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The Linear Non-threshold Extrapolation of Dose-Response Curves Is a Challenge for Managing the Risk Associated with Occupational Exposure to Carcinogenic Agents

Since its definition by the US National Research Council (1983) just 40 years ago, human risk assessment is the result of a process consisting of 4 steps, i.e., (i) hazard identification, (ii) dose-response assessment, (iii) exposure assessment, and, finally, (iv) risk characterization [1]. Hazard and risk are not synonyms, though the oldest volumes of the IARC Monographs on the evaluation of carcinogenic risks to humans [e.g., 2] start with a 'note to the reader' specifying that "the term 'carcinogenic risk' in the IARC Monographs series is taken to mean the probability that exposure to an agent will lead to cancer in humans". However, the title of recent monographs has been modified to recognize that *Hazard* refers to the strength of the evidence that an agent is a carcinogen, whereas *risk* refers to the probability that a given exposure to a carcinogen will result in cancer [3] thus limiting their relevance to the first step of risk assessment. The difference is even sharper with the inclusion of mechanistic evidence, particularly from biomarkers of effect in exposed humans, as a basis to classify agents as carcinogenic to humans (group 1) or probably carcinogenic to humans (group 2A) [3]. Including such widespread mechanisms as inflammation and oxidative stress among the key characteristics of human carcinogens is undoubtedly valuable for better understanding the mode of action. Understanding the potential of a given agent to induce changes relevant to a carcinogenetic process does not help to calculate the likelihood of its occurrence.

Regulatory agencies use quantal monotonic dose-response relationships to assess risks, including occupational ones. The dose-response relationship is usually sigmoidal or Italic S-shaped: small doses do not appear toxic up to a particular point of departure (threshold), which can be identified as a NOAEL (No Observed Adverse Effect Level), i.e., the highest dose at which no detectable adverse effects occur in an exposed population, including its most susceptible fraction. From the NOAEL, Occupational Exposure Limits (OELs) are derived as environmental concentrations not to be exceeded in managing the risk of adverse health effects at the workplace [4]. Such a deterministic approach is also applied to carcinogenic substances acting as promoters or epigenetic modulators, thereby increasing the carcinogenic risk with mechanisms other than a direct effect (damage) on DNA sequences coding for oncogenes.

It is generally considered that genotoxic carcinogens do not have a threshold, i.e., that no dose is safe. The dose-response relationship at low exposure levels is obtained by extrapolation from the LOAEL (Lowest Observable Adverse Effect Level). The LOAEL can be either a high dose of a carcinogen administered to experimental animals showing a significant increase in cancer incidence or the airborne concentrations occurring in occupational settings where epidemiological studies showed an excess of cancer incidence. From the LOAEL onwards, the dose-response curve fits experimental or empirical data. In contrast, the censored segment, for which data are missing, is extrapolated back to the origin (i.e., to zero for both dose and response), thus adopting the linear non-threshold (LNT) model [5]. Other models could be used, e.g., the one-hit, the multi-stage, and the multi-hit, but the risk estimate per unit of dose would differ by orders of magnitude from each other [1]. On the other hand, biological responses may be proportional to the logarithm of the dose, but there is no way to put negative values or zero on a logarithmic axis.

In his historical account published in this journal issue [6], Calabrese reports the fundamental role of

two scientists, Gofman and Tamplin, in adopting the LNT assessment of cancer risk due to ionizing radiation exposure. He also highlights the controversial and non-evidence-based aspects in this context, as he had already reported in previous papers [e.g., 7]. Acknowledging the weaknesses of the LNT foundations calls for a desirable debate on the extrapolation to zero of the dose-response curves for ionizing radiations, recognizing that they are biased. LNT extension to carcinogenic chemicals, particularly those with radiomimetic properties, should also be revised, considering new subsequent scientific acquisitions such as DNA repair enzymes or epigenetic mechanisms acting with deterministic, and hence threshold mode of action.

Risk assessment is evolving into new approach methodologies aimed to reduce or replace animal testing by using *in silico, in vitro*, omics, cellular, micro-arrays, and more complex system data to be analyzed in the framework of mechanism-based risk assessment. In addition to incorporating physiological, toxicokinetic, and toxicodynamic parameters in such models, other conceptual issues must be addressed to achieve a realistic risk assessment and to set exposure limits instrumental to implementing effective prevention strategies. Indeed, applying uncertainty and safety factors when deriving exposure limits from such models may imply challenging situations in risk management [8]. Such challenging situations are already apparent for the possible effects of low doses of ionizing radiation, as the so-called natural background in some areas of our planet often reaches values higher than either the limits set or the levels measured by personal dosimetry in occupationally exposed groups, e.g., in healthcare workers involved in diagnosis and treatment activities in hospitals. Setting a limit lower than naturally occurring airborne concentrations is nonsense because measuring doses inferior to the natural background is simply impossible.

