

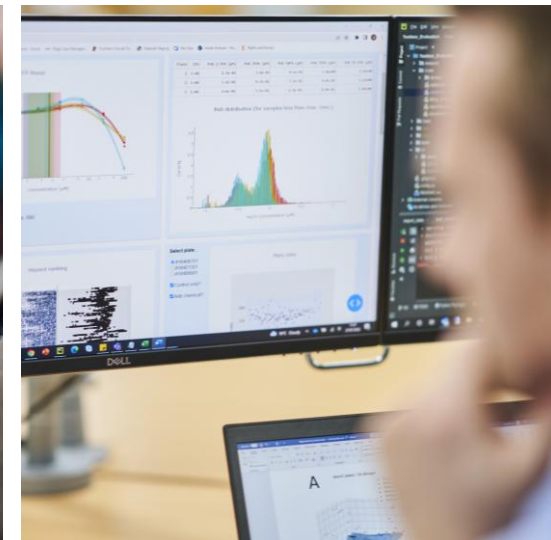
AI-based *in silico* Tools in Safety Risk Assessment

Dr. Predrag Kukic



JIFSAN

11th December 2025



Excitement about AI

- Need for **BIG data** and robust data governance frameworks (accurate, consistent, complete, compliant)
- AI models (transparent, traceable, compliant, robust)
- Rigorous Internal & External Validation
- Define Confidence in AI Predictions
- Ability to Interpret the Results
- Well-defined application (CoU)

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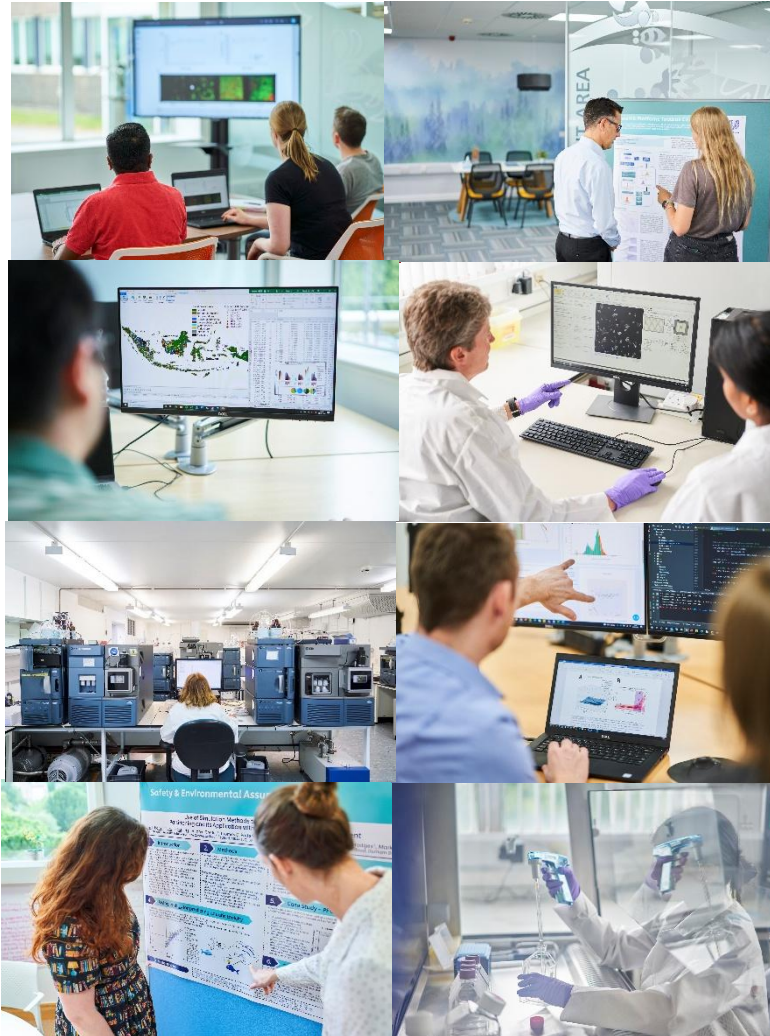
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AI models with meaningful impact:

- ChatGPT-3 – ca. 300 billion words
- DALL-E - ca. 2 billion images
- AlphaFold – Big Fantastic Database of ca. 66M of protein families and 2.5 B protein sequences



Safety, Environmental and Regulatory Science (SERS) Expertise



SERS is a diverse, multi-disciplinary team of ~180 scientists covering:

- Cell & Molecular Biology
- Chemistry
- Computational Modelling
- Environmental Safety
- Environmental Sustainability
- Exposure Science
- Informatics & Data Science
- Mathematics & Statistics
- Microbiology
- Process Safety
- Regulatory Science (chemical & food safety)
- Toxicology

Safety Risk Assessments

- Consumers, Workers, Environment

Life Cycle Assessments

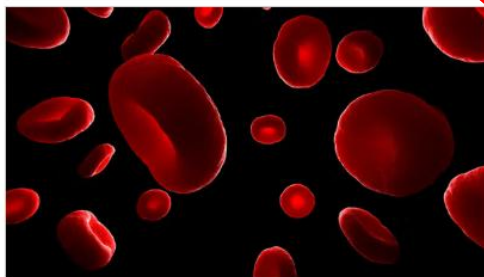
- Environmental Impacts

Product Compliance

- Regulatory Data & Dossiers

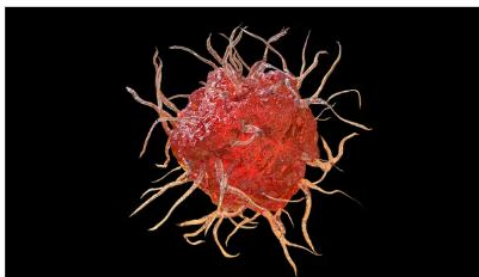


Safety Risk Assessment - Our Research Focus Areas



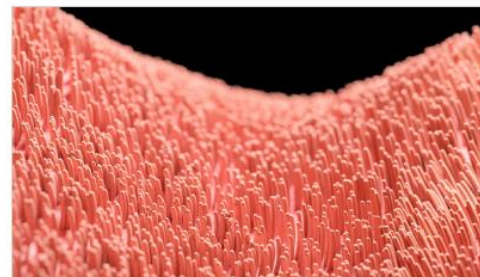
Systemic Safety

To understand the safety of ingredients if they are absorbed into the body (systemic safety), we do not use an animal study to...



