The challenge of determining the health risks of low-dose chemical exposures

openaccessgovernment.org/article/the-challenge-of-determining-the-health-risks-of-low-dose-chemical-exposures/190357

25 March 2025

Image: © Kittisak Kaewchalun | iStock

Rebecca J. Wilson and Pamela J. Lein, explore whether the dose makes the poison or not. Here, they discuss the challenges of determining health risks associated with low-dose chemical exposures

Nearly 500 years ago, Swiss physician and chemist Paracelsus originally expressed a fundamental tenet of toxicology: “All things are poison and nothing is without poison; only the dose makes a thing not a poison.” In other words, all substances are harmful at a high enough dose, but at low doses, the same substance is non-toxic or even therapeutic.

However, recent advances in analytical chemistry that enable the detection of chemicals in environmental samples and human tissues at levels equivalent to a teaspoon of water in an Olympic- sized swimming pool (parts per trillion), coupled with growing experimental evidence that extremely low chemical exposures can adversely impact human health, have triggered a debate regarding the applicability of Paracelsus’ paradigm to toxicity testing.

Addressing this issue is critically important to public health because the detection of vanishingly small amounts of chemicals in the environment is concerning, but reducing chemical contamination to zero is often cost-prohibitive, if not technically impossible.

Limitations of traditional toxicity testing

To establish safe levels of hazardous chemicals in air, water, food and consumer products, regulatory scientists often rely on tests that identify a no-adverse effect level (NOAEL), the highest dose of a chemical that does not cause toxicity. These tests are typically designed to detect immediate or acute effects of exposure to a single chemical in adult animals. However, toxicology research over the past few decades has revealed a number of limitations of this approach. For example, there is now extensive evidence that chronic, repeated exposure to chemicals at low doses that do not have immediate toxic effects can cause harm or elicit different adverse health outcomes than those observed following acute exposure to higher doses.

Paracelsus himself observed this phenomenon. Based on his initial studies of the acute effects of metallic mercury, he recommended low levels of mercury that did not cause acute toxicity for therapeutic uses. However, his later studies revealed that repeated administration of mercury at doses he thought safe, based on acute toxicity studies, caused tremors, headaches, cognitive impairment, kidney damage, and muscle weakness. Consequently, Paracelsus argued that mercury should never be used as a therapeutic agent because of the toxic risks associated with repeated low-dose exposures.

Another problem with traditional toxicity tests that evaluate one chemical at a time is that humans are exposed to many chemicals simultaneously. Significant experimental and clinical evidence demonstrates that a low level of a chemical that is not toxic on its own may become toxic in the presence of other chemicals. This is particularly likely if the chemicals in the mixture act via the same mechanism so that their effects are additive or if certain chemical(s) in the mixture influence metabolism to either increase the production of toxic metabolite(s) or decrease the detoxification of individual chemicals within the mixture.

It is now also appreciated that age at the time of exposure is a critical determinant of toxic outcomes. For example, lead levels that have no effects on adults cause significant neurotoxicity in young children, while higher lead levels that are toxic to adults elicit different adverse outcomes in children. Differential susceptibility to toxic chemicals at different life stages is due to age-related differences in the expression or activity of the molecular pathways that chemicals interact with to cause toxicity or changes in the metabolism of toxic chemicals with age.

Another challenge: Non-traditional dose-response relationships

The paradigm that the “dose makes the poison” assumes that toxic responses to chemicals are linear, such that the number of individuals affected and/or magnitude of the toxic response increases as the dose increases. While this is true for many chemicals, there are numerous examples of chemicals that exhibit a non-monotonic dose- response relationship, exemplified by U-shaped or inverted U-shaped curves. In the former, toxic effects are observed at the lowest and highest doses but not at doses in between, while in the latter, toxic effects are observed as doses increase until they reach a maximum response, at which point toxic effects decrease with increasing doses.

Essential metals, which are required in the diet for optimal health, and endocrine disruptors, which alter natural hormone systems, are examples of chemicals that exhibit non-monotonic dose-response relationships. Classic toxicity testing often misses non-monotonic dose-related toxic responses because the range of doses tested is too narrow to capture lower doses that cause toxicity not observed at the higher doses, or it is assumed that if the higher doses are without effect, then lower doses will be as well.

Quantifying human exposure is critical in assessing toxic risks

If toxicity testing identifies a chemical as toxic, it does not necessarily mean it poses a risk to human health. This is because the likelihood and level of human exposure are critical determinants of toxic risk. If there is minimal chance of human exposure to the chemical or if the chemical is present in the environment at levels below those that produce adverse effects, the chemical poses minimal risk to human health.

Quantifying human exposure is also important for interpreting the relevance of experimental toxicity data. For example, the plasticizer bisphenol A (BPA) is an endocrine disruptor that binds to the estrogen receptor but with a thousand times lower affinity than the natural hormone, estradiol. So, even though BPA has weaker effects on the estrogen receptor than estradiol, because of its pervasiveness in the environment and human tissues, BPA poses a toxic risk to human health.

Health risks of low dose chemical exposures: The path forward

Determining the human health risks posed by chronic exposure to low levels of chemicals in the human environment is challenging. Overcoming this challenge will require adapting toxicity testing strategies to better represent human exposures and an increased understanding of the human exposome, e.g., the totality of environmental exposures we experience throughout our lives.

The costs of these endeavors are significantly outweighed by the potential benefits: preventing or decreasing the impact of disease at both the individual and population levels via regulation of low-dose chemical exposures identified as significant toxic risks.