# DECONSTRUCTING RADIATION HORMESIS†

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*Abstract*—**This paper explores some factors that may explain why the possibility of hormesis has not been embraced by the radiation protection community. If shown to be sustainable, hormesis might ameliorate several serious issues plaguing radiation protection including the high economic cost of environmental regulatory compliance and public fear of radiation exposure. Some but not all analyses of data from various sources, including the Japanese survivors of the atomic bombs and residential radon studies, suggest that low levels of ionizing radiation may be beneficial to human health. The evidence, however, has not been viewed as compelling for the following reasons: (1) Data in support of radiation hormesis in human populations is limited and much of it is based on re-evaluation of selected epidemiological data that has been used to test a different hypothesis; (2) Hormetic effects are weak and inconsistent, and are subject to large statistical uncertainties as is the case for carcinogenic effects at small doses; (3) A consensus is lacking on how hormesis should be defined and quantified; and (4) It is unclear how hormesis can be incorporated into the regulatory framework when beneficial health effects exceed the requirement for protection of health.**
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**Key words: hormesis, radiation; health effects; radiation protection; epidemiology**

## INTRODUCTION

THIS PAPER explores some factors that may explain why hormesis has not been embraced by the radiation protection community. Two arguments are made in this paper. The first argument pertains to the evidence in support of radiation hormesis in humans. Is the evidence convincing enough to warrant abandonment of the linear no-threshold (LNT) theory in favor of hormesis as a basis for radiation protection? The second argument addresses implementation of hormesis in radiation protection. If, for the sake of discussion, it is assumed that the scientific evidence warrants support of hormesis, what are the consequences to radiation protection practice?

As discussed below, hormesis might ameliorate many of the difficulties associated with the LNT theory in radiation protection, yet the scientific establishment has been reluctant to incorporate it. Discussion of the large number of animal and human studies that have been identified as possibly supporting radiation hormesis is beyond the scope of this paper and may be found elsewhere (Calabrese and Baldwin 2000; Luckey 1992). Selected human studies are discussed as examples of the difficulty in measuring hormesis to the exclusion of other possible health outcomes (i.e., cancer) and because radiation regulations and radiation protection practices are concerned with the protection of humans.

Regulations to limit environmental and occupational exposures to radiation are based on the assumption that any dose of radiation, no matter how small, might cause cancer. The International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection and Measurements (NCRP) use a linear-quadratic theory of the form $\alpha D + \beta D^2$ to describe the relation between radiation dose and radiogenic health effects. However, at environmental and occupational doses of interest in radiation protection, the dose-response relation may be described by the LNT theory ($\alpha D$) because the quadratic term is insignificant. Standard setting organizations use a linear dose extrapolation to estimate health impacts resulting from environmental and occupational exposures. The LNT theory has led to the widespread belief that no radiation dose is safe. While regulatory decision-making was designed to protect the public health, its implementation has become punitive and burdensome in many ways. Regulatory compliance costs are steadily growing while desired public health benefits are increasingly difficult to measure. Ideally, strategies to allocate resources to reduce health risks should consider all sources of risk (radiologic and non-radiologic) and should be concentrated in areas where the greatest risk reduction may be expected.

According to some scientists there are now sufficient scientific data to indicate that the LNT theory is overly restrictive and is not correct for some types of cancer (e.g., leukemia) in the low-dose region. Other scientists believe that risks of low dose exposure are underestimated by the LNT theory. Of course, alternative theories that predict different risks in the low dose region (e.g., hormesis, quadratic, supralinear, or threshold) also have significant uncertainties because of the paucity of data in the low dose range. (For the purposes of this

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paper low dose is defined as <100 mGy in adult populations.) All biologically-plausible theories, including the LNT, are inadequate in the Popperian sense (Popper 1959) because they are untestable (i.e., unfalsifiable) in the low dose region. Theory falsification requires bona fide counter-evidence in the low-dose range. Falsification cannot be based on dose extrapolation because of the very large uncertainties when extrapolating over a wide range of doses (2 orders of magnitude or more). Therefore, selecting a particular theory to the exclusion of biologically plausible alternatives will remain an intractable problem until experimental approaches are developed to make observations of radiogenic health effects possible in the low dose range.

