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

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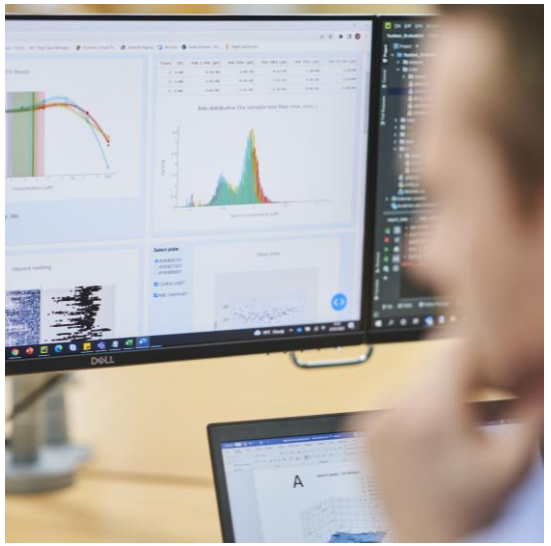
Unilever | SERS Safety, Environmental & Regulatory Science | Joint Institute for Food Safety and Applied Nutrition, University of Maryland, U.S. Food & Drug Administration | JIFSAN

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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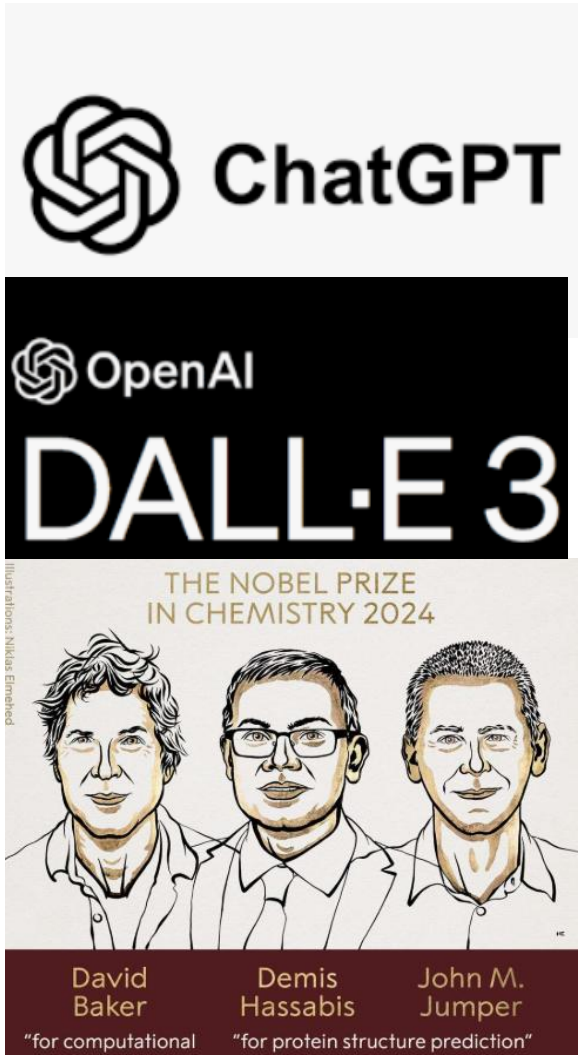
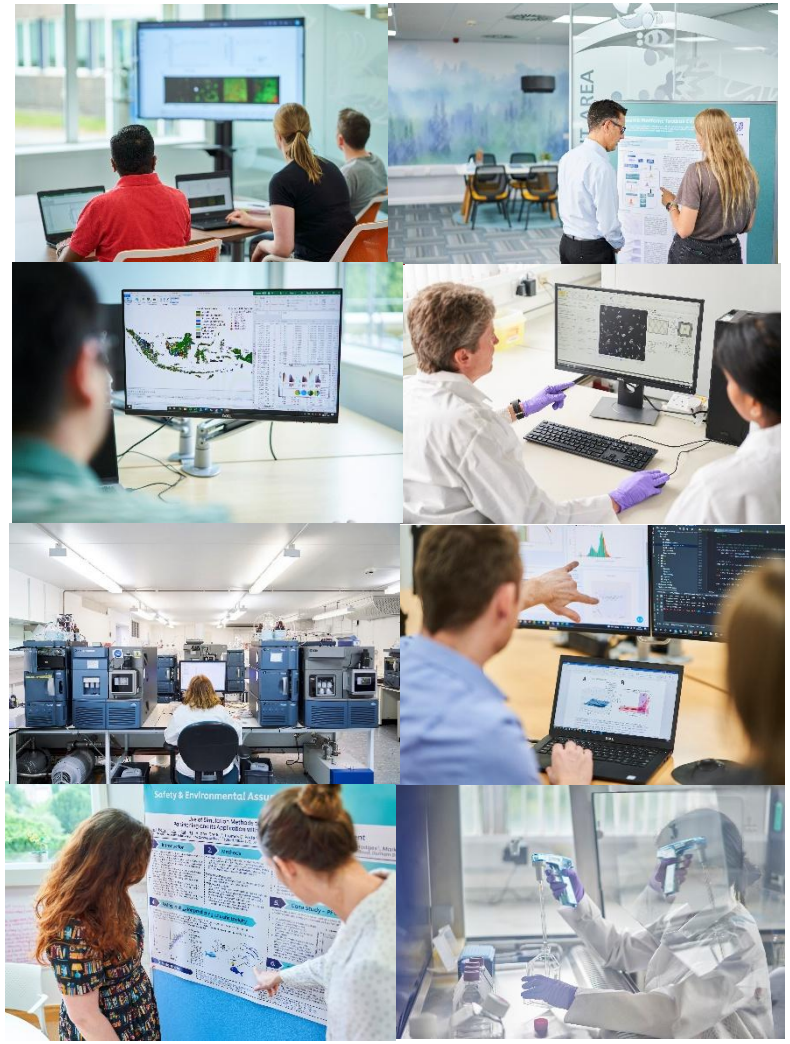
AI models with meaningful impact:

