

## WEBINAR

Métodos Alternativos ao uso  
de animais para indústria de  
Higiene Pessoal, Perfumaria e  
Cosméticos

# Modelos *in silico* e integração de AOPs na avaliação de ingredientes cosméticos com fins regulatórios

São Paulo  
2023

# Overview

- **Sobre nós e nossos trabalhos**
- **Entendendo os modelos *in silico* e alguns inteligência artificial**
- **Contexto regulatório: guias e exemplos de recomendação legal de modelos *in silico***
- **Exemplos de aplicação: AOPs / NGRA / IATA / Defined Approaches**

# Sobre a Alttox

Fundada em **2012** e localizada na Av. Vital Brasil, 305 – Butantã, São Paulo – SP.



Responsável pela **primeira plataforma brasileira de modelos *in silico*** validados com fins regulatórios do Brasil e América Latina, em projeto financiado pela FAPESP, a Is-Tox Platform.



- Mais de **70 clientes** atendidos e inúmeros projetos de sucesso
- Pioneira nos modelos *in silico* no Brasil com fins regulatórios

**Parceiro estratégico e renomado** para softwares e avaliações *in silico* de segurança



**Premiações** de inovação e pesquisa em congressos e associações acadêmicas.



# Softwares e projetos de pesquisa e inovação

- 1ª plataforma de modelos QSAR *in silico* do Brasil e América Latina → Real time



## Contaminantes

Soluções em avaliação toxicológica de impurezas e contaminantes



## Cosméticos

Estudos sem o uso de animais e com base na estrutura química



## Novas Moléculas

Soluções em avaliação toxicológica de novas moléculas e ingredientes



## Medicamentos

Soluções desenhadas para atender às legislações específicas



## Agroquímicos

Relatórios de avaliação de toxicidade impurezas para IBAMA, MAPA e ANVISA



## Alimentos

Avaliação toxicológica dos potenciais contaminantes neoformados (NFCs)



IrriTTest™



Pred-Oral™



Genotox-iS™



AOP-Sens™



iS-Liver™



Pred-CYP22D™



iS-Ocular™



Acute-Tox™



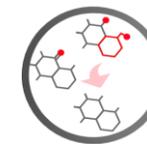
DevTox-iS™



BCF-Test™



Pred-Ecotox™



iS-Purge



DegradationPlot  
Prediction of degradation products and pathways



NitroRisk  
Risk Assessment for N-nitrosamines formation



Prioritizer  
Ranking of priority for nitrosamines risk assessment of drug substances



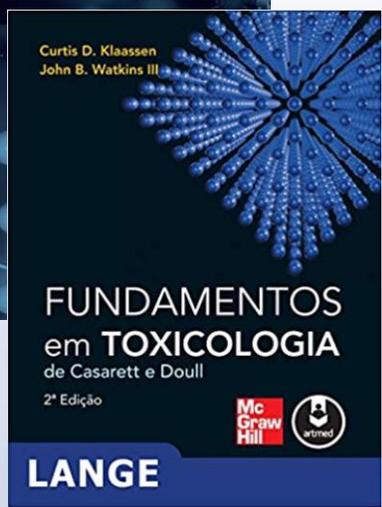
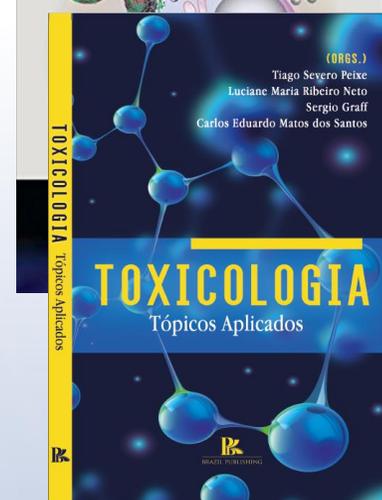
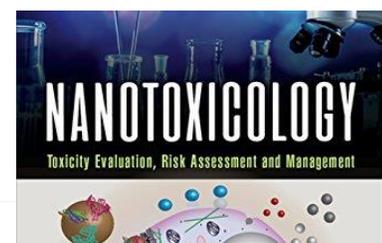
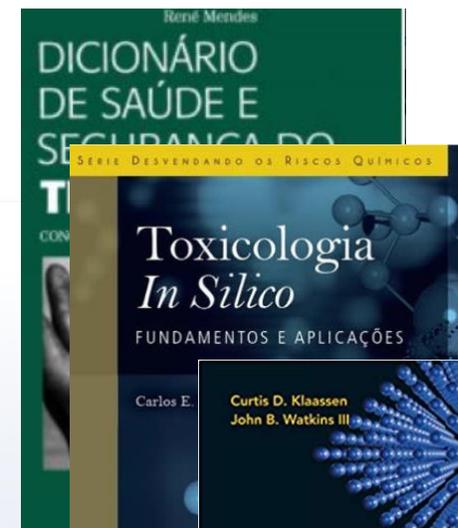
Projeto financiado:



<https://is-tox.com/our-models>



# ALGUMAS PUBLICAÇÕES



Regulatory Toxicology and Pharmacology 136 (2022) 105288

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

Journal homepage: [www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

Pharmaceutical Medicine  
<https://doi.org/10.1007/s40290-020-00357-6>

LETTER TO THE EDITOR

Setting limits for N-nitrosodimethylamine (NDMA) in read-across and structural analogs: N-nitrosopiperazine

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ARTICLE INFO

Handling Editor: Dr. Martin Van den berg

Keywords:  
Nitrosamines  
Mutagenic inquiry  
Risk assessment approach  
Read-across  
in silico

Dear Editor,

We read the review by Valeur et al. [1] about the safety of excipients in neonatal medicinal products, with many interesting points and an objective discussion about access to knowledge on the clinical pharmacology of excipients in neonates and its impact in improving the quality of risk assessment and decision making during drug development by a risk-benefit analysis. Although we think the article discusses relevant aspects about the safe use of excipients in medicines used to treat newborns, we have a few concerns, considering the importance of adequate interpretation of toxicological limits for the quality of risk assessments, and regulatory and/or clinical decisions.

First, in Table 2, the authors provided an overview of the supposed tolerance limits for ethanol, propylene glycol and benzyl alcohol as proposed by the European Medicines Agency (EMA) [2-4], highlighting a limit for benzyl alcohol of 5 mg/kg/day "for adults and children aged over 4 weeks". However, this limit is not for benzyl alcohol, but for the benzoic acid and its salts (e.g. sodium benzoate and other benzoates) orally in food [2]. Second, this is not a limit proposed or established by the EMA as was described in Table 2. This limit is only cited by the EMA, and as described in the EMA's report [2] is an Acceptable Daily Intake proposed by the JECFA (Joint FAO/WHO Expert Committee on Food Additives) [5].

Most importantly, contrary to the considerations about tolerance limits presented by the authors, no specific limits were set in the EMA's report for the excipient benzyl alcohol.

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MDPI

Article

## Challenges and Opportunities for Integrating *In Silico* Models and Adverse Outcomes Pathways to Set and Relate New Biomarkers

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check for updates

**Abstract:** The Adverse Outcome Pathway (AOP) framework has been considered the most innovative tool to collect, organize, and evaluate relevant information on the toxicological effects of chemicals, facilitating the establishment of links between molecular events and adverse outcomes at the critical level of biological organization. Considering the combination of the high volume of toxicological and ecotoxicological data produced and the application of artificial intelligence algorithms from the last few years, not only can higher mechanistic interpretability be reached with new *in silico* models, but also a potential increase in predictivity in hazard assessments and the identification of new potential biomarkers can be achieved. The current paper aims to discuss some potential challenges and ways of integrating *in silico* models and AOPs to predict toxicological effects and to set and relate new biomarkers for defined purposes. With the use of the AOP framework to organize the ecotoxicological, toxicological, and structural data generated from *in chemico*, *in vitro*, *ex vivo*, *in vivo*, and population studies, it is expected that the generated biological and chemical construct will improve its application, establishing a knowledge platform to set and relate new biomarkers by key event relationships (KERs).

**Keywords:** Adverse Outcome Pathway; *in silico* models; biomarkers; predictive toxicology

### 1. Introduction

*In Silico* Toxicology (IST) integrates different mathematical models to predict the toxicity of chemicals based on patterns of structural and physicochemical properties related to the toxicological activity.

With increasing relevance in different applications and as a cost-effective tool with a potentially higher mechanistic interpretability in evidence-driven assessments, *in silico* models (computer-based) are considered useful for predicting the toxicity of chemicals with unknown biological activity and are recommended by regulators and/or proposed by investigators for use in various contexts. Some types of substances assessed by *in silico* models in the last few years include drug impurities and degradation products [1]; pesticide metabolites and impurities [2]; additives, neo-formed contaminants (NFCs), and contaminants in food [3–5]; cosmetic ingredients [6]; industrial chemicals and emerging chemicals (ECs) [7]; and others.

