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PERSPECTIVE ON THE USE OF LNT FOR RADIATION PROTECTION AND RISK ASSESSMENT BY THE U.S. ENVIRONMENTAL PROTECTION AGENCY

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□ The U.S. Environmental Protection Agency (EPA) bases its risk assessments, regulatory limits, and nonregulatory guidelines for population exposures to low level ionizing radiation on the linear no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold. The use of LNT for radiation protection purposes has been repeatedly endorsed by authoritative scientific advisory bodies, including the National Academy of Sciences' BEIR Committees, whose recommendations form a primary basis of EPA's risk assessment methodology. Although recent radiobiological findings indicate novel damage and repair processes at low doses, LNT is supported by data from both epidemiology and radiobiology. Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future.

INTRODUCTION

The U.S. Environmental Protection Agency (EPA) is responsible for protecting the public from environmental exposures to radiation. To meet this objective the Agency sets regulatory limits on radionuclide concentrations in air, water, and soil. In other cases (e.g., for residential radon) it may establish nonregulatory guidelines for radionuclides. The purpose of these limits and guidelines is to prevent health effects and to establish an acceptable level of safety for members of the public, the primary concern being the minimization of radiogenic cancers.

Setting protective exposure limits and providing appropriate guidance requires an assessment of risks. Periodically, EPA updates its radiation risk models. In this process, EPA derives most of its assumptions and models from reports by scientific advisory bodies including the U.S. National Academy of Sciences, the International Commission on Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects of Ionizing Radiation (UNSCEAR), and the National Council on Radiation Protection and Measurements (NCRP), with additional input from its own independent review of the scientific literature.

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To assist the Agency in its assessment of the health risks from ionizing radiation, EPA has often helped sponsor reports from these organizations, particularly from the NAS "BEIR Committees." The risk models and supporting evidence is then reviewed by EPA's Scientific Advisory Board of outside distinguished scientists before becoming final and being implemented. Thus, EPA's estimates of risk to low dose radiation reflect a broad scientific consensus.

Based on extensive epidemiological and laboratory studies, radiation is a well-established human carcinogen; however, with the notable exception of radon exposures in homes, environmental levels of radiation are too low to produce detectable excess cancers in epidemiological studies. As a consequence, risks have to be extrapolated from results of epidemiological studies on more highly exposed individuals. A similar situation exists in connection with EPA's assessments of risk from chemical carcinogens: the cancer risk due to intake of a chemical is extrapolated from studies at higher doses. In the case of chemicals there is usually an additional extrapolation from laboratory animals to humans. For radiation, at least, there are direct human data upon which we can establish that it causes cancer and from which the magnitude of the risk at environmental doses can be projected, even if that estimated risk is too small to be observed.

Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold.

More specifically, it is common practice to project radiogenic cancer risk due to exposures of low level, ionizing radiation by a linear extrapolation of the dose response function observed for more highly exposed cohorts, especially the Life Span Study (LSS) cohort of Japanese atomic bomb survivors. For low-LET radiation, a dose/dose rate effectiveness factor (DDREF) is usually incorporated to reflect evidence that the risk coefficient for acute doses of ≈ 0.5 Gy is higher than what it would be for lower dose exposures or for exposures at low dose rates. The National Academy of Sciences BEIR VII committee (NRC 2006) recently estimated that the relevant DDREF for solid tumor induction is about 1.5: *i.e.*, the risk at low doses and low dose rates is expected to be only about a factor of 1.5 times lower than that projected from a simple linear fit to the LSS data.

Is this approach for extrapolating risk justified from a scientific standpoint? Is it reasonable from a radiation protection standpoint? What would it take to justify a change in this approach for the purposes of radiation protection or of radiation risk estimation, more broadly?

SCIENTIFIC PERSPECTIVE

Results from laboratory studies of irradiated animals and epidemiological studies of irradiated human cohorts are generally consistent with a linear, no-threshold dose-response, down to the lowest doses for which there is statistical power to measure (Brenner et al. 2003). For low-LET radiation, however, even the largest epidemiology studies are only sensitive down to incremental doses of ~100 mGy above background. At this dose, each cell nucleus is traversed by ~100 electron tracks. In comparison, at natural background levels, each cell nucleus is traversed by only on the order of 1 track per year. There is, nevertheless, a theoretical basis for excluding a threshold and for extrapolating the linear dose-response relationship to very low doses where the radiogenic damage is caused by single tracks.

