RulemakingComments Resource

From: Ricci <apricci@earthlink.net>
Sent: Tuesday, September 01, 2015 7:04 PM
To: RulemakingComments Resource
Subject: [External_Sender] Docket ID NRC-2015-0057 Submission by Dr. Paolo F Ricci
Attachments: US NRC_LATEST_Comments.docx

Dear Sir or Madam,

I attach my submission regrading this docket.

Sincerely,

Paolo F Ricci, PhD, LLM

Docket ID NRC–2015–0057

Paolo F Ricci PhD, LLM Response to the US Nuclear Regulatory Commission (*Fed. Reg*. Vol. 80, No. 120, Tuesday, June 23, 2015) Request for Comments on Linear No-Threshold Model and Standards for Protection Against Radiation (NUCLEAR REGULATORY COMMISSION, US NRC, Federal Register Vol. 80, No. 120, Tuesday, June 23, 2015 Proposed Rules 10 CFR Part 20. [Docket Nos. PRM-20-28, PRM-20-29, and PRM-20-30; NRC-2015-0057]. Linear No-Threshold Model and Standards for Protection Against Radiation.

Reason for This Response

The petitioners request that the NRC amend part 20 of Title 10 of the Code of Federal Regulations (10 CFR), "Standards for Protection Against Radiation," to be based on new science and evidence that contradicts the LNT hypothesis and request that the NRC greatly simplify and change 10 CFR part 20 to take into account the "vast literature demonstrating no effects or protective effects at relatively low doses of radiation."

Recommendations and Findings

1. We strongly support accepting the biphasic (hormetic) literature that has either demonstrated no effect at low doses or, from instance to instance, demonstrated "beneficial" effects – namely, the hormetic part of the curve, also known as the *J*-shaped part, that models percent decrease in cancer response from exposure to ionizing radiation).

2. We find that acceptance of published literature in peer reviewed journal should not be at issue. This accords with US Supreme Court decisions such as *Daubert*, *Joiner*, *Khumo* and more recent cases; those are law cases that have relevance to the US NRC but are not discussed. What is at issue is validity via confirmation by independent group or groups, which applies to any serious research. The LNT at low doses cannot be supported because it is, admittedly by those advocating it, a conjecture[1]. It is based on subjective belief that using it benefits society. This belief is in fact incorrect and may cause more damage than good.

3. We recommend the biphasic (hormetic) dose-response model as the justifiable model in lieu of the LNT conjecture. The rationale for our support is strictly based on the fact that

[1] An assumption is accepted as true without proof. A conjecture is a statement based on incomplete knowledge. The LNT at low dose is a conjecture, rather than an assumption. In some occasions it is a hypothesis, because the LNT has a basis in fact (albeit of limited mechanistic value).

the biphasic (hormetic) model is theoretically and empirically superior to the LNT conjecture.

4. We find that the LNT ma*y* serve public policy in specific instances, provided that the biphasic model is also discussed mechanistically and empirically, and is demonstrated not to be appropriate. So doing enhances human health protection and minimizes the social costs associated with regulating radiation exposures at low doses.

5. We suggest a policy paradox that may bias the allocation of diseases burden associated with ionizing radiations.

Docket ID NRC–2015–0057

Paolo F Ricci PhD, LLM Response to the US Nuclear Regulatory Commission (*Fed. Reg*. Vol. 80, No. 120, Tuesday, June 23, 2015) Request for Comments on

Linear No-Threshold Model and Standards for Protection Against Radiation

Response

Conjecture and Fact: LNT and biphasic (hormetic) models in science-policy for radiation protection

Paolo F Ricci, PhD, LLM

August 30, 2015

I certify that I have received no funding from any sources for the development, writing, and submission of this response to US NRC Notice of Request for Comments above-mentioned.

Docket ID NRC–2015–0057

Paolo F Ricci PhD, LLM Response to the US Nuclear Regulatory Commission (*Fed. Reg*. Vol. 80, No. 120, Tuesday, June 23, 2015) Request for Comments on

Linear No-Threshold Model and Standards for Protection Against Radiation

Conjecture and Fact: LNT *and* biphasic (hormetic) models in science-policy for radiation protection

Paolo F Ricci, PhD, LLM

… *We've got those linear . . . those linear no-threshold blues.* (M Rosenstein, A Musing Columntune, Feb. 1995, *Health Physics Newsletter*)

I. The Controversy Addressed in This Submission and Conclusions

The controversy we address is exemplified by the differences between the US and the French Academies (i.e., the US National Academies of Science, the French Academy of Sciences, and the French National Academy of Medicine) regarding the evidence of the effects of ionizing radiations at low doses. For example, although the US (e.g., BEIR VII, Phase 2 Report) supported the LNT, the French Academies raised doubts about this model's appropriateness (and scientific soundness).

We focus on the choice of regulatory dose-response models: the LNT at low doses and its alternative, the *J*-shaped biphasic (hormetic) cancer model. We only discuss chronic (i.e., long-term) exposures to carcinogens. The policy stance that best characterizes the LNT in US regulatory practice is (Puskin, 2009):

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.

Our reasoning and key conclusions $\mathbf{C_1}$ and $\mathbf{C_2}$ (under rule **R** := *use the LNT*) are the summary response to the US NRC request for comments, Table A. The details of the basis for this table are discussed after this Table.

Table A, Logic and Conclusions from the Analysis of the the Controversy Between the LNT at low doses and the J-shaped Hormetic Cancer Dose-response Model for Regulatory Actions

Our Work **Premises and Conclusion**	**Premises Regarding the LNT in Radiation Protection (Motivated by Puskin, 2009)**	***Our Work***	***Our work*** **Comments**[2]
Premise 1, p_1	The LNT is **presumed** to be conservative.	This is a rebuttable presumption under US administrative law. Often, epidemiologic studies can neither confirm or disconfirm the true shape of the model.	Biphasic data and models often – but not always -- rebut this presumption. When so, the LNT should be used instead.
Premise 2, p_2	Linear low dose **extrapolation to zero** is unlikely (**greatly**) to underestimate risk. This model (and the biphasic model) saturate at 100% response.	Conservative presumptions are asserted to be protective by not greatly underestimating cancer risk. An **extrapolation** is a mathematical exercise, the LNT is an **interpolation** from the data to the (0, 0) (dose = 0, response = 0) values of the + real axes. (If the LNT model's parameters are estimated, the wording should be ***constrained estimation*** because the values of the response intercept and exposure are forced to be zero)	**The LNT can do measurable damage at low doses** by negating the beneficial part of the biphasic -- *J*-shaped cancer model. See Figure 1, the *J*-shape is the hormetic model for cancer and the LNT at low dose, also for cancer.

