Belgrade Bioinformatics Conference

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Toxicology Transformed: Harnessing Artificial Intelligence for Advanced Research

TOXICOLOGY

THEN…

The science of poisons and intoxication

Paracelsus, XVI century

“The dose makes the poison”

NOW…

Focused mainly on prevention

ENVIRONMENTAL CHEMICALS → naturally occurring and man-made

Most reported toxic environmental chemicals:

- pesticides
- heavy metals
- polycyclic aromatic hydrocarbons (PAHs)
- polychlorinated biphenyls (PCBs)
- pharmaceuticals
- plastic-associated chemicals (e.g., flame retardants, phthalates, bisphenols, etc.)
- per- and polyfluoroalkyl substances (PFAS; e.g., PFOA, PFOS, etc.)

Human exposure is inevitable → most of these chemicals detected in human blood and other bodily fluids, hair and nails

350,000 chemicals and mixtures of chemicals registered on the global market!

ENVIRONMENTAL EXPOSURES → a significant disease burden

WHO Report → More than 2 million deaths and 53 million disability-adjusted life years (DALYs) attributable to environmental exposure

The largest contributors:

- cardiovascular diseases (42%, 848,778 deaths)
- chronic obstructive pulmonary disease (COPD, 26%, 517,734 deaths)
- cancers (17%, 333,867 deaths)

Regulatory agencies evaluate harmful effects of environmental chemicals → **setting safety limits to better protect the health of people**

CHEMICAL RISK ASSESSMENT

Whole animal toxicity studies

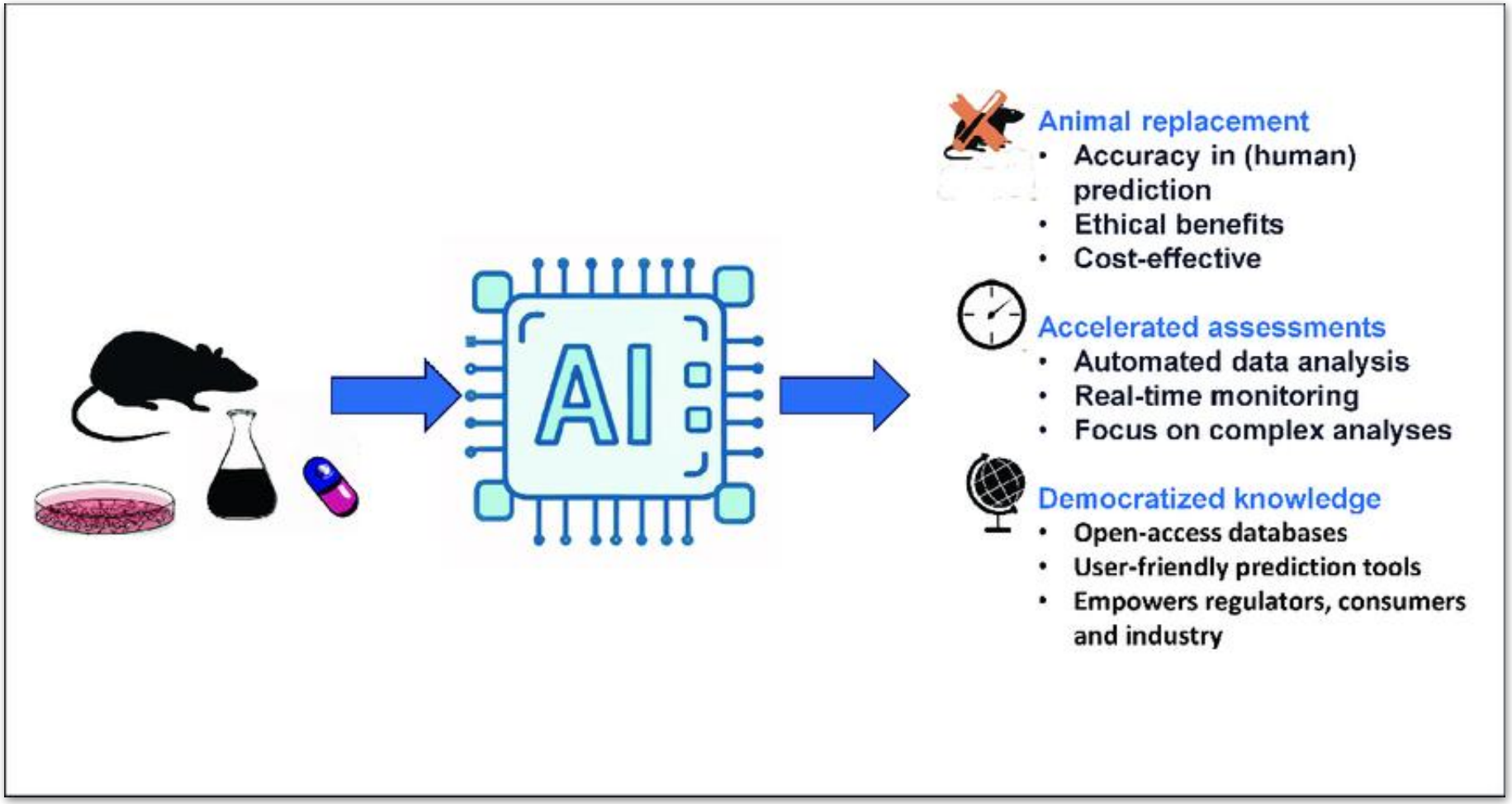
- costly and time-consuming
- ethical concerns
- uncertainty in translating data to humans
- lack of mechanistic endpoints

Epidemiological studies

- observational in nature
- associations without causality

Each year, about **2,000 new chemicals are introduced** → limited or no adequate toxicological information!

The Emerging Role of AI in Toxicology



Hartung, T. (2023): ToxAIcology - The evolving role of artificial intelligence in advancing toxicology and modernizing regulatory science. *ALTEX - Alternatives to Animal Experimentation*, 40(4), pp. 559–570. doi: 10.14573/altex.2309191.