Water 2020, 12, 3549; doi:10.3390/w12123549

[www.mdpi.com/journal/water](http://www.mdpi.com/journal/water)

# Modelos *in silico*

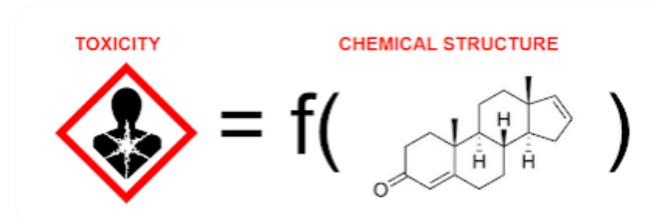
Fundamentos



# O que são modelos *in silico*?

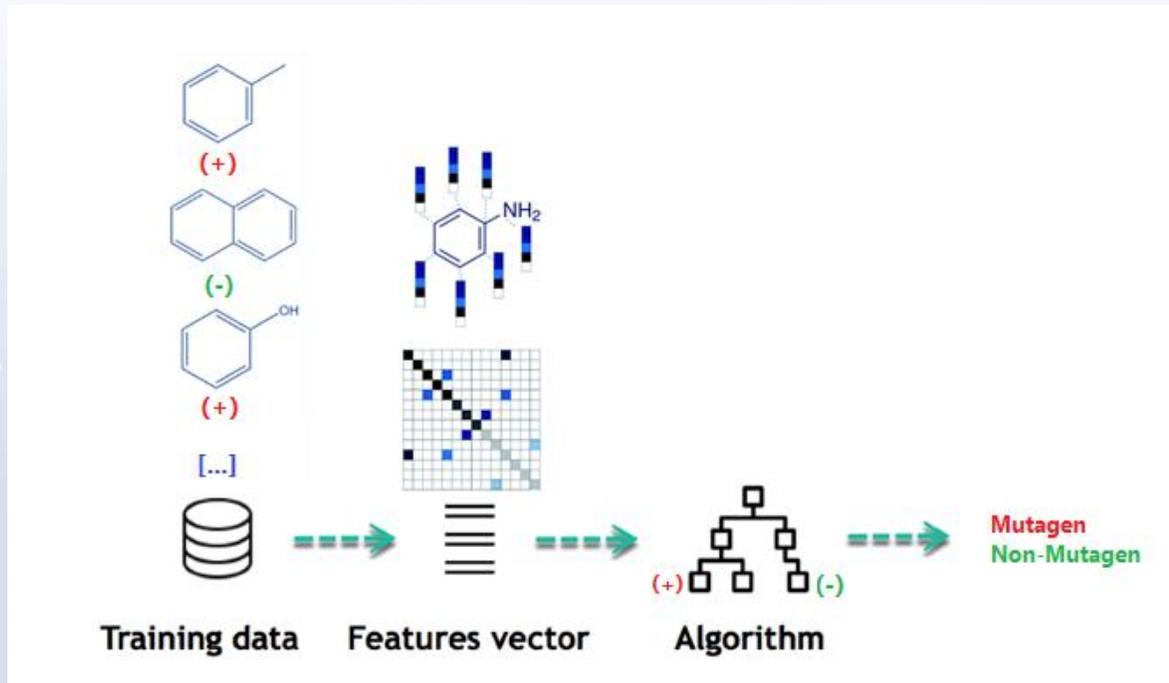
- Uma das **NAMs (New Approach Methodologies)** baseadas em uso de softwares / modelos computacionais

- SAR** – Relações Estrutura –atividade
- QSAR** – Relações Quantitativas entre Estrutura e Atividade
- (Q)SAR** – Referido-se a ambos, SAR e QSAR!
- **Métodos de extrapolação e interpolação baseada em similaridade estrutural ou mecanicista (Read-across, análise de tendência, formação de categorias e outros)**
- **Inteligência Artificial e algoritmos de machine learning (RF, redes neurais, kNN, SVM, Deep Learning etc.)**



# Como prever o potencial de toxicidade?

- Dados prévios -> Identificação de padrões (relação estrutura-atividade)
- Criação de algoritmos -> Predições



# Critérios de validação da OECD

- 1- Um endpoint definido
- 2- Um algoritmo inequívoco
- 3- Um domínio de aplicabilidade definido
- 4- Medidas apropriadas de qualidade de ajustamento, robustez e preditividade
- 5- Uma interpretação mecanística, se possível

Unclassified

Organisation de Coopération et de Développement Economiques  
Organisation for Economic Co-operation and Development

ENV/JM/MONO(2007)2

30-Mar-2007

English, French

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ENVIRONMENT DIRECTORATE  
JOINT MEETING OF THE CHEMICALS COMMITTEE AND  
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Cancels & replaces the same document of 15 February 2007

GUIDANCE DOCUMENT ON THE VALIDATION OF (QUANTITATIVE)STRUCTURE-ACTIVITY  
RELATIONSHIPS [(Q)SAR] MODELS

JT03224782

Document complet disponible sur OLIS dans son format d'origine  
Complete document available on OLIS in its original format

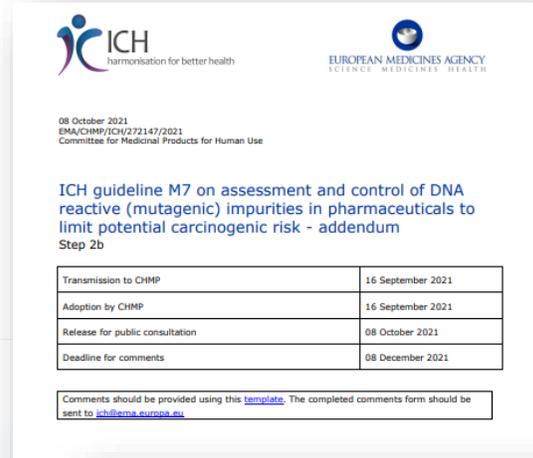


ENV/JM/MONO(2007)2  
Unclassified

English, French

# Modelos *in silico* são aceitos com fins regulatórios?

- ▶ Não apenas aceitos, mas em alguns casos **exigidos**
  - ▶ **Isoladamente; ou,**
  - ▶ **Combinados com testes *in chemico*, *in vitro* e/ou *ex vivo* (New Approach Methodologies)**
- ▶ Exemplos (lista não exaustiva)
- ▶ **Guideline OECD No. 497 (2021)** Guideline on Defined Approaches for Skin Sensitisation (contextos diversos, sobretudo o cosmético)
  - ▶ Recomendável inclusão de mais métodos e modelos *in silico* validados ao invés de “softwares” (boa prática regulatória)
- ▶ **ICH M7** (contexto farmacêutico)
- ▶ **ISO 10993-23:2021** (avaliação de componentes de dispositivos médicos)
- ▶ **SCCS Notes** - Guidance for Safety Evaluation of Cosmetic Ingredients (12<sup>a</sup> rev 2023)
- ▶ **Legislações relacionadas a inventários e registros de substâncias: REACH, TSCA, DSL**
- ▶ **E outras nos setores agroquímicos, alimentos e medicamentos;**



ICH harmonisation for better health  
EUROPEAN MEDICINES AGENCY  
SCIENCE · MEDICINES · HEALTH

08 October 2021  
EMA/CHMP/ICH/272147/2021  
Committee for Medicinal Products for Human Use

ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - addendum  
Step 2b

Transmission to CHMP	16 September 2021
Adoption by CHMP	16 September 2021
Release for public consultation	08 October 2021
Deadline for comments	08 December 2021

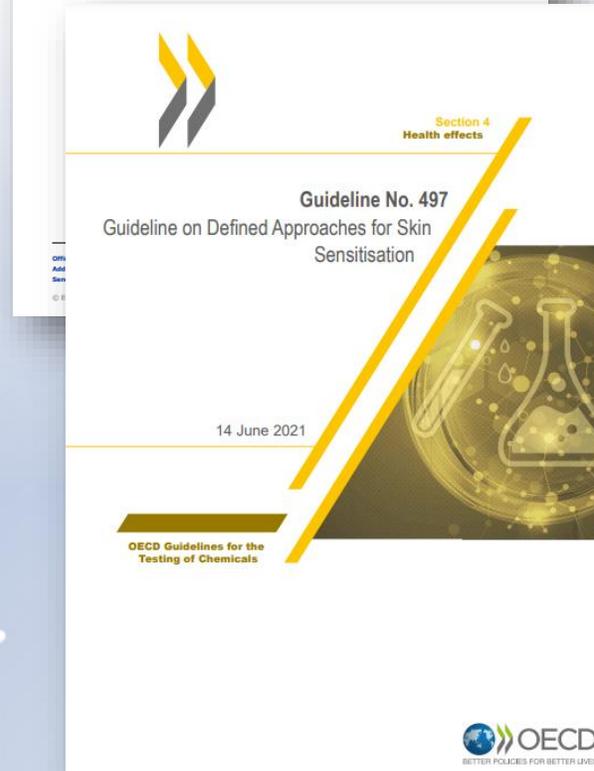
Comments should be provided using this [template](#). The completed comments form should be sent to [ich@ema.europa.eu](mailto:ich@ema.europa.eu)