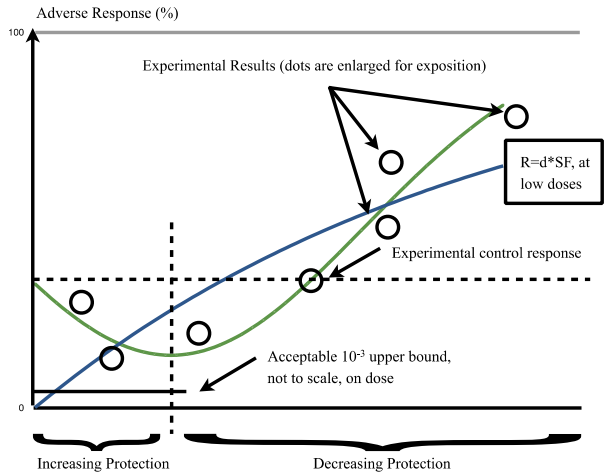
[2] A legal presumption is "*[a] conclusion made as to the existence or nonexistence of a fact that must be drawn from other evidence that is admitted and proven to be true*." If specific facts are established, a judge or jury must assume another fact that the law recognizes as a logical conclusion from the proof that has been introduced. A presumption differs from an inference, which is a conclusion that a judge or jury may draw from the proof of certain facts if such facts would lead a reasonable person of average intelligence to reach the same conclusion. A legal *conclusive presumption* is one in which the proof of certain facts places the existence of the assumed fact beyond dispute. A presumption cannot be rebutted or contradicted by evidence to the contrary. For example, a child younger than seven is presumed to be incapable of committing a felony. There are very few conclusive presumptions because they are considered to be a substantive rule of law. A rebuttable presumption is one that can be disproved by evidence to the contrary. An assumption is a taking for granted of a fact or statement without the need for proof (Merriam-Webster on line dictionary).

Premise 3, p_3	**Simplicity –** response is directly proportional to low doses.	Simplicity := proportionality at low doses; it is unknowably right or wrong at very low doses. It should not trump non-linearity when the stakes for those at risk are high (e.g., the disease is severe, dreaded, etc.). Non-linear models are often more consistent with actual behaviors, although they are difficult to explain to lay stakeholders and may be complicated to develop.	Simple explanations have their place, but not when they demonstrably cause damage to those at risk when the LNT is causally incorrect relative to the biphasic model. When the *J*-shape is correct but the default used is the LNT then the regulation does more harm than good, but the harm is left unstated. See Figure 1.
Incorrect Conclusions, C_1 and C_2, from ((p_1, p_2, p_3; R) $\rightarrow$ {C)	*… if radiation standards are promulgated under the* ***assumption*** *that (the) LNT is correct,* they will be protective. (Puskin, 2009)	The choice of one model over another should not result in a zero sum game for society. Rather, it is a matter of using the correct model advisedly, under the specific policy-science contexts justified by both substantial theory and empirical data and results.	***C_1 This strong conclusion is biased and circular (by p_1, p_2, p_3).*** ***C_2 The biphasic model correctly accounts for positive effect of exposures, when these are empirically and theoretically evident. This cannot happen when there is interpolation to zero from high doses inherent to the LNT.***

II. Introduction

The LNT and the hormetic (biphasic or even multiphasic) dose-response models can coexist (Ricci, Straja, and Cox, 2012). There may be limited instances where the LNT may be appropriate. There are many more instances where a biphasic model is more appropriate than any conjecture or assumption because it directly reduces risk (unlike the LNT) and indirectly minimizes the spending scarce resources on the illusion of increased safety. We depict, in Figure 1, the LNT (blue line) at low doses and the biphasic (or hormetic) *J*-shaped model (green line) fit to the same set of hypothetical experimental points (enlarged for ease of viewing) (Ricci and Sammis, 2012). Notably, the LNT uses the (0, 0) point as the origin of its curve; it is a statistical constraint for estimating the slope of the LNT curve at low doses; the *J*-shaped model does not (Cohen, 1995; Ricci, 2009; Ricci, Straja and Cox, 2012).

Figure 1, Hypothetical Fits of the LNT (at low doses) and the Biphasic (Hormetic) Models



The aspects that must be considered, for changing causation for regulating public and occupational exposures, range from risk-risk trade-offs to accounting for the evolution of scientific information and knowledge. The latter is at the core of this NRC proposal. Science has advanced to the point that biphasic mechanisms are established, and yet regulatory work in the US has not accounted for those advances. The inclusion of new evidence has lagged admittedly because of the simplicity of the LNT model.

Consider the evidence for the LNT at low doses. The *most important source of epidemiological data* is the study of Japanese survivors of the atomic bomb blasts who were exposed to acute (and thus sort-term) high doses of x-rays and neutrons (US EPA, 2011)). The basic model of radiogenic cancer adopted by the US EPA is the liner-quadratic dose-response (linear and quadratic in the dose term), such that "… at low doses and dose rates the dose-response for either low- or high-LET radiation appears to be linear with no evidence of a threshold" (US EPA, 2011, p.8). For low LET, response is also proportional to dose, but flatter than for the high LET scenario. Hence, these two scenarios are plausible bounds on risk – if the LNT conjecture is appropriate. This is a big if. As the US EPA (2011, p. 11) states:

Much recent research in radiobiology has focused on several new phenomena relating to the effects of low dose radiation, including: (1) the adaptive response, (2) genomic instability, and (3) bystander effects. These phenomena have raised questions about the reliability of the LNT model for radiation carcinogenesis.

This statement does not conflict with good science-policy. It allows validated evidence of a specific cancer model, the J-shaped hermetic model, to be used:

The preponderance of data regarding these effects has been obtained from experiments on isolated cells. There is limited information on the occurrence of these effects in vivo, and no understanding of how they might modulate risks at low doses. At first sight, it would appear that the adaptive response should be protective, whereas bystander effects and genomic instability might increase risk. Interpretation may be complicated, however, by the possibility

for triggering protective mechanisms in bystander cells, such as an adaptive response or apoptosis of precancerous cells (Citations omitted).

What is troublesome, however, is that according to this agency

The BEIR VII Committee was not convinced that these effects would operate in vivo in such a way as to significantly modify risks at low doses. It was a consensus of the Committee 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). A similar conclusion was reached by another group of experts assembled by the International Commission on Radiological Protection (ICRP 2005).