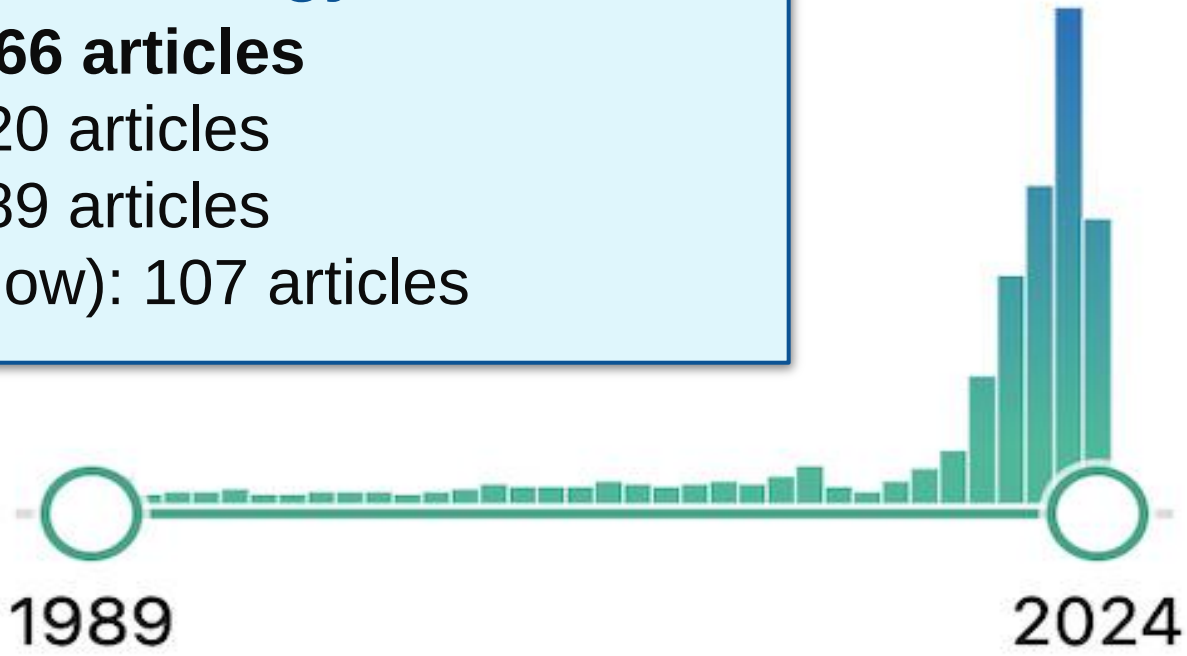
AI and Toxicology in PubMed

Total: 566 articles

2022: 120 articles

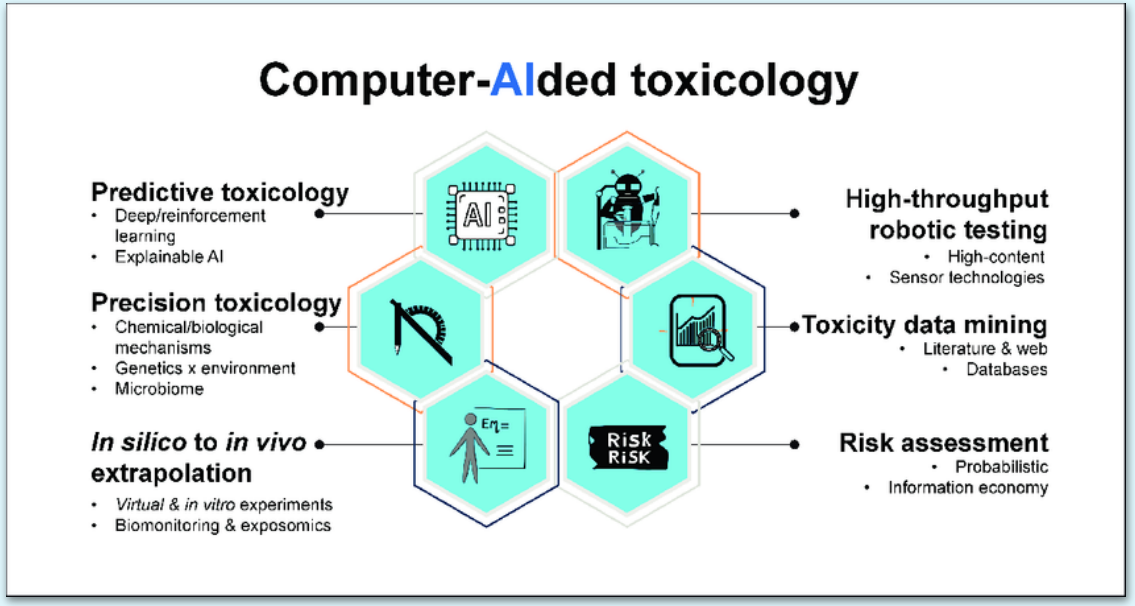
2023: 189 articles

2024 (-now): 107 articles



Key areas where AI is expected to transform toxicology:

- Predictive toxicology
- Data mining & analysis
- Risk assessment
- IVIVE
- Mechanistic research



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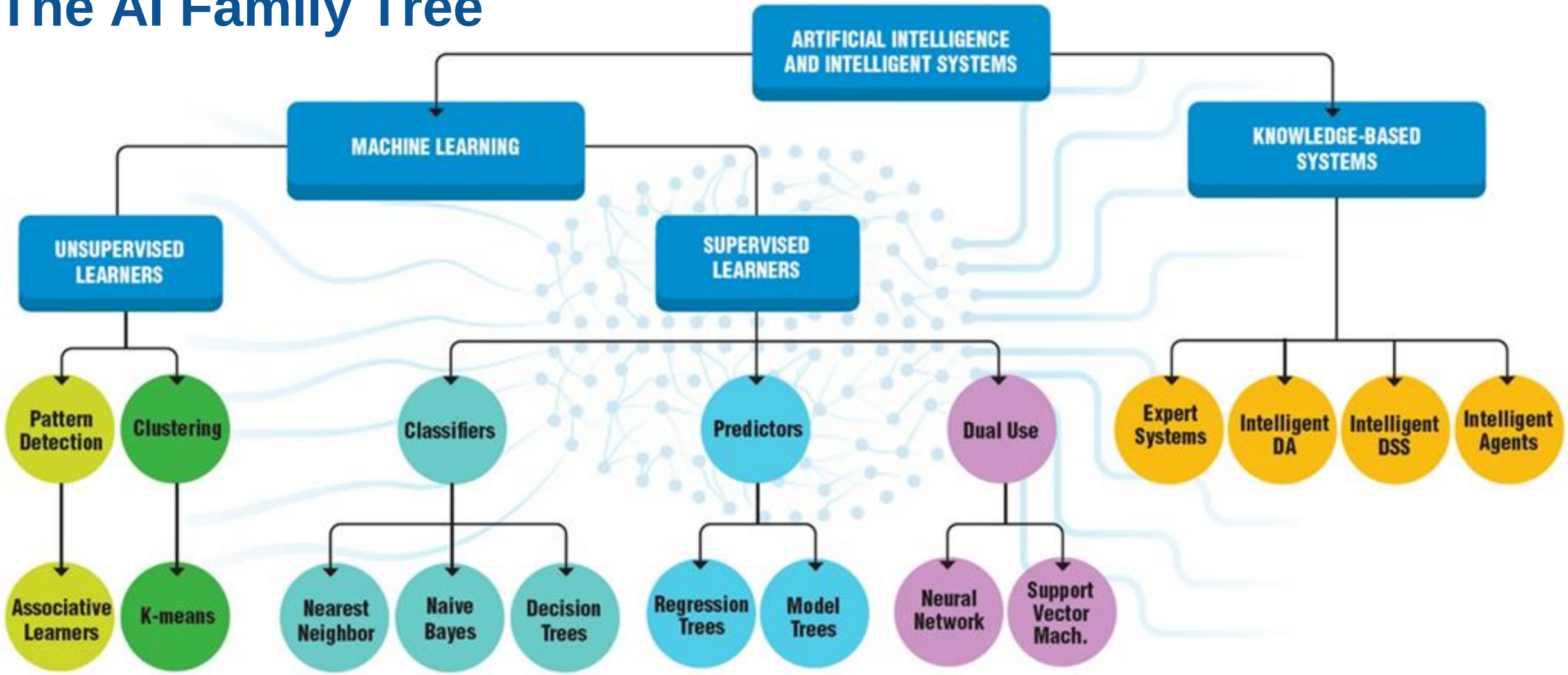
The AI Family Tree



