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LINEAR NON-THRESHOLD: SEPARATING FACTS FROM FICTION

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The Linear Non-Threshold (LNT) process is used by virtually all governmental agencies to compute incidence of cancer as a consequence of exposure to a carcinogen. This comment applies the concept of Best Available Science (BAS) Metrics for Evaluation of Scientific Claims (MESC) derived from BAS to issues related to reliability of LNT hypothesis. This paper identifies the level of maturity of the LNT hypothesis and the associated uncertainties.

Key words: Best Available Science; Metrics for Evaluation of Scientific Claims; Linear Non-Threshold.

INTRODUCTION

The formation of the U.S. Environmental Protection Agency (EPA) in 1970 and the need for regulating environmental pollutants, emission of chemicals from manufacturing plants, application of pesticides and emission of radioactive materials from various operations, and numerous other environmental problems led to the application of risk assessment. Eventually this also led to the establishment of regulatory science as a new scientific discipline defined as an interdisciplinary and multidisciplinary branch of science constituting the scientific foundation of regulatory, legislative, and judicial decisions. One of the primary tools of regulatory science is risk assessment, a component of risk analysis that also includes risk management (an administrative process for policy makers) and risk communication (a process for informing not only the stakeholders but also the general public).

Health risk assessment requires the establishment of a dose-response function. The Linear Non-Threshold (LNT) hypothesis is used primarily for establishing the relationship between the exposure and carcinogenic effect of specific agents. The origins of LNT go back to Hermann Joseph Muller who, in 1927, demonstrated that exposure to x-rays caused genetic mutations. Shortly thereafter, he published the results of his studies in English (Muller 1927). In 1928, the International Commission on Radiological Protection (ICRP) was formed, thus followed by the organization that eventually was named National Council on Radiation Protection and Measurements (NCRP). In 1955, the General Assembly of the United Nations formed the Scientific Committee on the Effects of
Atomic Radiation (UNSCEAR). One of the first comprehensive reports on health effects of ionizing radiation was prepared by the National Research Council, the research arm of the National Academy of Science, National Academy of Engineering, and the Institute of Medicine. The report known as BEIR III (NRC 1980) includes not only the status of science but also the history of the subject. In 1965, the International Agency for Research of Cancer (IARC) was formed, primarily to address exposure to chemical agents. One of the most famous and historic studies that included the LNT process was the so-called Rasmussen report (USNRC 1975) that attempted to use the probabilistic risk assessment to predict potential consequences of nuclear power accidents. That report used the LNT process for computing human health risks resulting from an accident.

Since that time, LNT has been used by virtually all government agencies in the U.S. and elsewhere to compute incidence of cancer as a consequence of exposure to a carcinogen. Although the decision of designating an agent as a carcinogen is associated with a significant number of assumptions and judgments, this paper is not intended to address them. Instead, we attempt to apply the concept of Best Available Science (BAS) Metrics for Evaluation of Scientific Claims (MESC) derived from BAS (Moghissi et al. 2010) to issues related to reliability of LNT hypothesis. In particular, the application of the BAS/MESC system would identify not only the reliability but also the level of maturity of the science upon which the LNT hypothesis is based. Finally, the BAS/MESC separates science from issues outside the purview of science.

Virtually all international organizations, regulatory agencies, and many scholarly organizations subscribe to the LNT process in addressing cancer risk. Although in describing LNT process both theory and hypothesis are used, in this paper we rely upon the most recent report of the National Research Council (NRC 2006) where the word hypothesis is used to describe LNT:

“The committee concludes that current scientific evidence is consistent with the hypothesis that there is a linear, no-threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans.”

It may be recalled that whereas hypothesis consists of an idea whose merit must be evaluated by experiments, computations, and other processes, a theory includes accepted principles, other reasoning, but also assumptions that attempt to explain a wide range of circumstances.

**FUNDAMENTALS OF LNT**

The primary objective of the LNT is to assess the risk associated with exposure to an agent. The carcinogen risk assessment consists of several
steps. Note that the LNT hypothesis is based on the single event process implying that either one photon or one molecule is needed to produce the effect. A discussion of the cancer risk assessment with the exception of LNT is beyond the scope of this comment. However, preceding the LNT, a decision must be made if there is sufficient evidence to designate an agent as a carcinogen. This step is known as hazard identification and is based on one or both processes.

1. There is sufficient human epidemiological data indicating that an agent is a carcinogen. Note that in virtually all cases, the number of exposed population is small and the exposure is at reasonably high levels.
2. Animals, mostly rodents, develop cancer in a long-term bioassay as a consequence of exposure to an agent. Again here, the exposure is at high levels and for a number of reasons the number of animals used in the study is small.