For carcinogenic elements and chemicals polluting the general environment, setting limits of exposure lower than the limit of quantification (LOQ) of techniques used for exposure assessment is also not applicable. Indeed, it would preclude exposure assessment, a fundamental step in risk characterization and management. Furthermore, a residual chance of getting cancer is conceivable even at zero exposure, as it would not avoid either spontaneous mutations or those occurring for other causes. Nor would it prevent failures to repair DNA damage. Therefore, for prevention purposes, it is more realistic either to propose a value graduation corresponding to normative guide values or to adopt the margin of exposure (MOE) strategy used for carcinogenic food constituents and contaminants, many of which are naturally occurring but at concentrations lower by several orders of magnitude than those necessary to cause cancer [8].

If the LNT extrapolation for ionizing radiations is affected by the severe limitations suggested by Calabrese's reconstruction, its extension to chemical carcinogens is also questionable. The quantal dose-response relationship is the one that characterizes the distribution of responses of individuals in a population of organisms [9]. The dose-response relationships can, in turn, be either monotonic (i.e., threshold or linear) or non-monotonic, where multiple points of inflection exist along the curve, determining U, U-inverted, and J shapes as occurs for essential nutrients or for hormesis in which we observe stimulatory effects at low doses and adverse effects at high doses, as described for radiation and many chemical agents [10, 11].

The correct definition of LNT is also crucial for another critical issue in predicting and preventing carcinogenic effects: the difference between carcinogens with demonstrable threshold and for which an exposure limit value is conceivable and chemicals without threshold. For the latter kind of chemical, it is impossible to set a limit such as that considered above. However, correctly answering the wrong question would not help prevent cancer. The right question is neither about hazard nor about exposure but rather about the risk entailed by any exposure, including zero exposure: does zero exposure mean zero risk? For agents with a demonstrable threshold, yes, whereas for genotoxic carcinogens acting by inducing mutations of critical genes, zero risk is unlikely to exist because mutations of critical genes can also occur spontaneously. Therefore, a risk as low as practically possible and measurable is the only realistic and achievable goal.

For chemicals with a deterministic mode of action and a threshold, the risk assessment should be based on the NOAEL to define exposures with no appreciable effects (e.g., the acceptable daily intake – ADI). For chemicals without a threshold, the type of risk assessment must be quantitative, i.e., based on dose-response modeling to calculate "the risk associated with a known exposure." LNT is but one risk quantification. Al-

ternatively, the need for intervention should result from the margin of exposure (MOE) between the dose known to cause cancer in experimental studies and the actual human exposure from different sources. European Food Safety Authority (EFSA) concluded that a MOE of 10,000, based on a BMDL for a 10% extra risk ($BMDL_{10}$) in a rodent carcinogenicity study, 'would be of low concern from a public health point of view and might reasonably be considered as a low priority for risk management actions [12].

Another aspect to be considered in risk management is the weight of evidence (WoE), i.e., the extent to which evidence supports possible answers to a scientific question. When reached, it may be expressed qualitatively or quantitatively. However, almost all cancers exhibit a baseline (background) incidence, even without specific agents. A background incidence implies that the population threshold – if one exists – has already been exceeded, and a positive dose-response gradient applies. Adding a small dose of the agent under study, with known and unknown agents causing the background incidence, will increase the lung cancer incidence proportionately to the added dose. Two assumptions are then possible: either it can be excluded that the agent under study and the background agents share some mechanistic components, and linearity is not assured, or it cannot be excluded, and linearity follows [14]. Beyond the issue of linearity, we can agree with Saracci that assumptions cannot be avoided, owing to the ubiquity, complexity, and potential impact of exposure to carcinogenic agents.

Calabrese's historical account of LNT adoption by regulatory agencies challenges a dogmatic approach to risk assessment for carcinogenic agents, demonstrating that the track has been disseminated by misconduct episodes and behaviors that lead to questioning the evidence on which the LNT has become a default "scientific" approach for genome-targeting agents. Lack of evidence does not necessarily disprove LNT. Still, it is a significant limitation of the WoE, and it calls for studies on the effects of carcinogens at low doses, contrasting with the extrapolations of expected effects from high and unrealistic doses to predict responses dogmatically.

Such studies include: (i) the systematic review of literature and assessment protocols, (ii) the appraisal and integration of the data, (iii) the assessment of biological relevance, (iv) the uncertainty assessment and communication, (v) the use of data from new approach methodologies (NAM). Furthermore, the growing knowledge of carcinogenesis's molecular mechanisms makes it possible to apply biomonitoring techniques to assess exposure and early effects. Independently of the mechanism of action of carcinogenic agents, the most reasonable approach to risk assessment and management of occupational carcinogenic risk is to ensure a safe MOE for the general population and biomarkers of exposure and effect not exceeding the reference values among potentially exposed workers.

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