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GUEST EDITORIAL

Application of *In Silico* and *In Vitro* Approaches to Assess the Toxicity of Inhaled Substances

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Scientific and ethical drivers have led to significant interest and investment in developing and using efficient human-relevant animal-free testing approaches to assess the toxicity of inhaled substances. Available methods range from computational models that predict the deposition pattern of a substance in the respiratory tract to physiologically based pharmacokinetic models that predict the absorption, distribution, metabolism, and excretion of a chemical to numerous *in vitro* models, including submerged monocultures or coculture systems, three-dimensional human respiratory tissue models grown at the air–liquid interface, precision-cut lung slices, and lung- or multiorgan chips. Although there is no shortage of methods—many of which are in use today for screening purposes or to support a weight-of-evidence approach—there remains a need to standardize, optimize, and share case studies of approaches that can be used for risk assessment and regulatory decision-making purposes.

In this special issue of *Applied In Vitro Toxicology*, work to advance animal-free testing approaches is presented. It includes 15 articles, including original research, reviews, a perspective piece, and a roundtable discussion. Topics include the use of three-dimensional reconstructed human tissue models for assessing respiratory tract absorption (W. Hoffmann et al.) and acute inhalation toxicity (G. Jackson et al.). Two original articles focus on testing tobacco and next-generation nicotine delivery products (H. Behrsing et al. and D. Thorne et al.), and two others discuss the development of a computational profiler for assessing chemical reactivity as a predictor of acute toxicity (D. Wilson et al. and S. Wijeyesakere et al.). The special issue also includes a report from a conference on air–liquid interface models (G. Lacroix et al.) and several review articles, including one on a human lung-on-a-chip. In the roundtable discussion, experts from government, industry, nonprofit, and academic sectors explore existing and emerging *in silico* and *in vitro* approaches, ongoing efforts, and steps needed to gain widespread use and regulatory acceptance of these approaches.

The most appropriate testing approach will vary, depending on multiple factors, such as the test substance and the purpose of the study. Consideration of existing information, the substance's physiochemical properties, the likely human exposure scenario, and data from *in vitro* and *in silico* models will be critical. Tiered testing can allow for early identification of highly toxic substances in assays that are more high throughput and less expensive, followed by more in-depth testing of the remaining substances with more sophisticated *in vitro* methods. Adverse outcome pathways can serve as a useful framework for designing these intelligent testing strategies, and existing data can be leveraged to gain confidence in emerging approaches.

Defining approaches that are sufficient to meet regulatory requirements will depend on a clear understanding of regulatory needs. The goal should be to identify information that is important for protecting public health and to determine how to predict that *in vitro*, rather than attempting to mimic animal tests. The high variability of many animal tests and their often unknown relevance to humans also need to be acknowledged so that nonanimal approaches will not be held to an unrealistic standard. In this way, we can develop approaches that are as good as or better than the currently used animal tests in producing reproducible results that will protect human health.

The ongoing work highlighted in this special issue shows the promise for a new and improved inhalation toxicity testing paradigm based on *in silico* and *in vitro* models and human mechanisms of toxicity, which will be better able to protect humans after inhalation exposure. To achieve this vision, it will be important to continue to foster dialogue among method developers and end users and to form multistakeholder partnerships across sectors.

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