Standards setting organizations continue to use the LNT theory because they believe it represents a reasonable middle ground and no other theory is more plausible on the basis of current scientific knowledge. The LNT theory in radiation protection appears resistant to falsification and overthrow because discrepancies between observations and theory can be explained either as an anomalous result or reconciled by introducing appropriate correction factors. The data from Cohen's residential radon study have been used to invalidate the LNT theory (Cohen 1995); however, most epidemiologists consider the data anomalous because of the ecological methods used and because of problems interpreting the ecological data due to the overwhelming confounding factor of smoking (Lubin 1998). By introducing the dose, dose-rate effectiveness factor (DDREF) (ICRP 1991; NCRP 1997; UNSCEAR 1977), the LNT theory could account for repair of radiation damage at low dose rate. DDREF is an external correction to the LNT theory because it is a divisor of the risk coefficient that does not alter the shape of the dose response curve.

The LNT theory poses enormous problems in radiation protection practice. The idea that no radiation dose is safe and concerns for "trivial risks" has contributed to a system of increasingly restrictive regulations. In its final ruling on radiological criteria for license termination, the U.S. Nuclear Regulatory Commission has determined that a site would be considered suitable for unrestricted release if the residual radioactivity, distinguishable from background, would result in an annual radiation dose that does not exceed 0.25 mSv (U.S. NRC 1997). This dose is about 3 orders of magnitude below doses associated with statistically significant radiogenic health risks in adult populations (as compared with background cancer rates), and is within the statistical variations of the natural radiation background in the U.S. (Mossman 1998).

The idea that any dose is potentially harmful has led to unwarranted fears about radiation. In one survey of primary care physicians in Pennsylvania, 59% of the doctors identified fear of radiation as the primary reason for their patients' refusal of mammography examinations (Albanes et al. 1988). Women who refuse mammography may be denying themselves an important medical benefit by compromising early detection and the subsequent management of disease. Following the Chornobyl accident in 1986, the International Atomic Energy Agency estimated 100,000–200,000 Chornobyl-related induced abortions in Western Europe (Trichopoulos et al. 1987). In Greece, as in other parts of Europe, many obstetricians initially thought it prudent to interrupt otherwise wanted pregnancies or were unable to resist requests from worried pregnant women in spite of the fact that doses were much lower than necessary to produce *in utero* effects (Trichopoulos et al. 1987).

If incorporated into the regulatory framework, radiation hormesis would ameliorate many of these difficulties. Small doses of radiation would be considered beneficial, or at least not harmful. Hormesis predicts a threshold dose below which the risk of adverse health outcomes is zero. Threshold doses could be used as a rationale for setting exposure limits. The notion that any dose of radiation is potentially harmful would be diffused, and public health concerns associated with environmental cleanup and radioactive waste disposal would be minimized.

Hormesis proponents have been pressing hard for credibility and reform (Airozo 1999; Hendee et al. 1998). However, the radiation protection establishment (e.g., ICRP and NCRP) has firmly held to the position that, based on current knowledge, the LNT is the most reasonable theory. Why has hormesis not been embraced by the scientific community? The issues are complex. Calabrese and Baldwin (1999) argue that hormesis has been marginalized because (a) hormesis has been historically linked to homeopathy, (b) detrimental effects at high doses have been emphasized ignoring possible hormetic effects at low doses, (c) mechanisms to explain hormesis are lacking, and (d) a coordinated effort by hormesis proponents is lacking to counter critics' views of the hormesis perspective. Elucidation of mechanisms has been problematic but the other three arguments have not been issues in the radiation protection community.

Cameron argues that hormesis can no longer be ignored because substantial scientific evidence exists to support the theory (Hendee et al. 1998). However, many scientists do not consider the evidence convincing. Hormesis proponents have failed to define clearly the phenomenon or develop a consensus on how hormesis should be quantified. Hormesis has been defined variously as stimulation (beneficial effects) by low doses followed by inhibition (detrimental effects) by higher doses (Stebbing 1982); effects unrelated to and unpredictable from effects of high dose exposure (Sagan 1987); and, a specific type of nonmonotonic dose-response function that results in beneficial effects at low doses (Luckey 1992).

Another factor bearing on the acceptability of hormesis is the inappropriate response by regulators and the public to "trivial risks." Such risks are associated with doses in the range of 0.1 mSv. Although health risks are either zero or too small to be measured at such levels, regulators and the public nevertheless respond as if these risks are real and serious. A belief that any dose of

radiation is potentially harmful leaves no room for possible beneficial effects at low levels.