Kleinstreuer N. & Hartung T. (2024): Artificial intelligence (AI)—it's the end of the tox as we know it (and I feel fine)*. *Archives of Toxicology*, 98, pp. 735–754. doi: 10.1007/s00204-023-03666-2.

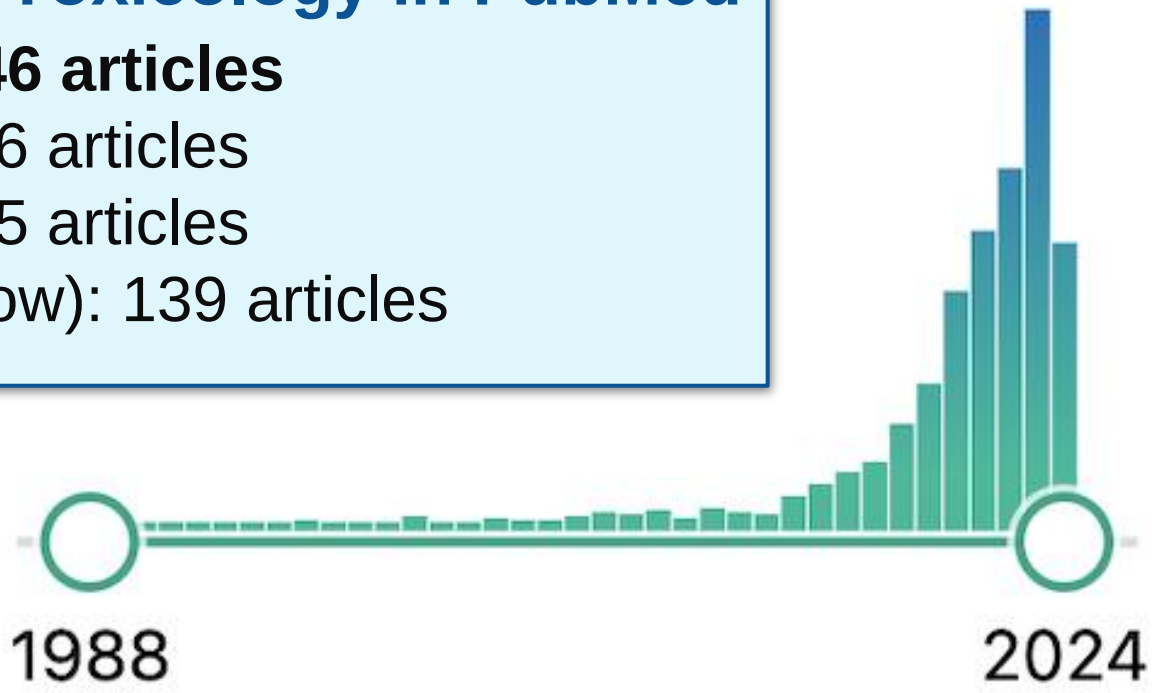
ML and Toxicology in PubMed

Total: 946 articles

2022: 176 articles

2023: 255 articles

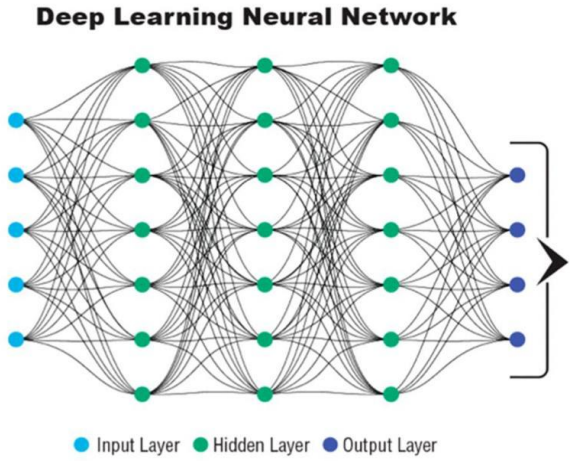
2024 (-now): 139 articles

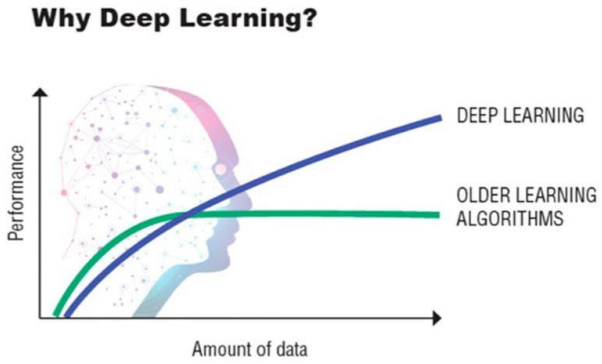


Predicting Chemicals' Toxicity Pathway of Female Reproductive Disorders Using AOP7 and Deep Neural Networks

- Previously defined **adverse outcome pathway (AOP)** of reproductive toxicity in adult females
- **Convolutional Deep Neural Network** models