In both cases, the risk assessment requires that the data obtained at high-levels of exposure be interpolated to low levels common at environmental and increasingly at occupational exposure levels. In addition, in the case of animal studies, the data obtained from animal studies must be converted to humans via allometric or physiologically-based pharmacokinetic models.

**THE BAS/MESC SYSTEM**

The impetus for the development of the BAS/MESC system came from the experience of the senior author of this paper who had to deal extensively with regulatory science issues—notably the LNT and related environmental issues. It required virtually three decades to bring the system to a reasonable conclusion (Moghissi et al. 2010).

**Core Principles of the BAS/MESC**

The BAS/MESC system envisions four basic core principles upon which the BAS concept is based.

*Open-mindedness Principle*

Society, including the scientific community, must consider new ideas that consist of scientific information that may contradict the existing and prevailing science.

*Principle of Skepticism*

Those who make a scientific claim must provide sufficient evidence supporting their claim. However, there must be a balance between the Open-mindedness Principle and the Principle of Skepticism.
Universal Scientific Principles

Regardless of the nature of the discipline, all scientific disciplines use methods, processes, and techniques that are common to all of them or Universal Scientific Principles (USP). The USPs are used in physics, chemistry, biology, medicine, and sociology—to mention a few.

Independent Reproducibility Principle

Independent reproducibility is the true proof of the validity of a scientific claim.

Three Pillars of the BAS/MESC

The concept of BAS rests on three independent and yet interrelated pillars consisting of: how the reliability of a scientific claim is assessed; the level of maturity science; and areas outside the purview of science.

Reliability

This Pillar categorizes information into personal opinions and gray literature, two unreliable scientific systems. It also includes peer-reviewed and consensus-processed scientific information that constitutes the foundations of scientific acceptability. As the overwhelming majority of LNT-related information is peer-reviewed and/or consensus-processed, this subject is not further discussed in this paper.

Classification of Scientific Information

Once the reliability of scientific information is assessed, it is necessary to evaluate the level of maturity of science. Whereas some scientific information is unambiguously proven, others may be evolving or speculative. The BAS/MESC system provides a classification of scientific information.

Class I – Proven Science: This class consists of scientific laws—sometimes called scientific principles—and their application. The cornerstone of this class is compliance with the Independent Reproducibility Principle implying that any investigator who has the proper equipment and the necessary skills can reproduce it. Scientific laws and applied sciences, notably engineering, constitute the core of this class.

Class II – Evolving Science: The overwhelming scientific advances in virtually all disciplines, including the foundation of LNT, fall into this class. There are likely to be many subparts to evolving science including the following:

Class IIA – Reproducible Evolving Science: Reproducible scientific information of a subject whose foundation or other scientific issues related to it is not completely understood constitutes the core of this class. A large segment of advancements in physics, chemistry, biology, and many other scientific disciplines is based on the desire of investigators to improve knowledge in this class.

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Class IIB – Rationalized Science: The scientific foundation of information placed in this class is derived from proven or reproducible evolving science. However, in contrast to previous classes it uses assumptions, extrapolations, and similar processes in deriving its results and conclusions. The key characteristic of scientific information that fall into this class is that in order to reproduce the information, one must accept its scientific foundation; assumptions; choice of mathematical processes; default data; and numerous other prerequisites. Examples of this class include certain aspects of the LNT hypothesis and numerous predictive models.

Class IIC – Hypothesized Science: This class consists of an organized response to an observation, an idea, or any other initiating thought process. Note that the information in this class is not necessarily based on Proven or Reproducible Evolving Science.

Class III – Borderline Science: Much of the information in this class is based on an educated guess or Scientific Judgment (Class IIIA) or Speculation (Class IIIB).

Fallacious Information: In the original version of the BAS/MESC, we considered this group—often called “pseudo science”, “junk science”, or “politically-processed science”—to be the fourth class in the scientific classification system. However, fallacious information is not science (and should be excluded from any analysis).

Areas Outside the Purview of Science

The third pillar of BASD/MESC is an often overlooked subject dealing with areas that are outside the purview of science. There is an increasing recognition that inclusion of societal objectives in science is detrimental to both science and the societal goals of science. Probably the best description on the role of the scientific community and the individual scientists is given by what has become known as the Ruckelshaus Effect. William Ruckelshaus (1983), the founding administrator of the U.S. Environmental Protection Agency stated:

"...all scientists should make it clear when they are speaking as scientists—ex cathedra— and when they are recommending policy they believe should flow from scientific information." He emphasized: “What we need to hear more from scientists is science.”

The Ruckelshaus Effect implies that once scientific issues are addressed, the individual scientists and the scientific community are as qualified to draw societal decisions from the science as are members of any other profession or their professional organization.
ASSESSMENT OF PREDICTIVE MODELS

Predictive models can fall within all three classes of scientific classes. Let us try to categorize predictive models. The first step in evaluating predictive models is to ensure that the determined association is indeed caused by the agent under consideration. An association is difficult to establish because of confounding factors, effect modifiers or proxy variables. On occasion, the association is caused by a common variable. For example, one should not be surprised to find a correlation between ice cream consumption and drowning. People consume more ice cream when the temperature is high, and swim more during the same period. Consequently, one should not blame consumption of ice cream for drowning.