## TESTING THE HORMESIS HYPOTHESIS

Evidence for radiation hormesis in human populations is limited, and much of it is based on re-evaluation of selected epidemiological data. Few studies used to support hormesis have been designed to test the theory directly. Hormesis is often inferred from analysis of data to test a different hypothesis. For instance, analyses of the Lifespan Study (LSS) data derived from the Japanese atomic bomb survivors have been conducted based on the assumption that the LNT theory is the most reasonable predictive theory (Pierce et al. 1996). Cohen's ecological radon data were evaluated as a test of the LNT theory (Cohen 1995). Interpretation of scientific data is influenced by the nature of the scientific questions asked and the experimental design and approaches used to answer the questions. Studies that appear to support an unexpected result are often not considered reliable because reliability is linked to support of the hypothesis being tested.

Hormesis, LNT, and other theories used to predict health effects at small doses of radiation cannot be easily supported or disproved in the low dose region. At low doses, effects are small and statistical uncertainties are high enough to embrace several possible theories. As shown in Table 1, both hormetic and carcinogenic effects have been reported in the same dose range (Cohen 1995, 1999; Miller et al. 1989; Ron et al. 1995).

The difficulty in selecting one theory to the exclusion of other biologically plausible alternatives is illustrated in Lubin and Boice's (1997) pooled analysis of eleven miner studies and meta-analysis of eight residential radon studies (Fig. 1). Although the LNT theory can be fit to the data with a positive risk coefficient, it is also reasonable to conclude that radon has no effect on lung cancer risk for radon concentrations $<400$ Bq $m^{-3}$ because the lower bound of the 95% confidence limits for data points cross unity relative risk (i.e., no radiation effect). However, from a regulatory perspective, it should be emphasized that the upper bound of the 95% confidence interval, rather than the lower bound, drives regulatory decision making.

The slope of Cohen's ecological regression, as shown in Fig. 1, is incorrectly drawn as continuously negative beyond 300 Bq $m^{-3}$. Actually, at about 150 Bq $m^{-3}$, the regression coefficient goes from negative to positive. Cohen's ecological regression is not statistically different from the meta-analysis data even though the slope of the Cohen regression is statistically significant from the LNT regression (Cohen 1999).

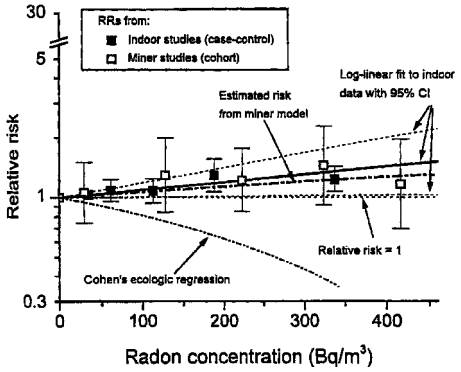


**Fig. 1.** Relative risks (RR) of lung cancer mortality derived from the meta-analysis of indoor radon studies and pooled analysis of underground miner studies (Lubin 1997). The solid line (and accompanying 95% confidence limits-dashed lines) is the fitted exposure response from the indoor radon studies. The dotted line represents RR = 1 (no radon effect). The dash-dot line represents Cohen's ecological analysis.

## HORMETIC EFFECTS ARE WEAK, INCONSISTENT, AND UNCERTAIN

Support for radiation hormesis has come from hundreds of cell and animal studies (Calabrese and Baldwin 2000; Luckey 1992). However, radiation hormesis in humans has not been firmly established. Table 2 lists three epidemiological studies commonly cited in support of hormesis (Cohen 1995; Kondo 1993; Miller et al. 1989). These studies are not entirely comparable because they relate to carcinogenesis in different tissues, and the dose-response relationships may be different. Accordingly, in a given dose range, hormesis may be demonstrated in one tissue, but increased cancer risk may be observed in another tissue. Acceptance of hormesis by the radiation protection community will depend on whether an overall net health benefit can be demonstrated. The evidence for hormesis in these studies is not compelling since the data may also be reasonably interpreted to support no radiogenic effect in the low dose range. In fact, as illustrated in Table 3, mutually exclusive models, including hormesis, have been fitted to the LSS data (Hoel and Li 1998; Kondo 1993; Little and Muirhead 1996; Pierce et al. 1996). Cohen's residential radon study (Cohen 1995) has been subject to criticism because of the ecological methods employed and because