Prediction of chemical hazards to the female reproductive system





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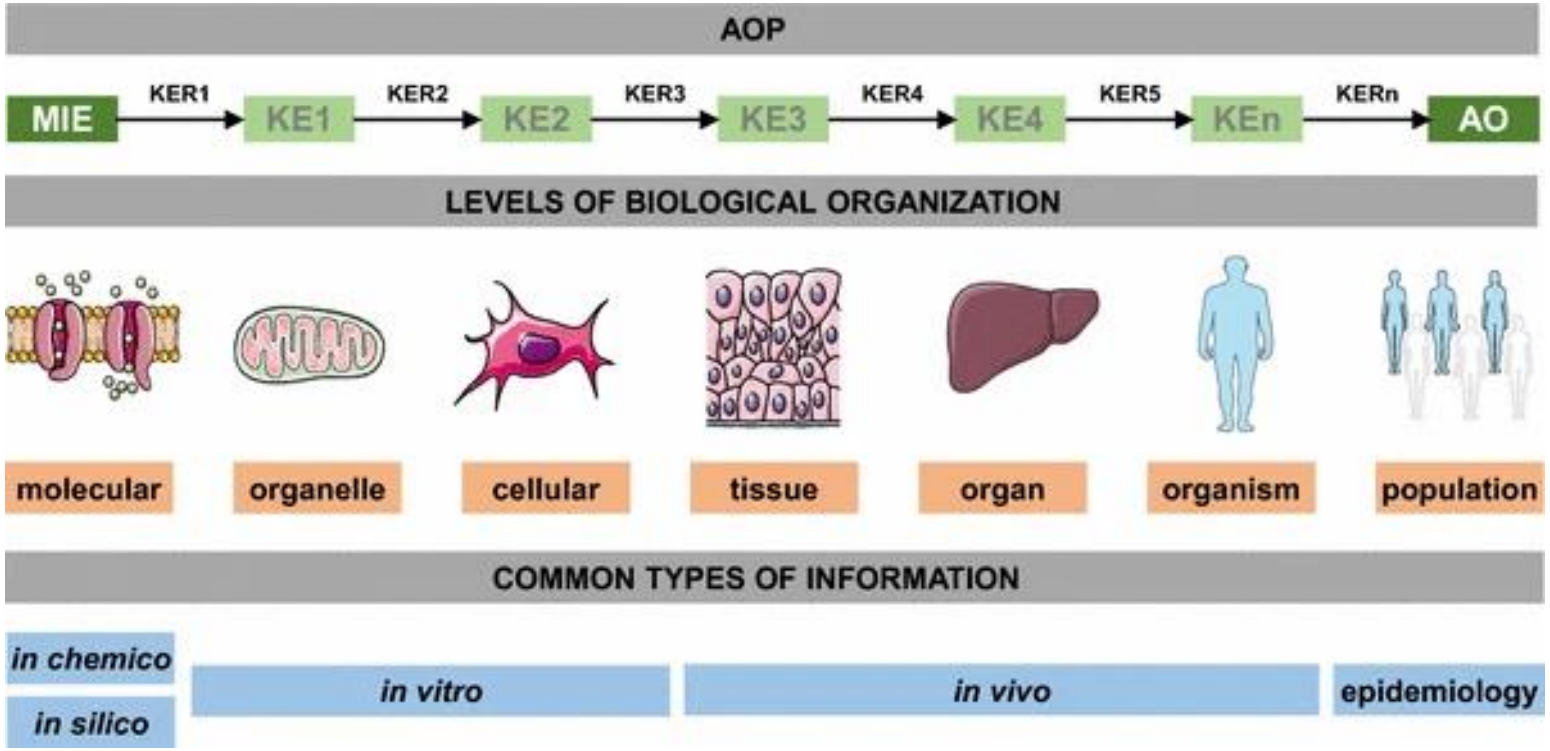
AOP – Basic Concepts



Key terms:

MIE – molecular initiating event

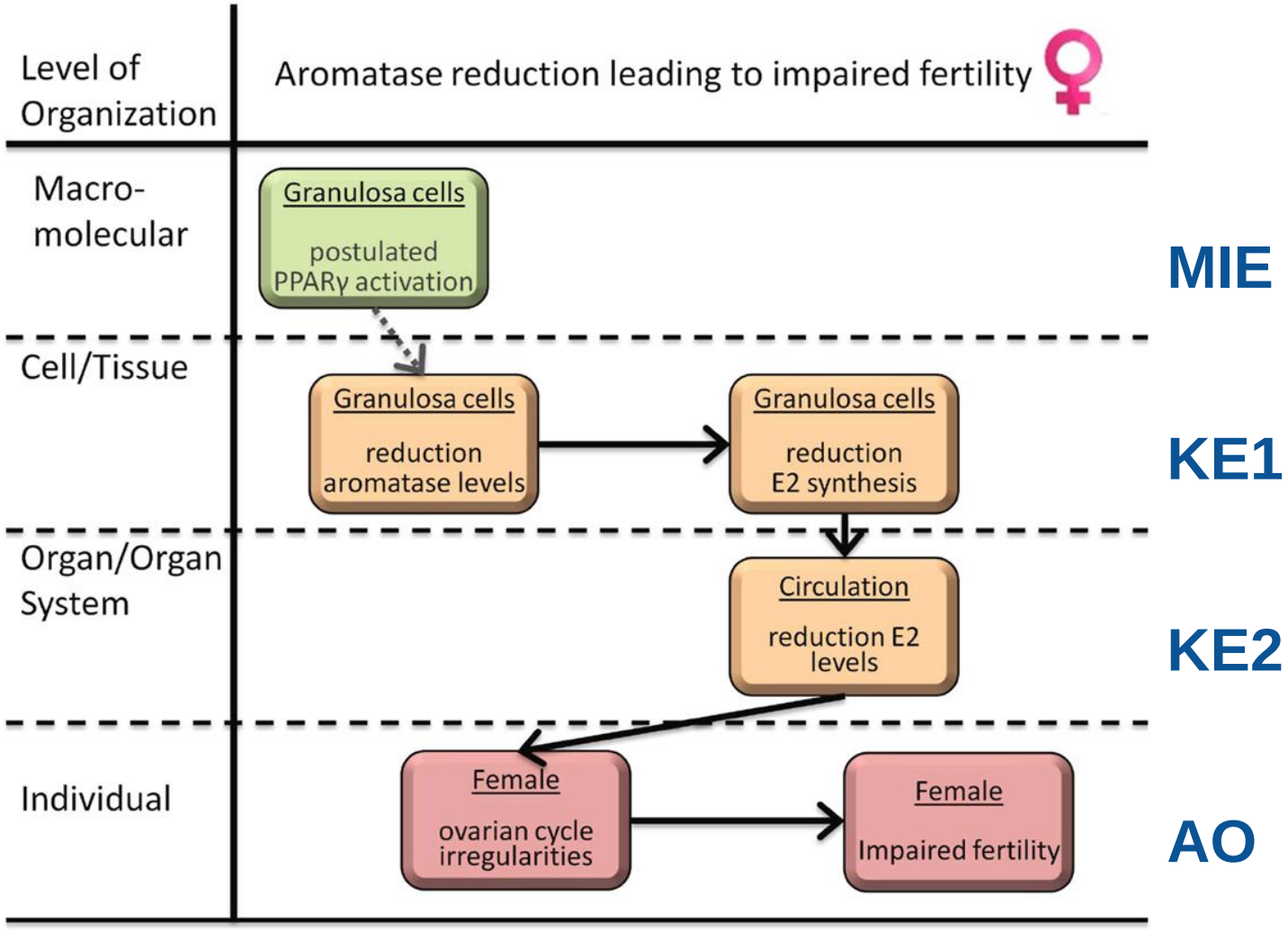
KE – key event

KER – key event relationship

AO – adverse outcome

Vinken M. et al. (2017): Adverse outcome pathways: a concise introduction for toxicologists. *Archives of Toxicology*, 91, pp. 3697–3707. doi: 10.1007/s00204-017-2020-z.

AOP7 → Aromatase (Cyp19a1) reduction leading to impaired fertility in adult female



From AOP-Wiki: https://aopwiki.org/aops/7

OECD status – Under review

17 assays relevant to AOP7 → retrieved from the US EPA CompTox Dashboard

https://comptox.epa.gov/dashboard/

ID	Assay Name	Assay Source	Assay Target
1	ATG PPARγ TRANS dn	ATG	PPARγ
2	ATG PPARγ TRANS up	ATG	PPARγ
3	TOX21 PPARγ BLA antagonist	Tox21	PPARγ
4	TOX21 PPARγ BLA agonist	Tox21	PPARγ
5	NVS NR hPPARγ	NVS	PPARγ
6	ERF ENZ hCYP19A1 dn	ERF	CYP19A1
7	NVS ADME hCYP19A1	NVS	CYP19A1
8	NVS ADME hCYP19A1 Activator	NVS	CYP19A1
9	TOX21 Aromatase Inhibition	TOX21	CYP19A1
10	CEETOX H295R ESTRADIOL dn	CEETOX	Estradiol
11	CEETOX H295R ESTRADIOL noMTC dn	CEETOX	Estradiol
12	CEETOX H295R ESTRADIOL noMTC up	CEETOX	Estradiol
13	CEETOX H295R ESTRADIOL up	CEETOX	Estradiol
14	CEETOX H295R ESTRONE dn	CEETOX	Estrone
15	CEETOX H295R ESTRONE noMTC dn	CEETOX	Estrone
16	CEETOX H295R ESTRONE noMTC up	CEETOX	Estrone
17	CEETOX H295R ESTRONE up	CEETOX	Estrone

MIE

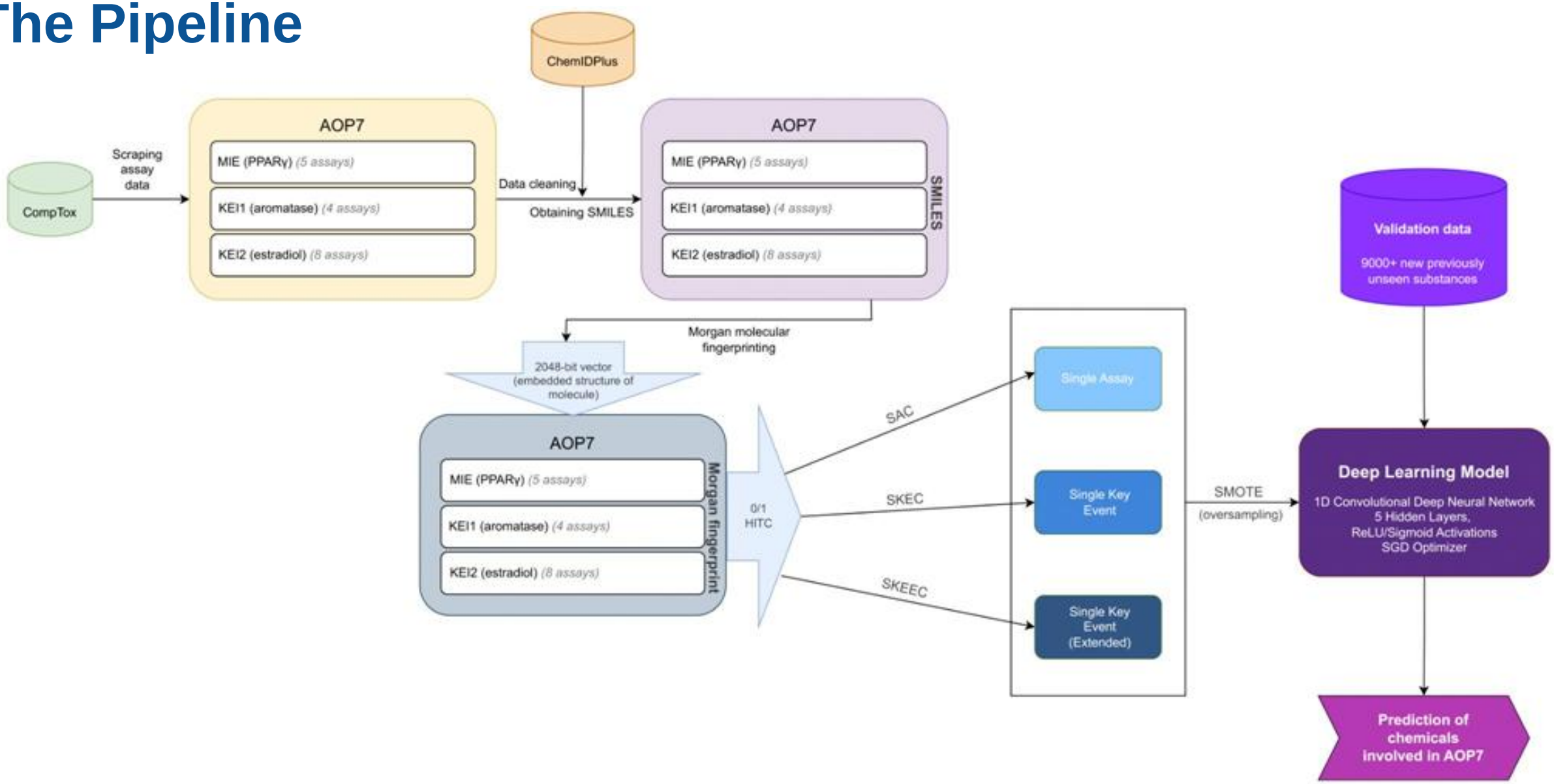
KE1

KE2

Obtained information on **8776 chemicals** and their activities

More than **99%** of chemicals **correctly identified**

The Pipeline



Training of Convolutional Neural Network Deep Learning Models

Single Assay Convolutional (SAC) Model

- One model was trained per assay
- 17 Neural Network Models were obtained
- Low number of active chemicals