The BAS concept divides predictive models into several groups based on their expected reliability.

Predictive Models Based on Proven Science: These models are entirely based on proven science (Class I) and thus are called applied science. The number of these “models” is large—too large to be included here. Let us consider models that predict the fall of an item on the surface of the earth. These models are normally based on the law of gravitation and can precisely predict the time required for the item to fall.

Primary Predictive Models: A large number of models used in contested areas of science are primary models. Most of these models have their foundation in either Proven (Class I), or Virtually Proven Science (Class IIA). However, these models use assumptions and numerous other parameter estimates and thus their predictions include uncertainty about models and variability. Consequently, Primary Predictive Models are entirely Rationalized Science (Class IIC).

Secondary Predictive Models: These models use primary models as their foundation, including those that rely somewhat or predominantly upon Rationalized Science (IIC). These models are likely to fall into the Borderline Science Class (IIIA; Scientific Judgment).

Tertiary and Lower Predictive Models: These models use secondary models as their foundation. The predictive ability of Tertiary Models is so large that they are at best Borderline Science (Class IIIB, Speculation) or more likely, Fallacious Information.

EVALUATION OF LNT BASED ON BAS/MESC

As described above, if human data are available, the predictive model based on the LNT hypothesis falls into the Rationalized Science Class (IIC). As shown in Fig. 1, the epidemiological data are presumably Class IIA (Reproducible Evolving Science), but the extrapolation is based on the assumption that the effect is linearly proportional to the exposure.

In the absence of scientific information regarding doses below the area where human data are available, the scientific community must pro-
vide the decision makers with a guide that is scientifically acceptable and yet reasonable for the decision maker to make a decision that is both publicly and scientifically acceptable. There are three potential approaches to address this problem:

**Practical Approach**

As shown in Fig. 1, there are data on high-level of exposure to carcinogenic agent and the induction of cancer. However, the decision maker accepts the notion that there is no scientifically acceptable approach to interpolate to regions applicable to the decision maker’s needs—implying that there is no scientific approach to move the information at least into the Reproducible Evolving Science Class (IIA). In this case, the decision maker arbitrarily decides to linearly interpolate to low levels. The decision maker announces the decision and defends it.

**Conservative Approach**

This approach is similar to that used in Approach I, except that the decision maker justified the decision by the desire to be protective. In effect, the decision maker concedes that the approach overestimates the potential risk by an unknown level, but indicates that absent the necessary knowledge, conservatism is justified by the desire to protect the public. In addition, this approach uses the upper 95th percentile of the statistical error or uncertainty in the extrapolation process.
Scientific Approach

The scientific approach would recognize the lack of credible information below the exposure where there are existing data. However, there are several scientific remedies that reduce the arbitrariness in simply linearly interpolating to zero. In this case, the errors associated with the data are used in the interpolation process.

DISCUSSION

The three choices described above indicate the problems the decision makers face. The practical approach is entirely inconsistent with the BAS/MESC process. There is no underlying science in such an approach. The conservative approach also violates the BAS/MESC, as it is based on societal objectives to be protective of the exposed population. Mossman (2007) suggests that “LNT theory is hard to argue against. Its simplicity and inherent conservatism are attractive to decision makers and policy makers.” They may be attractive but impose societal objectives into the decision process. In contrast to the two other approaches, the third approach does not violate the BAS/MESC. Instead, the risk assessor provides the decision maker with information that is void of societal objectives and is consistent with Universal Scientific Principles (USP). As stated in the report of the Bipartisan Policy Center (BPC 2009), “Policy makers should be wary of conclusions about risk that are expressed in a single number.” The characterized risk should include the upper 95th percentile, the lower 5th percentile, and the mid point of risk. The risk manager is responsible for choosing the appropriate number and justifying why that number was chosen.

This paper was intended to address the LNT hypothesis. The situation is more complex if one considers the conversion from rodents exposed at high-levels to humans at significantly lower levels. It is highly likely that an evaluation of this latter process will demonstrate that certain parts of that process fall into Hypothesized Science (Class IIC), Scientific Judgment (Class IIA), or even Speculation (Class IIIB).

CONCLUSIONS

This comment attempted to ascertain the level of maturity of the LNT hypothesis and identified uncertainties associated with it. It is essential to appreciate that the society must make decisions based on the knowledge at the time the decision is made. The information included in this paper should not be construed that, absent proven or reproducible scientific information, no decision should be made. Instead, the decision makers should make sure that scientific information excludes societal objectives.
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