It is noticeable that:

In contrast, the French Academy of Sciences issued a report that strongly questioned the validity of the LNT hypothesis (Tubiana et al. 2005). The French Academy report cited a paper by Rothkamm and Löbrich (2003) showing that repair of DSBs, as measured by the disappearance of γ-H2AX foci, was absent or minimal at low doses, presumably leading to apoptosis of cells with DSBs. The French Academy report claimed that this finding indicated that risks were greatly overestimated at low doses. Recent studies have cast doubt on the significance of this finding, however (Lőbrich et al. 2005, Marková et al. 2007).

By its very rationale (the *single hit* conjecture, Armitage and Doll, 1957) the LNT has an even weaker basis that that just discussed. Yet, the:

EPA accepts the recommendations in the BEIR VII and ICRP Reports to the effect that there is strong scientific support for LNT and that there is no plausible alternative at this point.

The BEIR VII preferred risk models for radiogenic cancers are (US EPA, 2011):

1. for solid cancers, both excess and absolute risks increase linearly with dose.
2. For breast cancer, the excess absolute risk increases linearly with dose;
3. for thyroid, the excess relative risk increases linearly with dose, and
4. for leukemia, the excess relative and excess absolute risks also increase linearly in dose but the dose-response model contains an additional quadratic term for dose (the linear-quadratic model).

III. The US NRC Position

The US NRC stance regarding radiation exposure (U.S. NRC, home page, *Page Last Reviewed/Updated Friday, October 17, 2014; accessed on July16 at 1100 PDT*); it is unambiguous, stating that (i) and ii) added for clarity):

i) Although radiation may cause cancer at high doses and high dose rates, public health data do not absolutely establish the occurrence of cancer following exposure to low doses and dose rates — below about 10,000 mrem (100 mSv).

…

ii) *A linear no-threshold (LNT) dose-response relationship is used to describe the relationship between*

radiation dose and the occurrence of cancer. This dose-response model suggests that any increase in dose, no matter how small, results in an incremental increase in risk. The U.S. Nuclear Regulatory Commission (NRC) accepts the LNT hypothesis as a conservative model for estimating radiation risk.

The regulatory question that arises from ii) has two aspects: 1) What is a prudent level of tolerable exposure (Ricci and Molton, 1986), given that no exposure is safe according to the LNT, and 2) What if that exposure is demonstrably benign at low doses? We address the second question, to be consistent with the USNRC request.

IV. LNT or Biphasic (Hormetic) Models at Low Doses?

The debate we address is well characterized by the differences of opinions held by Puskin and Pawel (2014) and by Stabin and Siegel (2014) regarding the regulatory use of the LNT. In the US, the LNT at low doses is based on the learned opinions of the BEIR, the NAS, and other scientific bodies. The state of affairs (Puskin and Pawel, 2014) is:

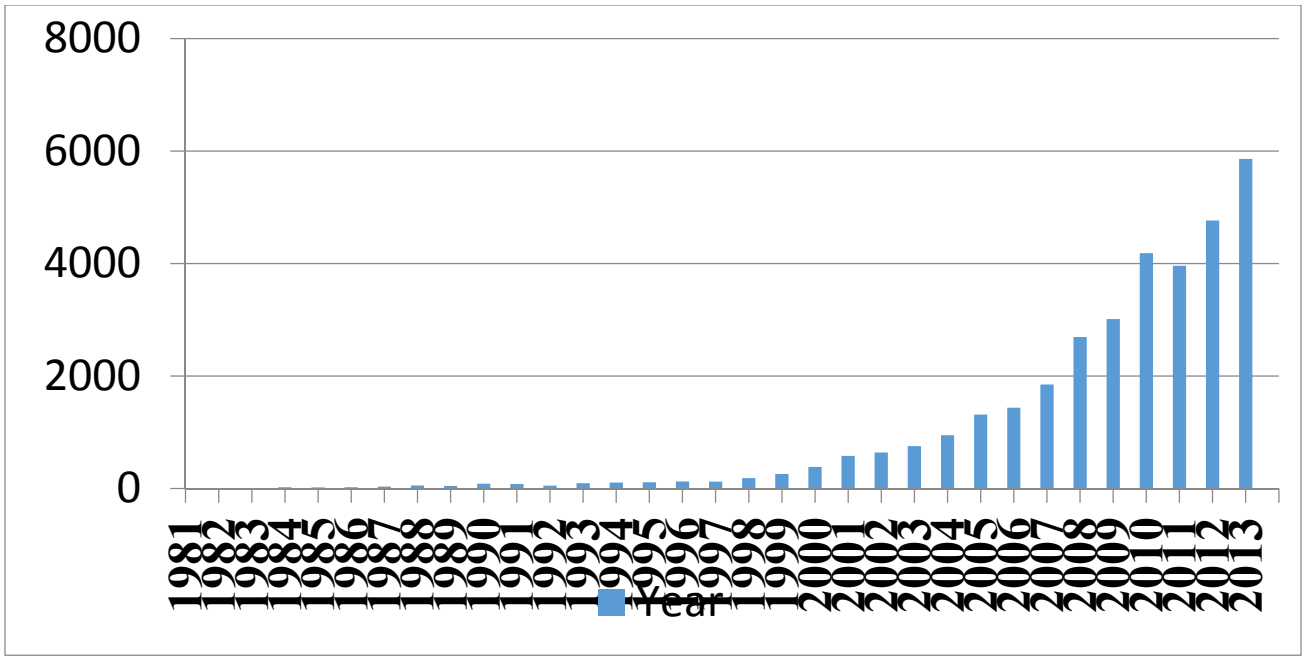
The position of EPA remains that, in view of current scientific information, LNT is the most suitable basis for assessing radiation risks at low doses. But, as emphasized elsewhere, LNT implies that, at low doses, risks, while not zero, are low (Puskin 2009).

