Key elements for better regulation of chemicals

Maurice Whelan

European Commission, Joint Research Centre (JRC)

BfR "20 year" Symposium,

Nov 2022

The EU's Chemicals Strategy for Sustainability

Ensure most harmful chemicals are not contained in consumer products

Extend Generic Risk Assessment approach

"One substance one assessment"

Common open data platform on chemicals

Address chemical mixtures

Promote safe and sustainable by design

Promote innovative testing and assessment methods

Better assessment of critical effects for more chemicals

Internationally recognised standards and tools

Make better use of 'academic' data in regulatory processes

https://ec.europa.eu/environment/strategy/chemicals-strategy_en

European Environment Agency

~ 100 000 chemicals on the market

~ 22 600 chemicals with a use over 1 tonne per year

~ 4 700 chemicals with a use over 100 tonnes per year prioritised in hazard characterisation and evaluation

RISKS

HAZARDS

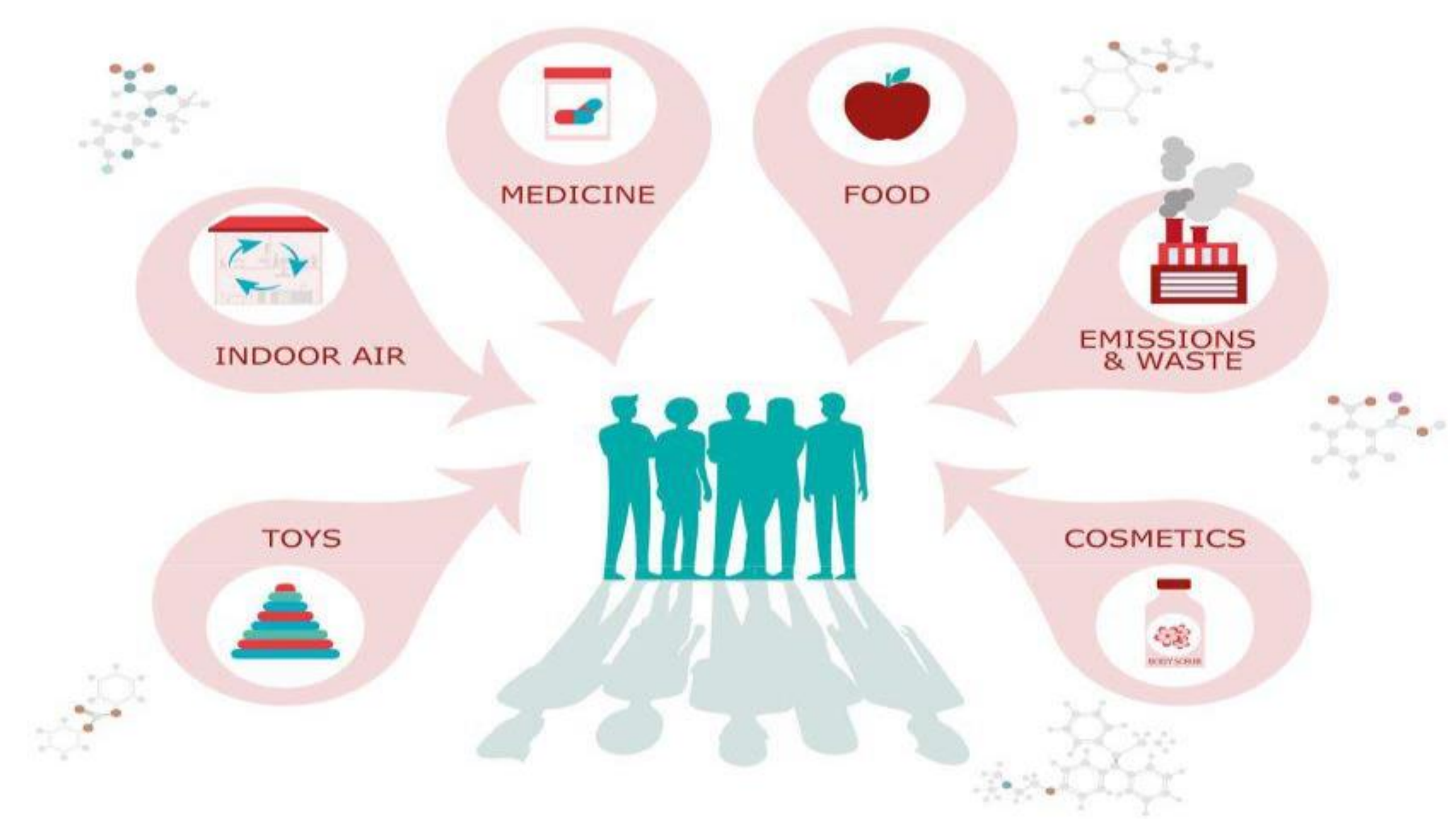
EXPOSURES

~ 500 chemicals
extensively characterised for their hazards and exposures

~ 10 000 chemicals
fairly well characterised for a subset of their hazards and exposures