BS EN ISO 10993-23:2021

BSI Standards Publication

Biological evaluation of medical devices Tests for irritation



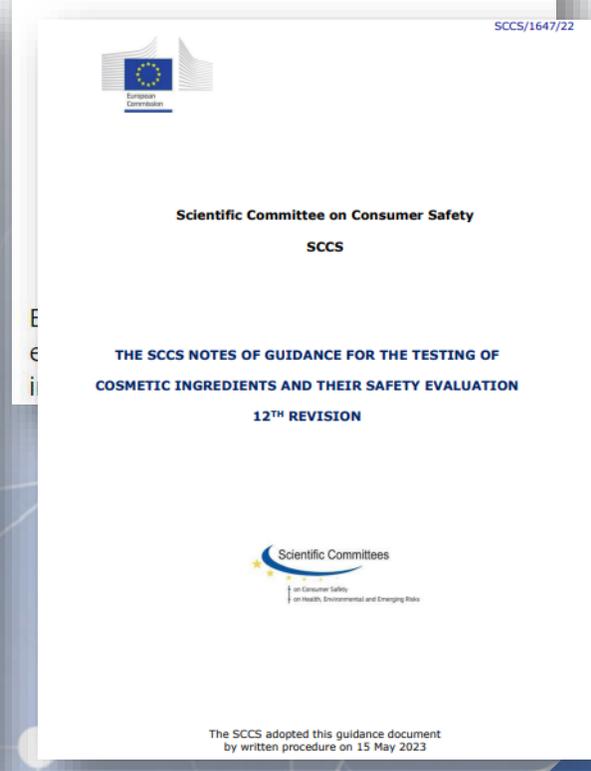
Section 4  
Health effects

Guideline No. 497  
Guideline on Defined Approaches for Skin Sensitisation

14 June 2021

OECD Guidelines for the Testing of Chemicals

OECD  
BETTER POLICIES FOR BETTER LIVES



SCCS/1647/22

European Commission

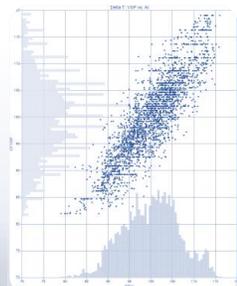
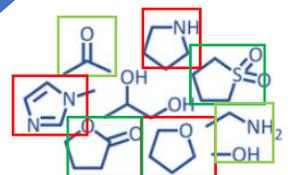
Scientific Committee on Consumer Safety  
SCCS

THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF  
COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION  
12<sup>TH</sup> REVISION

Scientific Committees  
on Consumer Safety  
on Health, Environmental and Emerging Risks

The SCCS adopted this guidance document by written procedure on 15 May 2023

# Exemplo de matriz SAR de alertas



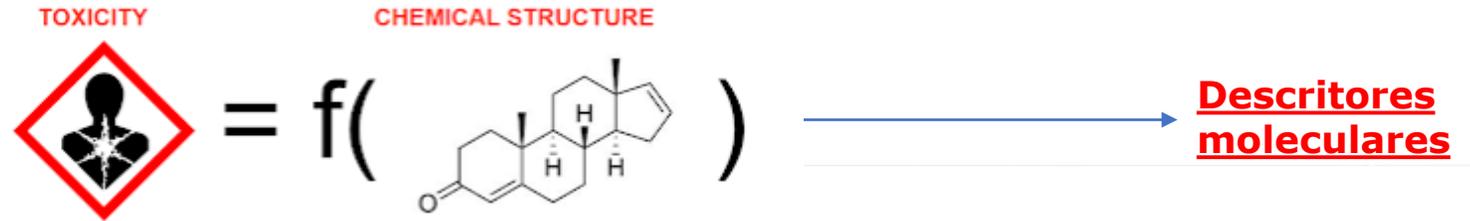
	EPs	Support	ρ	Structural Alert in ToxAlerts
MF_73		44	36.94	N-nitroso-N-alkylamides N-nitroso-N-alkylureas N-nitroso-N-alkylcarbamates
MF_0		67	27.92	Diazo
MF_1		55	22.76	Azide
MF_125		52	21.47	Aromatic and aliphatic aziridinyl derivatives
MF_156		47	12.60	Aromatic hydroxylamine ester
MF_72		27	9.09	Nitrosamine
MF_1651		178	6.79	Polycyclic aromatic hydrocarbons
MF_1841		26	6.59	Allylic halides
MF_824		48	6.01	Hydroxyl amine
MF_1667		226	5.84	Polycyclic aromatic hydrocarbons
MF_1831		36	5.33	Monohaloalkene
MF_75		162	5.19	Unsubstituted heteroatom-bonded heteroatom
MF_927		35	5.16	Aromatic N-acyl amine
MF_1298		27	4.94	Quinones
MF_920		964	4.70	Nitrosoarenes
MF_134		926	4.63	Aromatic nitro groups
MF_444		93	4.47	Nitrogen mustard

	EPs	Support	ρ	Structural Alert in ToxAlerts
MF_212		35	4.15	N mustard
MF_2188		29	4.12	Acyl halides
MF_2107		40	4.05	Alkyl ester of sulfonic and sulfuric acids
MF_34		74	3.68	Aliphatic azo
MF_1317		26	3.61	Heterocyclic polycyclic aromatic hydrocarbons
MF_1883		308	2.33	Aliphatic and aromatic epoxides
MF_916		656	2.17	Primary aromatic amine
MF_432		50	1.83	Alkyl carbamate
MF_41		151	1.54	Aromatic azo
MF_153		51	1.33	Aliphatic nitroso
MF_169		182	1.25	Tertiary aromatic amine
MF_2197		26	1.17	Aliphatic halogens
MF_1836		59	1.17	α,β-unsaturated carbonyl
MF_1470		43	0.82	Coumarins
MF_2220		1491	0.64	Simple aldehyde
MF_2097		47	0.58	Alkyl ester of phosphonic and phosphoric acids

# Modelos estadísticos - algoritmos



# Modelos estatísticos (QSAR)

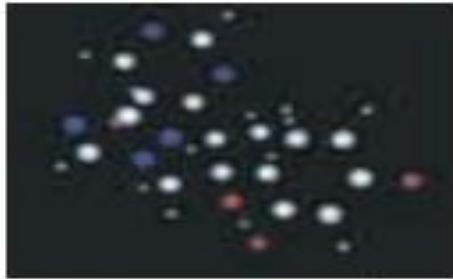


**Toxicidade =  $f$  (carat. FQ e/ou estruturais)**  
 Quantitative structure-toxicity relationship (QSTR)

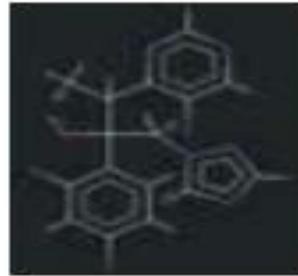
- ▶ Resposta contínua: IC50, EC50, DL50, CL50 etc;
- ▶ Respostas categóricas: +/-
- ▶ Classificatória (fraco, moderado, forte, extremamente forte etc.)
- ▶ Probabilística: 0 a 1 (0 – 100%)

Obs: a notação (Q)SAR ao invés de QSAR, é frequentemente utilizada na literatura para descrever modelos de todas as categorias, incluindo aqueles sem relação quantitativa entre estrutura e atividade, como SAR e regras.

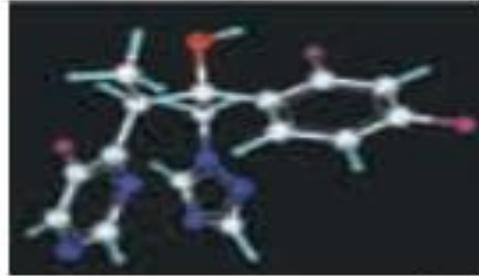
# Descritores e formas de representação estrutural QSAR 1-D, 2-D, 3-D e 4-D



1D Representation



2D Representation



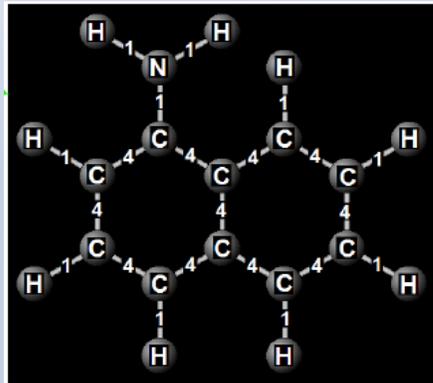
3D Representation



4D Representation

SMILES (Simplified  
molecular-input line-entry system)