First, traversal of cells by energetic charged particles produces ionizations and molecular excitations resulting in chemical damage to the DNA. Significantly, even low-LET radiation, for which the energy deposition events are, on average, more widely spaced, produces a substantial fraction of its DNA damage in the form of "clusters" or "multiply-damaged sites" (usually at the ends of electron tracks), which are difficult or impossible for the cell to repair faithfully (Goodhead 1994). Second, it appears that a single mutation in a cell can increase the probability that the cell will become malignant. Lastly, a foolproof biological mechanism for screening out malignant or pre-malignant cells appears to be ruled out by the high rate of cancer observed in the population. These mechanistic features of radiation carcinogenesis argue against a strict dose threshold below which there would be no risk of a radiation-induced cancer.

Although a strict threshold appears unlikely, mechanisms may exist to modulate risks at very low doses in such a way that actual risks are substantially below those projected by LNT. In effect, we might then have a "practical threshold"—*i.e.*, a dose below which the risk becomes negligible from a regulatory perspective. Before such a threshold is accepted for radiation protection purposes, however, there would almost certainly be a need for confirmation with human epidemiological data—or, at least, with some kind of biomarkers in human tissues that clearly relate to cancer.

Radiobiological research has recently focused on a number of low-dose effects, including the adaptive response (Azzam *et al.* 1996, Redpath and Antoniono 1998, Tapio and Jacob 2007), bystander effects (Mothersill and Seymour 1998, Nagasawa and Little 1999, Mitchell *et al.* 2004), and genomic instability (Morgan *et al.* 1996, Little *et al.* 1997), which might provide mechanisms whereby the linearity of the dose-response relationship would break down at low doses. In principle, the risk per unit dose could plausibly be either increased or decreased through these mechanisms. For example, bystander effects refer to

changes in unirradiated cells due to irradiation of nearby cells. Such changes may, in principle, be either harmful (*e.g.*, by producing carcinogenic mutations in bystander cells) or protective (*e.g.*, by stimulating repair or by inducing apoptosis of damaged cells). At this time, it is unclear whether or not any of these phenomena have an appreciable effect on the *in vivo* dose-response for ionizing radiation (NRC 2006).

Even the largest epidemiological studies lack the power to detect low-LET radiation risks unless the incremental dose above background is about 0.1 Gy or higher. Nevertheless, epidemiological studies of groups receiving fractionated or chronic exposures may shed light on risks at substantially lower doses (Puskin 2008). For example, studies have been carried out on scoliosis and TB patients (Doody *et al.* 2000, Howe and McLaughlin 1996), who received multiple diagnostic x-ray exposures of less than 10 mGy each, separated by more than a week. At these x-ray doses, no cell nucleus is traversed by more than a few radiation tracks during a single examination. As a consequence, the relevant DNA damage is expected to have been produced solely by single tracks. A positive dose response for cancer induction has been observed in both the scoliosis and TB patients. Moreover, the slope of the dose-response in the TB patients is remarkably consistent with that observed for breast cancer in the LSS (Howe and McLaughlin 1996). These results argue against an effective threshold—even at ~ 1 track per cell nucleus.

Even more sensitive tests for a low-dose practical threshold might be obtained through epidemiological studies of cohorts receiving chronic radiation exposures, either environmentally or occupationally. There are a number of such cohorts being investigated, notably: the population around Chernobyl (Hatch *et al.* 2005), Chernobyl cleanup workers (Hatch *et al.* 2005), people living downriver from the Mayak Plutonium Plant (Ostroumova *et al.* 2006, Krestinina *et al.* 2005), the population residing near the Semipalatinsk nuclear test site in Kazakhstan (Bauer *et al.* 2005), occupants of ^{60}Co-contaminated buildings in Taiwan (Hwang *et al.* 2008), and cohorts of workers from the nuclear industry and nuclear shipyards (Cardis *et al.* 2007, Muirhead *et al.* 2009, Schubauer-Berigan *et al.* 2007). Such studies can potentially provide evidence regarding risk at exposure rates of 0.1-1 mGy/day, corresponding to 0.1-1 ionizing track per cell nucleus per day, or even lower (Puskin 2008). Statistically significant positive associations between radiation dose and cancer incidence have been found for a number of these cohorts. A recent meta analysis of epidemiological studies of subjects exposed to chronic, moderate doses of radiation indicated that the risk per unit dose was about the same as that found in the LSS cohort (Jacob et al. 2009). Results are still somewhat preliminary, and improvements in both dosimetry and epidemiological follow-up are anticipated. If these findings do hold up, it would indicate that a practical threshold could only exist at very low daily doses,

which would put severe restrictions on any proposed biological mechanism (Puskin 2008).