**Table 1.** Conflicting epidemiological evidence at low dose.

| Dose | Positive health effect | Negative health effect | Reference |
|---|---|---|---|
| 100–200 mGy | Reduction in breast cancer mortality | | Miller et al. (1989) |
| | | Excess thyroid cancer in children | Ron et al. (1995) |
| [Rn] $<$ 150 Bq $m^{-3}$ | Reduction in lung cancer mortality | | Cohen (1995, 1999) |
| | | Excess lung cancer mortality | Lubin and Boice (1997) |

**Table 2.** Selected human epidemiology studies purporting to show hormesis.

| Study | Study population | Experimental design | Zero effect point | Maximum hormetic effect |
|---|---|---|---|---|
| Canadian fluoroscopy study (Miller et al. 1989) | Mortality from breast cancer in 31,710 women admitted to Canadian sanatoria between 1930 and 1952 for treatment of tuberculosis | Retrospective cohort analysis | ~300 mGy | ~27% |
| Japanese atomic bomb survivors life span study (Kondo 1993) | Mortality from cancer in atomic bomb survivors | Prospective cohort analysis | ~500 mGy | ~20% |
| Residential radon study (Cohen 1995) | Lung cancer mortality rates associated with mean levels of radon in homes in 1,610 U.S. counties | Ecological analysis | >350 Bq $m^{-3}$ | ~30% |

**Table 3.** Life span study data used to support mutually exclusive theories.

| Theory | Source of Data | Comment |
|---|---|---|
| Linear no-threshold | Pierce et al. (1996) | Statistically significant dose response for cancer mortality in the dose interval 0 to 50 mSv |
| Curvilinear or threshold | Little and Muirhead (1996) | Upward curvature in dose response for leukemia incidence and mortality; no curvature observed for solid cancers; evidence for threshold in non-melanoma skin cancer |
| Curvilinear or threshold | Hoel and Li (1998) | A-bomb cancer incidence data agree more with a threshold or nonlinear dose-response model than a purely linear model although the linear model is statistically equivalent |
| Supralinearity | Pierce et al. (1996) | Excess relative risk per Sv increases with decreasing dose |
| Hormesis | Kondo (1993) | Cancer mortality is reduced in male survivors of the Nagasaki bomb below ~50 mGy |

of problems presented by the overwhelming contribution of cigarette smoking as a confounder.

Biological mechanisms of radiation hormesis are not well understood. It is not clear how low concentrations of radon as found in the domestic environment might lead to a reduction in the baseline lung cancer mortality when high concentrations of radon are known to lead to an increased mortality rate. Most biological explanations for radiation hormesis have been based on cellular phenomena such as adaptive responsiveness and other repair mechanisms. Hormesis proponents have argued that cells undergo extensive oxidative damage during normal metabolism and are able to repair such damage. Ionizing radiation is believed to stimulate repair, thus further reducing the number of damaging oxidative species conferring overall benefit to the cell. Although these cellular phenomena are well known, it is unclear how they relate to an overall benefit to the body as reflected in reduction in cancer mortality. Cancer is a multifactorial disease; although DNA changes must occur in critical target cells to initiate cancer, the overall probability of occurrence of disease depends on numerous host and other environmental factors that may be independent of the initiating event in the target cell(s).

## INCORPORATING HORMESIS INTO THE REGULATORY FRAMEWORK

Hormesis theory presents a dilemma for regulators. If the purpose of health and safety regulations is the control of human activities to protect the public health, how does hormesis (i.e., beneficial effects of radiation) fit into the regulatory framework? In this regard, beneficial effects of radiation need to be carefully distinguished from prophylactic measures. Radiation protection practice is a system of prophylactic strategies whereby engineering and other controls are introduced in the workplace to reduce radiation dose in order to reduce the probability of radiogenic disease (e.g., cancer). Radiation hormesis, on the other hand, is concerned with reduction in non-radiogenic disease burden (i.e., health benefit). Hormesis theory predicts that small doses of radiation confer a public health benefit by reducing the natural incidence of disease in the population.

