Dose-Response: An International Journal

Volume 10
Issue 2 *Special Issue on the Role of Linear and Nonlinera Dose-Response Models in Public Decision-Making*

Article 7

6-2012

THE ROLE OF LINEAR AND NON-LINEAR DOSE-RESPONSE MODELS IN PUBLIC DECISION-MAKING (WHAT TO DO WHEN UNCERTAINTY AFFECTS ENVIRONMENTAL HEALTH CHOICES)

Paolo F Ricci
Holy Names University, Xiamen University, Xiamen, China and University of Massachusetts, Amherst

Ian R Sammis
Holy Names University

Dose-Response, 10:203–208, 2012
Formerly Nonlinearity in Biology, Toxicology, and Medicine

ISSN: 1559-3258
DOI: 10.2203/dose-response.11-024.Sammis

International Dose-Response Society
www.Dose-Response.org

THE ROLE OF LINEAR AND NON-LINEAR DOSE-RESPONSE MODELS IN PUBLIC DECISION-MAKING (WHAT TO DO WHEN UNCERTAINTY AFFECTS ENVIRONMENTAL HEALTH CHOICES)

P. F. Ricci □ Holy Names University, Xiamen University, Xiamen, China and University of Massachusetts, Amherst

Ian R. Sammis □ Holy Names University

INTRODUCTION

This Special Issue contains several articles that use theoretical and empirical findings about causation at low doses in an attempt to provide useful methodological insights to those concerned with making choices about the tolerable level of danger posed by carcinogens and toxic agents at very low exposures. The reason for our concern with the soundness of choices dealing with those exposures has been most vividly and tragically shown by the two natural events — earthquake and resulting tsunami — that caused the catastrophes that so greatly affect Japan. The nuclear power plans suffered failures that have had an almost immediate impact on the future of energy production and policies of countries that depend or consider on nuclear energy. Once again, the development and safety of nuclear power is questioned, in part because of the belief that very low exposure to the radionuclides emitted in those accidents causes cancers, regardless of dose. The question then is: Is there evidence—rather than either dogma or assumption or both—that low levels of exposure cause detriment to human health? Clearly, there is no argument that much larger exposures do cause cancer or can kill in very short order.

In regulatory risk analysis, causation, through dose-response models, is part of the legal basis for justifying the reduction of exposures to hazardous agents likely to cause cancer. When a sufficiently large population is exposed to a very low (near-background) dose, even nearly infinitesimal excess individual risks can in principle cause a substantial number of additional cancer cases. In the aggregate, the overall expected number of cancer cases, while large, may still be generally undetectable, given the large background number of cancers in a population. To set environmental and occupational standards, the law couples legal causation and the "best science" about cause and effect to regulatory policy-making. The potential

Address correspondence to Paolo F. Ricci, Holy Names University, Oakland, CA 94619; Phone: 510-436-1337; Email: ricci@hnu.edu

for judicial review of an unsound regulatory choice—review that occurs on both sides of the Atlantic—should limit the scope of an agency freedom to act arbitrarily. Throughout the special issue, we see that this is not true in practice. Hazardous exposures are regulated (e.g., via numerical standards limiting exposure, often considering hourly or other temporal window) at either acceptable or tolerable risks: for example, a one in a million chance of cancer death yields the corresponding tolerable exposure, for a given causal model of dose-response (Holland, 1986). The usual or default model used in setting those allowable exposures, for cancer risk assessment, is (regardless of its overall form) linear, no threshold (or beneficial effects), the LNT. Unfortunately, this is a conjectural model, as for any real carcinogen there must be some minimum level at which a response can be detected. Defaulting to the LNT—when incorrect—can do more harm than good. For toxic agents, the threshold model is generally used (often with factors of safety to further decrease the magnitude of the dose to an acceptable level of intake by humans. Because the threshold model cannot account for any beneficial effects at very low doses, it can also lead to suboptimal decisions.

