16-17 October 2024 | Sophia Antipolis

INTEGRATING AI INTO CHEMICAL SAFETY ASSESSMENT

OPPORTUNITIES, CHALLENGES, AND THE PATH FORWARD

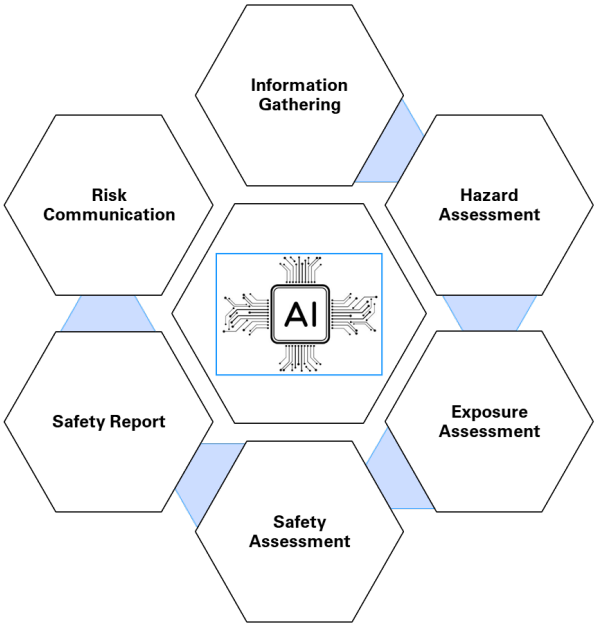
WORKSHOP FLASH REPORT

Background and objectives

Chemical safety assessment systemically analyses scientific data to evaluate potential adverse effects of chemical exposure on humans and the environment. Chemical safety assessment relies on a diverse array of data sources, incorporating both qualitative and quantitative information to form a comprehensive understanding of chemical impacts. The rapid advancement of artificial intelligence (AI) is transforming this field, enhancing capabilities to process and analyse vast datasets, including unstructured data types such as images, videos, and text. By leveraging AI's predictive power, risk assessors can better anticipate potential toxicity, uncover patterns in data previously difficult to detect, and improve the accuracy and efficiency of chemical safety assessments.

The workshop brought together key experts in the field of application of AI in chemical safety assessment, and aimed to:

1. Gain an overview of the "state of the art" in AI Technologies and Applications
2. Identify opportunities and challenges for AI application in chemical safety assessment.



Event participation

The workshop took place in Sophia Antipolis, France, on October 16-17, 2024, with online participation options on the first day to accommodate a broader audience. Day one counted thirty participants attending in person, and over 100 joining online. Attendees represented a diverse mix of professionals from regulatory agencies, policy making bodies, academia, and industry, reflecting a broad spectrum of expertise and perspectives on the integration of AI in chemical safety assessment. This interdisciplinary group contributed to rich discussions and a collaborative environment focused on advancing AI-driven innovations in regulatory and scientific frameworks for chemical safety. Day two was limited to face-to-face participants and included a series of breakout groups focused on: Data considerations; Existing and future applications of AI; Building trust in such applications.

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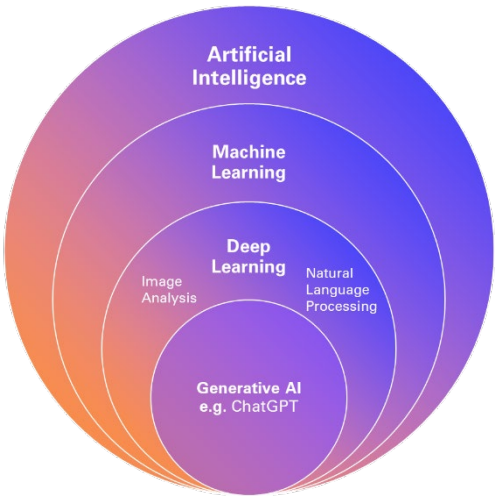
State of the art of AI technologies (Day 1 presentations)

Dr. Hua Qian (ExxonMobil Biomedical Sciences) gave a brief overview of AI and its different branches. Artificial intelligence (AI) refers techniques that enable computers to mimic human behaviour. Machine learning (ML) is a



subfield of AI, describing the ability to learn without explicitly being programmed. Deep learning, often used interchangeably with neural networks, can extract patterns from unstructured data like images and text (MIT Deep Learning). Generative AI, which emerged in late 2022, has been rapidly advanced and is widely adopted into many applications, like chat (Q&A), writing, and summarisation, through its easy accessibility: simple user interface and natural language prompts. *(Watch presentation here)*

