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Metamorphosis of human health risk assessment with artificial intelligence (AI) - a new paradigm in pharmaco-toxicological sciences

Toxicological Science, especially in the last five decades, has witnessed rapid evolution of different tools and techniques developed to address diverse issues related to studies dealing with adverse health effects of a variety of poisons, drugs, chemicals,ever-growing list of xenobiotics and human diseases. Traditionally these studies are performed using suitable animal (*in vivo*) models. There was a time when toxicologists/pharmacologists were searching models alternate to animal toxicity testing (Doke and Dhawale, 2015). Improved cell culture techniques, knowledge on stem cells and other microbiological systems led to the development of *in vitro* toxicology. It was soon followed by *DNA chips, micro fluidics, in silico toxicology , toxicogenomics and computational toxicology*. Several platforms are now discussing **machine learning (ML)** and **artificial intelligence (AI)** together as future tools of computational toxicology. For decades, quantitative structure-activity relationship (QSAR) methods have been employed to study the effects of drugs/chemicals (Cai *et al*., 2022). However, AI methods for toxicity assessment ranging from ADMEtox to AI_4TOX provide evidence to the immense potential of AI. Intriguingly, a few problems between theoretical developments and practice of AI by end users have been recognized.

AI is now being employed in cancer care. According to WHO (2022), cancer is responsible for 9.3 million deaths per year. AI is being used for cancer grading, classification, follow up services and diagnostic accuracy. However, certain limitations viz. testing, validation, certification and auditing need to be addressed (Cabral *et al.,* (2023). Potential of AI in diabetic care and management has recently been recognized. The huge burden of diabetic patients in India can be managed through AI tools. Diabetic risk can be predicted using genomic data, to diagnose diabetes using EHR data and to identify diabetes related complications i.e. retinopathy and nephropathy (Singhla *et al.,* 2019). Application of AI in the management of cardiovascular diseases like myocardial infarction has been highlighted with special reference to Chinese medicine (Chen *et al.,* 2022). There exists experimental evidence that AI tools can be used to assess, monitor and manage Parkinsons' disease (Bounsall *et al*., 2023). Perspectives of the application of AI in complimentary and alternative medicine were reviewed by Chu *et al.* (2022).

Several regulatory agencies are now adopting the concept of 3R *ie*., **replacement, reduction** and **refinement** of animal testing (EU REACH/3R principles; Toxicology 21 of U.S. Government) (Maestri, 2021).The application of AI in clinical toxicology through converging data resources, algorithms, real world information from sensors and health records has also been discussed (Sinha *et al.* 2021). Plausibility of toxicity prediction using AI tools was recently reviewed by Santin *et al.* (2021). Application of AI in recently emerged science of nanotoxicology is also being sought. The need for nanotoxicity databases, powerful nano descriptors, new modeling approaches, molecular mechanism analyses and designing of next generation nanomaterials are being debated (Jha *et al.,* 2014; Yan *et al*., 2023).

U.S. Food and Drug Administration (USFDA) has recently initiated and AI program in Toxicology known as **AI4TOX**. This program mainly consists of four initiatives-

AnimalGAN- to predict animal toxicology data for untested chemicals (*/about –fda/nctr-research-focus-areas/animalgan-initiative*); **SafetAI-** to develop novel deep learning methods for toxicological endpoints (*/about-fda/nctr-research-focus-areas/safetai-initiative*); **BERTox-** to develop the most advanced AI powered Natural Language Processing (NPL) (*/about-fda/nctr-research-focus-areas/bertox initiative*) and **PathologAI-** to develop an effective and accurate framework for analysis of histopathological data from animal studies (*/about-fda/nctr-research-focus-areas/pathologai-initiative*).

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Recently, Society of Toxicology (SOT) annual meeting held at Nashville from March 19-23, focused on a question-"How could AI be used for risk assessment?" There exists some skepticism weather AI may be used in human health risk assessment? How AI could be applied -to prioritize pharmaceutical/environmental chemicals, to identify potential off targets and decipher the mechanisms of toxicity and detect pathological effects? A Symposium session devoted to AI summarized international collaborative computational projects like CERaPP, COmPara and CATOMOS that have been designed to streamline the regulatory and safety assessments (Hartung, 2023). High throughput screening data (HTS) to predict drug induced liver injury (DILI) using AI is also being generated. AI can identify mechanisms for off target effects in drug development. AI can also be plausibly used to predict genotoxicity. Can AI tools automate the analysis of developmental or physiologically based assays? These discussions held during the symposium indicate exciting potential of AI in health risk assessment. It is speculated that, tools of nanotechnology hybridized with AI can metamorphose human health risk assessment to an extent that has never been achieved before.

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