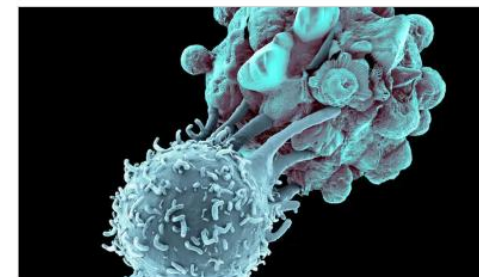
Skin Allergy Safety

Some ingredients used in consumer products have the potential to cause allergic contact dermatitis (ACD), a type of skin allergy. To...



Inhalation Safety

A significant proportion of Unilever's products are aerosols and sprays which include underarm antiperspirants, hair sprays...



Immune Effects Safety

We consider all potential adverse impacts on the human immune system resulting from exposure to an ingredient. These include...



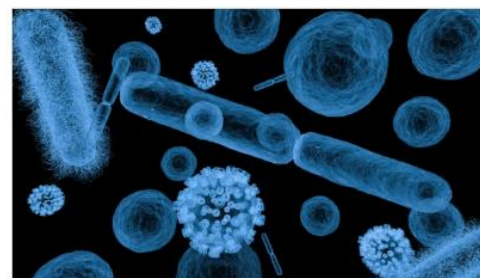
Microbiological Safety

Some of our consumer products have the potential to change the human microbiome or raise microbiological concerns...



Environmental Safety

Unilever ingredients are often disposed of down the drain after use, so it is important for us to assess the environmental safety of...

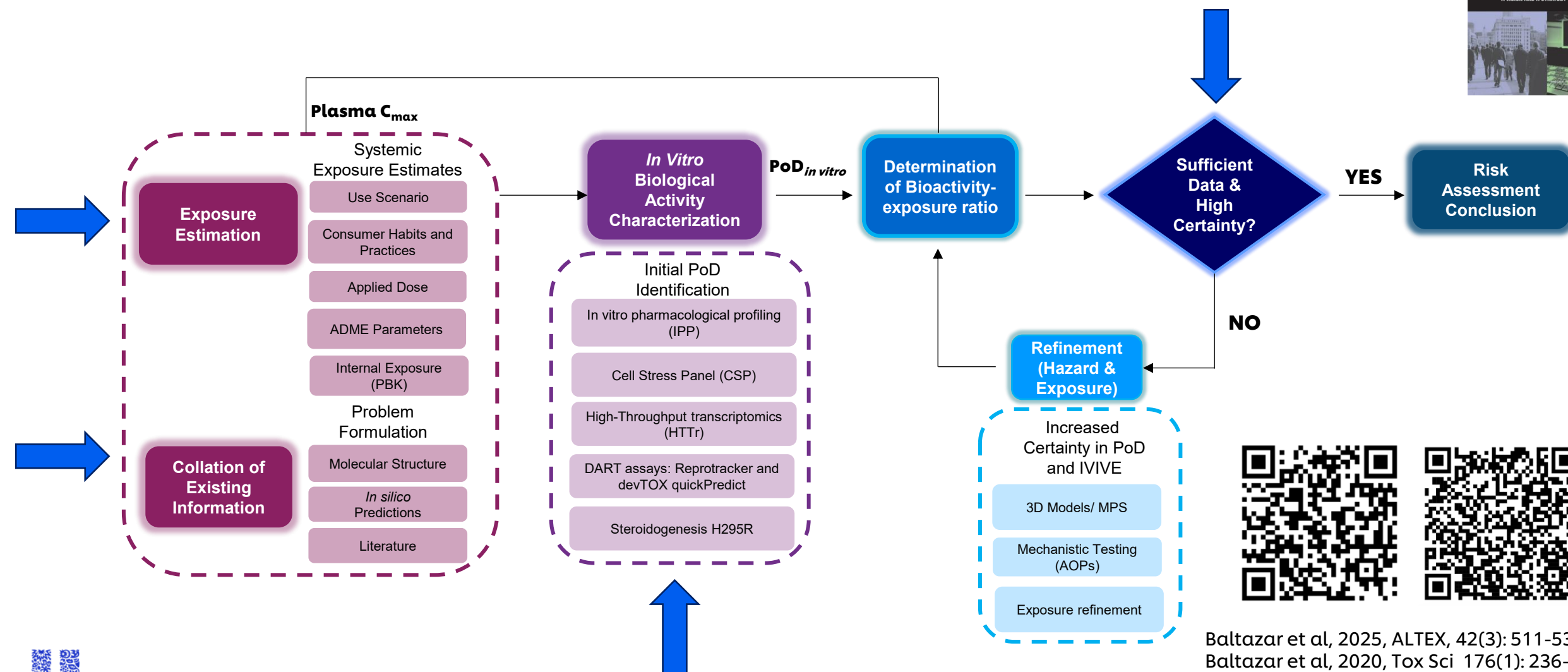
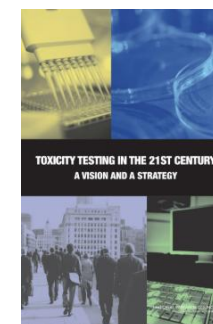


Biodegradation

Biodegradation is the process in which an ingredient is broken down through natural processes by microorganisms into simple substances...