Their statement, given the amount and weight of evidence for biphasic behaviors at low doses (Figures 2 and 3), conflicts with the US EPA (2004) objectives:

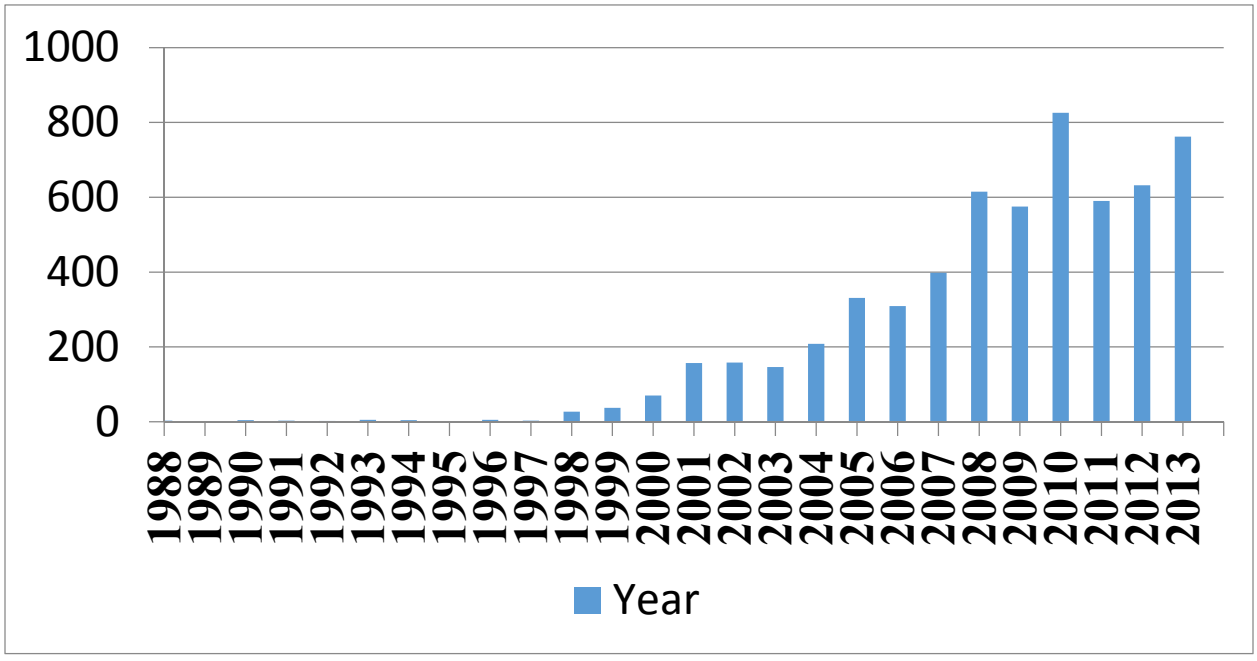
- *conducts risk assessment to provide the best possible scientific characterization of risks … on a rigorous analysis of available information and knowledge, … a summary of the confidence or reliability of the information available to describe the risk, …*
- *… can help guide risk managers to decisions that mitigate … risks at the lowest possible cost and which will stand up if challenged in the courts.* (Underlines added)

Specifically, the conflict is exemplified by the ever increasing (cumulative) evidence for biphasic models of dose response (Personal Communication, Calabrese, July 23, 2015), stated as the cumulative number of citations.

Figure 2, Cumulative Evidence for Biphasic (Hormetic) Dose-Response



The annual number of citations is depicted in Figure 3 (Calabrese, personal communication, July 23, 2015).



V. Low Doses: The LNT model versus the *J*-shaped biphasic cancer models

The nature of the LNT at low doses has two aspects. The first is mechanistic (cancer biology based). Its early basis was the *single hit, single target* Poisson distribution theory of cancer (Armitage and Doll (1957), Charnley (2015), Knudson (1971), Knudson (2001), Cairns (1975)). The

second is policy-based: it is asserted to be conservative in that it does not include a threshold (on the dose axis). Hence, an infinitesimal dose has an infinitesimal, positive probability of causing cancer: low doses do not give any advantage or "benefit."

The uncertainty affecting the LNT can be explained from the US EPA summary *(Linear Low-dose Extrapolation for Cancer Risk Assessments: Sources of Uncertainty and How They Affect the Precision of Risk Estimates*, www.usepa.gov/scipoly/sap/meetings/1998/july/session2.pdf). We note that the LNT falls squarely in the region of (apparently maximal) uncertainty, as depicted in Table 1 below [with added, bracketed text by the Author of this paper]:

Figure 1. Sources of uncertainties in risk assessments. The input parameters can vary from well conducted human toxicity studies with definitive supporting animal studies (Certain) to an exposure scenario which employs only model assumptions (Less Certain). The precision of the risk assessment is only as good as its least precise [*accuracy* is at least as important as precision, particularly when dealing with estimator functions] parameter [estimated by the correct estimator and after the assumptions buttressing that estimator are verified. If those assumptions cannot be verified, and the appropriate correction made, then the results are scientifically unsound because they may be biased, or have variability that is incorrect relative to what it should be]. [Text in square brackets added]

Table 1, Sources of Uncertainty in Risk Assessment (US EPA, op. cit.)

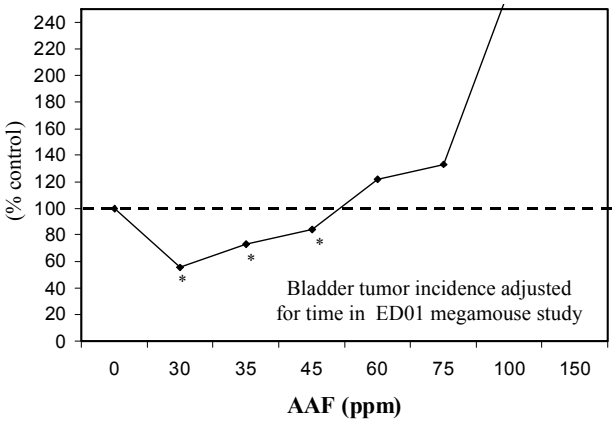
	CONFIRMED STUDIES	INCOMPLETE STUDIES	ASSUMPTIONS/ EXTRAPOLATIONS
TOXICITY EFFECTS	-Main studies -Mechanistic Studies -Epidemiologic Studies	-Surveys -Range-Finding -Literature Studies	-Interspecies extrapolation -Structure Activity Relationship -Route-to-Route Extrapolation
DOSE RESPONSE	-Closely spaced dosing -Multiple dosing	-Single Dose -Widely spaced dosing	-Toxicity Equivalent Factor -Benchmark Dose -Linear Low Dose -Potency Estimates
EXPOSURE	Monitoring Studies -Biomonitoring for occupational and residential exposure	PHED (surrogate data) -DRES	Default Assumptions -Exposure Factors/algorithms -Models -Activity Scenarios
	- CERTAIN	…	- UNCERTAIN

There is no argument that high levels of ionizing radiations decrease mean survival time of those exposed (UNSCEAR, 1982). There is incontrovertible evidence that, from approximately 300 mGy to 2 Gy, the cumulative probability of damage from exposure is approximately linear (Pollycove and Feinendegen, 2003). This is not the case for low levels of radiation because those levels are more likely than not "beneficial" through a variety of biological mechanisms.