- 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

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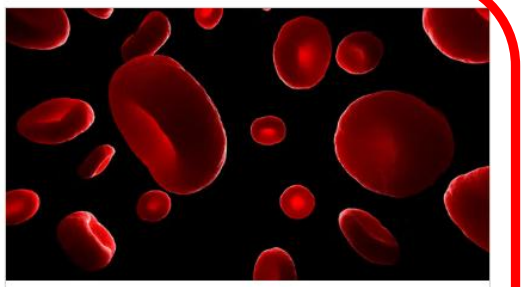
Collaborating to modernise the scientific data & tools we use for making safety decisions – 20 years of research & evaluation

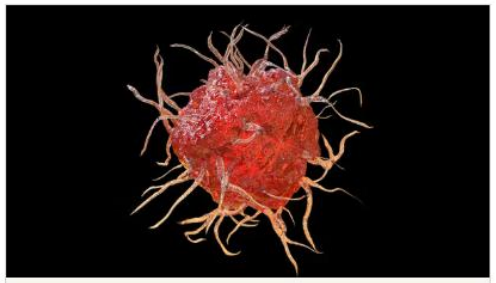
https://sers.unilever.com/our-science/safety-without-animal-testing/

Safety Risk Assessment - Our Research Focus Areas



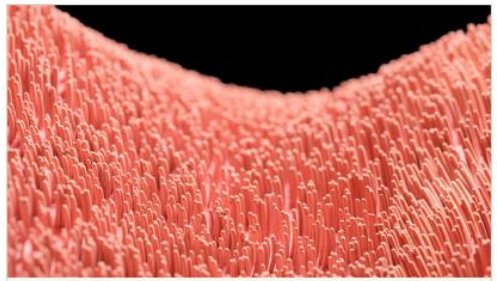
Systemic Safety

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



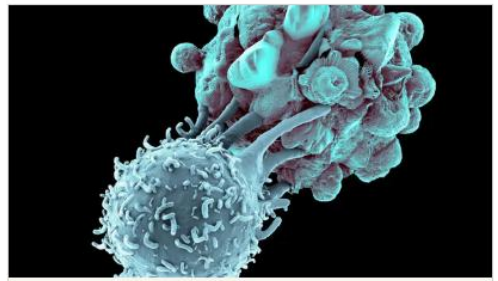
Skin Allergy Safety

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



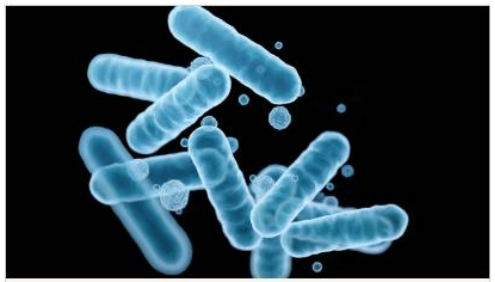
Inhalation Safety

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...

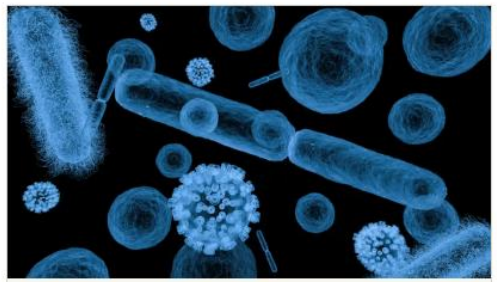


Microbiological Safety

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...