Next Generation Risk Assessment

Dr. Nicole Kleinstreuer (NIH) introduced the concept of augmented intelligence, where AI complements and enhances human intelligence. She emphasised the transformative role of AI in chemical safety assessment for collating, interpreting and generating testable hypotheses for high-volume, high-content, complex data streams. Dr. Kleinstreuer showcased international projects using machine learning (ML) to crowdsource development of predictive models for toxicology endpoints like endocrine disruption and acute toxicity, now available in OPERA. She also demonstrated how ML, including natural language processing (NLP) / large language model (LLM), can democratise access to computational tools by creating user-friendly workflows for chemical grouping and by integrating data, including from new approach methodologies (NAMs), turning it into actionable insights for chemical safety assessment, for example via ICE. *(Watch here)*

Professor Thomas Hartung (Johns Hopkins University) emphasised the value of AI in extracting and integrating large datasets to predict toxicity. He highlighted examples such as using ML for read-across structure activity relationships (RASAR) to predict nine key toxicological and ecotoxicological endpoints. He also showcased the Ontox project, which goes beyond structural similarity by incorporating biological similarity and integrating RASAR/QSAR data with AOP networks and physiological maps. Additionally, Prof. Hartung recommended better communication on how AI can reduce uncertainty in risk assessments. *(Watch here).*

Dr Weida Tong (US FDA) highlighted that while ML has long supported pattern recognition in toxicological data, recent advancements in generative AI now enable generation of synthetic animal study results for untested substances using legacy animal data. The FDA conducted a proof-of-concept study using Generative Adversarial

Networks (GAN) to generate clinical pathology and toxicogenomics data for untested substances. Dr. Tong also introduced CycleGAN, which can translate one type of data into another, such as converting toxicity data from one organ to another. For more information see AI4TOX. *(Watch here).*

Dr. Anne Kienhuis (RIVM) presented how AI was leveraged in the VHP4SAFETY project which aims to perform risk assessments using human scenarios and biology. She explained how LLMs are used to populate the virtual human platform (VHP), which integrates clinical, physiological, epidemiological data and in silico/in vitro data. Dr. Kienhuis emphasised two key factors for building trust in AI: transparency and explainability. She noted that hackathons have been effective in fostering engagement, building trust and encouraging cross-disciplinary collaboration and learning. *(Watch here).*

Toxicokinetics

Dr. Zhoumeng Lin (University of Florida) highlighted the potential of ML to develop physiologically based pharmacokinetic (PBPK) models for predicting internal chemical concentrations in target organs. He noted gaps in published research, including a lack of toxicokinetic models for food-producing animals (important for food safety) and a focus on small molecule drugs. Dr. Lin presented the FARAD programme, which developed a ML model to predict plasma half-life of drugs in food-producing animals. Dr. Lin also presented an AI-enabled PBPK model to predict nanoparticle delivery to target tissues in mice. *(Watch here).*

Systematic Review

Dr. Fulvio Barizzone (EFSA) introduced EFSA's AI Roadmap, which aims to expand evidence accessibility and improve the trustworthiness of the risk assessment process by 2027. A key focus is using AI, such as LLM, in systematic reviews, including tasks like identifying keywords, removing duplicates, assessing bias, and screening and classifying references. AI governance activities are still in progress. Challenges include clarifying data use from publications and obtaining permission to use it for AI purposes. For further information see: Cavalli, et al. 2022 and Bersani et al., 2022. *(Watch here).*

Innovative Chemistry

Professor Paul Rees (Swansea University) presented examples of how AI is being applied to cell imaging in drug discovery and disease progression analysis. He demonstrated how ML and deep learning, combined with advanced techniques like flow cytometry and cell painting, can be used to track disease progression. He also showed how such techniques can detect cellular changes caused by chemical exposure, such as micronucleus formation resulting from genotoxic effects. Prof. Rees highlighted ground truthing as a key challenge. *(Presentation available here).*

Dr. David Rouquié (Bayer) highlighted the use of AI in de novo design of compounds. He summarised Bayer's work predicting in vivo acute oral toxicity data from chemical structures using ML QSARs, and from in vitro cell painting data using ML morphological profile-based models. The results showed that cell painting data has potential to predict in vivo acute toxicity, even without overlap in chemical space between the training set and test set. Dr. Rouquié also showcased a generative AI model, built on large public datasets, used to

design molecules with a high probability to induce desired cell painting or gene expression profiles. This proof-of-concept was performed in the context of hit discovery and paves the way toward the concept of AI-guided safety-by-design. *(Watch here).*

