



These projects have received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 963845 (ONTOX), No. 965406 (PrecisionTox), No. 964537 (RISK-HUNT3R)

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Open **2-3 July 2026** Symposium

Maastricht
The Netherlands

ONTOX Probabilistic Risk Assessment (OPRA):
An AI-enabled framework

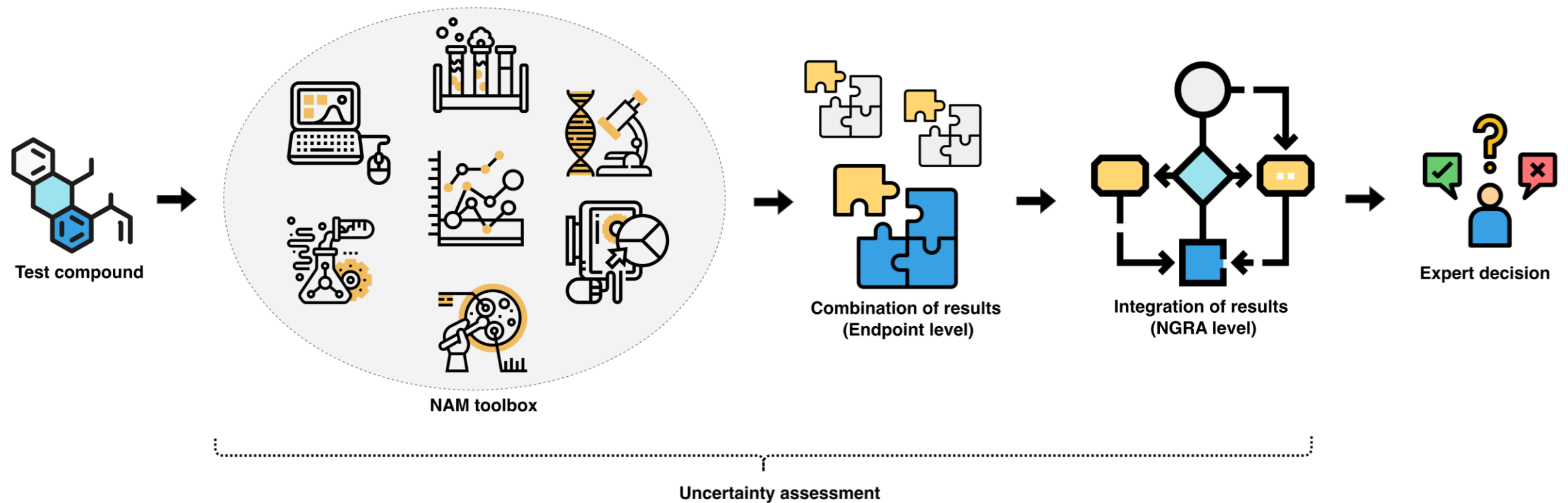
Karolina Kopańska, PhD

Johns Hopkins Center for Alternatives to Animal Testing (CAAT)

Project: ONTOX

aspis-cluster.eu

... is defined as a hypothesis-driven (and exposure-led) approach that integrates results derived from the New Approach Methodologies (NAMs)





Methods for uncertainty assessment and combination of evidence

Probabilistic methods

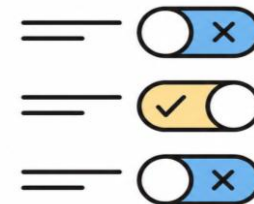
- Require data for calculations
- Assumes that uncertainty can be represented as distributions



Examples: Frequentist (MLE), Bayesian (inference, networks)...

Non probabilistic methods

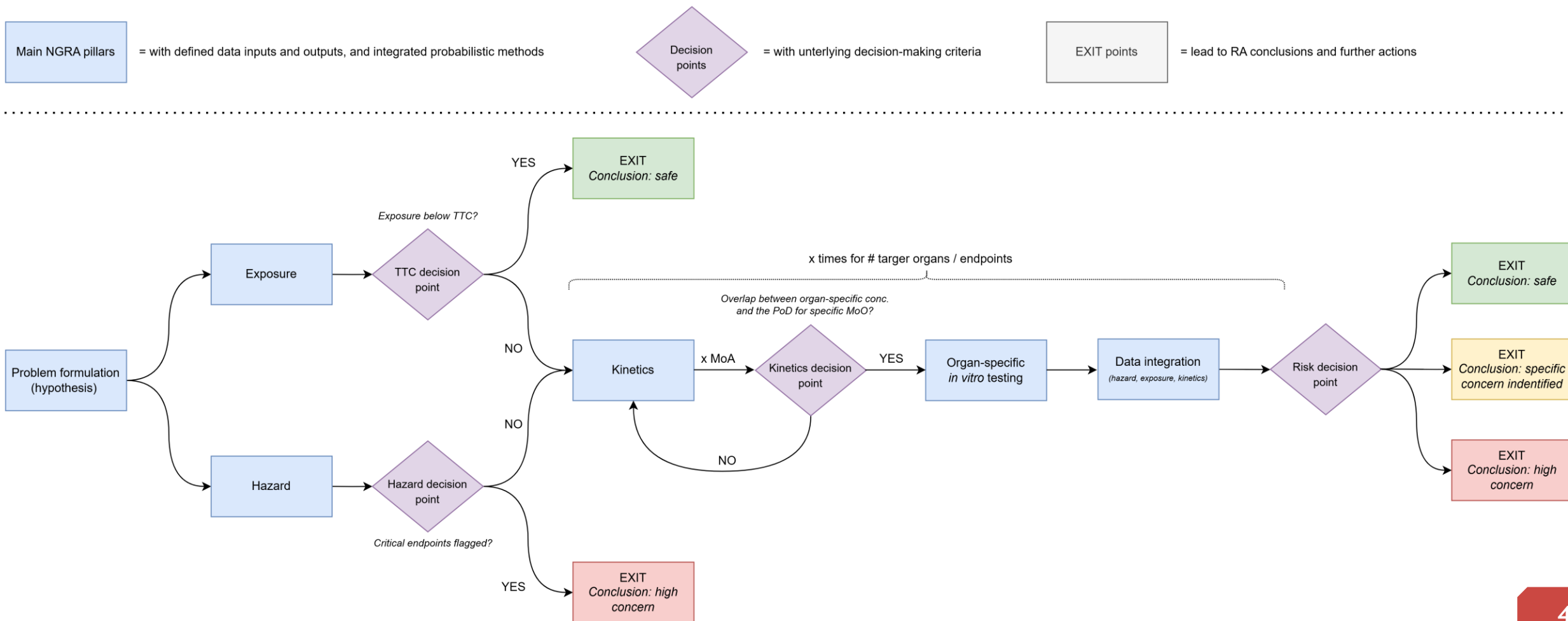
- When data is incomplete or low quality
- Output as range of possibilities, uncertainty represented as intervals, bounds, sets..