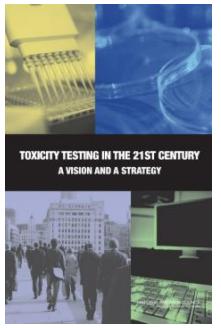


Biodegradation

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

https://sers.unilever.com/our-science/safety-without-animal-testing/

Non-animal Safety Risk Assessment for Systemic Toxicity



Plasma C_{max}

Systemic Exposure Estimates

Exposure Estimation

- Use Scenario
- Consumer Habits and Practices
- Applied Dose
- ADME Parameters
- Internal Exposure (PBK)

Problem Formulation

Collation of Existing Information

- Molecular Structure
- *In silico* Predictions
- Literature

In Vitro Biological Activity Characterization

Initial PoD Identification

- In vitro pharmacological profiling (IPP)
- Cell Stress Panel (CSP)
- High-Throughput transcriptomics (HTTr)
- DART assays: Reprotracker and devTOX quickPredict
- Steroidogenesis H295R

$PoD_{in\ vitro}$

Determination of Bioactivity-exposure ratio

Sufficient Data & High Certainty?

YES

Risk Assessment Conclusion

NO

Refinement (Hazard & Exposure)

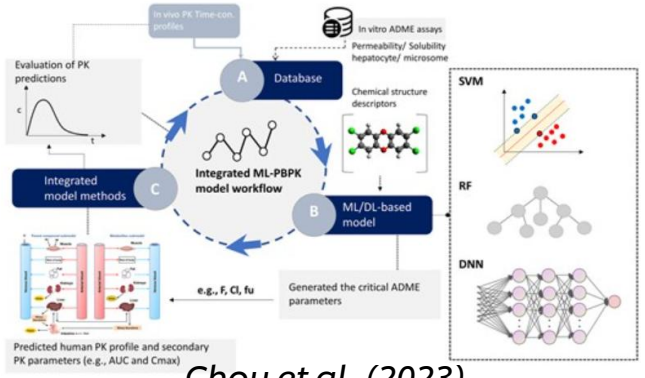
Increased Certainty in PoD and IVIVE

- 3D Models/ MPS
- Mechanistic Testing (AOPs)
- Exposure refinement

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.

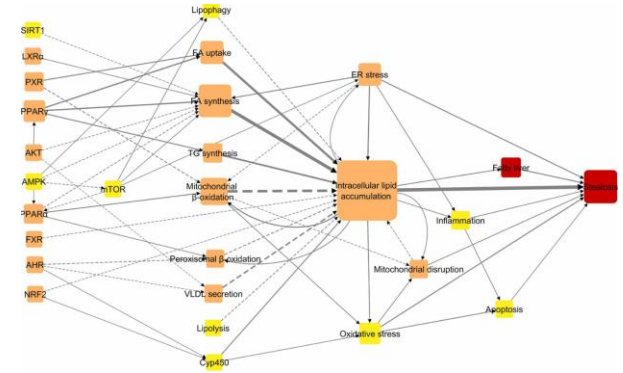
Examples of AI tools for Systemic Toxicity

Predict Absorption, Distribution, Metabolism & Elimination



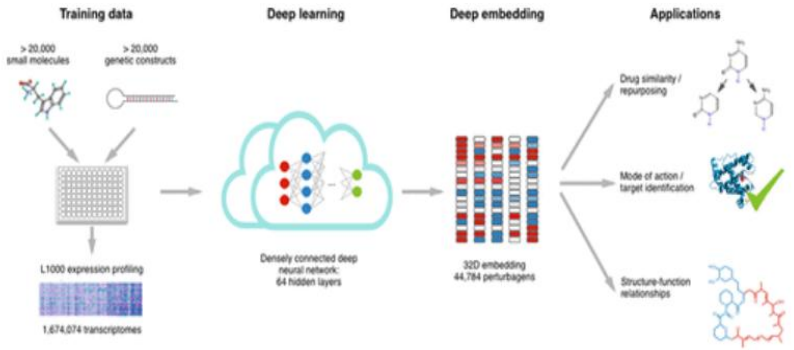
Chou et al.,(2023)

Predict Liver Steatosis and Cholestasis



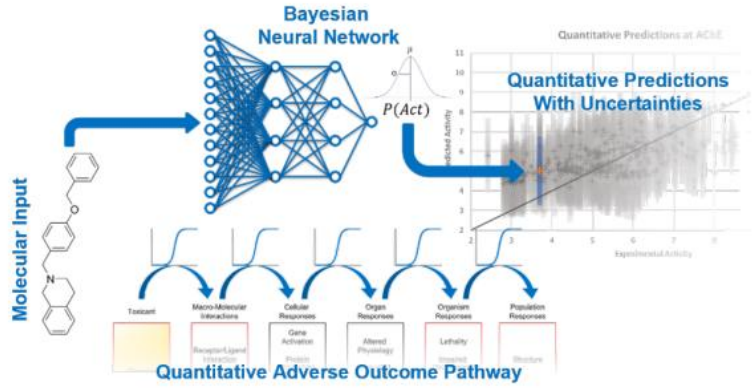
Verhoeven et al.,(2024) and Ertvelde et al.,(2023)

DNNs for toxicogenomic read-across



Donner et al., (2018)

Predict off-target effects



Allen et al., (2022)

