, but rather relies on the more informative approach of comparing cancer rates within the worker population by radiation dose. Using this approach, a statistically significant positive association of solid cancer with radiation dose was found, which certainly does not support hormesis as the petitioners claim. Updates of this study, including radiation workers in three of the 15 countries (France, UK, USA), but with nearly four times the number of deaths (for all cancer 19,748 vs 5,233 deaths), find statistically significant positive associations of radiation dose with both leukemia apart from chronic lymphocytic leukemia (8) and solid cancer (9). Risks are somewhat lower than in the previous analysis (7), in part because of the exclusion of the Canadian workers, who had particularly high radiation risks, which were inconsistent with those in the other groups of workers.
- TB fluoroscopy cohort (p.4 paragraph 2). The data cited are from a 1989 publication. A later analysis of the Canadian tuberculosis (TB) fluoroscopy cohort does not show any reduction in risk in the low dose range – indeed breast cancer risk increases progressively with increasing dose over the dose range up to 4 Gy (10); a similar pattern is observed in the Massachusetts TB fluoroscopy cohort (11).
- Persons in the Urals exposed to radioactive waste from Mayak (p.5, paragraph 2). Publications from 1994 are cited. Not cited are updated analyses using improved dose estimates that have demonstrated statistically significant dose-response relationships for leukemia (12), all solid cancers evaluated as a group (13, 14), and breast cancer specifically (15).
- Taiwan Co-60 study (p.5, paragraph 3). The petitioners cite an older analysis that compares cancer rates for this population to National Taiwanese rates. The results are largely uninterpretable because of difficulties with comparisons with external populations, (16). The petitioners fail to mention a later and more reliable internal analysis of this cohort that shows a significant excess risk of leukemia and a borderline significant excess risk for female breast cancer (17).
- Residential radon studies (p.5, paragraph 4). The work of Cohen is cited. His work is based on an ecological design which is a prone to many biases (based on geographic patterns of radon exposure and cancer incidence instead of individual data on lung cancer and exposure), and has been widely criticized (18-20). Not mentioned are pooled analyses of 7 North American (21) and 13 European (22) case-control studies involving nearly 11,000 lung cancer cases and 19,000 matched controls with individual estimates of residential radon exposure. Both studies found statistically significant associations of lung cancer risk and radon exposure, with estimates that were similar to those obtained through linear extrapolation from studies of underground miners exposed to higher levels of radon.
- Chernobyl studies (p.6, paragraph 2). The petitioners fail to cite several studies that show significant dose-response relationships for thyroid cancer in relation to internal doses of I-131 in childhood (23-26) (with mean thyroid doses of 0.65 Gy), or leukemia in relation to external doses in clean-up workers (27) (with mean red bone marrow dose to the controls of 0.08 Gy).

Above we have cited several studies that provide evidence of a dose-response at low doses. In addition, other studies provide evidence of excess risk of childhood leukemia associated with natural background radiation exposure at doses of the order of 5 mGy (28, 29), excess risk of leukemia and other childhood cancers associated with exposures of 10-20 mGy from diagnostic x-ray exposure *in utero* (30-32), and

increased risks of leukemia and brain cancer among children given multiple computerized tomographic examinations with doses of about 60 mGy (33). None of these studies can rule out the possibility of a small threshold dose. The shape of the dose-response curve may vary by characteristics the radiation exposure such as dose rate, and is known not to be the same for all types of cancer. For example, bone cancer (2, 34) and leukemia (35) have a more strongly upward-curving dose response (35). However, overall the epidemiologic evidence supports the LNT hypothesis as a useful approach for estimating cancer risks from low-dose radiation exposure.

Biological material

- Biological mechanisms (p.2, paragraph 2). It has been known for some time that the efficiency of cellular repair processes varies with dose and dose rate (36, 37), and this may be the reason for the curvature in cancer dose response (38) and dose rate effects observed in epidemiological and animal data (36). DNA double strand breakage is thought to be the most critical type of intracellular damage induced by radiation (36), although there is also evidence of other targets for radiation action within the cell (39, 40). Repair of double strand breaks (DSBs) relies on a number of pathways, even the most accurate of which, homologous recombination, is prone to errors (37); other repair pathways, e.g., non-homologous end joining, single-strand annealing, are intrinsically much more error prone (37, 41). The variation in efficacy of repair that undoubtedly occurs (41) will affect the magnitude of unrepaired and misrepaired damage and, whereas unrepaired damage is likely to result in cell death, misrepaired damage will invariably result in mutation, and a fraction of these mutations may lead to cancer (36).
- Dr Marcus alludes to the well-known involvement of the immune system in cancer, and more generally the role of adaptive response. The critical issue is whether the up-regulation of the immune system or other forms of adaptive response that may result from a radiation dose offsets the carcinogenic damage that is caused. The available evidence, summarized above, is that it does not, and that, given the similarities in risks per unit dose following exposures to very low doses of radiation and after moderate dose radiation exposure (28, 33, 42, 43), the non-linearities induced by any adaptive response cannot be substantial. While adaptive response modulating the effect of relatively high challenge doses of radiation (of several Gy) following a smaller priming dose (of usually at least several tens of mGy) is well known experimentally (mostly *in vitro*), it is not universally observed in all experimental systems, nor does it last more than a few days, and there is little or no evidence for its involvement at low priming and challenge doses (41, 44).

There is also data, not referenced by the petitioners, suggesting an increase in stable chromosome aberrations and other markers of biological damage in the peripheral blood lymphocytes of nuclear workers and other groups with protracted radiation exposures (45-49). Chromosome changes play a major role in carcinogenesis and there is increasing evidence that the presence of increased frequencies of chromosome aberrations in peripheral blood lymphocytes in healthy individuals could be a surrogate for the specific changes associated with carcinogenesis and therefore indicative of risk (50-52). There is much other *in vitro* and *in vivo* radiobiological data suggesting small but adverse effects of moderate dose exposure – in particular there is little data to suggest a threshold in dose, or possible hormetic (beneficial) effects of low-dose radiation exposure (2, 36, 43).

Conclusions

In summary, excess cancer risks have been observed in numerous epidemiologic studies of persons exposed at low to moderate doses. In addition, the available data on biological mechanisms do not provide general support for a low-dose threshold or hormesis. Although the possibility of a small threshold cannot be excluded, any moderately large threshold in dose (>10 mGy) seems unlikely.

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