Single Key Event Convolutional (SKEC) Model

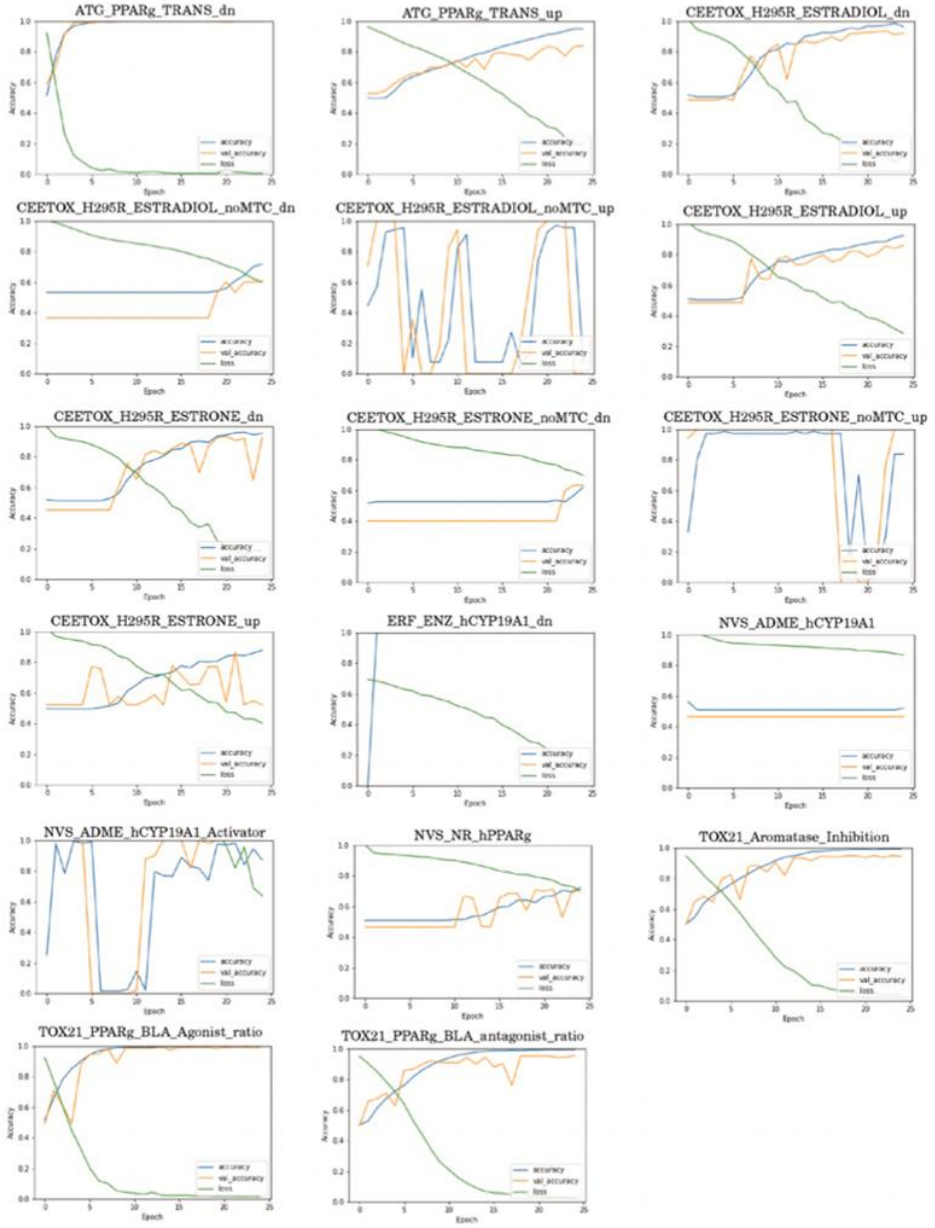
- Data grouped by MIE and KE (f.e., all 5 PPARγ assays were used to train the model)
- More data

Single Key Event Extended Convolutional (SKEEC) Model

- Two types of CompTox assays: “up” and ”down”
- Multi-class classification to predict loss-of-function and gain-of-function assays in MIE and KEs

Single Assay Convolutional (SAC) Model Training and Performance Overview

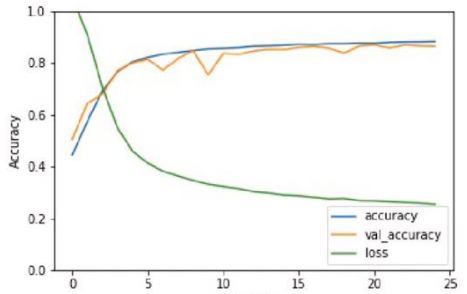
Assay Data	Accuracy	Validation Accuracy
ATG_PPARg_TRANS_dn	0.999651	0.997905
ATG_PPARg_TRANS_up	0.948351	0.838178
CEETOX_H295R_ESTRADIOL_dn	0.984724	0.934272
CEETOX_H295R_ESTRADIOL_noMTC_dn	0.716667	0.600000
CEETOX_H295R_ESTRADIOL_noMTC_up	0.970149	1.000000
CEETOX_H295R_ESTRADIOL_up	0.923171	0.859223
CEETOX_H295R_ESTRONE_dn	0.958234	0.933333
CEETOX_H295R_ESTRONE_noMTC_dn	0.620690	0.633333
CEETOX_H295R_ESTRONE_noMTC_up	0.985075	1.000000
CEETOX_H295R_ESTRONE_up	0.877653	0.865672
ERF_ENZ_hCYP19A1_dn	1.000000	1.000000
NVS_ADME_hCYP19A1	0.560000	0.463768
NVS_ADME_hCYP19A1_Activator	0.994872	1.000000
NVS_NR_hPPARg	0.720603	0.710843
TOX21_Aromatase_Inhibition	0.992276	0.949855
TOX21_PPARg_BLA_Agonist_ratio	0.996715	0.993592
TOX21_PPARg_BLA_antagonist_ratio	0.993719	0.954405
Average:	0.896620	0.866728