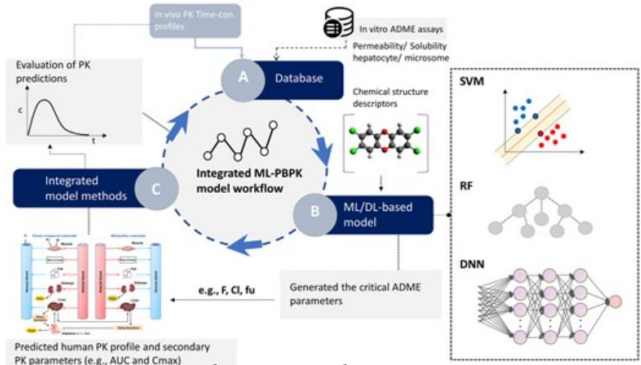
Non-animal Safety Risk Assessment for Systemic Toxicity



Baltazar et al, 2025, ALTEX, 42(3): 511-530
Baltazar et al, 2020, Tox Sci 176(1): 236-252.
Middleton et al., 2022 Tox Sci 189(1):124-147.
Cable et al., 2025 Tox Sci 204(1):79-95.

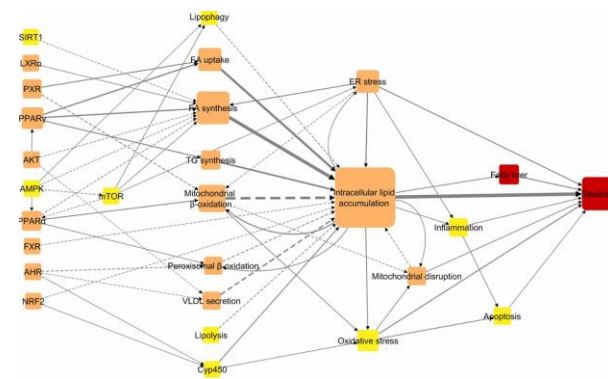
Examples of AI tools for Systemic Toxicity

Predict Absorption, Distribution, Metabolism & Elimination



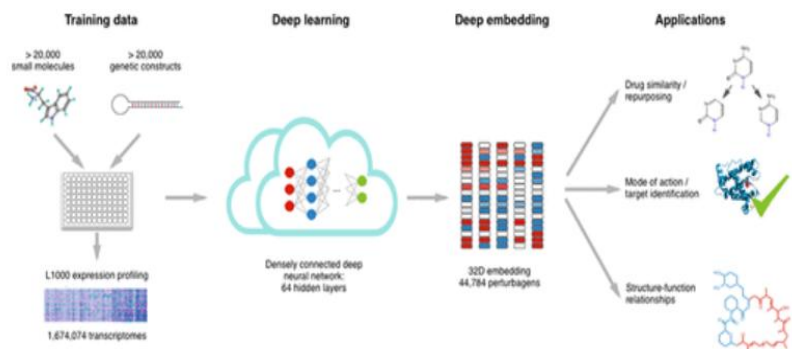
Chou et al.,(2023)

Predict Liver Steatosis and Cholestasis



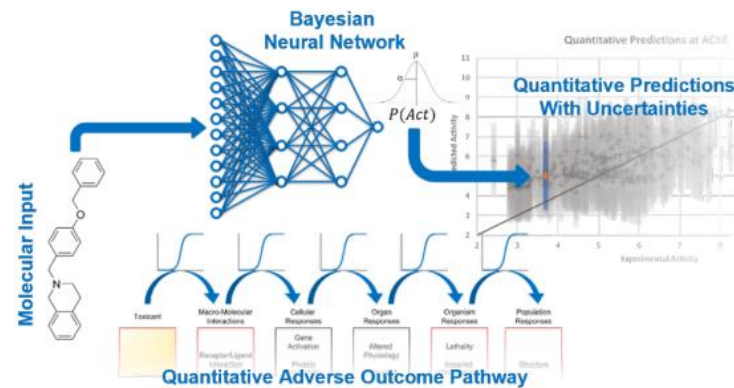
Verhoeven et al.,(2024) and Ertvelde et al.,(2023)

DNNs for toxicogenomic read-across



Donner et al., (2018)

Predict off-target effects



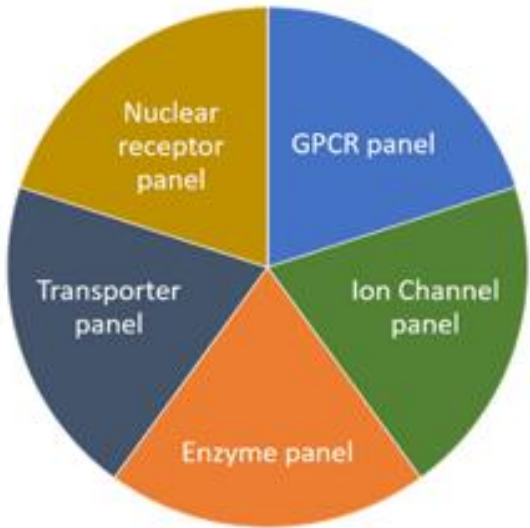
Allen et al., (2022)