C1(=CC=CC2=C1C=CC=C2)N



## MOL File

```

16 15 0 0 0 0 0 0 0 0999 V2000
-0.1958 -2.9667 0.0000 C 0 0 0 0
0.5147 -2.5500 0.0000 C 0 0 0 0
0.5135 -1.7250 0.0000 H 0 0 0 0
1.2292 -2.9625 0.0000 H 0 0 0 0
1.9417 -2.5458 0.0000 C 0 0 0 0
2.6542 -2.9583 0.0000 C 0 0 0 0
3.3667 -2.5417 0.0000 C 0 0 0 0
4.0792 -2.9542 0.0000 C 0 0 0 0
4.7917 -2.5375 0.0000 C 0 0 0 0
5.5042 -2.9500 0.0000 C 0 0 0 0
1.2250 -3.7875 0.0000 C 0 0 0 0
0.8083 -4.5000 0.0000 C 0 0 0 0
1.3917 -5.0833 0.0000 C 0 0 0 0
0.9750 -5.7958 0.0000 C 0 0 0 0
1.5583 -6.3792 0.0000 C 0 0 0 0
0.9708 -6.9625 0.0000 C 0 0 0 0
8 9 1 0 0 0 0 0 0 0 0 0 0 0 0
4 5 1 0 0 0 0 0 0 0 0 0 0 0 0
9 10 1 0 0 0 0 0 0 0 0 0 0 0 0
2 3 1 0 0 0 0 0 0 0 0 0 0 0 0
4 11 1 0 0 0 0 0 0 0 0 0 0 0 0
5 6 1 0 0 0 0 0 0 0 0 0 0 0 0
11 12 1 0 0 0 0 0 0 0 0 0 0 0 0
1 2 1 0 0 0 0 0 0 0 0 0 0 0 0
12 13 1 0 0 0 0 0 0 0 0 0 0 0 0
5 6 7 1 0 0 0 0 0 0 0 0 0 0 0
13 14 1 0 0 0 0 0 0 0 0 0 0 0 0
2 4 1 0 0 0 0 0 0 0 0 0 0 0 0
14 15 1 0 0 0 0 0 0 0 0 0 0 0 0
7 8 1 0 0 0 0 0 0 0 0 0 0 0 0
15 16 1 0 0 0 0 0 0 0 0 0 0 0 0
M END
  
```

**Vertices**  
(atomic type,  
coordinates etc.)

**Edges**  
(connectivity table,  
label-types of bonds)

Formas que a  
máquina pode  
entender!

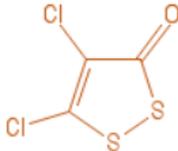
# Descritores fingerprints

- Fingerprints são descritores na forma de uma lista de valores binários (0 ou 1), que podem ser gerados por diferentes Keys (MACCS Keys, ECFP etc.)
- Um conjunto de padrões estruturais podem ser checados. Por exemplo, uma estrutura **OC=CN**, pode conter:



*0-bond paths:* **C**      **O**      **N**  
*1-bond paths:* **OC**      **C=C**      **CN**  
*2-bond paths:* **OC=C**      **C=CN**  
*3-bond paths:* **OC=CN**

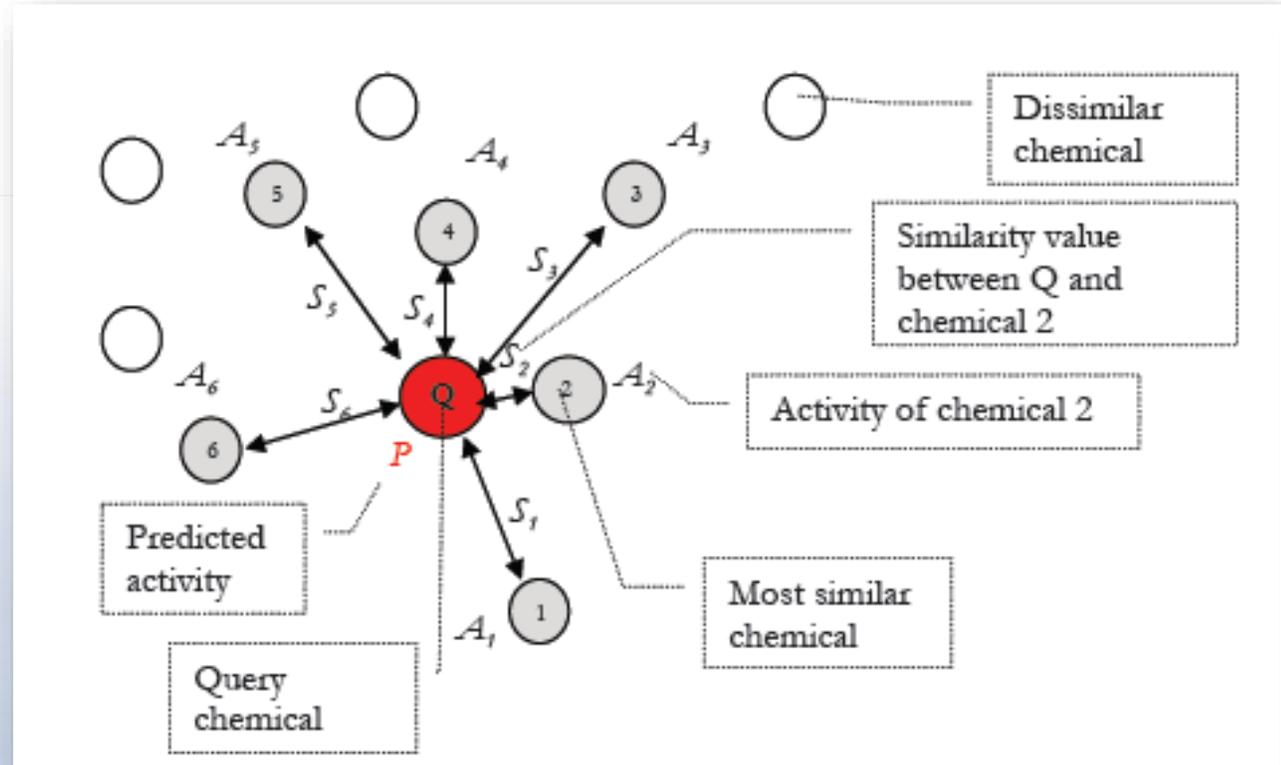
Exemplo Fingerprint MACCS

MACCS Keys (conjunto de questões)		
Há menos de 3 oxigênios?	Yes (1)	Yes (1)
Há uma ligação S-S?	Not (0)	Yes (1)
Há um anel de 5 membros?	Yes (1)	Yes (1)
É pelo menos um F, Cl, Br, ou me apresentar?	Not (0)	Yes (1)
Lista de bits ou bitstring		



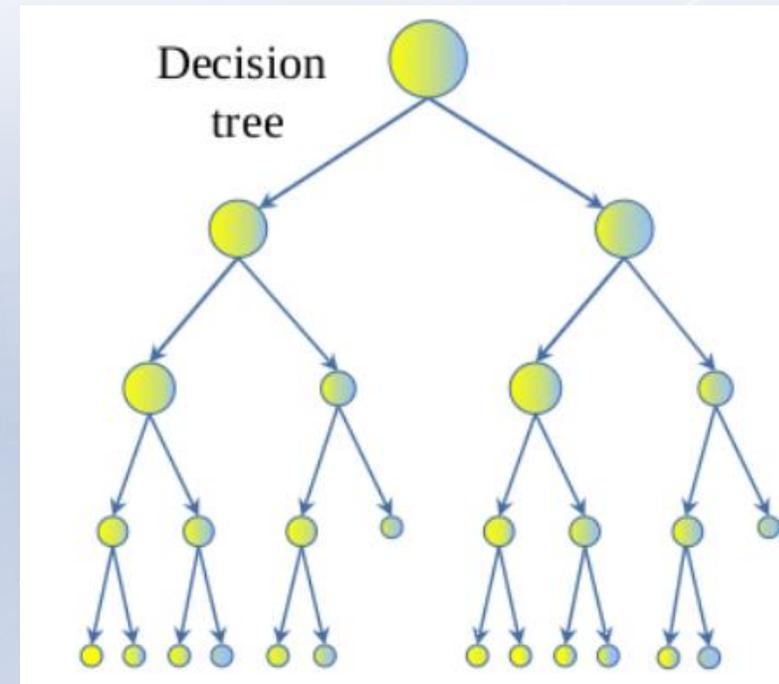
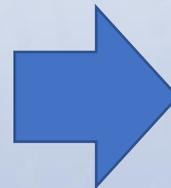
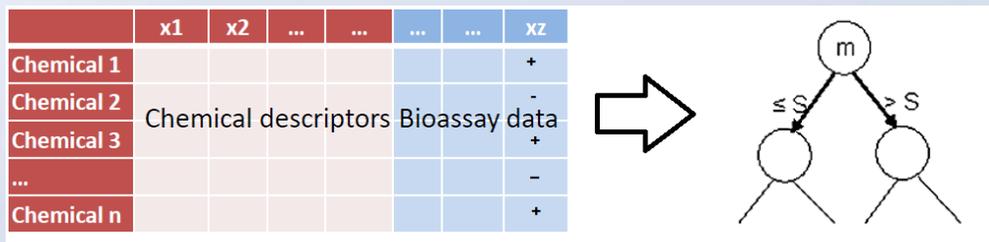
# kNN (Nearest Neighbor)

