

Acting on What We Know: A Progressive Path to Precision Chemical Regulation

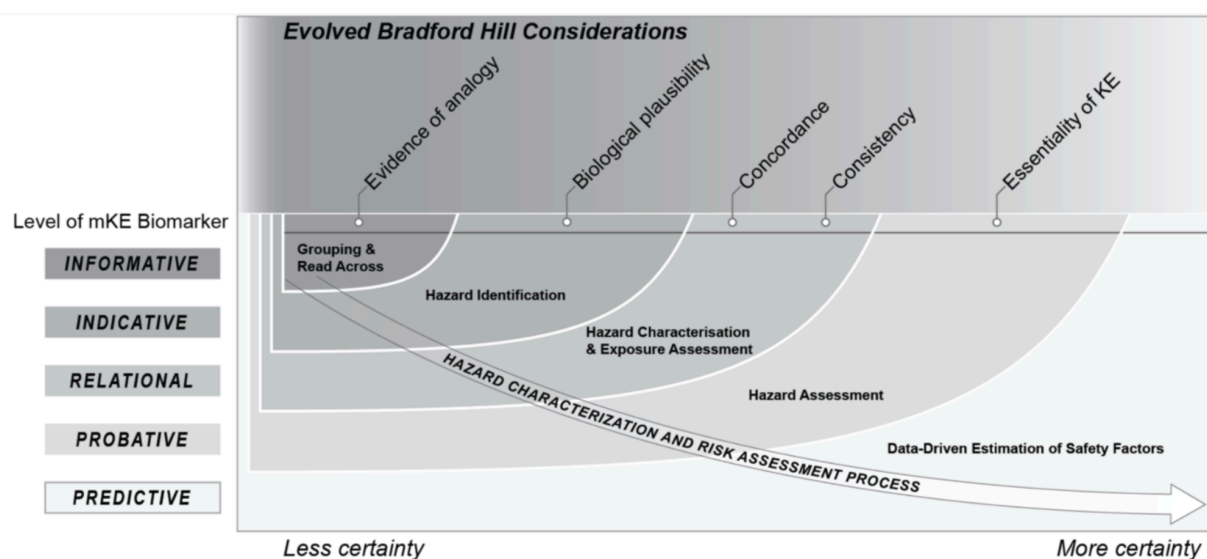
Editorial by Elisabeth Andrews

“All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.”

– Sir Austin Bradford Hill

Regulatory toxicology has long grappled with divergent understandings of causation across science and law. The legal definition implies a yes/no determination of culpability, designed to indict or exonerate willful human actors. In contrast, scientific investigation builds probabilistic models of causation that are continually expanded and refined. When legal readings of causation are applied to diffuse, complex, and cumulative biological effects of industrial compounds (about which new information is rapidly emerging), the result can be a paralyzing mismatch. Presently, even as regulatory bodies seek to incorporate New Approach Methodologies (NAMs) into assessment frameworks, decisions remain largely tethered to animal testing that can deliver a verdict through “apical endpoints” — mortality or failure to develop, grow, or reproduce. Contemporary scientific insights about gradual, often systemic biological changes at low exposures over long periods (and in chemical mixtures) may better reflect true hazards, but this nuance does not easily translate to law.

The **Progressive Precision Regulatory Framework** seeks to resolve this incongruity. Rather than asking if NAMs can stand in for apical-endpoint tests, the framework suggests a spectrum of regulatory responses calibrated to the strength and nature of NAMs. As was recently recognized in the [Recommendations of DEFRA's Hazardous Substances Advisory Committee \(HSAC\) for the Adoption of New Approach Methodologies \(NAMs\) in UK Chemical Regulation](#), this framework's progressive categorization of the level of evidence offered through molecular key event (mKE) biomarkers unlocks regulatory possibilities that expand with increasing precision. Each progressive class of NAMs evidence satisfies cumulative considerations, warranting the next set of actions along the regulatory path. At the most basic level, *evidence of analogy* (top left in figure) indicates that effects are occurring in a similar manner in response to distinct chemical compounds. This level of biomarker is sufficient to warrant grouping and read-across, even if the function of the biomarker (e.g. gene activation) is unknown. Details on all levels of mKE biomarkers, aspects of association, and applicability for chemical hazard characterisation and risk assessment are discussed in the HSAC document.



Progressive Precision Regulatory Framework

The logic of this approach builds on the insights of the epidemiologist and statistician Bradford Hill, who in 1965 proposed a set of considerations for implicating contaminants in the onset of illness. His nine factors range from *consistency* in outcomes across different populations to *coherence* of the proposed disease trajectory with established knowledge. Importantly, although these factors came to be known as the “Bradford Hill criteria,” they were not a checklist of requirements. Hill’s intent was not to *constrain* the admissibility of environmental health information, but the opposite: to demonstrate its usefulness even when incomplete. “What I do not believe,” he stated, “is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect.”

Today’s information is far more sophisticated than that of Hill’s era. What was in 1965 a “black box” of biological processes has been increasingly illuminated. To reflect these advancements, in 2014 M.E. (Bette) Meek and her colleagues outlined evolved Bradford Hill (EBH) considerations that draw on mode-of-action models tracing causal mechanisms from chemical exposures through adverse outcomes. The Progressive Precision Regulatory Framework builds on Meek et al.’s approach to apply the EBH considerations explicitly to mKE biomarkers, and to order them sequentially with increasing precision and expanded regulatory application.

NAMs will continue to advance and refine our understanding of toxicity, surpassing any knowledge that could be gained through traditional animal testing. Integrating NAMs into regulatory frameworks will require not only careful consideration but also willingness among decision makers to acquire expertise and familiarity with NAMs (and willingness among NAMs advocates to communicate clearly and patiently). Fortunately, we don’t need to wait for “complete” knowledge in order to share discoveries and act appropriately on what we know. As mKE biomarker data become more refined and precise, thereby satisfying more of the EBH considerations, further steps can be taken along the path to precision chemical regulation.