Dr. Alex Beatson (Axiom) presented Axiom's ML platform, designed to provide high quality toxicity data for chemical design. Currently focussed on liver toxicity, the platform is trained on a large dataset of drug-like molecules, agrochemicals and cosmetics, using cell painting data from primary human hepatocytes. It predicts liver toxicity, including point of departure, from chemical structure and includes an investigative assistant that identifies molecular substructures driving toxicity and suggests modifications to reduce toxicity. *(Watch here).*

From FAIR data to FAIR AI for Modern Toxicology

Dr. Erik Schultes (GO FAIR Foundation) highlighted that the FAIR[1] principles, introduced in 2016, were designed to enhance the ability of machines to automatically find and use data. He explained how the FAIR principles can improve data usage in AI, using OpenAI's ChatGPT as an example. Dr. Schultes suggested that applying a 'FAIR-ification' process to legacy data before using it in AI could help to address the key challenges of noise, bias and copyright. He also proposed that AI trained on FAIR data could be considered 'FAIR AI' or 'Fully AI-Ready'. *(Watch here).*

Dr. Barry Hardy (Edelweiss Connect) provided practical examples of preparing FAIR datasets for use in risk assessments and 'safer and sustainable by design' (SSbD) evaluations in projects such as RISK-HUNT3R, EU-ToxRisk. He highlighted several key areas where AI can contribute, including the development of knowledge graphs, curating metadata, and integrating different sources of evidence, including data from NAMs. Dr. Hardy also outlined use of Bayesian Networks for weight of evidence assessment and creation of an open standard for images as important future directions for AI in chemical safety assessments. *(Watch here).*

Key Learnings from Day 1

Dr. Maryam Zare Jeddi (Shell Global Solutions International BV) and Prof. Ben van Ravenzwaay (Wageningen University and Research), provided a summary of the Day 1 presentations.

The Day 1 presentations highlighted that AI is not just a tool for the future but is already shaping the way we approach safety - predicting hazards, reducing reliance on animal testing, advancing NAMs, and accelerating regulatory decisions. AI's ability to process massive datasets and uncover hidden patterns provides a new level of insight that traditional methods often do not reveal. ML and generative AI have the potential to transform toxicity prediction using existing data for training and new data to analyse and draw conclusions. LLMs are facilitating systemic literature reviews, whilst ML and generative AI are being used to design safer chemicals. AI can also facilitate implementation of Next Generation Risk Assessment and SSbD.

While AI is advancing rapidly and surpasses human capability for the analysis of large datasets it still must be used as complimentary to human intelligence which still provides the expert judgement required.

[1] Findable, Accessible, Interoperable, and Reusable

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The success of AI systems relies heavily on the data they are trained on - data must be both accurate (quality) and abundant (quantity) to ensure AI functions optimally. Applying the FAIR principles to datasets can support by ensuring data is computable, trustworthy, and equitable.

Application of AI in exposure science may be less developed and has potential for future growth.

Opportunities and challenges (Day 2 breakout group discussions)

Reflecting on the Day 1 presentations, small breakout groups explored opportunities and challenges in applying AI to chemical safety assessment across three key themes:

- Data considerations
- Existing and future applications
- Building trust

To provide further insights, Professor Tim Gant (Imperial College London) shared lessons from genomics on adoption of new technologies in chemical safety assessment. Key challenges included lack of confidence in data, limited technical guidance, and the need for clearer communication and case studies. He also noted that while 'omics is still developing, ML and generative AI offer potential for data training and interpretation. Prof. Gant encouraged proactive action: "Don't wait for technology to mature before establishing standards and methods."

Breakout group 1: Data considerations

The following challenges and opportunities were identified:

Challenge	Opportunity
Data Sharing	
Data ownership and intellectual property	Categorise copyright, c.f. Creative Commons. Communication of incentives.
Data security and confidentiality	Transparency in terms of data use. Federated learning ML. Honest broker entity. Data encryption.
Data accessibility, unknown datasets including lack of standardised/harmonised formats for metadata	Standardised, harmonised formats. Make IUCLID[2] FAIR. CADDY format. Incentivisation c.f. Data openness badge.
Data quality and Reliability	
Lack of fit for purpose data quality (reliability) assessment guidance; Poor training sets, data gaps, lack of minimum metadata requirement.	Consider **the trade-offs between data quality and quantity** for AI training. Use of AI for automated study quality scoring.
Data integrity and dynamic nature AI-generated knowledge	Establishing robust protocols for updating training data and re-evaluating AI models. Developing AI models whose decision-making processes can be understood and audited to ensure **transparency and explainability**
Data curation and management	
Who stores, who maintains, for how long and who pays	Address sustainability of database. Build effective data life cycle management and FAIR data principles implementation into project scope, especially if publicly funded.
Data Cleaning and curation	Detailed annotation of data points. Use of Controlled Vocabularies and Ontology.