Secondary Pharmacology assays



Targets (gene)	Hit rate*		Main organ class or system	Effects	
	Binding	Functional or enzymatic		Agonism or activation	Antagonism or inhibition
G protein-coupled receptors					
Adenosine receptor A _{2A} (ADORA2A)	High	Low (agonist)	CVS, CNS	Coronary vasodilation; ↓ in BP and reflex; ↑ in HR; ↓ in platelet aggregation and leukocyte activation; ↓ in locomotor activity; sleep induction	Potential for stimulation of platelet aggregation; ↑ in BP; nervousness (tremors, agitation); arousal; insomnia
Ingredient		Food Source		Interaction Type	
Caffeine		Coffee, tea, cocoa		Antagonist	
Theobromine		Cocoa, chocolate		Antagonist	
Theophylline		Tea		Antagonist	
Androgen receptor (AR)	Medium	Medium	Endocrine	↑ in prostate carcinoma; oedema; androgenicity in females; ↑ in muscle mass; ↑ in hostility; sleep apnoea; liver complications	↓ in spermatogenesis; impotence; gynecomastia, mastodynia; ↑ in breast carcinoma
Glucocorticoid receptor (NR3C1)	Medium	Medium	Endocrine, immune	Immunosuppression; hyperglycaemia; insulin resistance; muscle wasting; ↑ in body weight; osteoporosis; glaucoma; ↑ in BP; ↓ in plasma potassium and arrhythmia	Hypoglycaemia



44 most important targets
PERSPECTIVES

Reducing safety-related drug attrition: the use of *in vitro* pharmacological profiling

Joanne Bowes, Andrew J. Brown, Jacques Hamon, Wolfgang Jarolimek, Arun Sridhar, Gareth Waldron and Steven Whitebread

Abstract | *In vitro* pharmacological profiling is increasingly being used earlier in the drug discovery process to identify undesirable off-target activity profiles that could hinder or halt the development of candidate drugs or even lead to market withdrawal if discovered after a drug is approved. Here, for the first time, the rationale, strategies and methodologies for *in vitro* pharmacological profiling at four major pharmaceutical companies (AstraZeneca, GlaxoSmithKline, Novartis and Pfizer) are presented and illustrated with examples of their impact on the drug discovery process. We hope that this will enable other companies and academic institutions to benefit from this knowledge and consider joining us in our collaborative knowledge sharing.

safety testing of drug candidates and are designed to prevent serious ADRs from occurring in clinical studies.

The only *in vitro* pharmacology assay that is absolutely required by regulatory authorities is one that measures the effects of new chemical entities on the ionic current of native (*I_h*) or heterologously expressed human voltage-gated potassium channel subfamily H member 2 (KCNH2; also known as hERG)¹. The mechanism by which blockade of hERG can elicit potentially fatal cardiac arrhythmias (torsades de pointes) following a prolongation of the QT interval is well characterized^{2,3}, and the seriousness of this ADR is one reason why this assay is a mandatory regulatory requirement. Receptor binding studies are also recommended as the first-tier approach for the assessment of the dependence potential of novel chemical entities⁴.

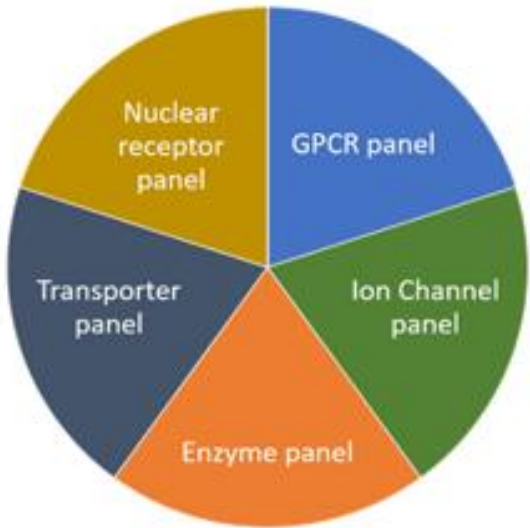
However, current regulatory guidance does not describe which targets should constitute an *in vitro* pharmacological profiling panel and does not indicate the stage of the discovery process at which *in vitro* pharmacological profiling should occur.



¹⁰Bowes et al., Nat Rev Drug Discov. 11(12):909-22, 2012.

Secondary Pharmacology assays

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Adenosine	High	Low (agonist)	CVS, CNS	Coronary vasodilation		Potential for stimulation
Compound Class		Food Source			AR Interaction Type	
Flavonoids		Fruits, vegetables, tea			Antagonist	
Isoflavones		Soy products			Antagonist	
Lignans		Flaxseed, sesame seeds			Anti-androgenic	
Polyphenols		Grapes, berries, tea			Modulator	
Contaminants		BPA, phthalates (packaging)			Antagonist	
Androgen receptor (AR)	Medium	Medium	Endocrine	↑ in prostate carcinoma; oedema; androgenicity in females; ↑ in muscle mass; ↑ in hostility; sleep apnoea; liver complications	↓ in spermatogenesis; impotence; gynecomastia, mastodynia; ↑ in breast carcinoma	101,102
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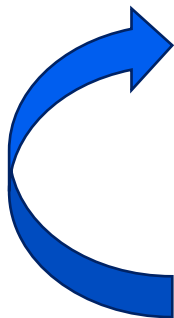
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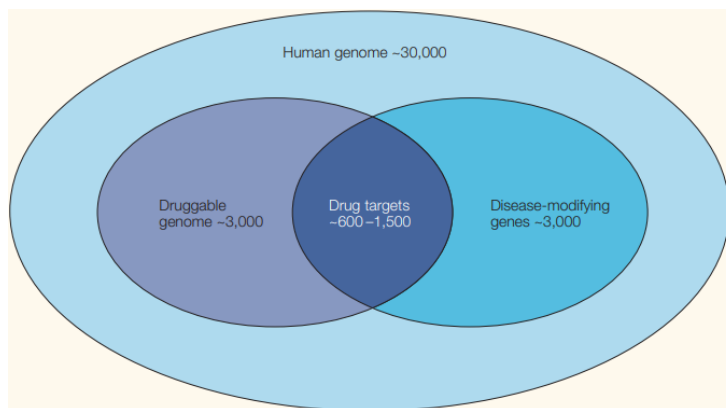
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AI models to extend Secondary Pharmacology Screening