Examples: Dempster-Shafer Theory, Fuzzy theory, Interval analysis...



NGRA + uncertainty assessment methods + AI = OPRA



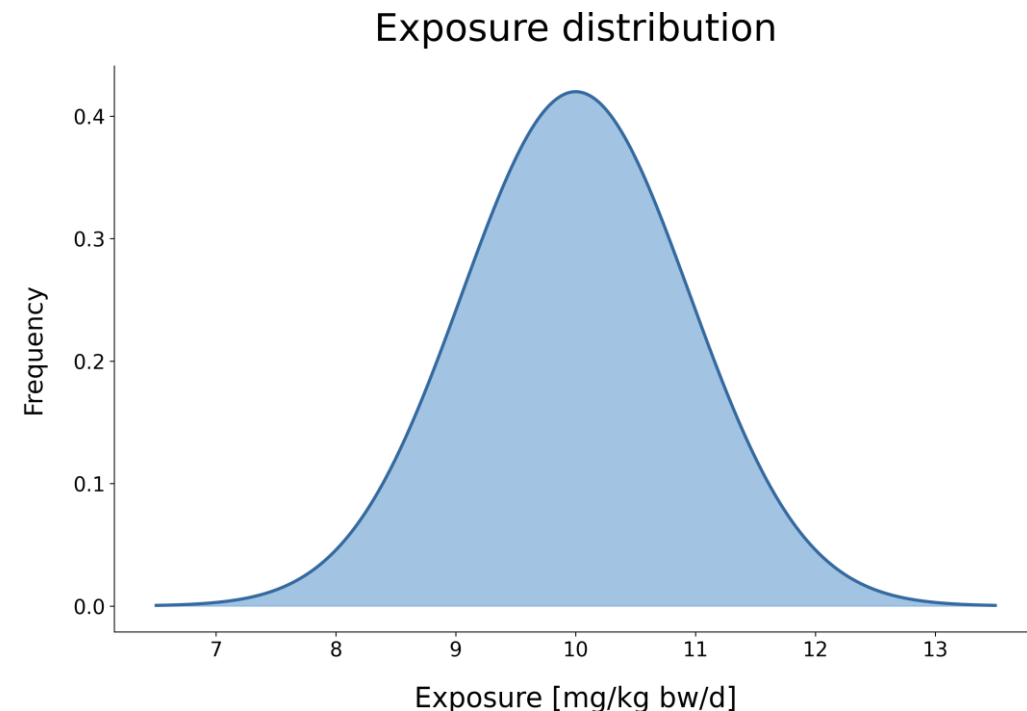


Clearly defined inputs and outputs are essential for effective AI implementation

Input:

- **Exposure scenario**
 - Exposure frequency, duration, route
 - Population of interest
- **Probabilistic framework**
 - Frequentist (MC)
- **Exposure simulation**
 - Mean
 - Data spread (e.g., standard deviation)
 - Data distribution (e.g., normal)