[2] International Uniform Chemical Information Database - software application to capture, store, maintain and exchange data on intrinsic and hazard properties of chemical substances.

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Challenge	Opportunity
	Standardisation. "Little" Parameters: Capturing all relevant study parameters, even those that might seem insignificant, is crucial (Rich Metadata)

Breakout group 2: Existing and future applications

Over fifty applications of AI in chemical safety assessment were identified, including data identification, extraction, interpretation, prediction and generation (toxicological and exposure) as well as testing design and retrospective safety assessments. Each application was evaluated for development status, reliability, acceptability and priority.

High priority and relatively mature applications identified included:

- Data identification
- Data extraction and analysis

Mature and relatively well accepted applications identified included:

- Image analysis (e.g. cell painting)
- Systematic reviews
- Analysis of incident data
- Physico-chemical parameter prediction

High priority but less mature areas identified included:

- Safety assessment of mixtures
- Data read-across
- Data quality assessment (e.g. via CREED)
- Exposure assessment including toxicokinetics

Breakout group 3: Building trust

Building trust in AI is essential for its effective adoption in chemical safety assessment. This trust hinges on both **social** and **technical** factors. By addressing these dimensions, AI can be better integrated into workflows, gaining confidence from all stakeholders. The breakout group identified several opportunities to strengthen trust:

Social Aspects:

- Incorporate human oversight to ensure transparency and reliability.
- Promote understanding of AI technologies through education and easy access to tools.
- Demonstrate AI's strengths in minimising human bias and uncovering deeper insights in data.

Technical Aspects:

- Develop standardised reporting frameworks and validation guidelines, potentially led by international organisations like the OECD.
- Prioritise the use of high-quality datasets for model training and exercise care with the use of Generative AI for self-learning.
- Showcase AI's capabilities through proof-of-concept studies, such as grouping, data curation, or effects recognition, to build credibility.

By addressing these opportunities, AI can become a trusted ally in advancing chemical safety assessment.

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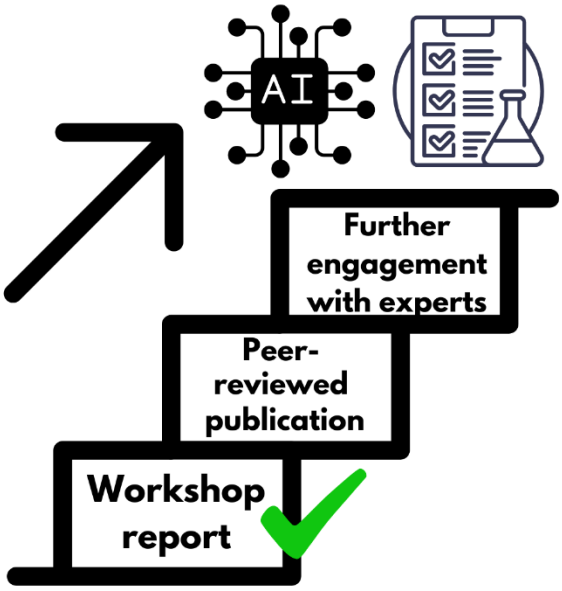
Key take home messages

AI in Chemical Safety: AI is transforming chemical safety assessment, complementing human expertise while still relying on expert judgment.

Data is Key: High-quality, accessible data in harmonised formats, along with transparent data practices, are essential for AI success. Tools like the IUCLID software, maintained by the European Chemicals Agency (ECHA), could become even more impactful if adapted to FAIR principles

Building Trust in AI: Standardised reporting, validation frameworks, and accessible tools are critical to overcoming trust barriers.

Emerging Priorities: Key focus areas include assessing mixtures, data read-across, exposure, and data quality evaluation.



Next steps

Dr. Blanca Serrano Ramon, ECETOC Secretary General, wrapped up the workshop by outlining the next steps and the path ahead.

A peer-reviewed publication is planned to capture and build upon the wealth of knowledge,

ensuring the impact is maximised and the journey continues.

The ECETOC Scientific Committee will actively explore how ECETOC can best contribute to advancing the use of AI in chemical safety assessment, driving innovation and shaping the future of safer, more efficient practices in the field.