Chemical carcinogenesis provides an example of the existence of the *J*-shaped dose-response. Bruce et al., 1981) studied mouse response to 2-AAF. The AAF experimental results, obtained in the mid 1970s by an US FDA long-term bioassay study with over *24,000* mice can determine the shape of the dose response at low doses (for that context). Despite the very large number of animals used, the results were only sensitive to an excess risk of *1/100*, much higher than the risk

levels used by regulatory agencies to set tolerable (or, less correctly, acceptable) doses or exposures. A Society of Toxicology (SOT) expert panel reviewed these results and reported that the study supported a biphasic (hermetic) dose response model, when the analysis included a time component based on interim sacrifices. The SOT found that *2-AAF* had a *J*-shaped dose response for bladder cancers that was consistent in each of the six separate rooms in which large number of animals were housed: it is easy to visualize the alternative LNT, by constraining it to begin at (0, 0) and, via a best fit plot through the data (Figure 4).

Figure 4, *J*-Shaped Dose-Response Relationship Between exposure to AAF and Percent Mouse Response



V. Qualitative and Quantitative Aspects: Modeling low dose-response

Qualitative -- The key problem with modeling response at low doses is that measuring the response directly is exceedingly difficult. This study points to a practical problem when considering live animal mammalian species lifetime cancer studies. The size of the study to detect low dose response becomes so large and expensive that it is unfeasible to carry out. When the predicted response is very low, as in cases of chronic exposure to radiation at levels similar to or slightly above background levels (levels of a few mSv/y), extracting a signal from the noise of the host of confounding factors—other carcinogens, varying levels of health at pre-exposure, and other risk factors—may well be impossible. This means that the *qualitative* features of the response may be unknowable. In trying to create public policy around such exposures, we are thus confronted with the worst possible case — a tiny, unknowable signal that must be multiplied by a vast number of potential cases to determine the possible level of harm involved.

Quantitative -- Systems in which a tiny error is magnified to create a much larger signal are said to be *ill-conditioned*. The thoughtless use of an ill-conditioned procedure runs the risk of producing an approximate solution —a solution in which errors can easily grow to be large enough that even the basic nature of the answer—much less its magnitude—may be fundamentally wrong. To exemplify, Ricci and Sammis (2014) have developed three scenarios.

Consider the following three models for a carcinogen, where *x=0* represents 0 dose and *x=1* represents the highest dose under consideration, at which we expect a rate of *R*. In these models, x_t may be interpreted as a very low dose, much lower than any expected background dose. Let:

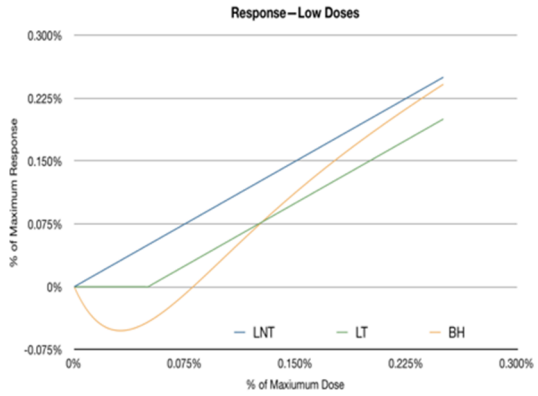
$f_1(x) = Rx$,

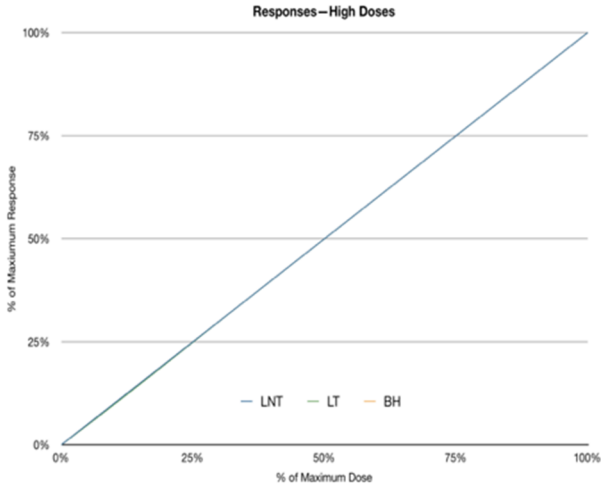
$$f_2(x) = \begin{cases} 0 & x < x_t \\ R(x - x_t)/(1 - x_t & x \geq x_t \end{cases}$$, and

$f_3(x) = Rx - (R_1 + r)xe^{-x/x_t}$.

These three curves are nearly indistinguishable for most values of *x*. At values of a few x_t, though, they show strikingly different behavior— f_1 continues to show positive harm, f_2 exhibits no harm below the threshold exposure x_t, and f_3 exhibits *J*-shaped (biphasic hormetic) behavior. Figure 5 plots these functions first at significant fractions of 1, then around x_t.

Figure 5, Alternative Behaviors of Dose-response Models at High Versus Low Doses





At significant fractions of the maximum dose, the three curves appear to be identical. At smaller scales, the distinct behavior of the three curves becomes apparent. If the measured exposure is $\frac{x_t}{2}$ on a large population P, policymakers are in an unenviable position. According to response function f_1, the small exposure should give rise to an expected $\frac{PRx_t}{2}$ cases of cancer; according

to f_2 none at all, and according to f_3 the exposure should actually prevent $P\left[R_1\frac{x_t}{2}e^{-1/2}-R\frac{x_t}{2}\left(1-e^{-1/2}\right)\right]$ cases per year. There are three aspects to consider. First, the actual dose *x* must be measured as accurately as possible. Any such measurement will necessarily have some degree of error. Second the response to this dose must be estimated using the best available science. This is straightforward for large *x* (in our example, for $x > x_t$), where the linear dose-response curve is well established, but enormously difficult for small *x*. Ricci and Sammis (2014) considered three possible policy situations.

(1) *One polluter, well determined dose* -- Here *x* is well determined, *f(x)* is not. In fact, as *sgn(f(x))* is not known, the science cannot even establish the *existence* of harm, much less its magnitude. In a heavily-populated region, *Nf(x),* the expected number of cases per year, now can be very large. In this case, claiming that the conservative decision is the one that avoids the greatest possible harm is questionable.