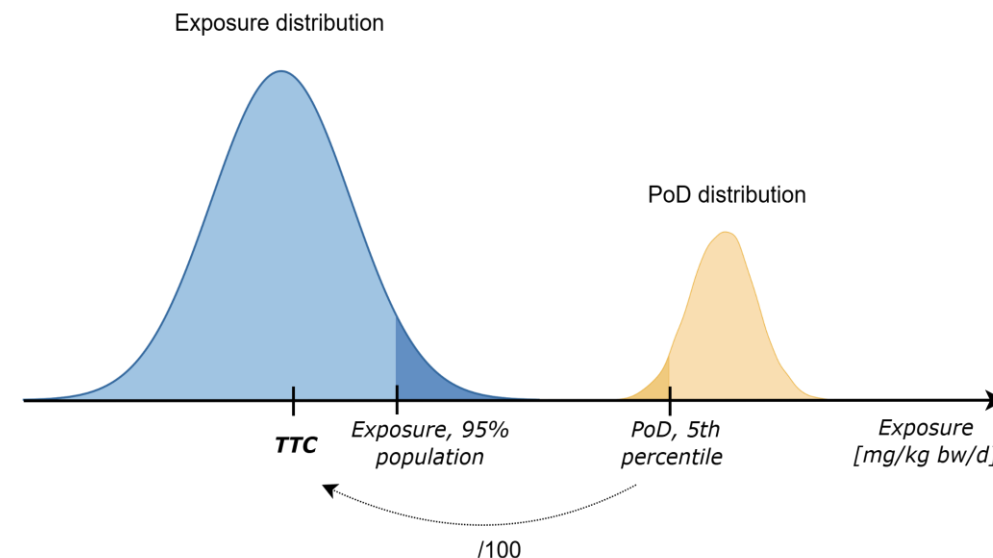
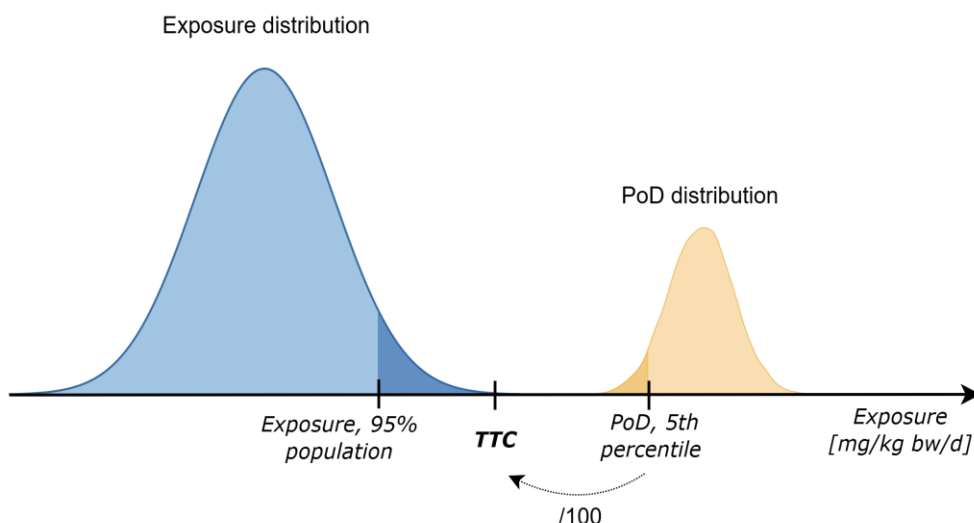
Output:





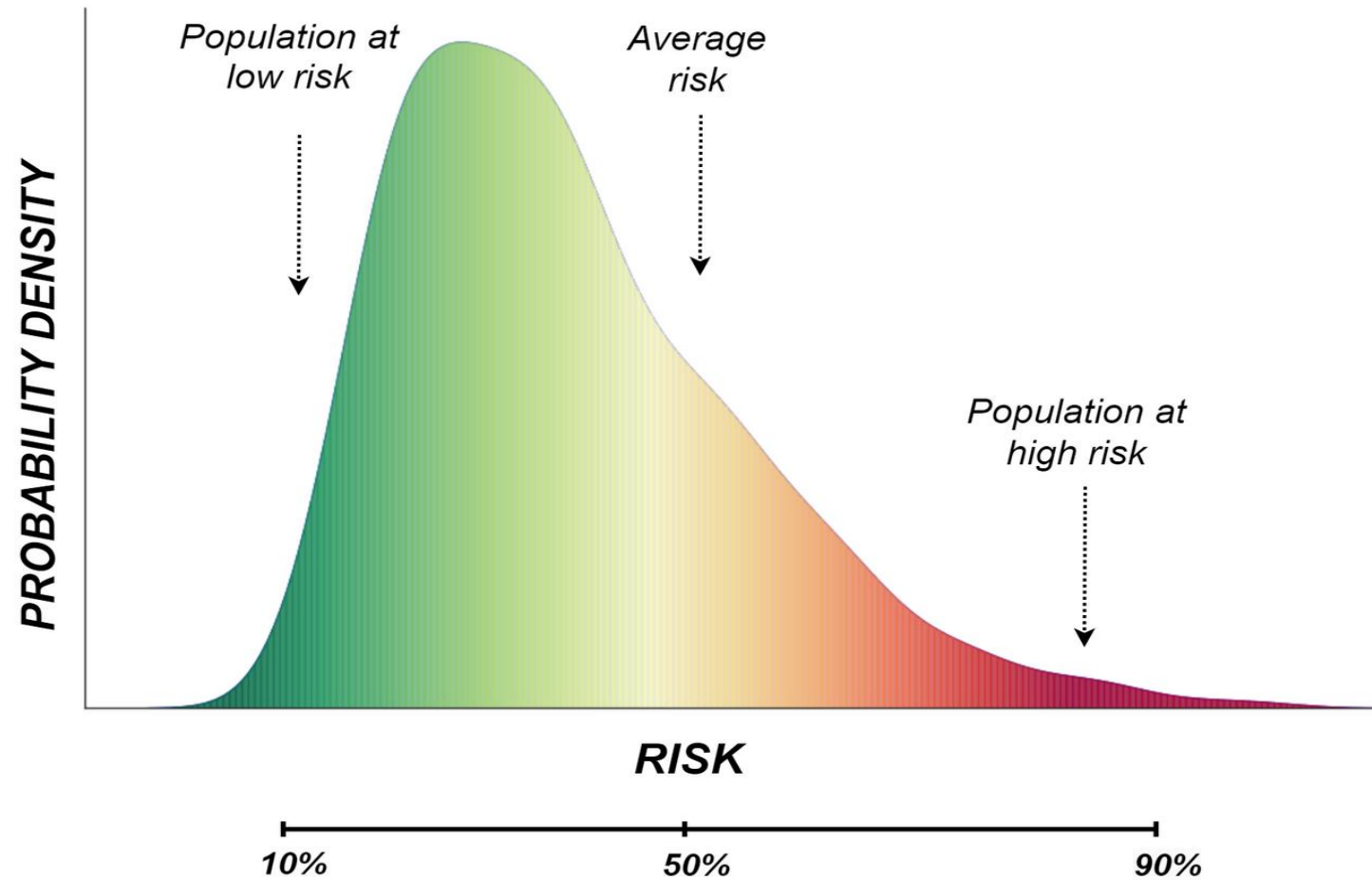
Modernized Threshold of Toxicological Concern (TTC)-based approach