- Modelo baseado em um espaço químico reduzido com **moléculas vizinhas mais próximas**
- Premissa de que moléculas similares devem ter **atividade biológica similar**
- Quando uma nova molécula é inserida, um conjunto de moléculas estruturalmente relacionadas semelhantes é obtido no banco de dados e utilizado para classificar a nova instância de consulta
- Limitações e incertezas



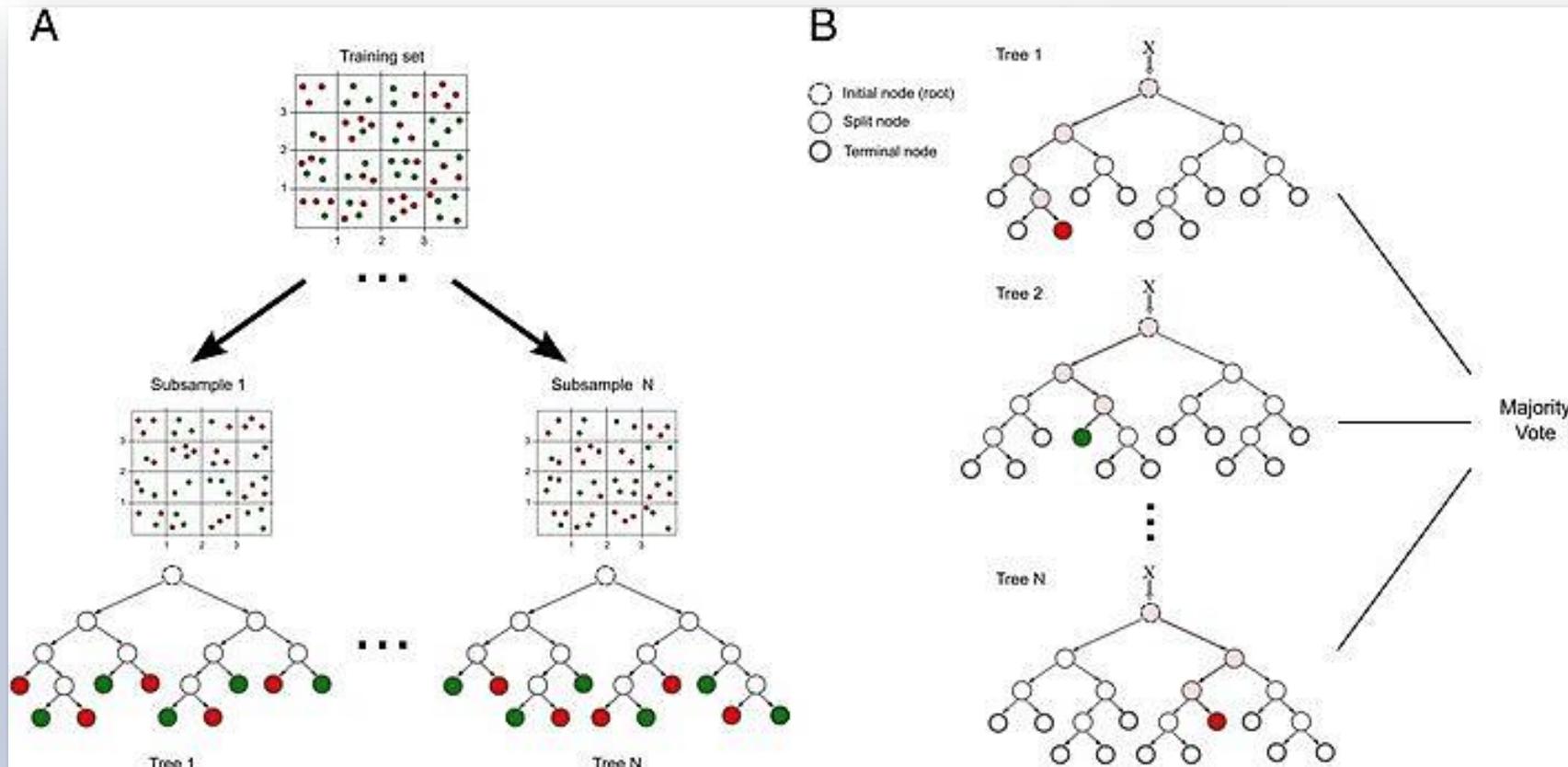
# Árvores de decisão e deep decision

- CART – Classification and Regression Tree
- Procura entre todos os valores de todos os preditores a divisão em 2 grupos
  - Em classificação: garantir maior pureza em cada grupo



# Random forests

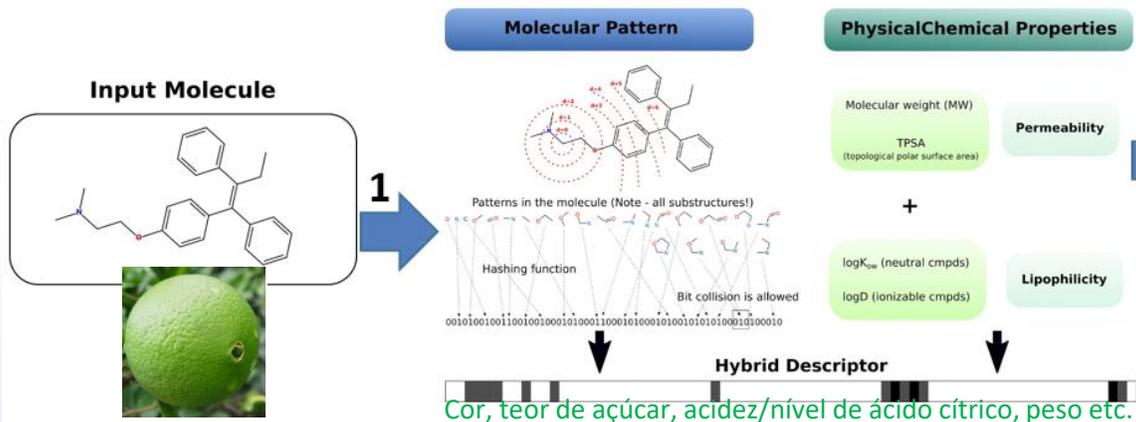
- Bagging (sorteio com aleatorização e reposição)
- Randomização na seleção de preditores em cada nó
- Menos variáveis em cada nó
- Predição segundo voto da maioria das árvores



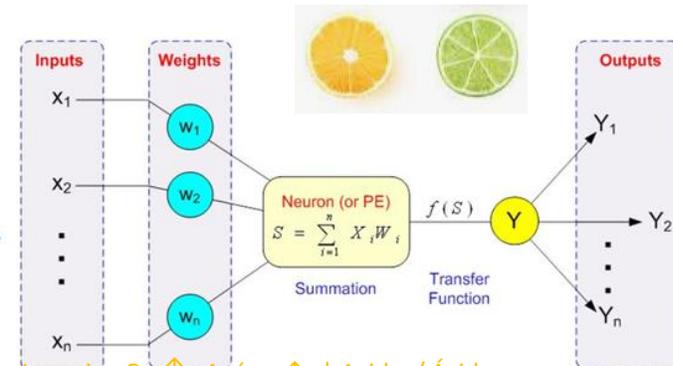
# Deep Learning com laranja e limões



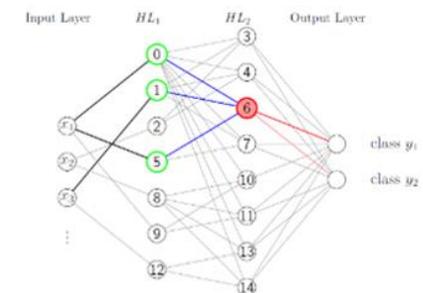
**Fingerprint Híbrido**  
 União do fingerprint ECFP e propriedade físico-química:  
 MW, TPSA, log<sub>Kow</sub>, logD



**deep learning (ANN)**  
 Machine learning decision model implemented with  
 the Hybrid fingerprint

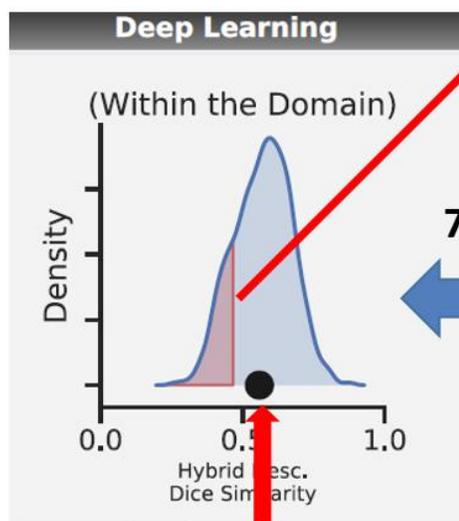


Laranja= Cor↕, Açúcar↑, ↓Acidez/ Ácido cítrico, ↕peso, caipirinha↓  
 Limão= Cor↕, ↓Açúcar, ↑ Acidez/ Ácido cítrico, ↕peso, ↑ caipirinha



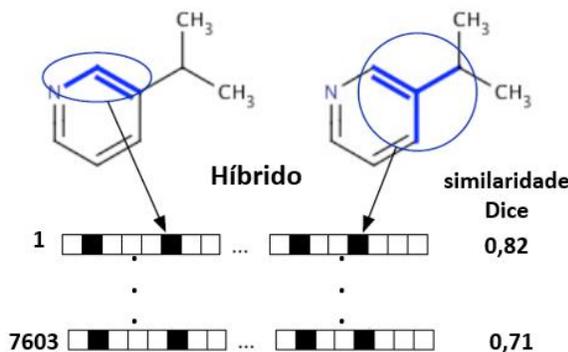
Laranja – Conf. 80%

**Predição composta pelo voto majoritário. Exemplo para resultado mutagênico com 70% de confiança.**  
 Durante a amostragem externa (5-fold externo), 70% das amostras apontavam combinação de pesos nas camadas profundas de neurônio para decisão de potencial mutagênico.