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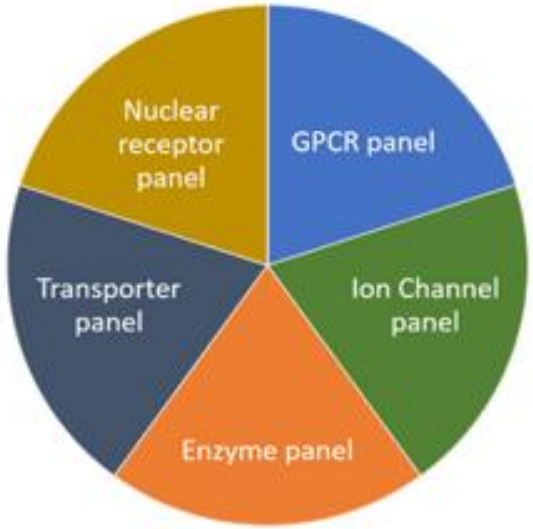
Secondary Pharmacology assays

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	
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
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	103

Ingredient	Food Source	Interaction Type
Caffeine	Coffee, tea, cocoa	Antagonist
Theobromine	Cocoa, chocolate	Antagonist
Theophylline	Tea	Antagonist



44 most important targets

PERSPECTIVES

A GUIDE TO DRUG DISCOVERY — OPINION

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_{Kr}) or heterologously expressed human voltage-gated potassium channel subfamily H member 2 (KCNH2; also known as hERG)[3]. 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[7,8], 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 entities[9].

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.

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

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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

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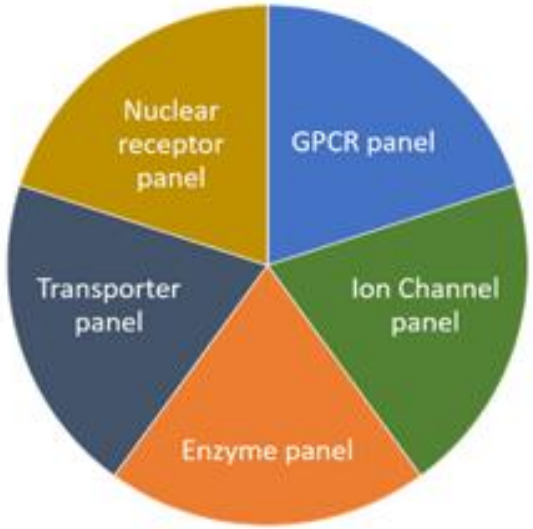

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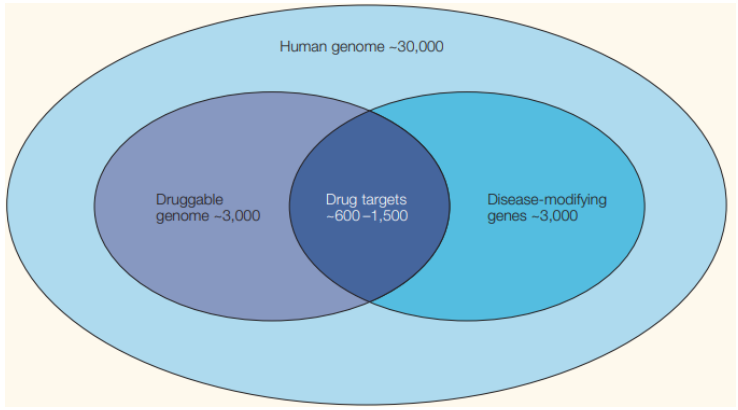
AI models to extend Secondary Pharmacology Screening