The purpose of this Special Issue is to address several policy-science implications of default dose-response models, their biphasic (hormetic) alternatives, and the consequences of using these defaults (LNT and threshold models) when the evidence is contrary to those defaults. Rather than reducing the burden of disease, they can actually add to it. Rather than preventing cancer, defaults actually add to the burden of disease by preventing any beneficial effect and thus increase to the overall social costs associated with a policy that disallows, de facto or de jure, a biphasic alternative—*even when that alternative is demonstrably correct.* To achieve our objective, the special issue deals with:

- Aspects of dose-response use in US regulatory law
- Aspects of dose-response use in the EU countries
- Overview of Chinese uses of risk assessment and management based on cancer and toxicological end-points
- Linear and non linear dose-response models with an emphasis on ionizing radiations at low doses (or dose rates)
- Aspects of costs and benefits analysis associated with the choice of dose-response models

The Special Issue also suggests ways to deal with policy postulates, such as the precautionary principle, that generally stand for the proposition that "*when there are threats of serious or irreversible damage to the environment, scientific uncertainty should not prevent prudent actions to prevent potentially large or irreversible damage*, as well as the critical issue of linearity at low doses" (Cameron, 1994). A *threat*, of course, may just be the result of igno-

rance or an incorrect perception. The combination of precautionary stance and use of a hypothesis that cannot be tested creates complex policy issue that can have large and unintended societal effects. The foundational basis for precautionary principle (O'Riordan and Jordan, 1995) in many conventions and treaties, as well as pronunciations by a number of entities, requires differentiating them between legally binding forms (e.g., Title XVI, Art. 130r of the Maastricht Treaty on European Union (1992); the Delaney Clause to the US FFDCA). Precautionary principles tend to place the burden of proof about who causes the hazardous situation leading to risk on those who market or develop a product, as the EU does in the REACH Directive. An example of such a shift (Commission of the European Communities, 2001) is that the

> "[r]responsibility to generate knowledge about chemicals should be placed on industry. Industry should also ensure that only chemicals that are safe for the intended purposes are produced."

The theoretical possibility that biphasic models can be used in regulating exposures, nonetheless, can be traced to EC's Commentary, which also states that:

> "A scientific evaluation of the potential adverse effects should be undertaken based on the available data ... [T]his requires reliable scientific data and logical reasoning, leading to a conclusion which expresses the possibility of occurrence and the severity of a hazard's impact on the environment, or health of a given population ... " (Commission of the European Communities, 2001).

More specifically, this Commentary concludes that *precautionary measures must not be applied to address conjectured risks*. As some of the papers in this Special Issue indicate, it is not clear that the difference between conjectured risk – a result of using a LNT model – and actual risks is explicitly recognized either in the EU or in the US. To the extent that other countries, e.g., China, follow US or European regulatory risk assessment frameworks, the overall result is less that societally optimal. The Canadian government proposed guiding principle for risk analysis includes the precautionary principle (Government of Canada, 2001, *The Need for a Federal Approach*) as follows:

A. Follow-up scientific activities, including further research and scientific monitoring, are a key part of the application of the precautionary approach. ... (a)
B. "Sufficiently sound information base" should be interpreted as sound and reasonable scientific information, including uncertainties that,

through evaluation ... [T]hat is, while scientific information would not need to demonstrate definitively the cause-and-effect relationship between risk and serious harm, it would demonstrate that such a risk exists. (And)

C. Generally, the responsibility for providing the scientific information base (the burden of proof) should rest with the party who is taking an action associated with potential or serious harm. ... "

An important issue that often goes unstated is well captured by Canadian Government (Gov of Canada, 2001). Specifically, it states that:

> "... it is impossible to prove a negative (e.g., to prove categorically that something will cause no harm, or to prove with absolute certainty that something bad might not happen or to prove that something is not harmful), but possible to demonstrate that "reasonable testing" was done with no evidence of harm ... The real and potential impacts of making a precautionary decision (whether to act or not to act), including social, economic and other relevant factors, should be assessed."

US law contains several variants of precaution to justify the regulation of toxic agents. For example:

- "The Administrator shall, specify, to the extent practicable: 1) Each population addressed by any estimate of public health effects; 2) The expected risk or central estimate of risk for the specific populations; 3) Each appropriate upper-bound or lower-bound estimate of risk ..." (Safe Drinking Water Act, § 300g-1(b)(3)),
- "Provide an ample margin of safety to protect public health or to prevent an adverse environmental effect" (Clean Air Act, §112(f)).
- "To assure chemical substances and mixtures do not present an unreasonable risk of injury to health or the environment" (Toxic Substances Control Act, TSCA §2(b)(3)).
- "Adequate to protect public health and the environment from any reasonably anticipated adverse effects" (Clean Water Act, CWA §405(d)(2)(D))."