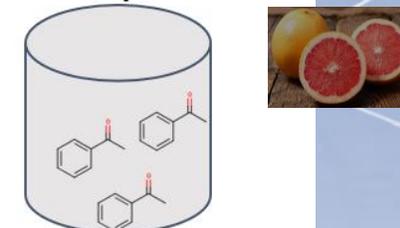
$$D_c = Z\sigma_{ec} + y_{ec}$$

Na Equação, o  $y_{ec}$  é a média aritmética e  $\sigma_{sec}$  o desvio padrão das similaridade dice dos  $k$  vizinhos mais próximos de cada composto na série treinamento. O parâmetro empírico  $Z$  controla o nível de significância, sendo que seu valor de 1,0. O valor de  $k$  ideal pode ser obtido pelo valor empírico calculado usando  $n^{1/3}$  ( $n$ =dataset tamanho).



1. Cálculo da similaridade da matriz de dados contra ela mesma para gerar uma matriz quadrada.
2. cálculo da similaridade dice entre a "input molecule" e todas as substâncias da dataset.

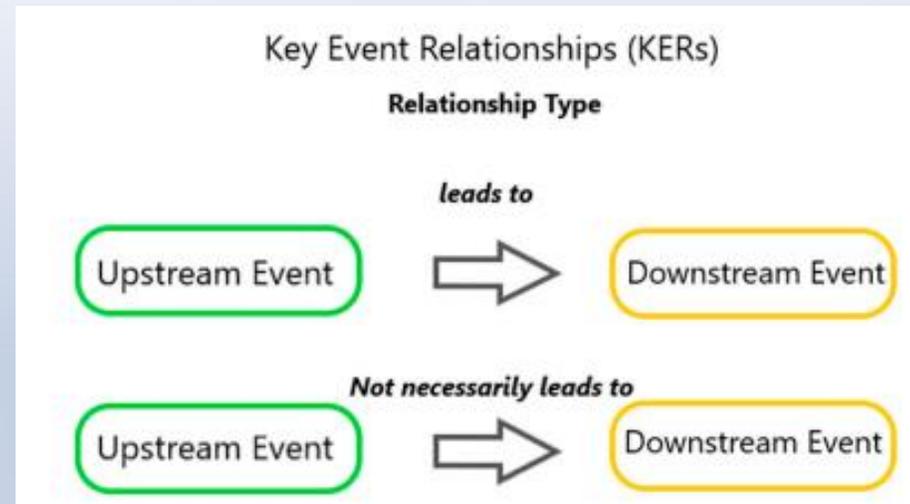
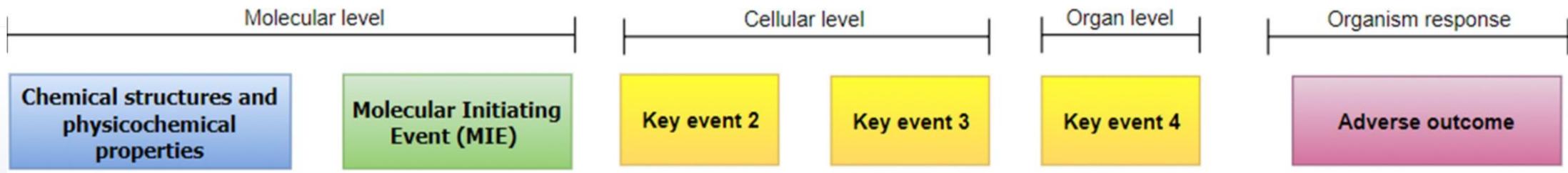
**Domínio de aplicabilidade**



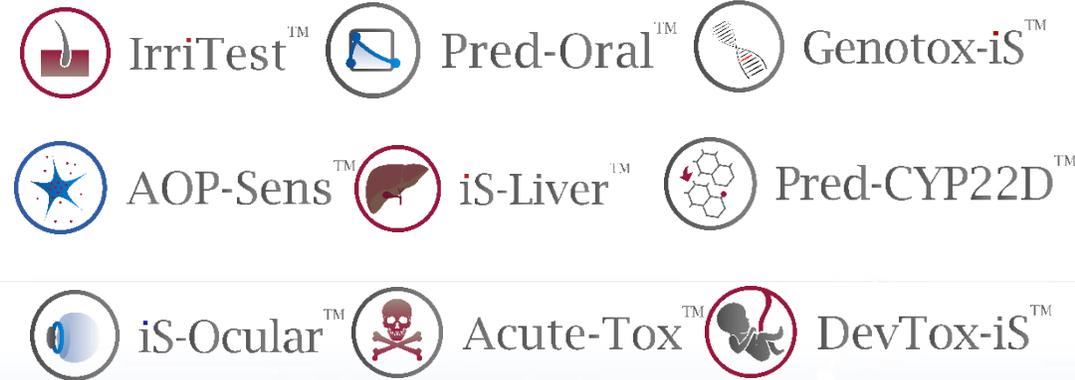
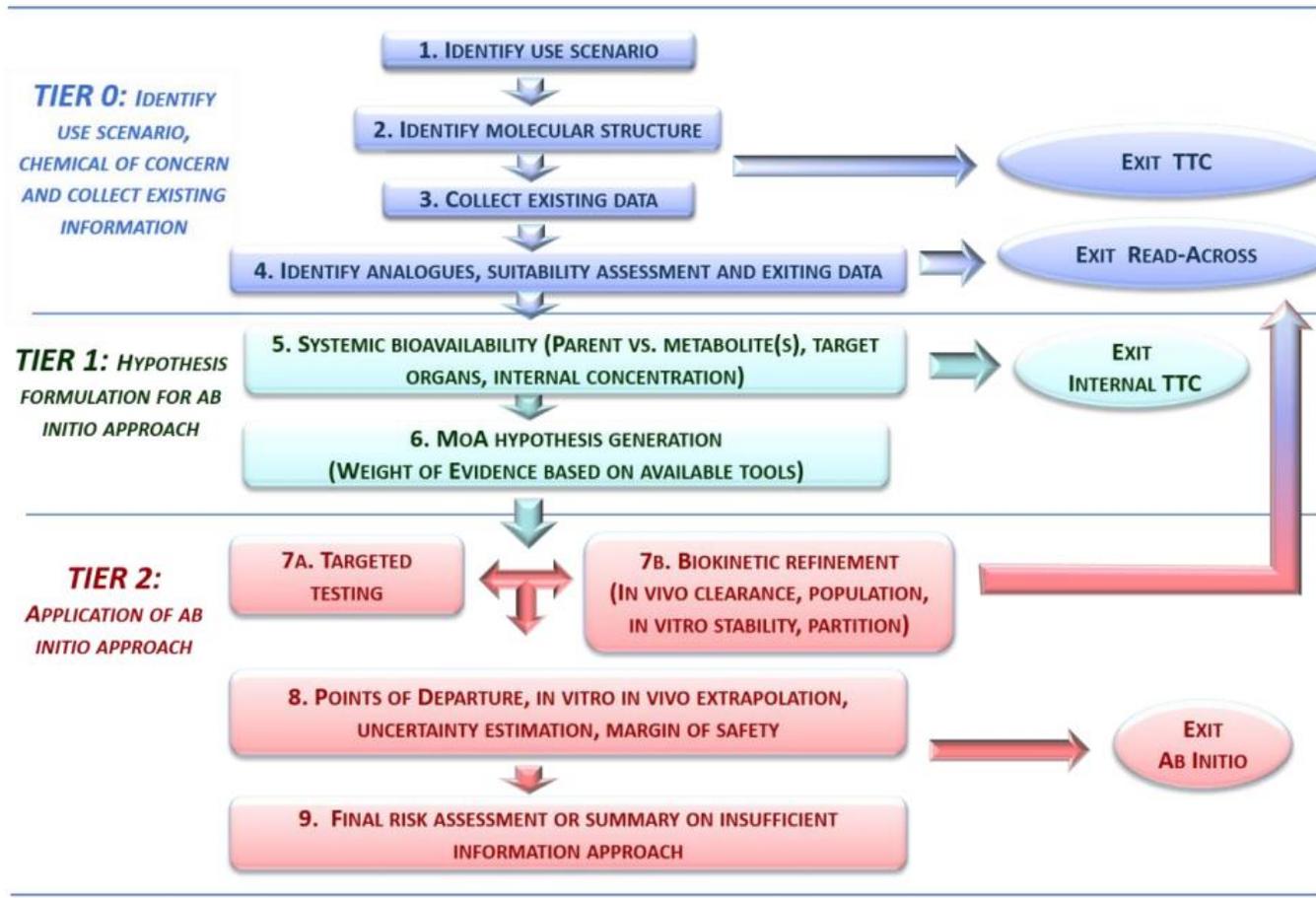
quimioteca com 7603 substâncias avaliadas para mutagenicidade *in vitro*.