(2) *Many polluters, well-determined collective dose* $x \gg x_t$*, delivered in partial doses such that each polluter* P_i *causes* $x_i < x_t$ *of the total dose.* This time f is on the solidly established linear response portion of the curve. The ultimate result depends entirely upon how the specific jurisdiction decides to apportion damages. If the damages are apportioned according to the fractional responsibility for the dose, then the ultimate damages will be precisely those expected by LNT, albeit with a significantly different justification.

(3) *A single polluter polluting near* x_t*; background rate* R_b *of the adverse event.* Here a single polluter is polluting near the threshold level. We assume a background rate for the adverse event is R_b , even in the absence of the pollutant. What is the probability that a *specific* adverse event has been caused by the pollution? In this case, the total rate of the adverse event is $f + R_b$, so the fraction of the rate due to the pollution is $\frac{f}{f+R_b}$ for positive f . When these claims are addressed by the legal system, then, harm is said to have occurred whenever $\frac{f}{f+R_b}$ exceeds some threshold probability T . In this case, if the standard is something like "better than even odds" that the specific harm is due to the low-level exposure, then the difference between LNT and the biphasic model is irrelevant; by that point the danger should be readily measurable. Cases1) and 2) suggest that the LNT model makes sense as a regulatory device if one expects the number of polluters to be quite high, so that the total dose may be much larger than the dose for which any individual polluter might be responsible. It is a much more dubious proposition in cases in which a sole low-level polluter exists. It is much more reasonable to scale down a well understood harm to the scale at which individual entities can respond than to scale up a poorly understood harm by multiplying it by a large population. Finally, regulations are usually designed

to prevent exposures well below the level at which the rate of adverse effects doubles. This can be problematic in the face of a difficult-to-detect gap between possible dose-response curves at low-levels.

VI. Regulatory Inconsistency and Resulting Paradox

Against this background, Stabin and Siegel (2014) suggest that the stringency of the LNT causes regulatory inconsistency because:

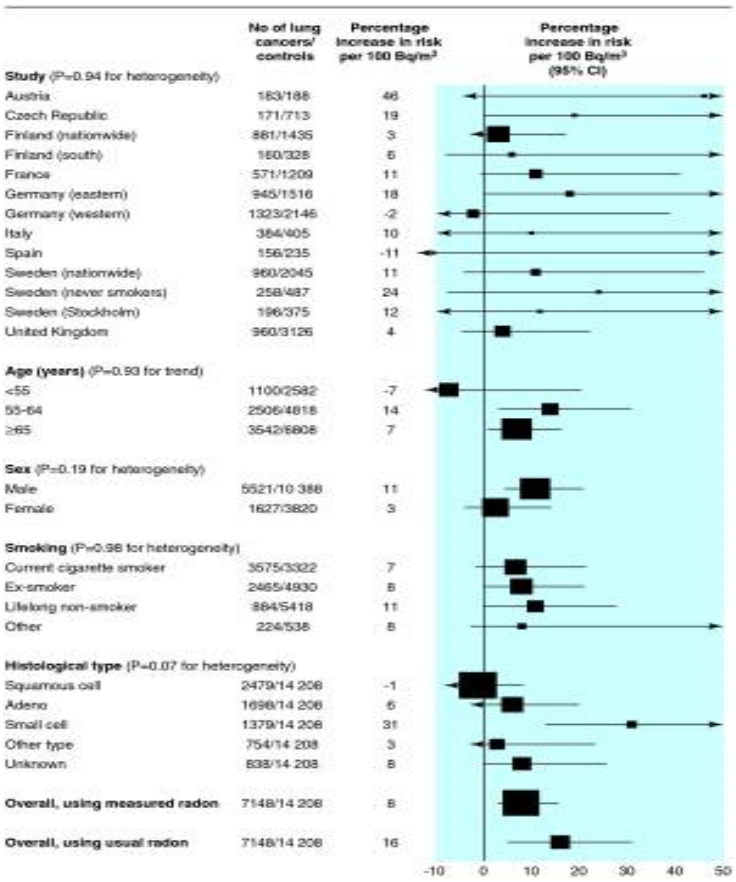
… the LNT hypothesis implies that any radon exposure, no matter how small, is associated with a lung-cancer risk. By its support of the LNT hypothesis, the EPA accepts that the only safe level of radon gas is no radon gas. According to the information on the EPA web page (epa.gov/radon), the estimated risk of lung cancer for a nonsmoker exposed to radon gas levels of 0.15 Bq L^{-1} is 0.7 percent using the LNT method—that is, 7 out of 1,000 nonsmokers are at risk for developing lung cancer from this exposure. Nevertheless, EPA has set 0.15 Bq L^{-1} as the action level above which EPA recommends that a homeowner take corrective measures and below which no action is needed. So most homeowners will not take any remedial action if their homes contain levels of radon gas at 0.15 Bq L^{-1} and below. Thus the 0.15 Bq L^{-1} action level represents a de facto "acceptable" level and a de facto threshold since most homeowners believe no action is required at or below the action level. This contradicts the EPA's endorsement of the LNT hypothesis. (Bq is Becquerel, L is liter).

Puskin and Pawel (2014) response suggests the continued reliance on *mainstream science-based evidence*, as adopted by BEIR and similar organizations. Consensus and not the direct evidence itself (which cannot be available by the very definition of a conjectured model), is that:

Stabin and Siegel's rejection of LNT is indefensible when it comes to radon. Citing a 1995 paper by Bernard Cohen, they claim that LNT "may grossly overestimate cancer risks associated with radon [sic] inhalation." They appear to be unaware of the pooled analyses of residential case-control studies (Darby et al. 2005; WHO 2009), which directly show that LNT provides a reasonable estimate of risk at radon levels only slightly above the EPA action level. It should also be pointed out that EPA's action level was not chosen on a health-risk basis, but it was driven by the technical feasibility of achieving reliable and verifiable reductions by homeowners.

For example, Puskin and Pawel (2014) rely on epidemiological results, aggregated via meta-analysis in a study by Darby et al., (2005), from whom we reproduce one of their key results, Figure 6.

Figure 6, Aggregate Analysis of Several International Studies (from Puskin and Pawel, op. cit.)



This *aggregation* (last two lines of Figure 6), points to an increase in risk per 100 Be/m^3 of air exposure. Yet, a quick assessment of each of the separate studies included in Figure 6, suggests that 17 of the total 26 studies yield statistically insignificant (they straddle 0 percent) increase in risk per 100 Be/m^3 of air.

