

Challenges in assessing the impact of environmental health hazards on populations

According to the recent COVID-19 Excess Mortality Collaborators (CEMC) report [1], COVID-19 deaths between Jan 1, 2020, and Dec 31, 2021, are about three times the recorded casualties. Instead of 5.94 million worldwide, they estimate that 18.2 million (95% uncertainty interval 17.1–19.6) people died worldwide because of the COVID-19 pandemic (as measured by excess mortality) over that period. In Italy, recorded and estimated deaths attributable to the COVID-19 pandemic were 137,000 and 259,000, respectively. In this issue of our journal, based on official data delivered by the Italian Statistic Institute (ISTAT), a paper shows that 161,000 deaths from March 2020 to December 2021 exceed the mortality observed in the previous five years after allowance for population ageing, and can reasonably be ascribed to the COVID-19 pandemic [2]. Such a figure – obtained over an extended but logical time span – is higher than that reported above [1] but much lower than calculated relying on artificial intelligence and Bayesian algorithms, leading to an overestimation by over 60%. To a different degree, this may also apply to low- and middle-income countries: the CEMC estimate for India was 4.07 million, over 25% greater than that obtained by a nationally representative survey of 3.2 million deaths [3]. Death certificates and integrated administrative databases are not error-free and depend on protocols applied by default. Likewise, machine learning depends strictly on parameters and assumptions translated into coefficients to be applied to data input.

The health impact assessment is challenging even in a relatively simple exercise (i.e., retrospective excess mortality attributable to a single agent, the SARS-CoV-2). The excess mortality ascribed to COVID-19 includes not only SARS-CoV-2 lethality but also such indirect causes as delayed assistance to other patients and overall health care possible in hospitals and ICUs saturated by people suffering from COVID-19, which add to deaths for reasons other than COVID-19 in patients positive for SARS-CoV-2. Furthermore, COVID-19 may have contributed to a sort of harvesting effect anticipating some deaths; it may have been an occasional finding in subjects who died for other reasons but tested positive for COVID-19; finally, recorded excess mortality does not include the possible health impact of the pandemic because of late effects. The so-called “long-COVID” and postponed screening procedures during the pandemic will delay diagnoses of cancer and other diseases, thus impacting mortality over forthcoming years. In 2021, excess mortality associated with the COVID-19 pandemic also includes the effect of vaccination (and, above all, of missing or incomplete vaccination). This example shows how difficult it is to assess something elusive in nature, as in the case of excess mortality due to either causally associated (both directly and indirectly) or concomitant deaths.

Assessing the health impact of environmental pollution is even more challenging for epidemiology than that of a single infectious agent: mixtures of contaminants are much more elusive, as they are very complex and originate from multiple sources, they interact not only with the health status and susceptibility of populations but also with many other agents and risk factors, and they act for decades.

In 2023, we will celebrate the 40th anniversary of the book proposing the four-step paradigm of risk assessment, intended as “the characterization of the potential adverse health effects of human exposures to environmental hazards. Risk assessments include several elements: description of the potential adverse health effects based on an evaluation of results of epidemiologic, clinical, and toxicologic research; extrapolation from those results to predict the type and estimate the extent of health effects in humans under given conditions of exposure; judgments as to the number and characteristics of persons exposed at various intensities and durations; and summary judgments on the existence and overall magnitude of the public-health problem.” [4]

Whereas the default paradigm for risk assessment used for decades still holds for deterministic effects of xenobiotics, it gives rise to concern and controversy when applied to multifactorial outcomes. In the latter case, uncertainties associated with inference largely exceed available evidence. A recent article presenting an original viewpoint on health impact assessment (HIA) is stimulating a discussion originating from the failure to acknowledge critical assumptions inherent in different models, a weakness that gets somehow lost among the mathematical formulae proposed by epidemiologists.

The point on which the HIA gives rise to controversial positions is the baseline rate to compute the cases attributable to a project under evaluation. According to Zocchetti's proposal, it should multiply the fraction of the baseline rate attributable only to the exposure under assessment [5]. According to other authors, it should apply to the overall baseline rate of the population [6]. On the one hand, the etiological fraction attributable to environmental exposures for most diseases is limited compared to other factors, such as genetic traits, diet, and lifestyle. Therefore, the incremental effect of such exposures is expected to increase only the marginal fraction of attributable cases. On the other hand, a new source of pollution will act on the whole population, and therefore it is expected to cause new additional total cases.

The outcome will depend on the interaction between exposures resulting from the novel setting and pre-existing risk factors. However, in deriving the standard HIA interactions have to be assumed when intervention is still at the planning stage, i.e., when it is still unknown whether risk factors will act in an additive, multiplicative or competitive mode. Considering that we cannot anticipate the interaction among multiple exposures before its occurrence, any *a priori* "assessment" is challenging.

Whereas in risk assessment, the probability is calculated for an adverse effect under specific exposure conditions, i.e. based on empirical data possibly adjusted for uncertainties of extrapolations, the challenge of HIA is to calculate the occurrence of measurable outcomes (impact) of something elusive in nature. Indeed, the health impact to be assessed will result from multiple factors behaving differently at subsequent stages, depending on unknown interactions among multiple factors. In standard HIA procedures, the relative effect of exposure is assumed to be constant across strata of confounders (and therefore applies equally to all individuals independently of their characteristics). Such an assumption does not seem to rely on the necessary pathophysiological ground.

That authoritative institutions adopt a particular methodology does not necessarily mean that such a methodology is error-free. For example, voting to classify a given substance or process as a human carcinogen based on epidemiological evidence alone may be misleading. The strength of the association between exposure and excess mortality is just one of the nine criteria or "viewpoints" listed by Austin Bradford Hill, "none of which can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as *a sine qua non*" [7].

Defining a range of possible scenarios would be more appropriate than a numerical outcome calculated with a dogmatic formula that does not include the potential role of confounders and effect modifiers, requiring unsupported assumptions. Instead of being "assessed", the health impact should be "evaluated" by either political or technical decision-makers, considering such additional criteria as costs, social acceptability, and risk-benefit balance.

Epidemiology faces challenges in identifying causal links between several factors contributing to any given outcome in its *post hoc* assessments, such as estimating the excess mortality ascribed to the COVID-19 pandemic. Attempts to predict the future relying on assumptions and calling them "assessments" does not *per se* confer validity to a forecast, which should not become divination. Several known unknowns and many unknown unknowns contribute to uncertainties that should always be considered. We should never forget that "Risk assessment also includes characterization of the uncertainties inherent in the process of inferring risk" [4].

Algorithms for artificial intelligence may show surprising performance associated with big data correlation analysis. They could make the traditional scientific method of using hypotheses, causal models, and tests ob-

solete. However, causality is an essential part of human thinking, and it is particularly relevant to prevention science. We simply need to maintain the necessary rigour, critical attitude, prudence and wisdom, resisting the temptation to delegate our judgment on complex issues to simple formulae or sophisticated algorithms.

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