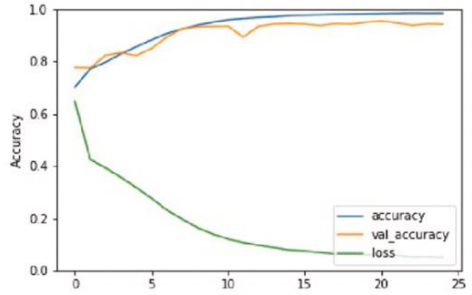
Single Key Event Extended Convolutional (SKEEC) Model Training and Performance Overview

Key Event	Accuracy	Validation Accuracy
MIE (PPARγ)	0.881929	0.868239
KEI1 (aromatase)	0.983826	0.953599
KEI2 (estradiol)	0.950586	0.946741
Average:	0.935698	0.922526

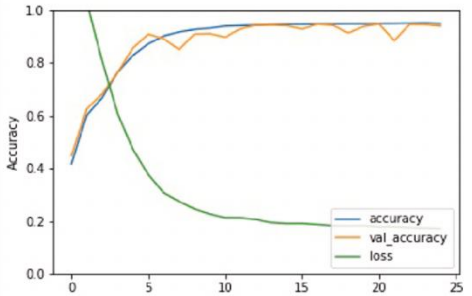
MIE (PPARgamma)



KEI1 (aromatase)

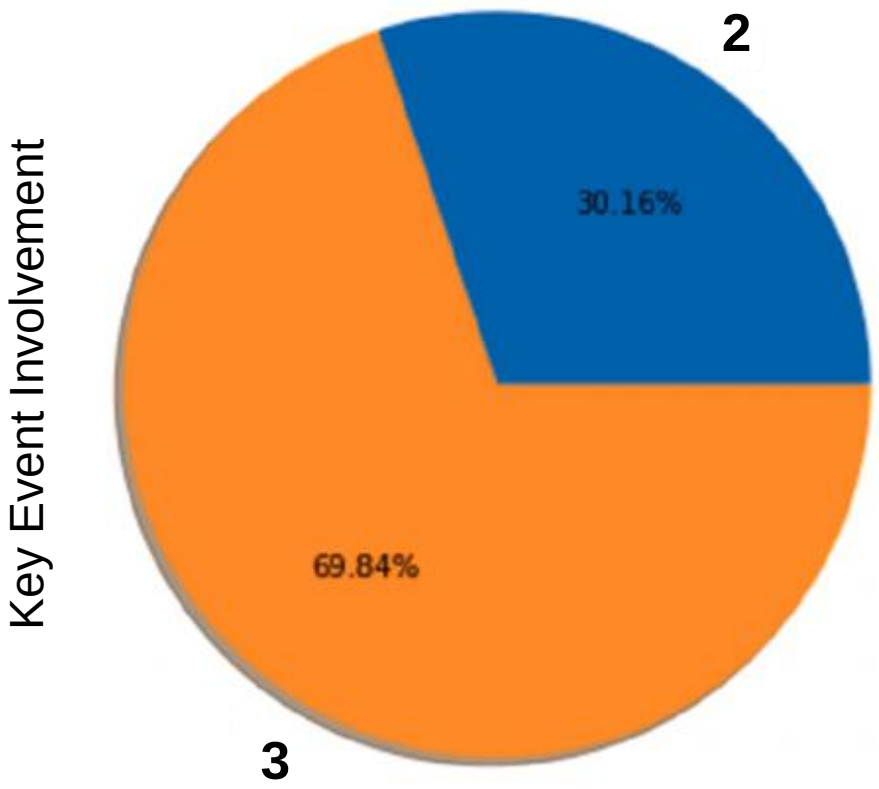


KEI2 (estradiol)