- 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

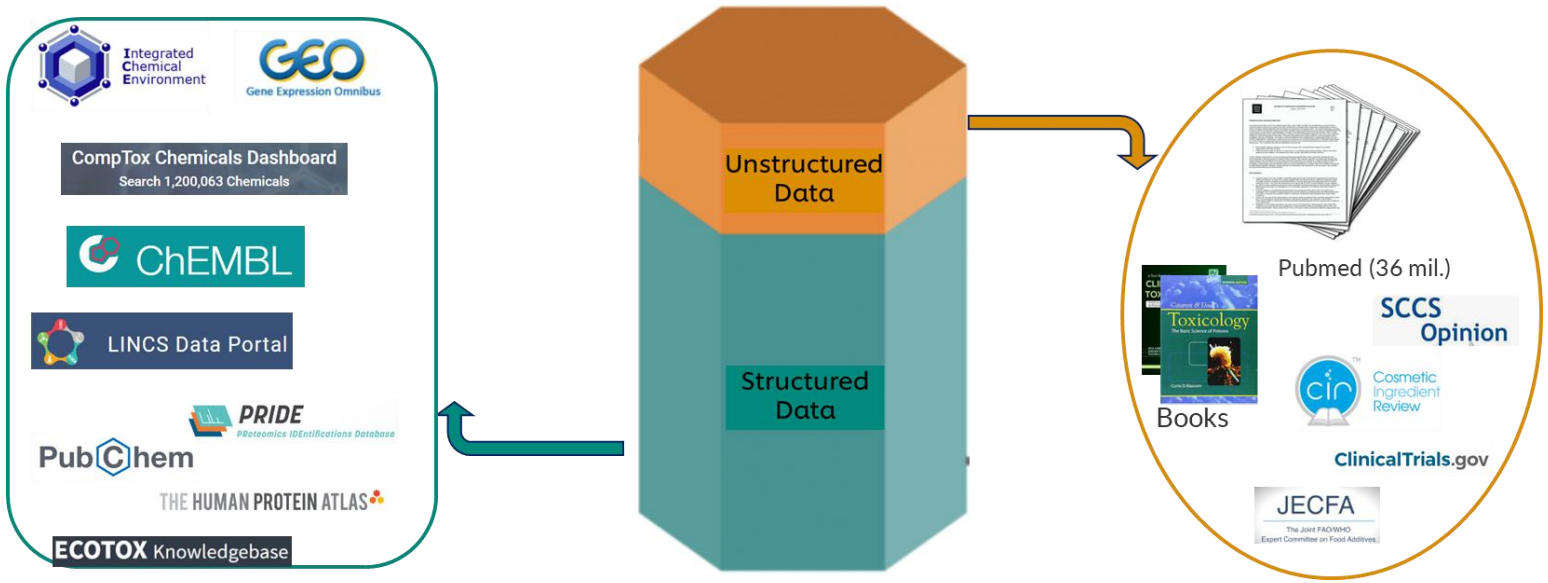


Hopkins & Groom, Nature Reviews, 2002

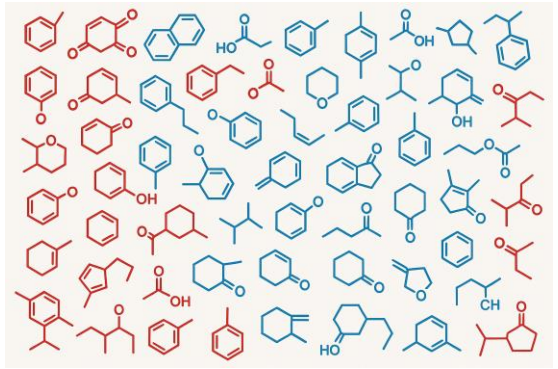
Target	Biological Role	Associated Effect
VEGFR2 (vascular endothelial growth factor 2	glutamate gated ion channel playing role in dendritic spine development	VEGF signaling involved in blood vessel formation
NMDA		Brain development
CYP19A1 inhibition	Conversion of testosterone to DHT	Reproductive disfunctio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

Availability of Experimental Data

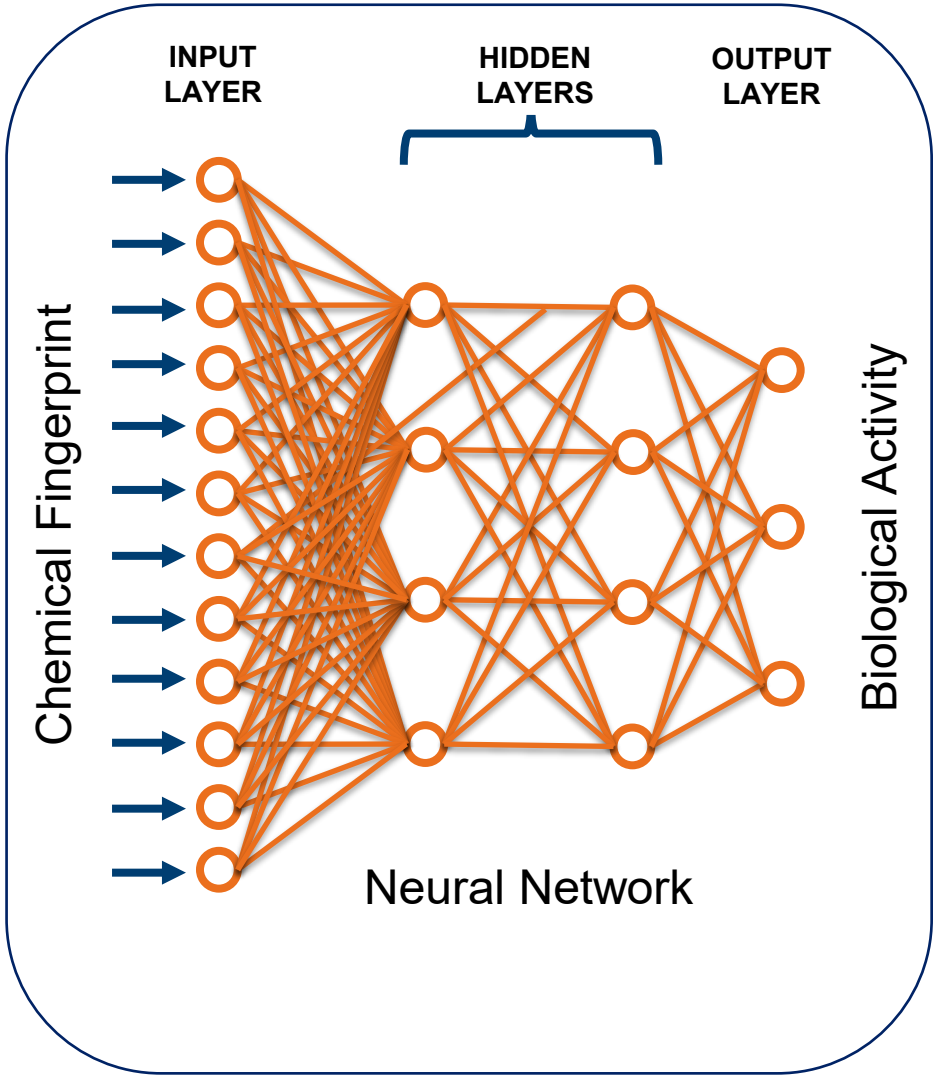
- This is becoming feasible due to the emergence of big and diverse *in vitro* tox data:
  - significant increase in high throughput data in the last 20 years (Tox21 and ToxCast programs, NIH Lincs, TEX-VAL, Pharma HTS data, Omics data from literature, etc.)
  - emergence of large curated databases (CompTox 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