- Secondary Pharmacology panels are pragmatic and include the most important targets with safety liabilities (around 40 to 80 targets)
- Increase in availability of **data and AI** allows us to **screen for more protein targets** associated with adverse effects
- Extending the list of safety pharmacology targets will be very beneficial to **increase confidence** in safety risk assessment

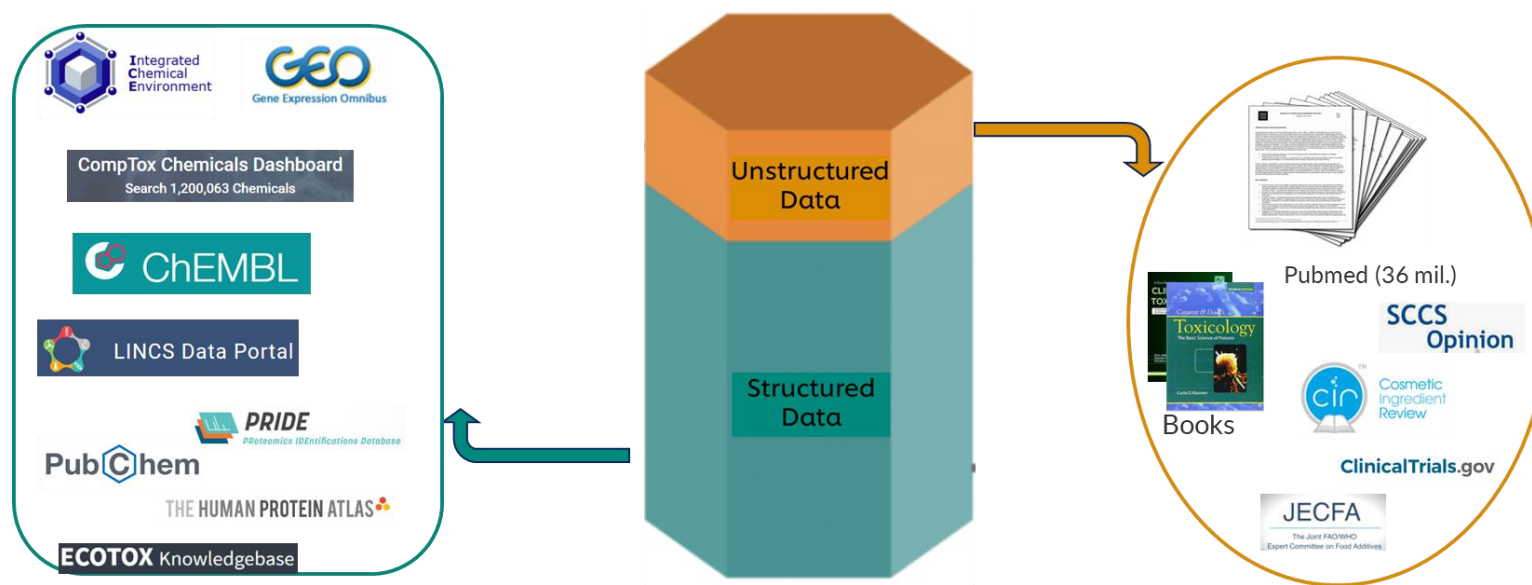


Hopkins & Groom, Nature Reviews, 2002

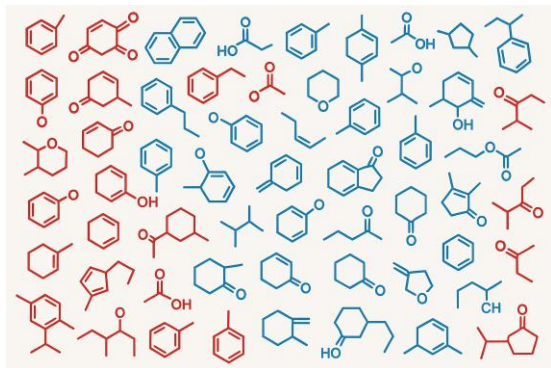
Target	Biological Role	Associated Effect
VEGFR2 (vascular endothelial growth factor 2)	glutamate gated ion channel playing role in dendritic spine development	VEGF signaling involved in blood vessel formation
NMDA		Brain development
CYP19A1 inhibition	Conversion of testosterone to DHT	Reproductive dysfunction
Sodium Iodide Symporter (NIS) Inhibition	Neurodevelopment	Development of the central nervous system and lungs
5α-reductase	Reproductive	Reproductive