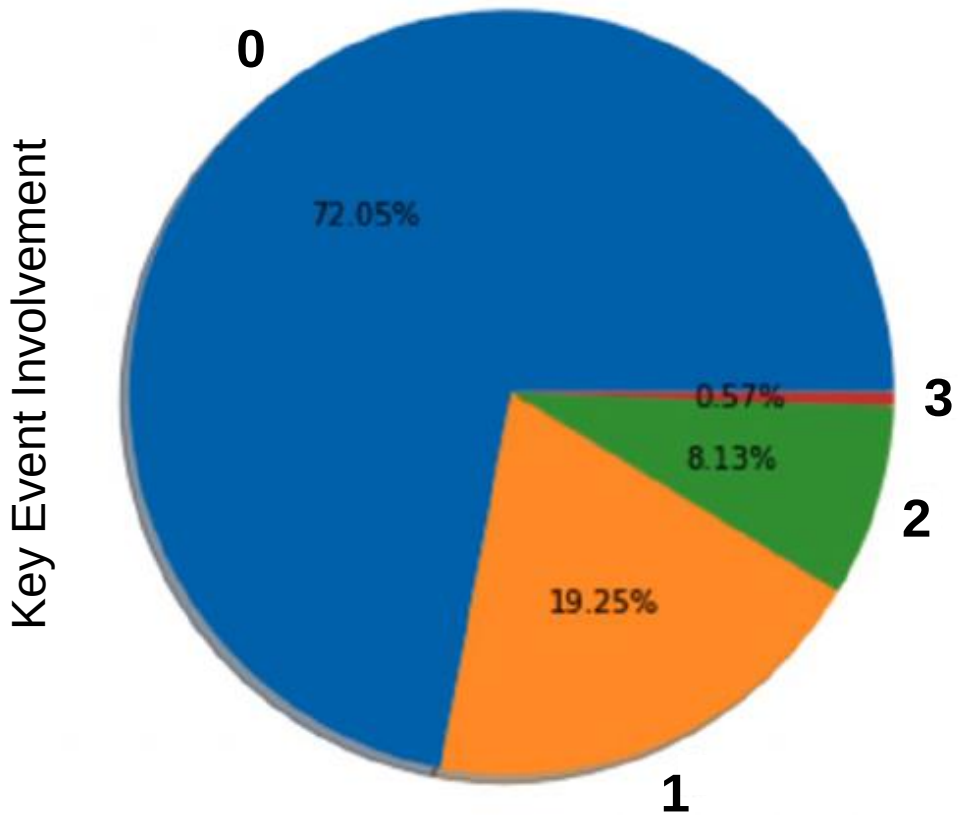


Comparison Between the SAC Model and the SKEEC Model in Key Event Involvement

SAC Model

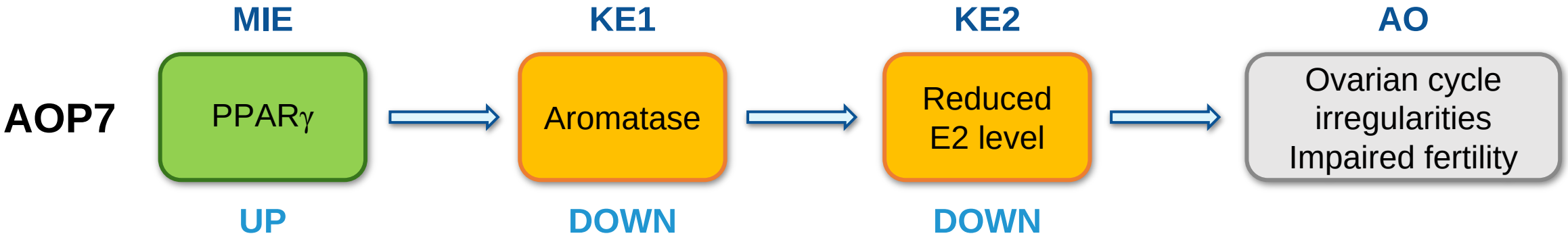


SKEEC Model



Identification of Chemicals Involved in AOP7

Chemicals active in the PPARγ gain-of-signal (“up”) assays and in the aromatase and estradiol loss-of-signal (“down”) assays could be candidate chemicals with the potency to cause female reproductive dysfunction through the following mechanism:



Number of chemicals predicted to affect **all events in AOP7** in this specific order:

- **SAC Model → 12 chemicals**
- **SKEEC Model → 9 chemicals**

In the CompTox database:

- imazalil
- triflumizole
- flusilazole

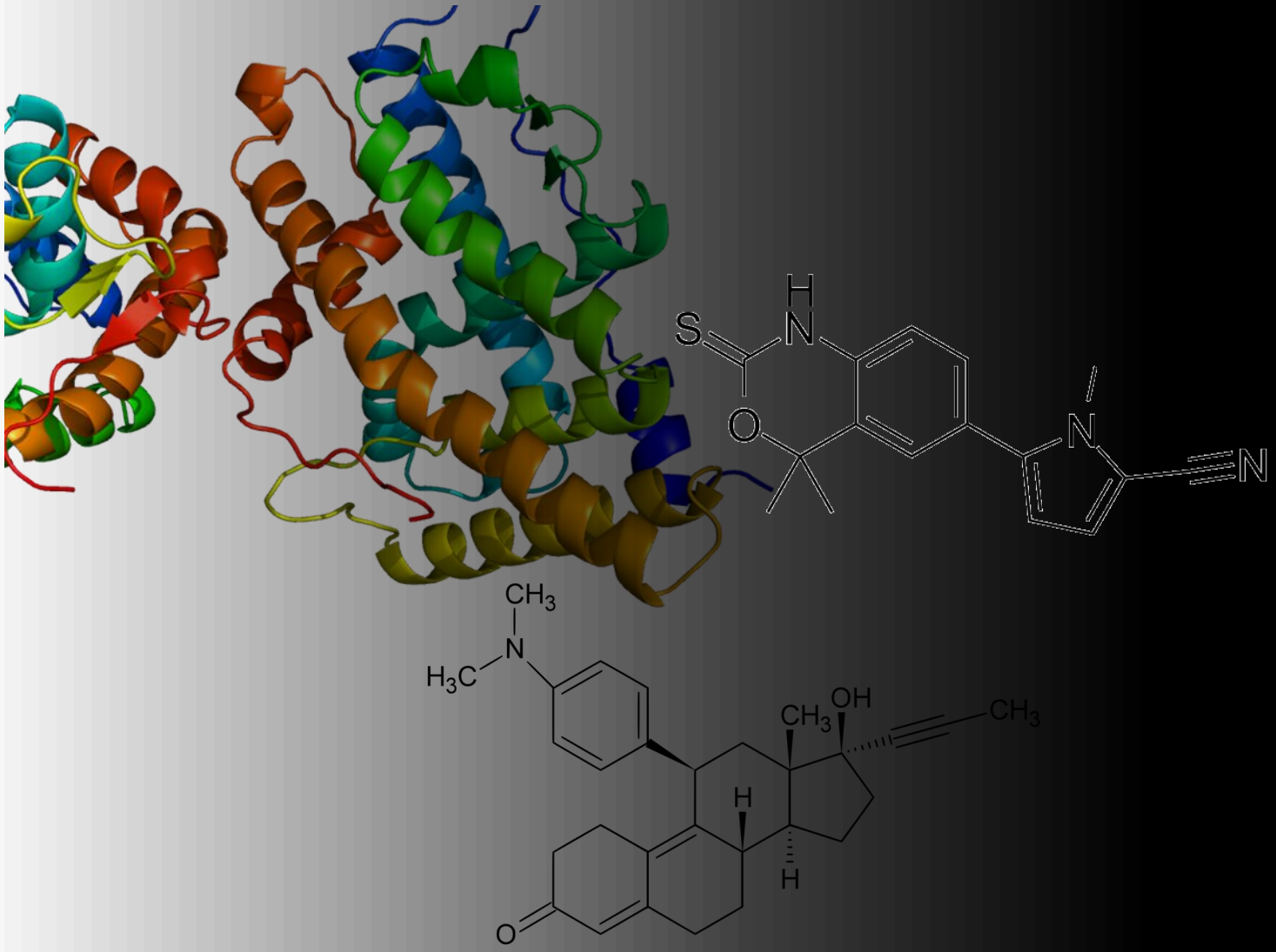
Predicted by the SAC Model:

- oxabentrinil
- chlorthalmonomethyl
- kinoprene
- trichloromelamine
- S-kinoprene
- C.I. fluorescent brightening agent 28

Predicted by the SKEEC Model:

- methanesulfonamide, N-[2-[(4-amino-3-methylphenyl) ethylamino]ethyl]-sulfate (2:3)
- 2,4′-dihydroxydiphenyl sulfone
- alpha-pimaric acid

Novel or previously unidentified chemicals that can exert female reproductive toxicity through the mechanism described in AOP7 → **Negative impact on the female reproductive system**



Predicting the Binding of Environmental Chemicals to the Progesterone Receptor Using Machine Learning

Progesterone receptor → regulates several functions in both reproductive and non-reproductive tissues

Our work is focused on predicting:

- Potency – **strong, moderate, weak**
- Agonist or antagonist

WORK IN PROGRESS

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