- Scenario with no concern
- Scenario with concern



From thresholds to odds: the role of thresholds of toxicological concern (TTC) in modern risk assessment

Karolina Kopańska^{1,2,**}, Costanza Rovida^{2,3**}, Eric Antignac⁴, Tara Barton-Maclaren⁵, Ian Corgreave⁶, Sylvia E. Escher⁷, Matthias Herzler⁸, Heli M. Hollnagel⁹, Eliška Kuchovská¹⁰, Alexandra Maertens¹¹, Julia M. Malinowska¹², Grace Patlewicz¹³, Tomasz Sobański¹⁴, Thomas Hartung^{1,2,11,15,16***}





Main NGRA-related challenges (I)

Substance

Cyproconazole — 2-(4-chlorophenyl)-3-cyclopropyl-1-(1,2,4-triazol-1-yl)butan-2-ol | **CAS 94361-06-5** | MW 291.77 Da | C₁₅H₁₈ClN₃O

A 1,2,4-triazole systemic fungicide. Not approved in the EU (Reg. 1107/2009) and withdrawn in GB.

Classified as a **Highly Hazardous Pesticide** (HHP Types I and II) by FAO/WHO and PAN criteria.

Regulatory Classifications (Revision 2 — Gaps Closed)

Authority	Classification	Source
CLP (2013)	H301 + H373 (STOT RE 2, liver) + H360D (Repr. 1B) + H400 + H410	PPDB (A5)
US EPA (1992)	Group B2 — Probable human carcinogen	OEHHA CIC 2011
WHO	Class II — Moderately hazardous	PPDB
HHP Type I (FAO/WHO)	Yes — Criterion C4 (Reproductive tox 1A/1B = H360)	PPDB (Doc 02)
HHP Type II (PAN)	Yes — R04 (Reproductive tox 1A/1B), R05 (Confirmed ED per WHO)	PPDB (Doc 02)

Regulatory Reference Doses (Revision 2 — Gap Closed)

Parameter	Value (mg/kg bwd)	Quality	Source
ADI (Acceptable Daily Intake)	0.02	A5	PPDB
ARfD (Acute Reference Dose)	0.02	A5	PPDB
AOEL (Acceptable Operator Exposure Level)	0.02	A5	PPDB
AAOEL (Acute AOEL)	—	—	PPDB

1. Key Physicochemical Properties				2. Environmental Fate (Modelled/Experimental)				3. Toxicokinetics (Summary)				4. Toxicity Data (Experimental)										
Property	Value	Unit	Source	Endpoint	Value	Unit	Source	Parameter	Value	Unit	Source	4.1 Acute Toxicity				4.2 Repeated Dose / Chronic Toxicity						
Molecular weight	291.77	g/mol	Doc 01	DT ₅₀ soil (aerobic)	110	days	Doc 02	Oral absorption	≥ 70	%	Doc 03/04	Endpoint (Species)	Value	Unit	Source	Study	Species	Dur.	NOAEL	LOAEL	Unit	Source
Log K _{ow} (exp.)	2.90	(—)	Doc 01, Ref 3	DT ₅₀ soil (anaerobic)	422	days	Doc 02	Dermal absorption	5–20	%	Doc 03/04	LD ₅₀ Oral (Rat)	1095	mg/kg	Doc 09, 10	90-day	Rat	90 d	2.2	6.4	mg/kg/d	Doc 12
Water solubility (20 °C)	126 (± 140)	mg/L	Doc 01, Ref 3/23	DT ₅₀ water (hydrolysis)	Stable	(—)	Doc 02	Oral bioavailability	80–90	%	Doc 03/04	LD ₅₀ Dermal (Rat)	>2000	mg/kg	Doc 12	90-day	Mouse	90 d	1.4	4.2	mg/kg/d	Doc 12
Vapor pressure (25 °C)	2.59 × 10 ^{−7}	mmHg	Doc 01	DT ₅₀ sediment	> 365	days	PPDB	Plasma protein binding	80–90	%	Doc 03/04	LD ₅₀ Inhalation (Rat, 4 h)	>5.85	mg/L	Doc 10	90-day (dermal)	Rat	90 d	>50	—	mg/kg/d	Doc 13
Melting point	107.5	°C	Doc 01	K _{oc} (exp.)	364	mL/g	PPDB A5	BBB penetration	Probable	(—)	Doc 03	LD ₅₀ Oral (Mouse)	942	mg/kg	Doc 09	1-year	Dog	1 y	0.5	1.5	mg/kg/d	Doc 14
Boiling point (pred.)	>250 (exp.)	°C	Doc 02	BCF (fish)	15–59X	(—)	EPA EFED	Metabolism (rat)	Extensive	(—)	Doc 04	LD ₅₀ Dermal (Mouse)	>2000	mg/kg	Doc 09	2-year	Rat	2 y	0.25	1.0	mg/kg/d	Doc 14
Henry's Law constant	7.1 × 10 ^{−10}	atm·m ³ /mol	Doc 02	BAF (exp.)	11–13	L/kg	Doc 02	Elimination t _{1/2} (rat)	1.21 (n=36)	h	Doc 03	LD ₅₀ Inhalation (Mouse, 4 h)	>5.85	mg/L	Doc 09	18-month (onc)	Mouse	18 m	0.1	0.3	mg/kg/d	Doc 15
pK _a (triazole N)	2.9	(—)	PPDB A5	K _{foc}	3.04	(—)	Doc 02	Primary route	Feces (65–80%)	(—)	Doc 03	LC ₅₀ Fish (96 h)	0.23	mg/L	Doc 10	Carcinogenicity (rat)		2 y	Negative	—	—	Doc 15
Dissociation constant (pH 7)	No dissociation	(—)	Doc 02	GUS leach. index	3.04	(—)	Doc 02	Renal excretion	16–33	%	Doc 03	EC ₅₀ Daphnia magna (48 h)	0.026	mg/L	Doc 10	Reproductive tox (2-gen) Rat	2 gen	0.22	0.7	mg/kg/d	Doc 16	
Density (20 °C)	1.26 (g/mL)	g/mL	Doc 02	Level III fugacity (air)	Low	(—)	PPDB					EC ₅₀ Algae (72 h)	0.028	mg/L	Doc 10	Developmental tox (rat) Rat	GD 6-15	0.2	0.6	mg/kg/d	Doc 17	
Octanol/water K _d (pred.)	125	L/kg	EPI Suite 4.11									LD ₅₀ Honeybee (contact 48 h)	>100	µg/bee	PPDB A5	Neurotoxicity (DNT)	90 d	—	—	—	Doc 18	
UV-Vis λ _{max} (MeOH)	295–297	nm	PPDB A5																			

