Integrated Environmental Assessment, Part IV

Human Health Risk Assessment

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Human health risk assessment (HRA) is a key approach in estimating the environmental and public health burdens that result from chemical emissions in the life cycle of a product or service. This column presents the fourth in a series of overviews of the state of the art in integrated environmental assessment—earlier columns described emissions estimation, fate and transport modeling, and exposure assessment. In this article, we review how estimates of intake dose are translated into metrics of human health damage or risk, as the ultimate step of an emission to damage assessment. An appendix available as Supplementary Material on the Web contains a more extensive list of references on HRA methods and applications in life cycle assessment (LCA).

The human health component of an LCIA aims to assess in a comparative way the multiple impacts and large number of toxic substances that are involved in the life cycle of products. This often differs from the scope of regulatory toxicological assessments, which generally focus on ensuring that safe doses are not surpassed by exposures at any location or point in time.

Human Risk and Dose–Response Assessment

Dose–response relationships for HRA are commonly estimated from either epidemiological data or animal toxicity (bioassay) studies; the former are preferred for the limited cases in which reliable data are available for current or historic human exposures and corresponding health outcomes. Animal bioassays are conducted under controlled conditions but require extrapolation from high to low dose and from the test animals to humans. Nonetheless, dose–response relationships and resulting health criteria for most chemicals are based on animal studies, and we thus focus on this approach, noting alternative methods under development at the conclusion of this column.

Traditionally, major human health impacts of concern have been differentiated between cancer and noncancer effects of toxics, with separate risk assessment guidelines:

- For *carcinogenic effects*, estimates are based on toxicological studies that use rats or mice exposed at (typically four) different doses. The initial 1986 U.S. Environmental Protection Agency (EPA) guidelines determined the potency (or *slope factor*) for cancer risks on the basis of the upper confidence limit of the dose–response slope at low dose. Because bioassays only provide limited information in the low dose range, the new 2005 U.S. EPA guidelines

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use the lowest reliable effect dose (ED; this dose typically yields a 10% response over background—i.e., the ED_{10}) as a point of departure.[1] A lower confidence limit for this benchmark dose is linearly extrapolated to the origin to obtain the slope factor. Alternative functional forms are used to fit the dose–response relationship, depending on the assumed mode of action of the toxin—for example, genotoxicity (gene mutation) versus cytotoxicity (cell damage). Alternative assumptions are also available for animal to human extrapolation (Small 2008).

- For *noncancer effects*, one determines benchmark doses in a similar manner, then divides them by chemical-specific uncertainty factors to determine a reference dose (RfD)—the daily "safe" dose that is likely to be without appreciable risk of deleterious effects, even to sensitive subgroups of the human population. These uncertainty factors account for uncertainties associated with animal-to-human extrapolation, interindividual variability between humans, and data quality. For noncancer effects, risk is characterized according to a dose-based hazard quotient, the ratio of the exposure dose to the RfD. Specific guidelines have been issued for reproductive and developmental toxicity, mutagenicity, and neurotoxicity as well as for early-life exposure and chemical mixture risk assessment.

Adaptations for Industrial Ecology

The focus of industrial ecology on issues such as LCA fosters the need for simple but informative and comparable metrics of potential health effects. The goal of the life cycle impact assessment (LCIA) is to characterize impacts over the whole life cycle of a product, from the production of the raw materials to the ultimate disposal of the product. The human health component of an LCIA aims to assess in a comparative way the multiple impacts and large number of toxic substances that are involved in the life cycle of products. This often differs from the scope of regulatory toxicological assessments, which generally focus on ensuring that safe doses are not surpassed by exposures at any location or point in time (Pennington et al. 2006). Regulatory risk metrics therefore need to be adapted to meet LCIA requirements, with recognition of the following:

- Overall impact for use in LCA should be integrated over the population, including but not driven by the most sensitive individuals—thus the use of population-based exposure metrics, such as the intake fraction.
- Effects on human health include both mortality and morbidity and can occur at different ages. Metrics combining these effects have been developed, such as the DALYs (disability-adjusted life years) or QALYs (quality-adjusted life years) lost due to exposure (Huijbregts et al. 2005).
- The assessment should be based on best estimates of dose–response rather than upper confidence limits, with uncertainty noted and treated separately. Although the uncertainty of chemical toxicity estimates often spans many orders of magnitude, a workable subset of compounds (~10 to 30) can often be identified as the most likely contributors to potential health risk over a product life cycle, which allows a better focused analysis (Rosenbaum et al. 2008).
- The LCA scope does not allow for full-scale, site-specific risk assessments, so there is a need for aggregate "effects factors" that can be used to weight pollutant emissions at a generic, continental, or regional level.

These adaptation needs have been discussed in various international panels and workshops convened to recommend guidelines for human health evaluation in LCIA (e.g., McKone et al. 2006). Their recommendations are reflected to varying extents in available LCIA methodologies, such as IMPACT2002+ (Pennington et al. 2006), ReCiPe (Huijbregts et al. 2005), the USEtox™ approach (Rosenbaum et al. 2008), and the latest developments of the EPA TRACI

model (Bare et al. 2003). The efforts made to address issues of aggregation, uncertainty, and weighting in LCIA have also yielded general improvements to the practice of comparative risk and decision analysis.

Challenges and Future Developments

Several challenges and opportunities remain both for risk assessment and comparative LCIA. First, how do we address the more than 100,000 substances now used in product manufacturing? It is clear that human data, although they are preferred to animal studies, are and will only be available for a handful of chemicals, such as fine particulates (PM2.5) or benzene. Due to the high costs of in vivo animal studies (~ $2 to 4 million), these will only be conducted for a limited number of high-priority chemicals. Screening approaches will therefore need to rely on the results of in vitro and high-throughput genomic tests, combined with advances in computational toxicology for relating health effects to molecular structure. Current research also considers advances in exposure and dose assessment needed for improved HRA. In particular, newly developed biomarkers allow for better characterization of exposures and the development of improved dose–response relationships.

New technologies and materials bring new types of exposures with uncertain health effects. Traditionally, chemical dose–response relationships have been based on mass concentration or dose. With the increasing use of nanomaterials and the potential emissions of nanoscale particles, other dose metrics may be needed, based, for example, on particle surface area. Finally, the need to estimate the health effects of exposures to complex mixtures, rather than one chemical at a time, remains perhaps the greatest challenge.

Note

1. U.S. Environmental Protection Agency. 2005. *Guidelines for carcinogen risk assessment*. Risk Assessment Forum, EPA/630/P-03/001F. Washington, DC: U.S. Environmental Protection Agency. See http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283.

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Supplementary Material

Additional Supplementary Material may be found in the online version of this article:

Supplement S1: This supplement provides additional references to the research literature related to this column's discussion of human health risk assessment.

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