Puskin (2009) suggests that scientific consensus is both necessary and sufficient to justify estimations of radiogenic risk:

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.

The LNT causation is a conjectured risk model for humans in which an infinitesimal exposure causes an infinitesimal response. Lack of evidence at low doses is resolved by adoption through policy fiat, technologically limiting dose to be greater than zero, the whole being justified by consensus. The EPA's technical feasibility for exposure standards is not determined by risk analysis; it is designed to achieves a practical level of exposure. Yet, federal agencies have moral and legal duties unbiasedly to inform those at risk about their likely cancer burdens due to involuntary exposure to ionizing radiations.

Under the LNT conjecture, this policy causes a number of individuals exposed to incur radiogenic cancers: but those at risk cannot be informed. Hence the paradox:

Avoiding the stricture of the low dose LNT by adopting it and then setting a standard to the right of the 0-value results in a de iure regulatory threshold.

Using the LNT, the regulatory threshold is surely known to increases the burden of radiogenic cancers by a finite amount, computable using the J-shaped model (Ricci, Straja, and Cox, 2012)

The regulatory threshold actually decreases that number of cancers whenever the correct model is biphasic. Protection occurs up to the minimum of the biphasic model.

Protection goes unnoticed.

The decreased disease burden is incorrectly assigned to some other policy actions.

VII. Evidence: Further comment

The *J*-shaped behavior had been demonstrated by Vilenchik and Knudsen (2006) with regressions for the excess relative risk of DSB mutations. Bogen et al., (1997) developed a cytodynamic *2*-stage model predicting a *J*-shaped response for ionizing radiations and shows that his model fits the observed uranium miner data. Scott *et al.* (2007) developed a model that links different cellular states to the probability of transition from one state to the other as a function genomic damage induced by different level of exposure to ionizing radiation. Using a MCMC simulation, Scott and his coworkers find a multiphasic response that depends on the amount of radiation and repair mechanisms. A Canadian epidemiological study of female mortality involving breast cancer, where the patients had had several fluoroscopies, was reassessed by Pollycove (1988). The original report of a LNT effect from those exposures was not LNT-like but, rather, it was *J*-shaped. Redpath (2007) commented that the LNT hypothesis is inconsistent with the empirical results from in vitro studies involving exposures to low energy photons (which are used for imaging work, such as mammography). Radiation damage to cellular DNA (pre- or post-exposures to mSv levels) has also shown to be characterized by *J*-shaped functions for *X*-and gamma rays.

Upton, (2001) states that:

Although the existence of such adaptive responses is no longer in doubt, it is not clear from the existing data whether the dose-response relationships for mutagenic, clastogenic, and carcinogenic effects of radiation are comparably

biphasic in the low-dose domain (citations omitted for brevity). Pending further research to resolve this question, the implication of adaptive responses or the setting of radiation exposure limits will remain uncertain.

Regarding mechanistic modeling, Puskin (2009) suggests that:

… 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.

The logical jump from (*appears to be ruled out)* to *([t]hese mechanistic features of radiation carcinogenesis argue against a strict dose threshold)* does not justify the LNT. The granularity of the former (*single mutation*) does not transfer to that of the other (*the high rate of cancer observed in a population*), absent a complete model that justifies such aggregation, both theoretically and empirical. Puskin (2009) also states that:

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.

What is *practical* is in the eyes of a regulatory beholder and the courts that will review the agency's (or Commission's) work. As to the epidemiological evidence, the meta-analysis results (Figure 6) cast doubts on the universality and validity of the LNT at low doses.

Causation is essential to science policy – stakeholders, science and the courts expect it. Corroborated evidence (confirmation) may be provided by mechanistic models. These are likely to lead to a biphasic response – not just a threshold. For instance, Bogen, Conrado, and Robinson (1997), Cox (2006), Scott, Haque, and Di Palma (2007), Zhao and Ricci (2010), Lou, Zhao, Wu, and Ricci (2013)) have done work directed to including the fundamental mechanisms leading to biphasic and threshold behavior of exposure and demonstrating such behavior for cancer.

Different findings can show when exposure can be *safe*, *beneficial* or unsafe on the same disease continuum; this is not novel. It was used in the FDA's determination that selenium, in a rodent study, was not a mutagenic (i.e., it is not a direct carcinogen) at low doses, although it was a liver carcinogen at high doses. Cadmium was thus not banned as a food additive: under the FFDA&CA in small doses it was tolerable as an additive to the diet of livestock animals.

VIII. Conclusion

The effect of ionizing radiation on many species has been studied for longer than a century (erythema from exposure to high levels of x-rays as our rough starting point). Yet, we find that society still needs clearer guidance than that currently available through regulatory policy's

continued reliance on a conjecture justified by appeal to a higher authority. Seemingly, that authority either disregards or minimizes the contribution of mounting empirical and theoretical evidence. What is learnt from the debate between Stabin and Siegel, on the one hand, and Puskin and Pawel on the other, is that the *battle of experts* is alive and well. This is good for the progress of science. But questionable for science-policy, as our paradox shows. When there is a regulatory view that adopts consensus about a conjecture as a way out of a difficult scientific issue, it may appear to lead to regulations for the sake of regulating. That view must be tempered and become secondary when new evidence trumps the conjecture.

Finally, biphasic models are not always correct (Ricci, Straja, and Cox, 2012). There are instances, as when the mechanisms causing a disease occur at very low doses and do not exist or are much less effective at higher doses -- unlike that of most carcinogens dealt with in regulatory analyses. In those situations, it is probable that the LNT may be appropriate: the result may be a shallow, rather than steep, LNT relative to the dose axis.

REFERENCES AND BIBLIOGRAPHY

Armitage P. and Doll R, (1957), A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. *Br. J. Cancer*, 11: 161–169.

Bruce RD, Carlton, WW, Ferber KH, Hughes DH, Quast JF, Salsburg DS, and Smith JM 1981, Re-examination of the ED01 study -- adjusting for time on study. *Fund. & Appl. Toxicol*., 1:67-80.

Charnley G, One-Hit Model. Encyclopedia of Public Health. 2002. *Encyclopedia.com.* 16 Jul. 2015 <http://www.encyclopedia.com>,

Cairns J (1975), Mutation selection and the natural history of cancer. *Nature*, *255*, 197–200.

Knudson AG, (1971), Mutation and cancer: statistical study of retinoblastoma. *Proc. Natl. Acad. Sci. USA*, *68*, 820–823.