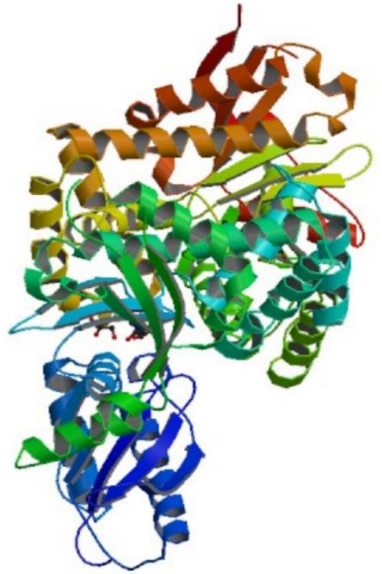
Building an AI model for a Target of Interest



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

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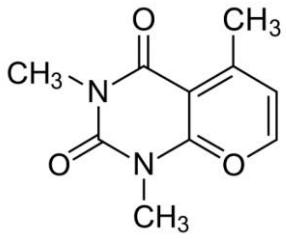
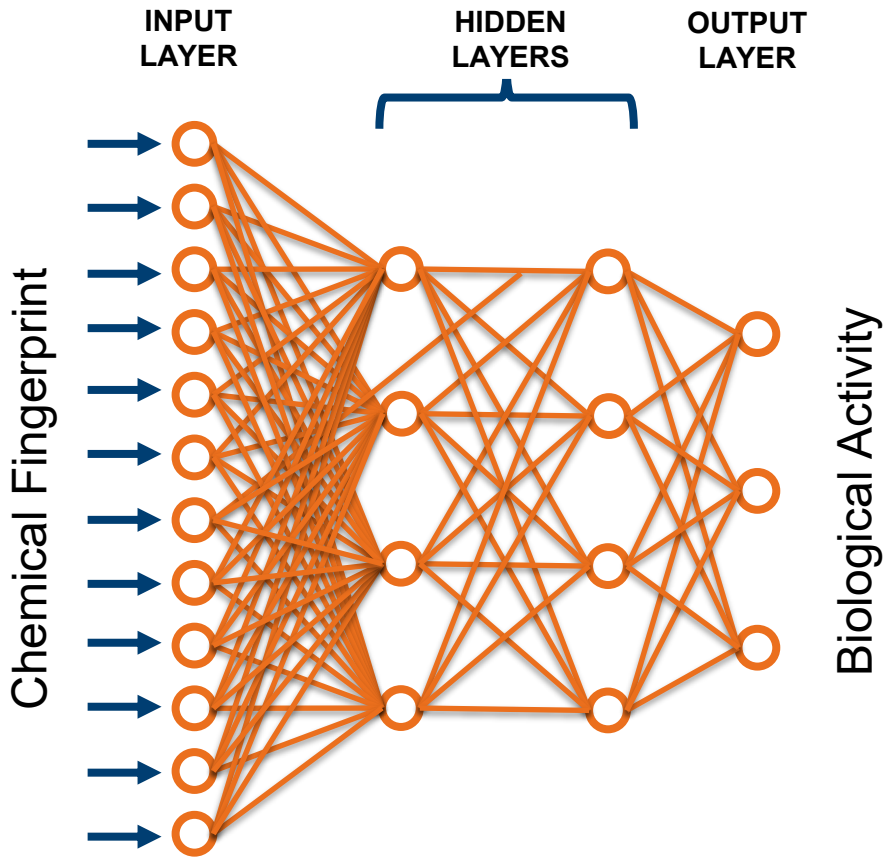
Testing an AI model for ADORA2A receptor