Availability of Experimental Data

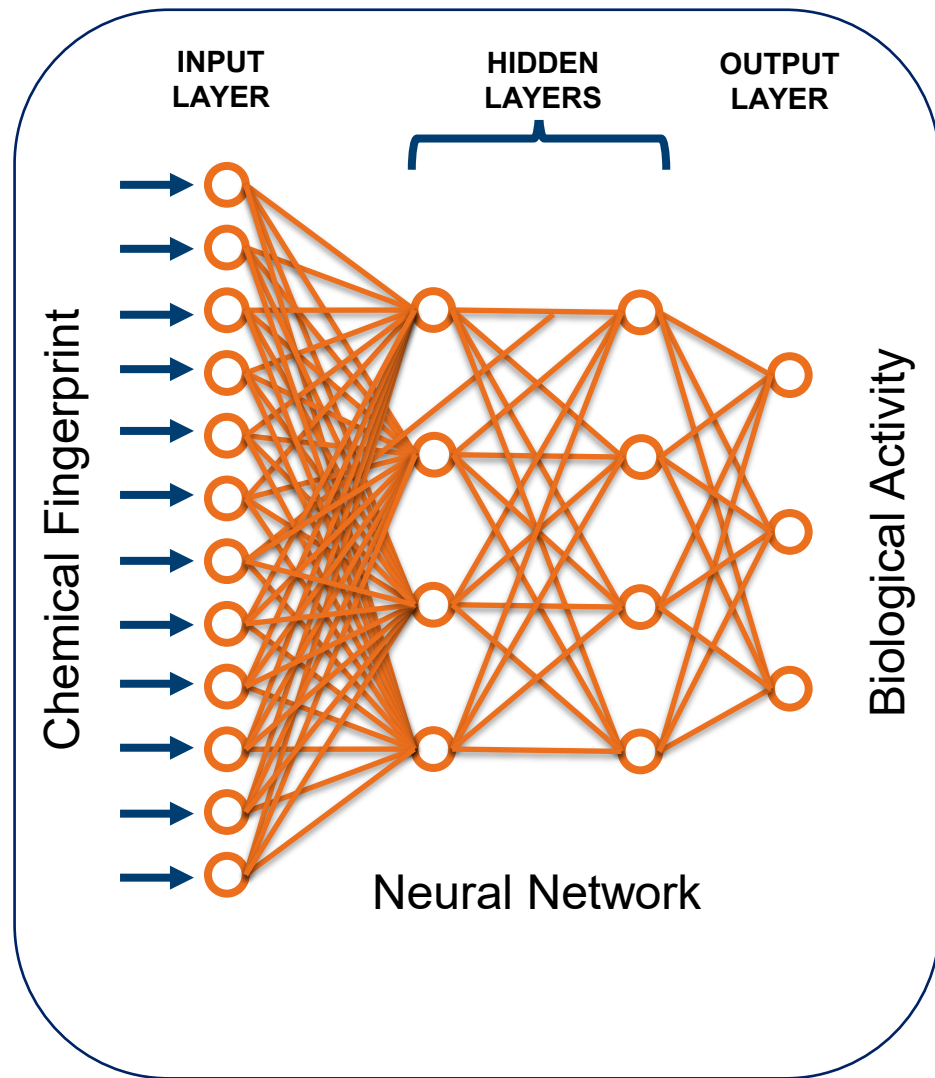
- This is becoming feasible due to the emergence of big and diverse *in vitro* tox data:
 - significant increase in **high throughput data** in the last 20 years (Tox21 and ToxCast programs, NIH Lincs, TEX-VAL, Pharma HTS data, Omics data from literature, etc.)
 - emergence of **large curated databases** (CompTox Dashboard, ChEMBL, etc.)
- Accumulating large-scale *in vitro* data allow for **systematic grouping of chemical compounds** by the biological target that they modulate and build AI model for that target



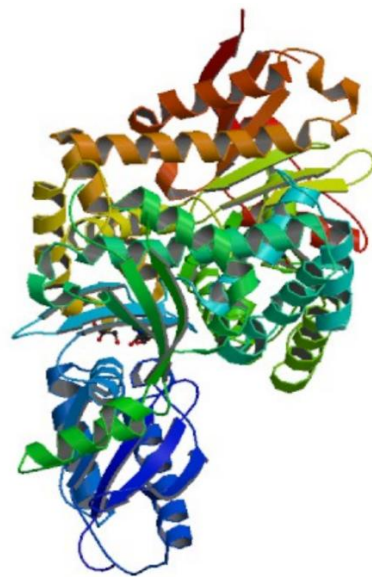
Building an AI model for a Target of Interest