Current health and safety regulations are based on statutory authorities designed to protect, rather than improve (i.e., hormesis), the public health. The public health protection provisions of representative nuclear regulations are provided in Table 4 (Mills et al. 1989). If hormesis can be appropriately demonstrated, it is unclear how beneficial health effects can be incorporated into the current system of regulations. Improved health as a result of exposure to small doses is beyond the requirement of health and safety regulations to protect the public health.

However, the hormesis-derived threshold (the zero effect point or ZEP) may have some regulatory utility if responses below the threshold were considered to be non-harmful rather than beneficial (i.e., below the threshold the risk of detrimental effects is zero). Exposure

**Table 4.** Selected nuclear regulations to protect public health.[a]

| Radiation protection standard | Authorizing statute | Radiation protection provisions |
|---|---|---|
| EPA Air Emissions Standards for Radionuclides 40 CFR 61 | Clean Air Act amendment of 1977 42 U.S.C. 7401 *et. seq.* | to promote public health; to determine whether or not emissions of radioactive pollutants endanger public health |
| NRC Basic Standards for Radiation Protection 10 CFR 20 | Atomic Energy Act of 1954 as amended and Energy Reorganization Act as amended | to establish rules, regulations and standards to protect health or minimize danger to life or property |
| OSHA Radiation Protection Standards 29 CFR 1910.96 | Occupational Safety and Health Act of 1970 29 U.S.C. 65 *et. seq.* | to protect workers from exposure to radiation |
| Federal Guidance on Diagnostic X-ray Exposures 43 FR 4377 | Radiation Control for Health and Safety Act of 1968 and other statutes | to develop a program of radiation protection including performance standards to control emission of electronic product radiation |

[a] Source: Mills et al. 1989.

limits could then be defined in terms of the threshold dose with appropriate inclusion of safety factors.

From an operational perspective, a system of radiation protection based on hormesis theory would be problematic (Fig. 2). As low as reasonably achievable (ALARA) is a central philosophy of radiation protection practice. ALARA developed from and is a rational extension of the idea that radiogenic dose response is monotonic in the dose range of interest in operational radiation safety, i.e., reduction in dose results in a concomitant reduction in radiogenic risk. However, hormesis is described by a non-monotonic dose response relation. Over the dose interval (0, ZEP), the slope of the dose response relation switches from negative to positive. Accordingly, in this dose interval, ALARA is no longer operationally meaningful because radiation produces beneficial effects and the risk of detrimental health effects is zero. Thus, implementation of hormesis theory creates an intractable problem in radiation protection practice. At doses above the ZEP, ALARA should remain the guiding operative philosophy but below ZEP the ALARA philosophy appears to have no utility. Doses typically encountered in radiation protection practice are below the ZEP as suggested by the estimated ZEP values in Table 2.

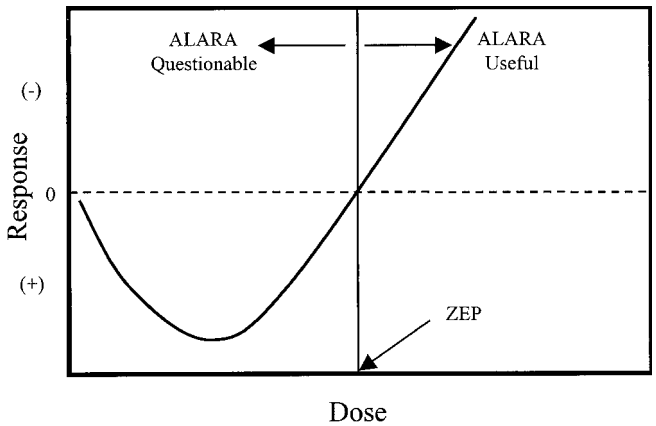


**Fig. 2.** Non monotonic dose response curve illustrating hormesis. The dashed line at zero response indicates no effect. Above this line effects are detrimental (-); below the line effects are beneficial (+). Hormesis theory predicts a threshold or zero effect point (ZEP) below which the probability of detrimental health effects is zero. The ALARA philosophy would appear to have no utility in radiation protection practice at doses below the ZEP.