food additive, colour additive, contact material



Molecule Name	Adenosine receptor 2A ADORA2A
Dexamethasone	0 (0.983)
Glutaraldehyde	0 (0.981)
Glybenclamide	0 (0.982)
Hydralazine hydrochloride	0 (0.714)
Metformin	0 (0.976)
Metoclopramide	0 (0.932)
Verapamil hydrochloride	0 (0.945)
Butylated hydroxyanisole	0 (0.97)
Sodium cyclamate	0 (0.98)
4-(3-Ethoxy-4-hydroxyphenyl)-2-buta	0 (0.959)
Sodium warfarin	0 (0.908)
2-Ethylhexanoic acid	0 (0.99)
Diethyl phthalate	0 (0.985)
Theophylline	1 (0.82)
Sodium salicylate	0 (0.968)
Diethylstilbestrol	0 (0.951)
Retinoic acid	0 (0.992)
Dolutegravir	0 (0.567)
Retinol	0 (0.993)
Dibutyl 1,2-benzenedicarboxylate	0 (0.98)
Methotrexate	0 (0.528)
Caffeine	1 (0.558)

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Molecular Initiated Event (MIE) Atlas

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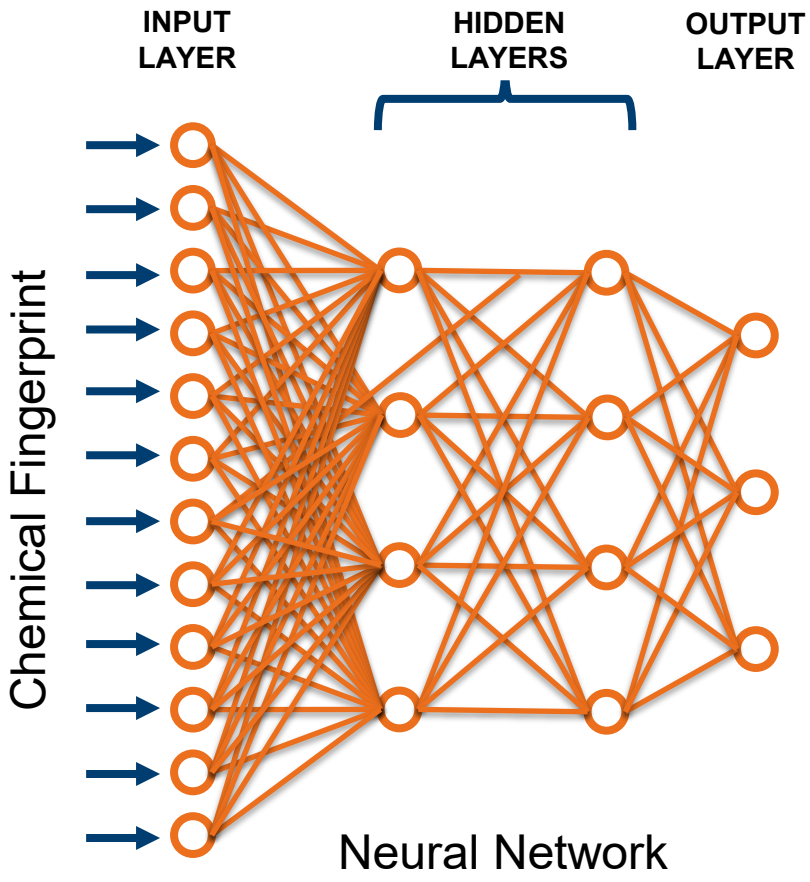
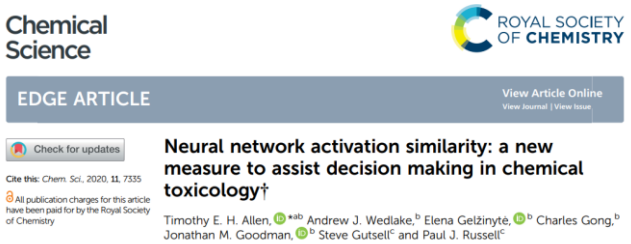
Data extracted and curated from ChEMBL and ToxCast databases

Target	Inactives
144,109 actives	141,796 inactives



MIE Atlas V1 (2019)	MIE Atlas V2 (ongoing)
79 biological targets	~600 biological targets


Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

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

Timothy E. H. Allen, Andrew J. Wedlake, Elena Gelžinytė, Charles Gong, Jonathan M. Goodman, Steve Gutsell and Paul J. Russell