1000s of chemicals compounds with measured binding activity against the target

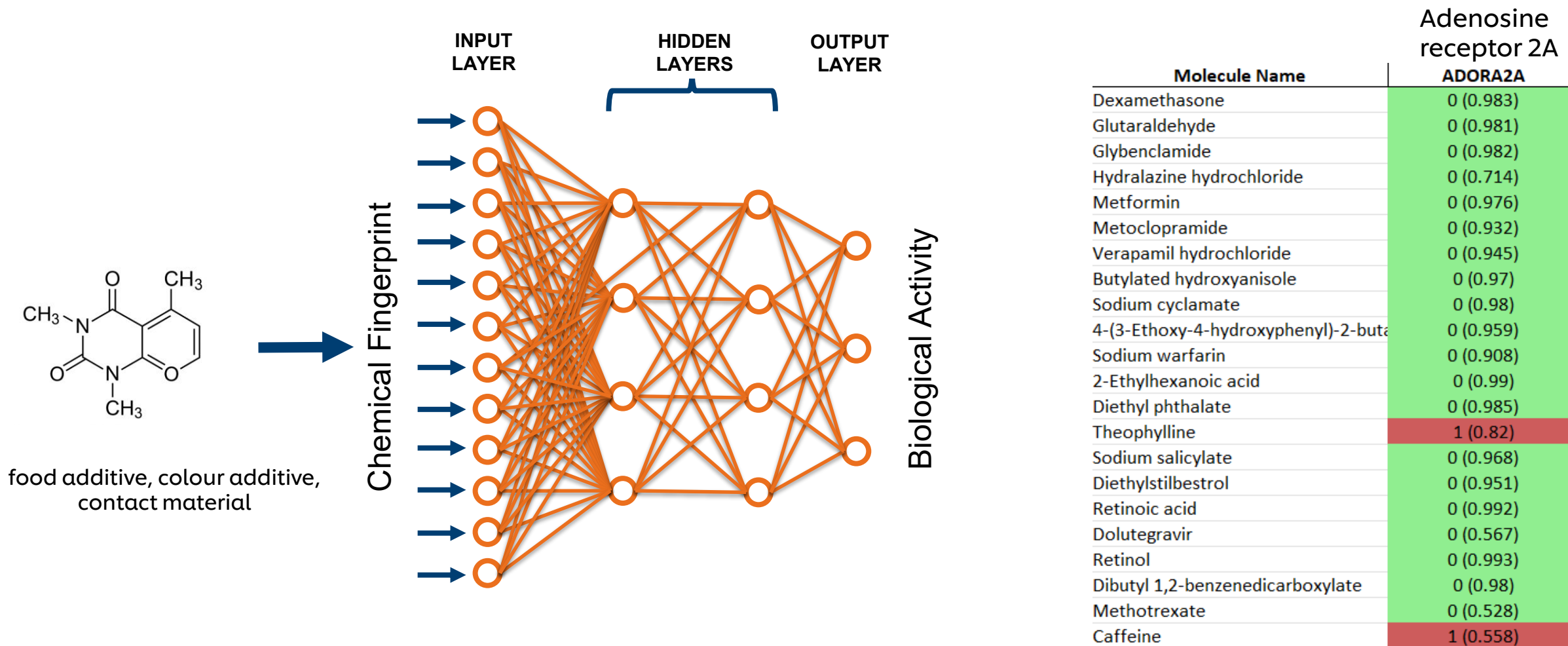


Adenosine receptor 2A



	Training data					Validation data				
	SE	SP	ACC	MCC	ROC-AUC	SE	SP	ACC	MCC	ROC-AUC
AVERAGE	92.1	96.5	95.8	0.901	0.99	86.9	93.2	92.5	0.822	0.96
SD	8.8	4.2	3.1	0.069	0.02	11.7	5.9	4.1	0.091	0.04

Testing an AI model for ADORA2A receptor

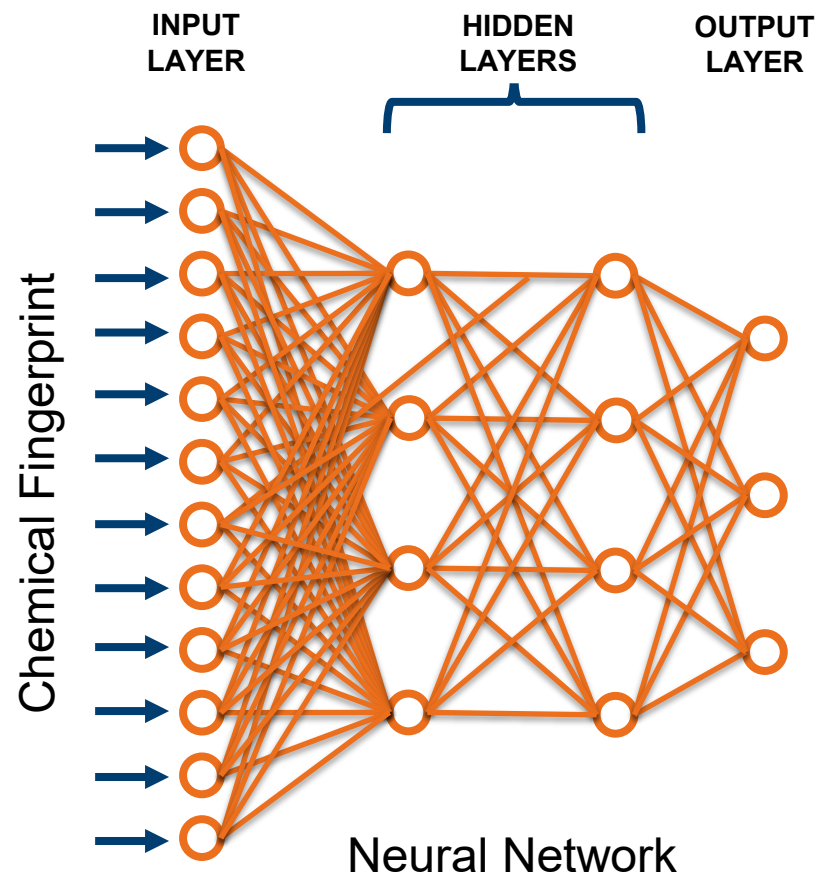


Molecular Initiated Event (MIE) Atlas



Data extracted and curated from ChEMBL and ToxCast databases

Target	Inactives
144,109 actives	141,796 inactives



MIE Atlas V1 (2019)

79 biological targets

MIE Atlas V2 (ongoing)

~600 biological targets

Chemical
Science



EDGE ARTICLE

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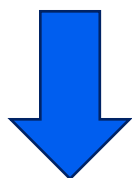
All publication charges for this article have been paid for by the Royal Society of Chemistry

Neural network activation similarity: a new measure to assist decision making in chemical toxicology†