5. Mechanistic / Mode of Action (Key Endpoints)			6. Key Gaps / Uncertainties			7. Summary Benchmarks (Regulatory Context)					8. Consolidated Hazard Profile (Top Findings)		
Endpoint	Finding	Evidence	Area	Description	Impact	Benchmark	Value	Unit	Basis	Source	Endpoint	Classification / Outcome	Confidence
Aromatase (CYP19) inhibition	Yes — decreased estrogen production	In vitro, rat	Acute inhalation LC ₅₀	Only limit test available	Moderate	ADI	0.02	mg/kg bw/day	NOAEL 2.2 mg/kg/day / 100 (rat, 90-d)	PPDB	Acute oral toxicity	GHS Cat. 3 (H301)	Very High
ER binding	Antagonist	In vitro	Aquatic chronic NOEC	Limited species coverage	Moderate	ARfD	0.02	mg/kg bw	NOAEL 2.2 mg/kg / 100	PPDB	Genotoxicity	Negative (in vitro caveat)	Very High
AR binding	Antagonist	In vitro	ED (endocrine disruption)	MOA data supportive but not conclusive	High	AOEL	0.02	mg/kg bw/day	Same as ADI	PPDB	Carcinogenicity	EPA Group B2 (probable) / CLP Cat. 2	Very High
Oxidative stress	Increased ROS in vitro	Cell-based	Immunotoxicity	No data	Moderate	ORfA	0.012	(mg/kg/day) ⁻¹	Q1*TR = 2.4 (upper bound)	EPA (Rereg)	Reproductive toxicity	Repr. 2 (H361f)	High
Genotoxicity (Ames)	Negative	Bacterial reverse mutation	Mixture effects	Not evaluated	Low	Margin of Exposure (MOE)	250	(—)	BMDL10 (liver) 5 mg/kg/day / ADI 0.02	Internal calc	Endocrine disruption	Confirmed ED (per WHO/PPDB)	Very High
Chromosomal aberration	Positive (EPA)	In vitro (CHO)									Aquatic toxicity (acute)	Cat. 1 (H400)	Very High
Micronucleus	Negative	In vivo (rat BM)									Aquatic toxicity (chronic)	Cat. 1 (H410)	Very High
											Persistence	Very Persistent	Very High
											Bioaccumulation	Low (BCF 15–59X)	High
											Neurotoxicity	Possible class concern	Medium



ONTOX Probabilistic Risk Assessment (OPRA): An AI-enabled framework

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Propylparaben (CAS 94-13-3): Toxicological Risk Assessment



CONTENTS

- ✓ 1. Substance ID
- ✓ 2. Metabolites
- ✓ 3. Chemical Transform...
- ✓ 4. Toxicokinetics (AD...
- 5. Environmental Fate
- 6. Acute Toxicity
- 7. Repeat-Dose Tox
- 8. Genotoxicity
- 9. Carcinogenicity
- 10. Reproductive Tox
- 11. Developmental Tox



Automated Assessments

REACH dossiers, chemical risk assessments, OEL/HBEL reports, ingredient safety reviews. Provide a substance and get an assessment with an audit trail you can hand to a regulator.



Conversational AI

Ask a question in plain language, get a cited answer. The AI has access to the full dataset and model library, so you can explore data, run predictions, or kick off assessments without leaving the chat.



Knowledge Graph

Hundreds of curated datasets linking chemicals to their hazards, classifications, and study results



Literature

Full-text search across 4M+ regulatory documents from EPA, ECHA, WHO, and 50+ other sources



Predictive Models

ToxTransformer, QSAR Toolbox, and hundreds of other models covering 4,000+ endpoints

2000 Databases

100 bln Data Points

90 mln Regulatory Documents

127 Computational Tools



Conversational AI

New conversation

d53173d6

Try one of these to get started

 Build a comprehensive report on the endocrine disruption potential of Bisphenol A

 Screen triclosan for mutagenicity, hepatotoxicity, and endocrine disruption — should it still be in consumer products?

