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GUEST EDITORIAL

Is LNT anti-evolution dose response model?

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Evolution is the central dogma of the biological sciences. As Theodosius Dobzhansky stated decades ago, "nothing makes sense without evolution." Despite this biological truism, there is a central aspect of advanced societies where evolution-based principles have been replaced by what seems best referred to as anti-evolutionary thinking in the environmental health sciences. This refers to cancer risk assessment and its long-institutionalized belief in and use of the linear non-threshold dose–response model (LNT).

Evolution is founded on key principles, including natural selection and mutational change, with both linked to the capacity to adapt to ongoing and unanticipated challenges or threats of any type. At its core, evolution is about change and the capacity to adapt to stress or threats. In this process, successful organisms are not passive recorders of energy depositions, like passive radiation dosimeters, but dynamic entities that experience challenges, damage, repair and recovery. Likewise, the great majority of organisms display the potential for preconditioning. This occurs when a low dose of stress (e.g. toxic agent) upregulates a plethora of adaptive responses that protect against subsequent and potentially life-threatening exposures or events within a protective temporal window, typically continuing for a few days to several weeks depending on the agent, model organism, and preconditioning scheme (Calabrese 2009, 2013, 2016). The major evolutionary paradigm then is that cells and organisms are not passive players in the process of life, but entities that display energy requiring adaptive qualities via constitutive and inducible mechanisms that are biologically displayed via dose-time-response relationships. Dose–response concepts that incorporate these evolutionary-based adaptive features reflect hormetic and threshold models, not the descriptive and mechanistic qualities of the LNT-non-repair model (Calabrese et al. 2022). Observations of such adaptive processes are highly generalizable, with the precise nature of these adaptive processes, including their generality, specificities and efficiencies varying by species, individual, and across the lifespan. When seen within the context of the above evolution dictum, it readily becomes clear that this also applies to understandings of the dose–response and the principles of risk assessment. Not viewed within this evolutionary perspective, the LNT mindset (called the Proportionality Rule) was adopted in the 1930s for radiation-induced gene mutation. The LNT extrapolates over many orders of magnitude of dose (i.e., total dose/dose rate), down to a single ionization with all damage assumed to be cumulative, irreparable, and irreversible rather than representing an adaptation-repair-recovery based dose–response framework (Calabrese 2019). This conceptual leadership eventually came to direct the field of risk assessment along a path leading to the present time, excluding repair/adaptation-based evolutionary thinking from environmental/ecological health, toxicology and the principles of cancer risk assessment.

The perspective offered here is that dose–response models should be evolution-based, being built from the bottom up, that is, from basic evolutionary principles rather than a top-down approach as originally led by the creators of LNT. This means that LNT is a model that fails to recognize the existence and functionalities of both constitutive (i.e. ongoing operations) and inducible adaptive processes (i.e. hormesis). Supporting of the evolutionary view is that most regulated chemical carcinogens (e.g. drinking water) are predicted to induce tumors at risks of about one in a million people over an 80-year lifespan due to exposures that could only be understood to be gigantic, with cumulative lifetime exposures (e.g. two liters/day throughout the lifespan) often approaching 10^{23}molecules. This perspective finds support in the detailed analysis of Waddell (2003), which estimated the threshold dose for 30 chemical carcinogens to range from approximately 10^{17} to 10^{22} molecules per kg/day. These massive daily and gigantic cumulative molecule-based dosages

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illustrate the limitations of the LNT concept and evoke concepts of thresholds and hormesis. It is time to see toxicology, the dose–response, and ecological/human risk assessment, within the framework of evolution, rather than a concept (i.e. LNT) that pretends to be scientific. If Dobzhansky were alive today and asked to opine on cancer risk assessment, he would likely conclude that "LNT makes no sense" because it has been decoupled from an evolutionary perspective.

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Declarations

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