# Adverse Outcome Pathways (AOPs)

Constructo que descreve a cadeia sequencial de eventos-chave relacionados a um desfecho toxicológico (efeito adverso)



# New Generation Risk Assessment (NGRA)



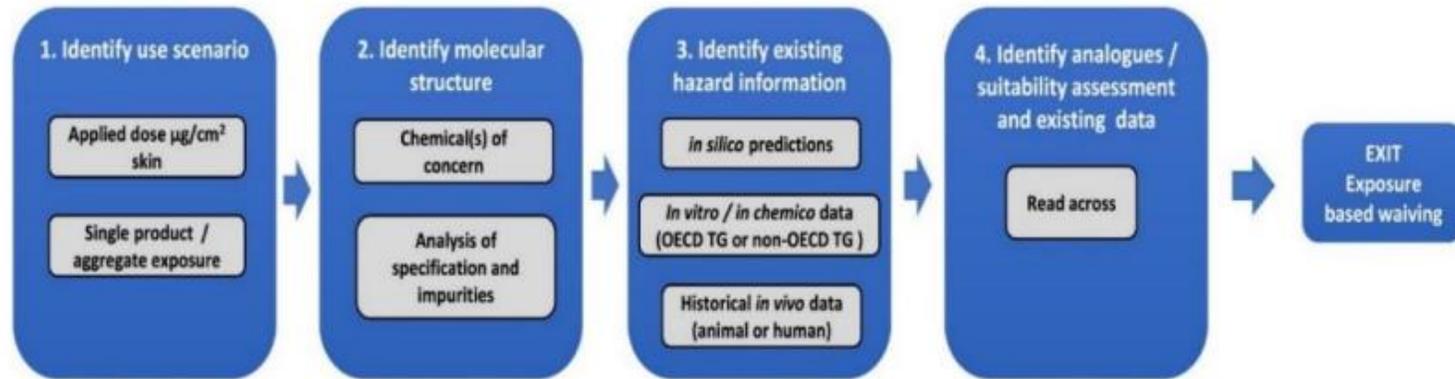
- ▶ Avaliação de características FQ, biodisponibilidade, metabolismo
- ▶ Avaliação de toxicidade sistêmica e para órgãos-alvo
- ▶ Avaliação para descartar potencial genotóxico, para proposição de limites baseados em toxicidade geral

- ▶ TTC: Classes I, II e III
- ▶ iTTC: 1µM

# NGRA para sensibilização cutânea

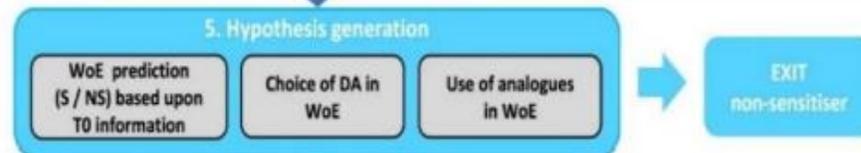
## Tier 0

Identify use scenario, chemical of concern and existing information



## Tier 1

Hypothesis generation; how will data be used in risk assessment?