 Evaluate the carcinogenic potential of glyphosate — where does the evidence actually land?

↓ Resume auto-scroll

Problem formulation: What is the health risk(s) for cyproconazole resulting from chronic oral exposure via food and drinking water for the European adult healthy population, with focus on systemic health effects.

 Claude Opus 4.6  Deep

 send  newline 

New conversation

d53173d6

TB

TJ Bozada 03:04 PM

Problem formulation: What is the health risk(s) for cyproconazole resulting from chronic oral exposure via food and drinking water for the European adult healthy population, with focus on systemic health effects.



Sagent claude-opus-4.6 · deep ● working

 Plan published 1 / 6 done · see Plan panel

 Assessment · **Identify Chemical** query=cyproconazole 6s >

 Tox Data · **Phys-Chem** q=cyproconazole 12s >

 Tox Data · **Repeat Dose** q=cyproconazole 1s >

 Tox Data · **Carcinogenicity** q=cyproconazole 1s >

 Tox Data · **Genotoxicity** q=cyproconazole 1s >

 Tox Data · **Dev/Repro Tox** q=cyproconazole 1s >

 Tox Data · **Acute Toxicity** q=cyproconazole 1s >

 Tox Data · **Regulatory Lists** q=cyproconazole 1s >

 Tox Data · **Endocrine** q=cyproconazole 1s >

 Crawler · **Search Documents** q=cyproconazole ADI acceptable daily intake EFSA peer review limit=5 1s >

 Crawler · **Search Documents** q=cyproconazole chronic dietary exposure assessment European population 1s >

 Crawler · **Search Documents** q=cyproconazole drinking water guideline value EU chronic toxicity 1s >

 Assessment · **Exposure Data** smiles=CC(C1CC1)C(CN2C=NC=N2)(C3=CC=C(C=C3)Cl)0 name=Cyproconazole <1s >

 Assessment · **Hazard Summary** smiles=CC(C1CC1)C(CN2C=NC=N2)(C3=CC=C(C=C3)Cl)0 name=Cyproconazole 1s >

 Thinking...

☐ Cancel esc to stop

↓ Resume auto-scroll

Queue a follow-up...

 Claude Opus 4.6  Deep

 send  newline ☐ Cancel



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1 Choose workflow

2 Configure & launch

X Cancel

Q Search workflows...

ICH M7 Mutagenic Impurities Assessment

ICH M7 compliant assessment for mutagenic impurities in pharmaceuticals. Evaluates structural alerts, Ames mutagenicity, and determines acceptable limits based...

1

Risk Assessment (Full CSR)

End-to-end Chemical Safety Report pipeline (63 stages, v2). Discovery + parallel evidence gathering across YARD, BioBricke-KG, ToxCast/ToxJobs,...

63

IUCLID Dossier Preparation

Generate REACH registration dossier content mapped to IUCLID sections 1-7. Covers substance identification, physicochemical properties, environmental fate,...

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ONTOX Probabilistic Risk Assessment (OPRA)

Probabilistic NGRA framework developed within the ONTOX project; currently under implementation.

Working on it!



Monte Carlo simulation is a useful method for estimation when it is difficult to obtain an analytical solution (Vose, 1996). To estimate the expected value of the quantity of interest, let $\theta_1, \dots, \theta_M$ be random samples drawn from the posterior distribution $f(\theta | \mathbf{x}, t_0)$. For each $j \in \{1, \dots, M\}$, let $x_{n+1}^j, \dots, x_{n+N}^j$ be random samples drawn from the assessment variable conditional on θ_j . Then, $\hat{h}(\theta_j)$ is a Monte Carlo estimate for $h(\theta_j)$:

$$h(\theta_j) \approx \hat{h}(\theta_j) := \frac{1}{N} \sum_{i=1}^N \mathbf{1}_{\{g(x_{n+i}^j) \geq g^*\}}. \quad (6)$$

Thus, sample j of the quantity of interest $\hat{h}(\theta_j)$ is not directly computed from θ_j , but from the samples $x_{n+1}^j, \dots, x_{n+N}^j$.

The posterior expected value of the frequency of exceeding a threshold can be estimated by

$$E(h(\Theta) | \mathbf{x}, t_0) \approx \frac{1}{M} \sum_{j=1}^M \hat{h}(\theta_j). \quad (7)$$

Extension to more than two evidence sources is straightforward. For example, the ground probability masses needed for combination of three DST structures are

$$q(f_k) = \sum_i \sum_j \sum_l m_1(f_i) m_2(f_j) m_3(f_l) \text{ for any } f_k \neq \emptyset \quad (40)$$

$$q(Y) = m_1(Y) m_2(Y) m_3(Y) \quad (41)$$

$$q(\emptyset) = \sum_i \sum_j \sum_l m_1(f_i) m_2(f_j) m_3(f_l) \text{ for } f_i \cap f_j \cap f_l = \emptyset \quad (42)$$