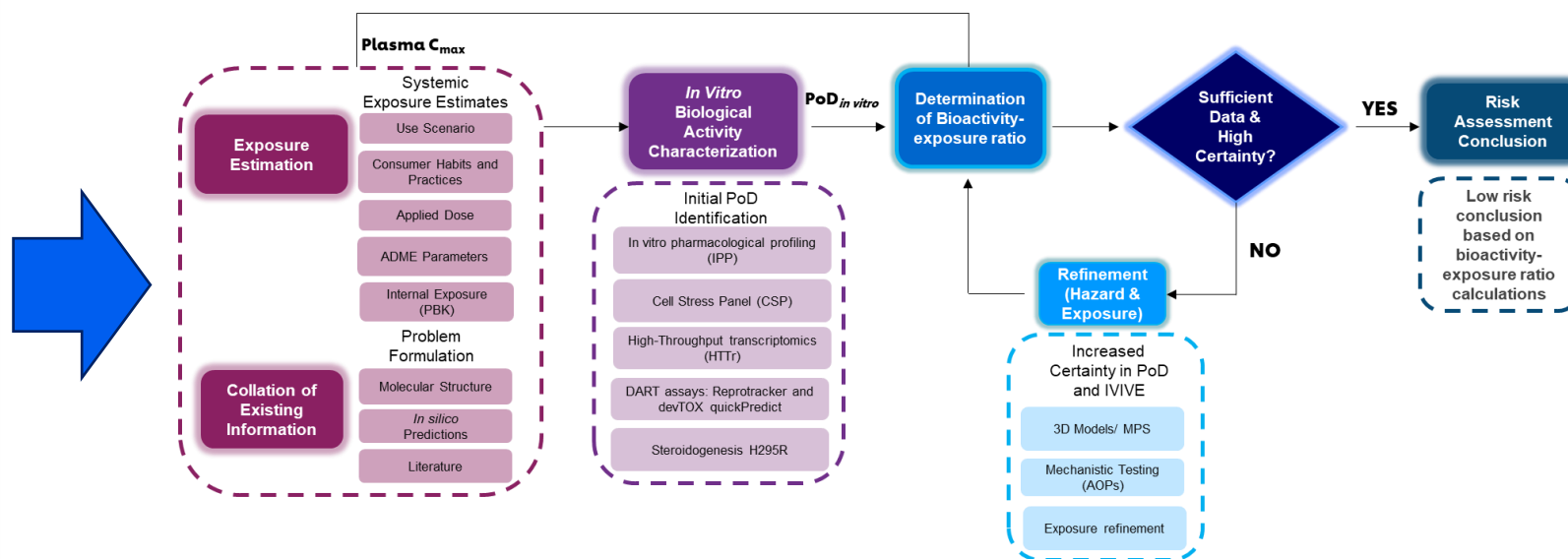
Timothy E. H. Allen,^a Andrew J. Wedlake,^b Elena Gelzinyte,^c Charles Gong,^b Jonathan M. Goodman,^c Steve Gutsell^c and Paul J. Russell^c

Application of AI in Safety Science: Future Trends

- Increased access to chemical, biological, exposure and toxicological data that are FAIR (expected exponential increase in global data volumes*).



- More accurate AI models that can help with individual steps in safety risk assessment.



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- **Data-driven** approach to complement Expert-driven approach.



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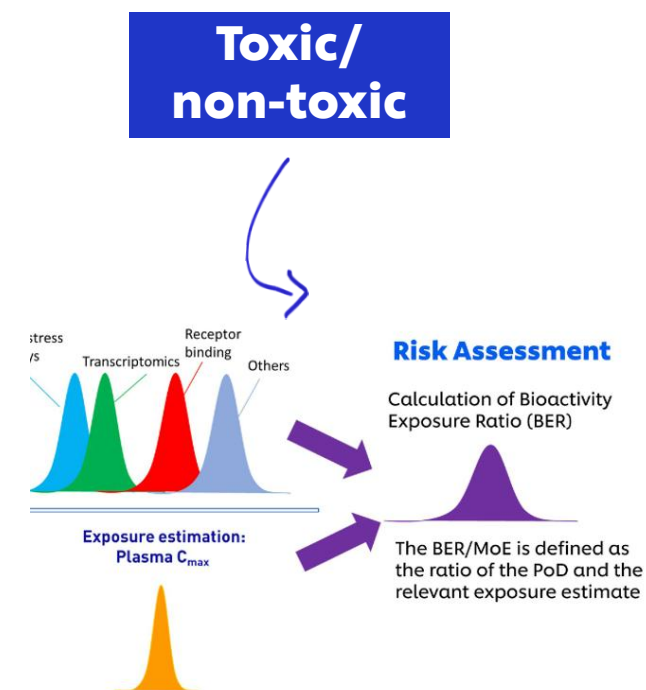
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Probabilistic Risk Assessment
(exposure and bioactivity probability distributions, probability of risk, uncertainty quantification, subpopulations, etc.)

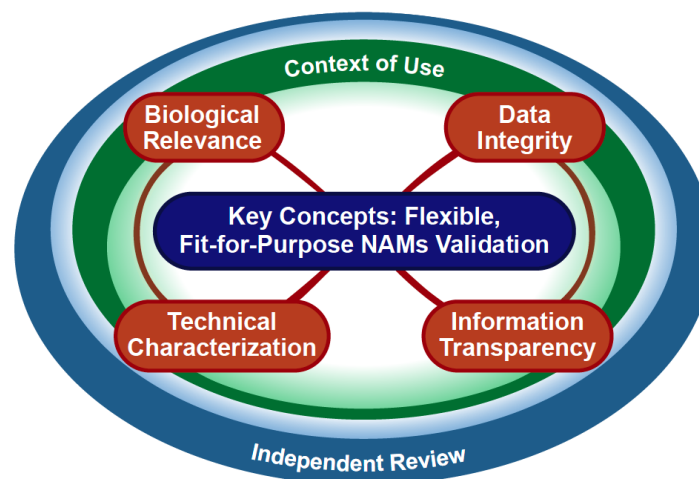


Application of AI in Future Safety Science: Build Confidence Step by Step

Increased industry: academia: regulatory exchange to amplify positive impact of AI on future toxicology, while also managing governance challenges.



- Leverage scientific and technological progress to advance exposure science, understanding of human biology and risk assessment.



- Guidance and guidelines that will pave the way for regulatory acceptance.

*ICCVAM Validation Report, Figure 1
(adapted from van der Zalm et al. 2022 Arch Tox)*



- Design educational programmes.
- Training and access to information that will support confidence in the use of AI.