Knudson AG (2001), Two genetic hits (more or less) to cancer, *Nature Reviews*, 1:157-162.

Environmental Protection Agency (1987). The risk assessment guidelines of 1986. EPA-600/8-87/045. (Guidelines for carcinogen risk assessment; Guidelines for mutagenicity risk assessment; Guidelines for the health risk assessment of chemical mixtures; Guidelines for the health assessment of suspect developmental toxicants; Guidelines for estimating exposures.) U.S. EPA, Office of Health and Environmental Assessment, Washington.

Environmental Protection Agency (1996), *Proposed Guidelines for Carcinogen Risk Assessment*, Fed. Reg., 61:17960-18011.

Ibid (2011), *EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population* (April 2011), EPA 402-R-11-001, Wash., DC.

Toth DJA, Gundlapalli AV, Schell WA, Bulmahn K, Walton TE, Woods CW, et al. (2013), Quantitative Models of the Dose-Response and Time Course of Inhalational Anthrax in Humans. *PLoS Pathog* 9(8): e1003555. doi:10.1371/journal.ppat.1003555

Stabin MG and Siegel JA (2014), Does the EPA contradict its own policies? *Health Physics News*, pp 17-19.

Puskin JS and Pawel DJ (2014), Response to Stabin and Siegel, *Health Physics News*, pp 19-20).

US EPA, Office of the Inspector General, *Improvements to EPA Policies and Guidance Could Enhance Protection of Human Studies Subjects*, March 31, 2014, Wash. DC.

Cohen BL (2010), Letter to the editor: Response to EPA position on cancer risk from low level radiation. *Dose-Response*, 8:384–386.

Puskin JS (2009), Perspective on the Use of the LNT for Radiation Protection and Risk Assessment by the U.S. Environmental Protection Agency, *Dose-Response*, 7: 284-291.

Pollycove M and Feinendengen LE (2003), Radiation-induced versus Endogenous DNA Damage: Possible Effect of Inducible Protective Response in Mitigating Endogenous Damage, *Hum. Exp. Toxicol*, 6:290-306

Cox LA. (2011) Universality of J-Shaped and U-Shaped dose-response relations as emergent properties of stochastic transition systems. *Dose-Response*, 3(3): 353–368.
http://doseresponse.metapress.com/app/home/contribution.asp?referrer=parent&backto=issue,6,11;journal,13,13;linkingpublicationresults,1:119866,1

Scott BR, Haque M, Di Palma J (2007), Biological basis for radiation hormesis in mammalian cellular communities. *Int J Low Radiat.* 4(1):1–6.

Bogen KT, Conrado CL, Robison WL 1997), Uncertainty and variability in updated estimates of potential dose and risk at a U.S. nuclear test site—Bikini Atoll. *Health Phys*; 73:115–126.

Cohen BL (1995), Test of the linear-no-threshold theory of radiation carcinogenesis for inhaled radon decay products. *Health Phys*.68:157–174.

Calabrese, EJ and Ricci,PF (2009), Hormesis and Risk Assessment, Part 10. In: *General and Applied Toxicology*, 3rd Edition (B Ballantyne, TC Marrs, T. Syversen, Editors). John Wiley and Sons. NY, NY

Conolly RB and Lutz WK (2004). Non-monotonic dose-response relationships: mechanistic basis, kinetic modeling, and implications for risk assessment. *Toxicol Sci* 77: 151-157.

Pollycove M, (1988), Non-Linearity of Radiation Health Effects, *Env. Health Persp*., 106:363-368

Vilenchik NM and Knudsen AG (2006), Radiation Dose-rate Effects, endogenous DNA damage, and signaling resonance, *Proc. Nat. Acad. Sci. USA* (2006) 103(47): 17874-9

Schollenberg H, Mitchel RE, Redpath JC, Crawford-Brown DJ, and Hoffman W (2007), Detrimental and Protective Bystnader Effects: A model approach, *Rad. Res*., 168(5):614-26 (Erratum, *Rad. Res*, 2008, 169(4): 481.

Ricci PF, Straja SR, and Cox jr LA (2012), Changing the Risk Paradigms Can be Good for Our Health: J-Shaped, Linear and Threshold Dose-Response Models*, Dose Response*, 10(2): 177–189. Published online 2011 Sep 29.

Upton AC. (2002). Carcinogenic effects of low-level ionizing radiation: problems and prospects. *In Vivo* 166: 527-533.

Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Bermann F, Cowper G, Fix J, Hacker C, Heinmiller B, Marshall M, Thierry-Chef I, Utterback D, Ahn YO, Amoros E, Ashmore P, Auvinen A, Bae JM, Bernar J, Biau A, Combalot E, Deboodt P, Diez Sacristan A, Eklöf M, Engels H, Engholm G, Gulis G, Habib RR, Holan K, Hyvonen H, Kerekes A, Kurtinaitis J, Malker H, Martuzzi M, Mastauskas A, Monnet A, Moser M, Pearce MS, Richardson DB, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, T 1101 urai I, Usel M, Veress K. (2007), The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Estimates of radiation-related cancer risks. *Radiat Res.* 167(4):396-416.

Ricci, PF and Sammis, IR (2014), Regulatory-Science: Biphasic Cancer Models or the LNT—Not Just a Matter of Biology!, *Dose-Response: An International Journal*: Vol. 10: Iss. 2, Article 3. Available at:
http://scholarworks.umass.edu/dose_response/vol10/iss2/3

Zhao Y and Ricci PF (2010), Modeling Dose-Response at Low Dose: A Systems Biology Approach for Ionization Radiation, *Dose-Response: An International Journal*: Vol. 8: Iss. 4, Article 7. Available at: http://scholarworks.umass.edu/dose_response/vol8/iss4/7

Lou, I C; Zhao, Y; Wu, Y; and Ricci, P F. (2013) Systems Cancer Biology and the Controlling Mechanisms for the J-Shaped Cancer Dose Response: Towards relaxing the LNT hypothesis, *Dose-Response: An International Journal*: Vol. 11: Iss. 4, Article 4. Available at: http://scholarworks.umass.edu/dose_response/vol11/iss3/4

P F. Ricci PF and Molton, LS, (1985) Regulating Cancer Risks, *Environ. Sci. Technol.*, *19*: 473–479; DOI: 10.1021/es00136a001

Ricci PF, (2009) Dose-response models: how might we think about linearity and nonlinearity? *Human & Experimental Toxicology*; 28:29-38. DOI:10.1177/0960327109103524 ·