Dempster's combination rule

In the original DST combination rule proposed by Dempster, the joint basic probability mass m_D associated with each joint focal element f_k is obtained by

$$m_D(f_k) = \frac{q(f_k)}{1 - q(\emptyset)} \text{ for all } f_k \neq \emptyset \quad (43)$$

$$m_D(\emptyset) = 0 \quad (44)$$

Eq. (43) also applies to the universal set, so

$$m_D(Y) = \frac{q(Y)}{1 - q(\emptyset)} \quad (45)$$

Error propagation through ensembles is also useful to estimate errors on derivatives of the model target with respect to a continuous parameter λ that characterizes the samples—e.g. forces acting on atoms, that are derivatives of the potential with respect to atomic coordinates. Defining derivative errors based on a direct variance estimator is not trivial [32], whereas a calibrated ensemble allows to do so straightforwardly, as we shall discuss later

$$\begin{aligned} \bar{y}'(A) &= \frac{1}{n_{\text{ens}}} \sum_{k=1}^{n_{\text{ens}}} \frac{\partial y^{(k)}(A)}{\partial \lambda} \\ \sigma_{y'}^2(A) &= \frac{1}{n_{\text{ens}} - 1} \sum_{k=1}^{n_{\text{ens}}} \left[\frac{\partial y^{(k)}(A)}{\partial \lambda} - \bar{y}'(A) \right]^2. \end{aligned} \quad (13)$$

In standard Bayesian analysis, the posterior probability for this event can be written as the integral of the quantity of interest for a given value of the parameter θ , times the posterior distribution of θ :

$$P(g(X_{n+1}) > g^* | \mathbf{x}, t_0) = \int P(g(X_{n+1}) \geq g^* | \theta) f(\theta | \mathbf{x}, t_0) d\theta. \quad (3)$$

If we define the quantity of interest as a function of assessment parameters θ :

$$h(\theta) := P(g(X_{n+1}) \geq g^* | \theta), \quad (4)$$

and Θ the random variable corresponding to uncertainty in the parameter θ , Equation (3) can be written as:

$$\int h(\theta) f(\theta | \mathbf{x}, t_0) d\theta = E(h(\Theta) | \mathbf{x}, t_0). \quad (5)$$

With the MVE approach, the prediction of a model is not a definite number but a random variable. Given a model with weights θ and input x , the conditional expectation and variance of the prediction $\hat{y}$ are:

$$E[\hat{y} | \theta, x] = \mu(\theta, x) \quad (8)$$

$$\text{var}(\hat{y} | \theta, x) = v(\theta, x) \quad (9)$$

where $\mu(\cdot)$ and $v(\cdot)$ are two deterministic functions. Under the Bayesian perspective, the weights of a trained model are also random variables following posterior distribution $p(\theta | \mathcal{D}^A)$:

$$p(\theta | \mathcal{D}^A) = \frac{p(\theta) p(\mathcal{D}^A | \theta)}{\int p(\theta) p(\mathcal{D}^A | \theta) d\theta} \quad (10)$$

where $p(\theta)$ is the prior and $p(\mathcal{D}^A | \theta)$ is the likelihood. Combining Eqs. 8–10, the posterior distribution of the prediction is:

$$p(\hat{y} | x, \mathcal{D}^A) = \int p(\hat{y} | \theta, x) p(\theta | \mathcal{D}^A) d\theta \quad (11)$$

whose expectation and variance are:

$$E[\hat{y} | x, \mathcal{D}^A] = E[\mu(\theta, x)], \theta \sim p(\theta | \mathcal{D}^A) \quad (12)$$

$$\text{var}(\hat{y} | x, \mathcal{D}^A) = E[v(\theta, x)] + \text{var}(\mu(\theta, x)), \theta \sim p(\theta | \mathcal{D}^A) \quad (13)$$

Due to conjugacy, the posterior distribution for these parameters is also a normal-gamma distribution with hyperparameters $\alpha_k^A, \beta_k^A, \gamma_k^A$, and δ_k^A :

$$\tau_k^A | \mathbf{a}_k \sim \text{Gamma}(\alpha_k^A, \beta_k^A), \quad (22)$$

$$\mu_k^A | \tau_k^A, \mathbf{a}_k \sim \mathcal{N}(\gamma_k^A, \delta_k^A \tau_k^A), \quad (23)$$

force errors can be readily computed based on the derivatives of the committee members

$$\begin{aligned} \bar{f}_{i\alpha}(A) &= \frac{\partial \bar{V}(A)}{\partial r_{i\alpha}} = \frac{1}{n_{\text{ens}}} \sum_k \frac{\partial V^{(k)}(A)}{\partial r_{i\alpha}} \\ \sigma_{f_{i\alpha}}^2(A) &= \frac{1}{n_{\text{ens}} - 1} \sum_k \left[\frac{\partial V^{(k)}(A)}{\partial r_{i\alpha}} - \bar{f}_{i\alpha}(A) \right]^2. \end{aligned} \quad (16)$$



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Theory (understand frameworks)

Practice (find and pool tools)

nonconformist 2.1.0 documentation

This website contains the API documentation for the nonconformist Python package, generated using Sphinx. For an introduction to the basic usage of nonconformist, please refer to [README.ipynb](https://nonconformist.readme.io/).

Source is available on [GitHub](https://github.com).

TOXTRUST

TOXTRUST is a flexible package allowing for a probabilistic evaluation of toxicological evidence as well as for the combination of individual evidence pieces using rigorous rules based on the Dempster-Shafer theory (DST).



Unilever-NGRA-LCL

NGRA Case Study using LCL for population variability

This repository contains the R code used for Alshammari et al. 2026 "Quantitative Estimates of Toxicodynamic Variability for New Approach Methodologies-Based Systemic Safety Toolbox Using a Population-Based Human in Vitro Model". Note that GWAS analysis was not conducted in R so is not included here.

Food for Thought ...