## DISCUSSION

If hormesis can be justified, it presents an attractive solution to key problems in radiation protection. However, discarding an established theoretical foundation is difficult. Is substantial evidence for hormesis necessary to overthrow LNT? The possibility of obtaining such convincing evidence is unlikely. The LNT theory itself is supported by little evidence in the low dose range. In the context of policy decisions, choosing one theory to the exclusion of plausible alternatives is a difficult exercise and includes consideration of non-science factors (e.g., economic costs).

The National Council on Radiation Protection and Measurements (NCRP), the U.S. National Research Council, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the U.K. National Radiological Protection Board and other authoritative bodies have assembled committees of experts to review the available scientific data on low-level ionizing radiation health effects and issued reports analyzing the scientific literature in which the LNT and other theories have been used in estimating risk. The LNT theory has been the theory of choice used by most of these expert organizations over the decades as the basis for their recommendations. These organizations are heavily committed to the LNT theory because they believe it offers a credible and defensible middle ground given the uncertainty in the shape of the dose response curve in the low dose region. UNSCEAR reviewed the available literature on hormesis only to conclude that further studies should

be carried out but, at this time, there is little reason to reject the LNT theory (UNSCEAR 1996). Scientists who present evidence in support of radiation hormesis (or any other nonlinear theory) should bear the burden of explaining why their views are right and the expert scientific committees are wrong. Regulatory bodies depend on recommendations from scientific committees, and are not likely to reject the LNT theory for a less conservative one unless such action is defensible in a scientific and public policy context.

The debate about beneficial effects of low levels of radiation will continue indefinitely unless radiation hormesis is systematically evaluated by the scientific community. The following recommendations are suggested:

- A consensus definition of hormesis that facilitates quantification of the effect is needed.
- Since the LSS data is the primary source of information to estimate human health risks from ionizing radiation and has been used as evidence for hormesis by some scientists, independent analyses of the LSS database should be conducted. Availability of the raw, unreduced LSS data is critical in independent tests of the hormesis hypothesis. The LSS database is well-characterized and encompasses a wide range of absorbed doses. The LSS database is large enough, particularly in the low dose range, such that a hormetic effect may be detectable if it is present. A systematic analysis should be coordinated by a scientific committee (under the auspices of UNSCEAR or other suitable organization with international standing) made up of individuals representing all perspectives of the low dose radiation problem. The credibility of the committee's findings will hinge on how well the committee is balanced, and on the commitment of participants to the committee's objectives.
- Coupled with epidemiological investigations, mechanistic studies need to be conducted. What biological processes (at the level of the organism) are stimulated or induced by low doses of radiation leading possibly to the hormetic effect? Epidemiological data alone may be insufficient in answering the hormesis question since the magnitude of effects is small. Even if epidemiological evidence for hormesis can be found, the credibility of the theory will hinge on elucidation of biological mechanisms to explain the effect.
- Given that further epidemiological studies are not likely to resolve the LNT controversy, molecular and cellular studies to characterize unique biomarkers or unique carcinogenic processes that can be used to identify radiogenic disease at low doses would appear to be critical (Brooks 1999). No biomarkers unique for radiogenic damage have been identified to date. However, even if such biomarkers are identified in the future, it is unclear how marker information can be used to clarify the shape of the dose-response curve if it is not possible to distinguish damage from natural background radiation sources from other sources (e.g., medical or occupational exposures). Several U.S. federal departments and agencies, including the recently established U.S. Department of Energy's "Low Dose Radiation Research Program," conduct basic science research on the health effects of low level radiation. These research programs should include specific research directives pertaining to hormesis.

The central role of the LNT theory in radiation protection philosophy needs to be carefully examined. Is it appropriate to continue to support LNT simply because no other predictive theory is more plausible? If not, what should be the basis for choosing an alternative theory? In a purely scientific sense, support for a particular theory should be based on sufficient scientific evidence such that all biologically plausible alternatives may be rejected. However, in the case of the LNT theory in radiation protection, such scientific evidence does not exist. There is scientific evidence to support several predictive theories (see, for example, Table 3). The radiation protection community continues to support LNT because they believe the theory is simple, LNT derived risk estimates are conservative, and the LNT theory offers a reasonable middle ground among alternative theories. In the regulatory context, theory selection is driven by more than just science because of the large statistical uncertainties in health effects at low doses. Although policy and regulatory decisions should be based on the best science available, it is clear that non-science factors such as economic and political considerations are also important.

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