## Tier 2

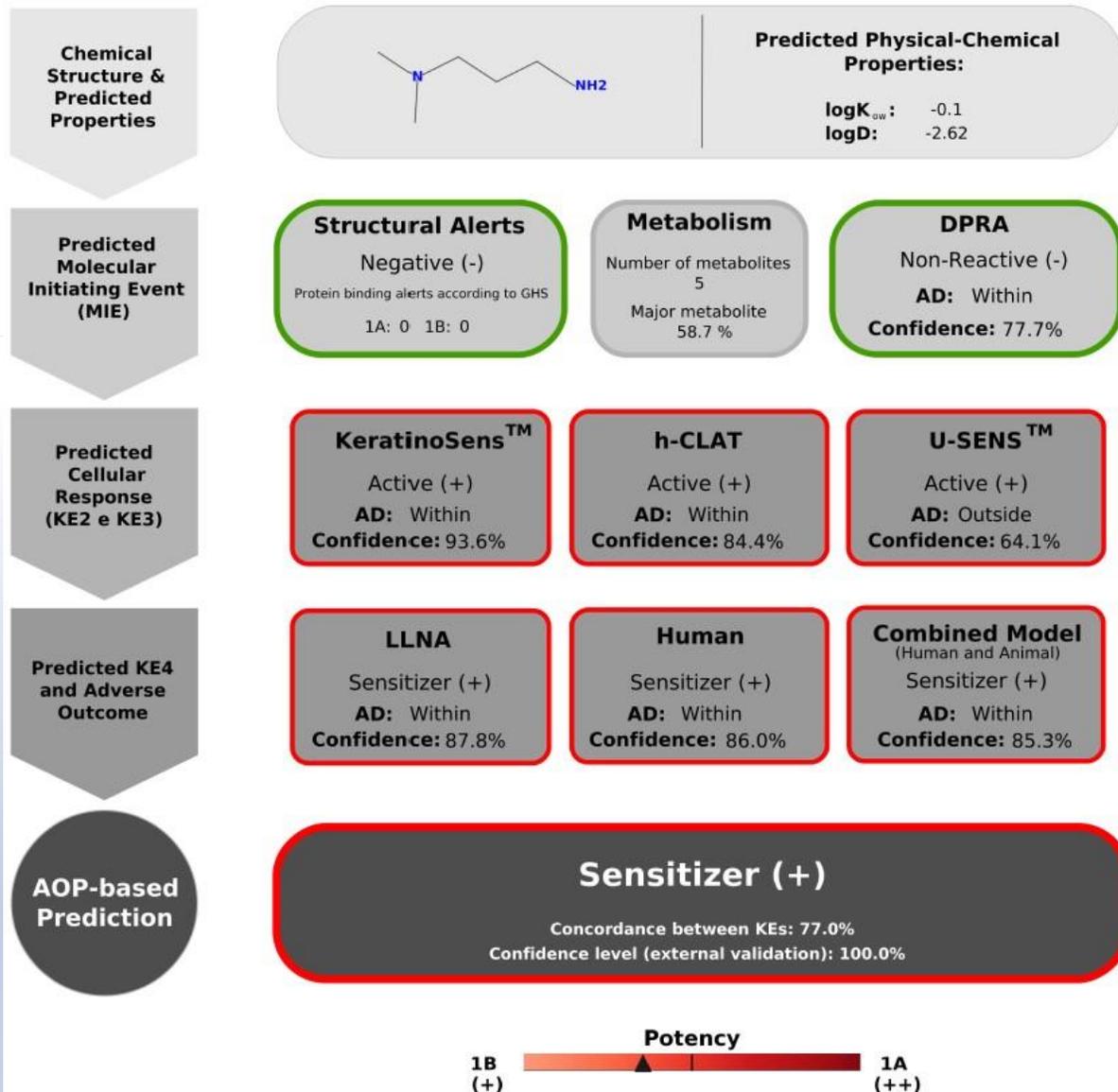
Risk assessment





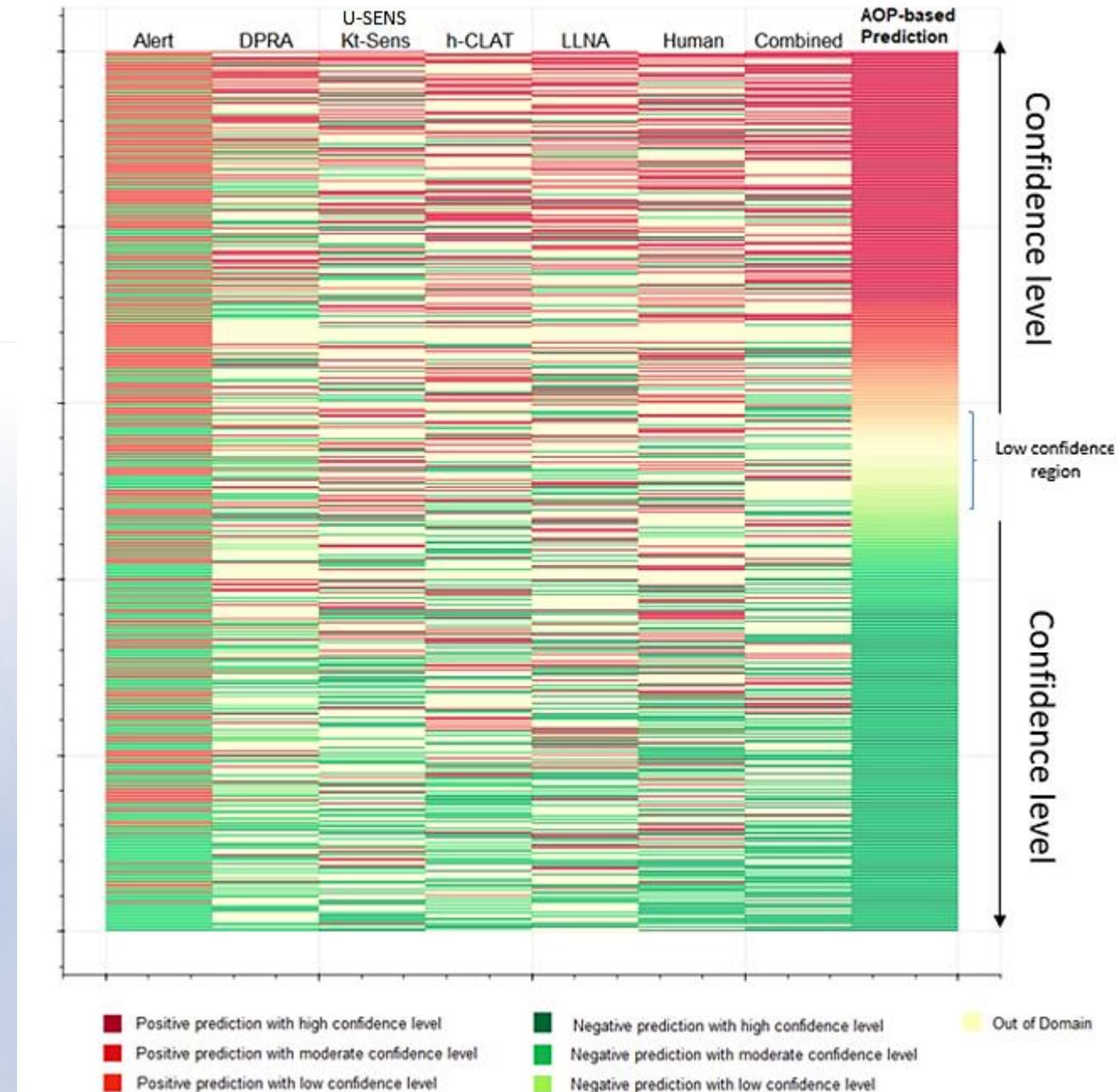
# AOP-Sens<sup>TM</sup>

- Modelo *in silico* “AOP-based” for NGRA e Defined approaches on skin sensitisation (DASS)
- Avaliação de dados físico-químicos
- Verificação de alertas na estrutura e nível de preocupação de metabólitos previstos (eventuais pró-haptenos)
- Predição de cada um dos eventos-chave e desfecho de sensibilização
- Estimativa do peso de evidência (WoE) através de Key Events Relationships
- Estimativa de potência de sensibilização (Classes do GHS) que podem ser utilizadas para estimativas da DST (dermal sensitization threshold)
- Dados de análogos para RAX



# Avaliando o peso de evidência (WoE)

- Avaliação mecanicistica
- Avaliação da concordância e relações entre os eventos-chave
- Regiões de alta ou baixa confiança
- Avaliação de análogos similares



# Aplicando na prática

**Name:**

(R)(+)Limonene

**CAS:**

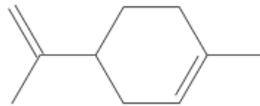
5989-27-5

**SMILES:**

CC1=CCC(CC1)C(=C)C

**logK<sub>ow</sub>:**

3.31



**Name:**

1,2-Dibromo-2,4-dicyanobutane (MDGN)

**CAS:**

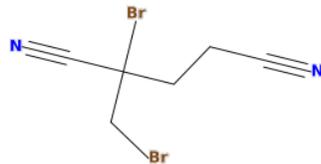
35691-65-7

**SMILES:**

C(#N)C(Br)(CC#N)CBr

**logK<sub>ow</sub>:**

2.34



**Name:**

Isopropanol

**CAS:**

67-63-0

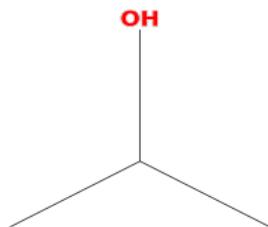
**SMILES:**

CC(C)O

**logK<sub>ow</sub>:**

0.39

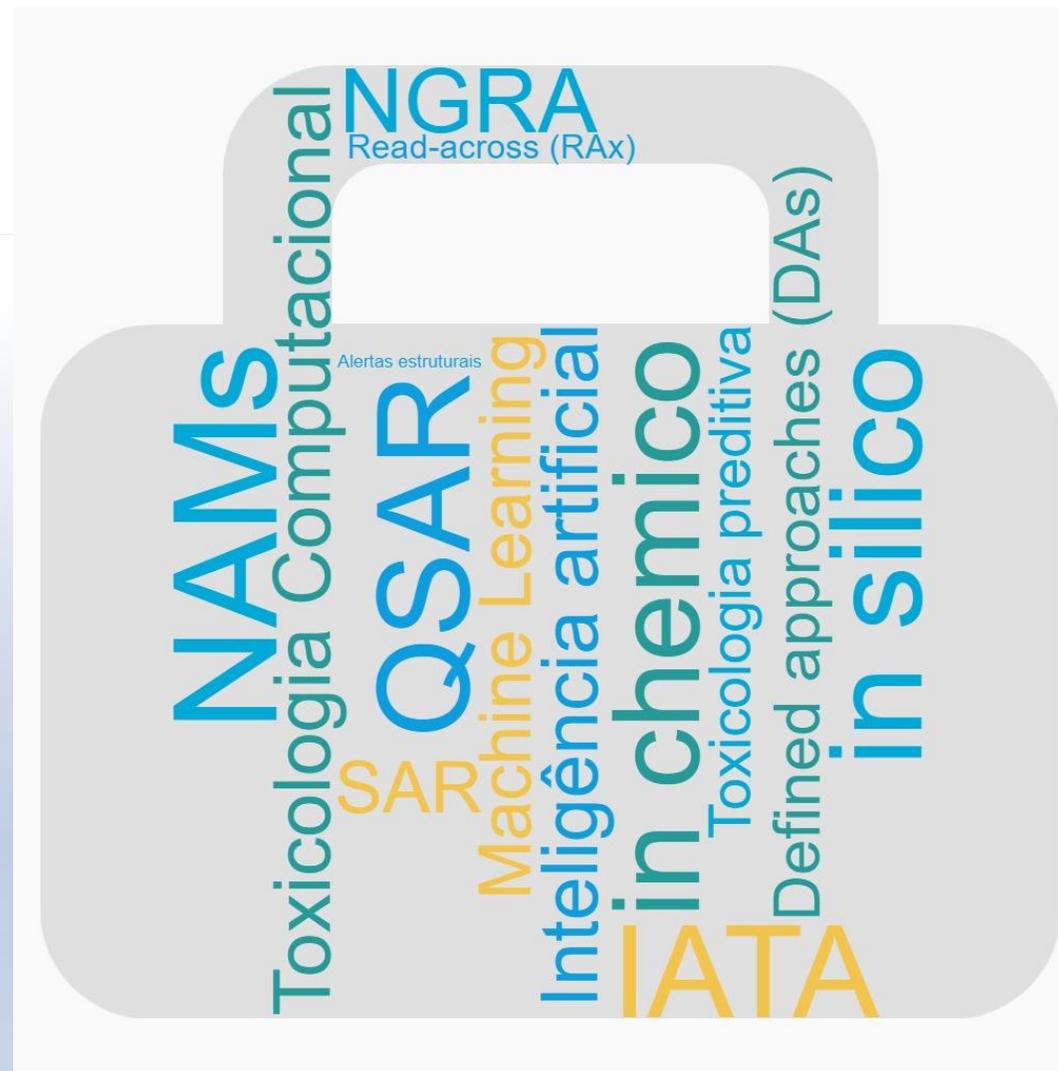
**logD:**



# Perspectivas para desenvolvimento e aplicação regulatória no Brasil?

- ▶ **Diálogos e capacitação:** diálogos mais diretos, CPs e atualização das gerências de órgãos reguladores sobre estes novos métodos, práticas e abordagens;
- ▶ **Atualização regulatória:** Ausência de guias locais e normativas sobre avaliação de segurança atualizadas de acordo com avanços internacionais
- ▶ **Projetos de inovação entre empresas:** co-desenvolvimento de novos modelos *in silico*, estratégias NGRA, DAs e IATAs com foco em endpoints relevantes

Qual nível de atualização regulatória e inovação?



# Nossos agradecimentos

GrupoBoticário 



 **ABIHPEC**  
Associação Brasileira da Indústria de  
Higiene Pessoal, Perfumaria e Cosméticos

**Obrigado pela atenção!**

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