Probabilistic Risk Assessment – The Keystone for the Future of Toxicology

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t4 Workshop Report*

The Probable Future of Toxicology – Probabilistic Risk Assessment

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t4 Workshop Report*

From Cellular Perturbation to Probabilistic Risk Assessments

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Uncertainty assessment of proarrhythmia predictions derived from multi-level in silico models

Karolina Kopańska¹ · Pablo Rodríguez-Belenguer^{1,2} · Jordi Llopis-Lorente³ · Beatriz Trenor³ · Javier Saiz³ · Manuel Pastor¹ 



TOXTRUST: a tool leveraging the Dempster-Shafer Theory for robust integration of NAM results in decision-making considering uncertainty

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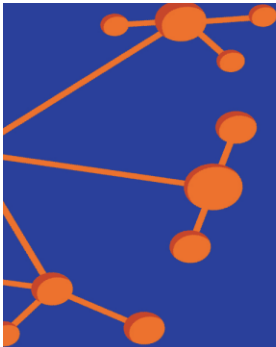


Uncertainty in toxicological assessments in the era of artificial intelligence

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Working Party on Hazard Assessment (WPHA) and WPHA Systemic Toxicity Expert Group



Introducing ONTOX AI-supported Probabilistic Risk Assessment - OPRA

Helena Kandarova
Deputy coordinator for dissemination, exploitation, communication and data management of the
ONTOX project
WG 6 – Risk Assessment and Implementation
WG14 – Communication



Funded by the Horizon 2020
Framework Programme of the
European Union



OECD SYSTOX Expert Group WPHA
June 3, 2026





OECD Working Party on Hazard Assessment (WPHA)

PROJECT PROPOSAL FORM

Project Title

OECD High-Level Guidance for the Integration of Artificial Intelligence in Chemical Safety Assessment

Submitted by:

Date of Submission to the Secretariat:

Details of Lead Country(ies)/Organisation

Country /Organisation:

ITALY, Slovakia

Agency/ministry/Other:

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Other Countries/Organisations Consulted:

Briefly describe if interest of other (non-lead) countries/organisations has been identified

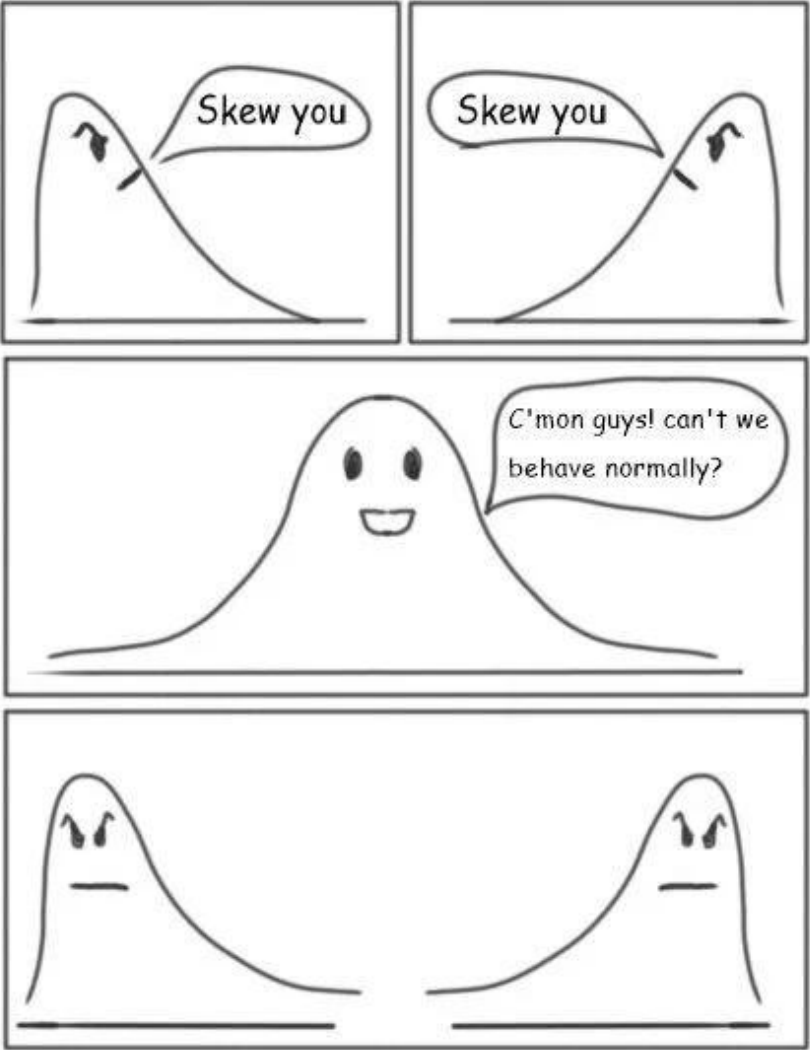
Preliminary discussions with the Netherlands, ECHA, and EFSA. Also potential input and examples from EU-funded research projects including ONTOX and PARC.

The aim of the project is to develop a practical **Framework for Trustworthy AI** to translate general OECD AI Principles into concise, sector-specific guidance.

The proposed high-level guidance will be **aligned**, to the greatest extent possible, with the **evolving requirements of major regulatory authorities**.

This project ensures all AI applications remain "**human-in-the-loop**" where AI acts as a "co-pilot" for expert risk assessors rather than a standalone decision-maker.

Aligned with the EU AI Act
and OECD AI Principles



<https://coolinfographics.com/news/2021/10/4/statistic-joke>

Our **OPRA** team:

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