It would seem that, if an agent were provably beneficial, such finding would not trigger its regulation under any of these statutes, until an unacceptably unsafe dose is reached. We think that this precept applies to the EU's as well, which uses the concept of *zero tolerance*. Specifically, the regulatory aspects of exposure to toxic agents (a combination of Regulations and Directives issued by the EU) based on the principle of *zero tolerance* means that no concentration is safe for human use or consumption, if a

substance has not been issued a maximum residue limit (MRL). The MRL is a requisite (Directive 2001/82/EC, the "cascade provisions", from Commission of the European Communities, 2001) for the marketing of any veterinary products used as sources of food for humans: if there is no MRL, then the product containing certain listed substance for which there is no MRL is cannot be marketed unless there is zero mass quantity of pharmacologically active of the listed substances. Thus, for those substances, unless the MRL exists, exposure to them is not tolerable. But, as the limits of analytical detection are increasing (lower and lower concentrations are increasingly detected), zero tolerance is equivalent and seemingly much more stringent that the *zero risk* of US law (used in the Delaney Amendments to the FFDCA, PL86-618; 21 U.S.C §376(b)(5)(B)).

UNCERTAIN OUTCOMES AND CHOICES

Uncertainty and causation are inevitable aspects of public heath decisions based on causal models and thus the correct assessment of risky outcomes must also include the uncertainty in those outcomes. Yet, some interpretations of the precautionary principle – such as *political will* in the EU — either dismiss or ignore this tenet in favor of actions that are guided by qualitative, deterministic (but often not testable) assumptions. Avoiding costly mistakes, even when made in good faith, suggests achieving a convergence between legal principles and their practical application in a socially efficient way (Wynne, 1992; Wynne and Mayer, 1993). Some of the aspects decision-making that are relevant to this point and to the issues and methods discussed in this Special Issue include considering:

- *Initiating Events and Outcomes* for which there is no past experience thus requiring great attention to the measures of uncertainty used and the way choices are made
- *Deterministic representations* where formal description of biological cancer processes (e.g., via a system of ordinary or partial differential equations) gives the illusion of complete and certain knowledge of future outcomes and their magnitude (given initial and boundary conditions)
- *Sensitivity to initial and boundary conditions* for certain types of models used to describe a causal biological process
- *Need for sensitivity analysis,* when scenarios describe seemingly plausible case-and-effect relationships
- *Misspecified models* that exclude important factors, and wrongly or incompletely formulate the causal relations between those factors and response
- *Statistical uncertainties* that combine estimation and inference with the variability of data (e.g., sampling variability), heterogeneities, confounders, measurement errors, and missing data

Probabilistic reasoning provides a formal and coherent method (not accepting a gamble that surely leads to loss and that, on average, more is preferred to less) for describing uncertain knowledge and for updating it with new data, while accounting for variability. Probability distributions, in contrast to deterministic numbers, indicate the variability in quantities that may be essential for stating and evaluating data-driven causal arguments (Shafer, 1996; Pearl, 2000).

REFERENCES

Cameron, J. 1994. The status of the precautionary principle in international law, In T O'Riordan and J Cameron, Eds *Interpreting the Precautionary Principle*, pages 262-89. Earthscan

Commission of the European Communities, 2001. Brussels.

Delaney Clause to the US FFDCA, PL86-618; 21 U.S.C §376(b)(5)(B)).

Government of Canada, 2001, http://www.tbs-sct.gc.ca/pubs_pol/dcgpubs/RiskManagement/rmf-cgr_e.html 3

Holland, P. W. 1986. Statistics and Causal Inference, *J. Am. Stat. Assoc.*, 81:945 – 970

O'Riordan, T and Jordan, A. 1995. 'The precautionary principle in contemporary environmental politics', *Environmental Values*, 4(3), pages 191-212

Pearl, J. 2000. *Causation*,MIT Press, Cambridge, MA

Shafer, G. 1996. *The Art of Causal Conjecture*, MIT PressWynne, B. 1992. 'Uncertainty and environmental learning: reconceiving science in the preventive paradigm', *Global Environmental Change*, 2, pages 111-27

Title XVI, Art. 130r of the Maastricht Treaty on European Union, 1992

Wynne, B. and Mayer, S. 1993. 'How science fails the environment', *New Scientist*, 5 June, pages 33-5