REGULATORY PERSPECTIVE

LNT has long been accepted as the basis for assessing risks from ionizing radiation. This approach has been repeatedly endorsed by National Academy of Sciences (NAS) "BEIR" committees, beginning with the 1972 BEIR Report (NRC 1972) and by the International Commission on Radiological Protection (ICRP), the National Council on Radiation Protection and Measurement (NCRP), and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). More generally, a 1985 policy directive from the Office of Science and Technology Policy (OSTP 1985) establishes the linear, no-threshold assumption as the default method for extrapolating cancer risks to low doses for the U.S. government. A recent directive by the U.S. Environmental Protection Agency allows deviation from the LNT approach (EPA 2005), but only in cases where there is strong scientific support for a mode of action that would give rise to a different dose-response relationship. In view of these recommendations and the supporting science, EPA has consistently applied LNT as part of its regulatory and risk assessment framework for radiation.

The use of LNT for radiation protection purposes is often justified as being "conservative"; *i.e.*, it is presumed that, while we may not be able to estimate the risk at low doses accurately, linear extrapolation is unlikely to (greatly) underestimate risk. Hence, if radiation standards are promulgated under the assumption that LNT is correct, they will be protective. LNT also has the great advantage of simplicity, risks from multiple exposures being proportional to the total dose. Given these features of protectiveness and convenience, there is very wide support for LNT in the context of radiation protection, even among scientists and regulators who harbor serious doubts about its scientific validity.

It is difficult to imagine any relaxation in this approach unless there is convincing evidence that LNT greatly overestimates risk at the low doses of interest. For example, before EPA would adopt a "threshold" for regulatory purposes, there would probably have to be a strong recommendation to that effect from authoritative bodies such as a National Academy of Sciences' BEIR committee, endorsed by the Agency's Scientific Advisory Board, with ample opportunities for public comment and Agency response. No such change can be expected soon in view of the recent BEIR VII Committee's position that "the balance of evidence from epidemiologic, animal and mechanistic studies tend to favor a simple proportionate relationship at low doses between radiation dose and cancer risk" (BEIR VII, p. 14).

Even if a practical threshold could be convincingly demonstrated, it remains unclear what effect this would have on radiation protection. A threshold lower than the level of radiation received from unavoidable sources would obviously have no impact on regulations. Demonstration of a practical threshold substantially above background might allow certain regulations to be relaxed or reinterpreted. Examples might include derived soil cleanup levels for Superfund sites and maximum allowed concentrations of radionuclides in drinking water. However, a number of issues would have to be considered in setting threshold-based standards, including the uncertainty in the threshold dose, the possible existence of sensitive subpopulations, and the contribution of multiple sources. Such considerations would likely dictate that a sizable safety factor be incorporated to ensure that a sufficiently large fraction of the population would fall below the threshold. For example, even if it were to be demonstrated that a dose rate of 10 mGy per year posed negligible risk to the great majority of people, the regulatory limit on a given source might still be set substantially lower than this.

Opposition to the LNT approach for radiation protection, in some cases, arises from concerns that the presumption of finite risk, even at background levels of exposures, generates unreasonable fears among members of the public, which may cause them to reject nuclear power or other useful technologies, such as diagnostic medical procedures. At the very least, basing radiation protection on the LNT assumption may impose large economic costs on the nuclear industry and on those footing the bill for cleanup of radioactively contaminated sites. Nevertheless, unless compelling evidence for a practical threshold can be obtained, it must be acknowledged that there is likely to be a risk even at the lowest doses of ionizing radiation. Denials only fuel distrust. It is better to acknowledge that the science, so far, is consistent with a non-zero risk at low doses, even if direct verification is lacking.

It can also be pointed out that LNT implies that risks at low doses are very low, providing reasonable assurance that current radiation protection measures, based on the LNT assumption, are adequately protective. In addition, it should be emphasized that any large-scale technology imposes some risk and that alternative technologies should be compared in terms of their respective benefits, health risks, environmental impact, and economic costs. In particular, electrical power generation based on nuclear reactors and on burning of fossil fuels should be evaluated in terms of: (1) their relative contributions to global warming and (2) their potential health impacts due to release of hazardous chemicals and radionuclides into the environment.

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