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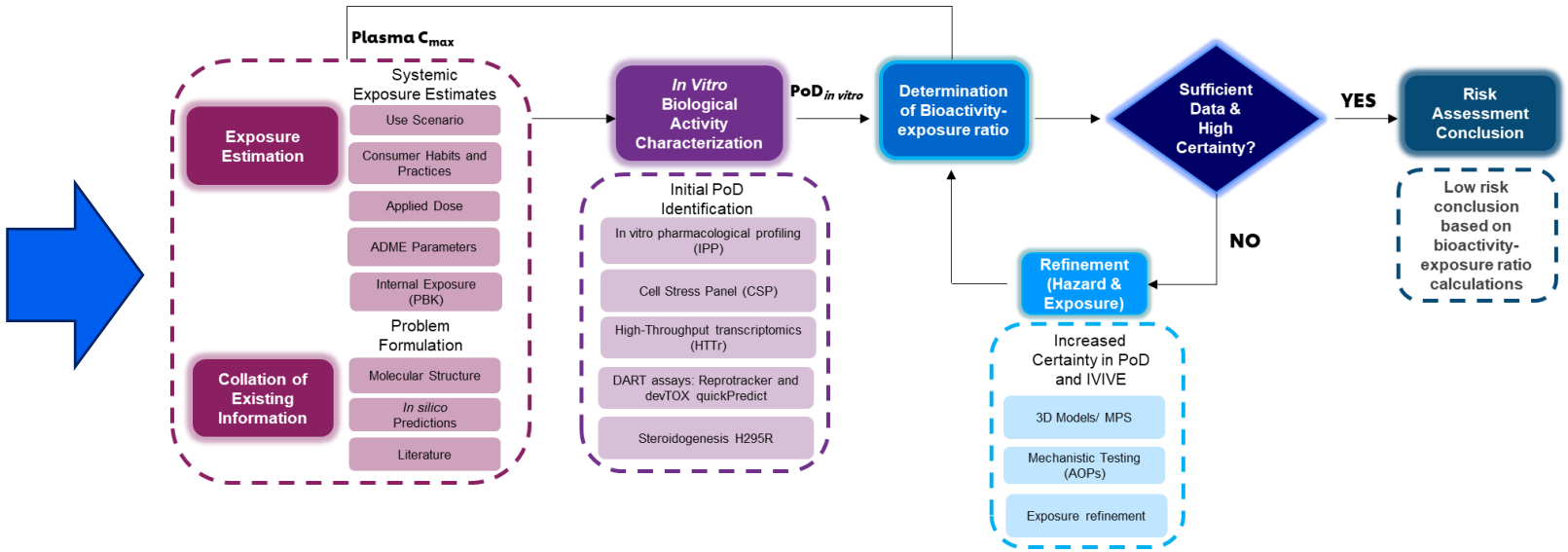
Application of AI in Safety Science: Future Trends

- 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.



* Source: Statista, Bernard Marr & Co

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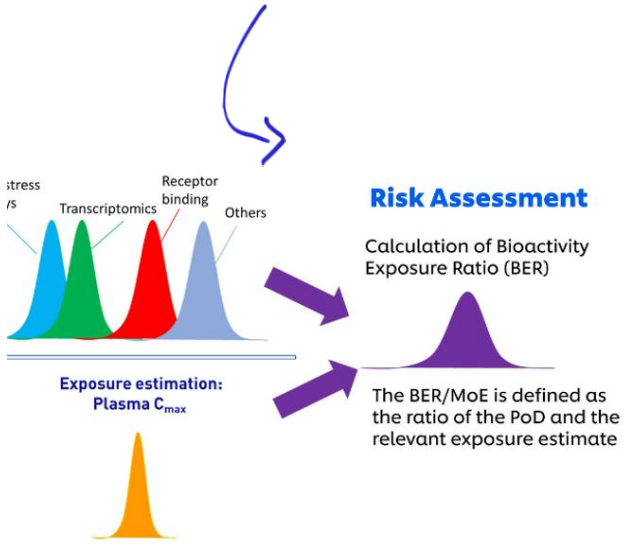
Toxic/ non-toxic



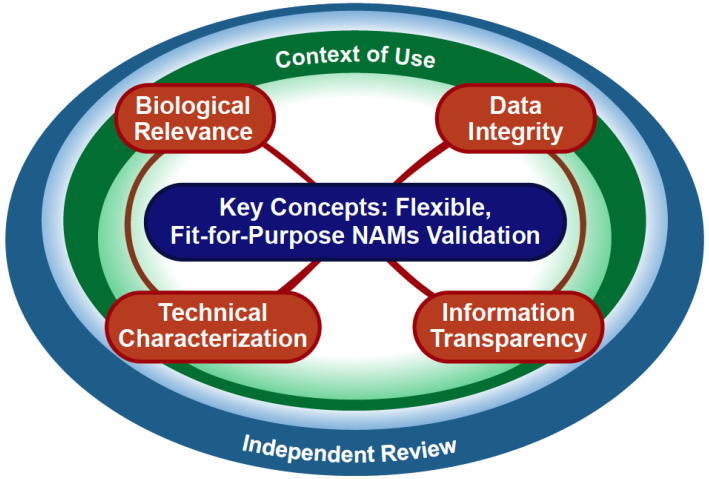
Probabilistic Risk Assessment (exposure and bioactivity probability distributions, probability of risk, uncertainty quantification, subpopulations, etc.)

* Source: Statista, Bernard Marr & Co

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.

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