



Future of pharmacology

Editorial

Toxicology has contributed to a shift in pharmaceutical toxicology, from a descriptive to an evidence-based, mechanistic discipline. Outside the boundaries of regulatory toxicology, Investigative Toxicology has the flexibility to embrace new technologies, enhancing translational steps from *in silico*, *in vitro* to *in vivo* mechanistic understanding to eventually predict human response. One major goal of Investigative Toxicology is improving preclinical decisions, which coincides with the concept of animal-free safety testing. The benefits of such 'in silico' models would be in enabling the rapid and robust prediction of the effects of compounds over a range of exposures, improving *in vitro*-*in vivo* correlations and the translation from preclinical species to humans. Systems toxicology models of organ toxicities that result in high attrition rates during drug discovery and development, or post-marketing withdrawals (e.g., drug-induced liver injury (DILI)) should facilitate the discovery of safe new drugs. Here, systems toxicology as applied to the effects of paracetamol (acetaminophen, N-acetyl-para-aminophenol (APAP)) is used to exemplify the potential of the approach. This goal is only fully achieved with primary prevention, which requires us to identify and prevent harms prior to human exposure through research and testing that does not involve human subjects. For that reason, public health policies place considerable reliance on nonhuman toxicological studies. Currently, compounds under preclinical development are being discarded due to the use of inappropriate animal models. Progress in Investigative Toxicology

could lead to humanized *in vitro* test systems and the development of medicines less reliant on animal tests. The adoption of evidence-based principles and methods will enhance the validity, transparency, efficiency, and acceptance of toxicological evidence, with benefits in terms of reducing delays and costs for all stakeholders (researchers, consumers, regulators, and industry).

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