~ 20 000 chemicals
with limited characterisation for their hazards and exposures

~ 70 000 chemicals
with poor characterisation for their hazards and exposures


MEDICINE
FOOD
INDOOR AIR
EMISSIONS & WASTE
TOYS
COSMETICS

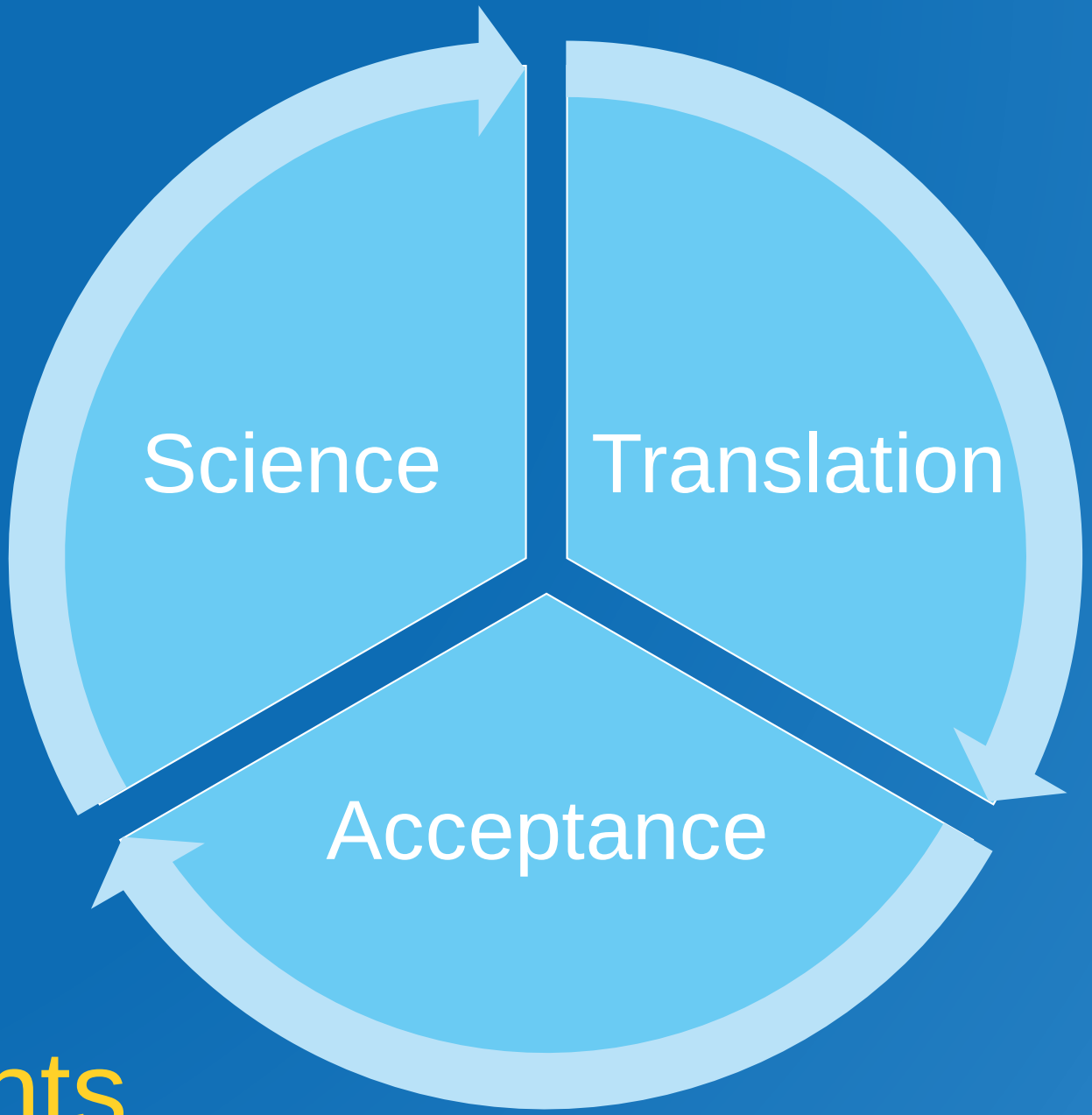
TOXICOLOGY

Can Europe replace animal testing of chemicals?

As revisions to the EU's regulatory system look certain to increase toxicity tests on animals, the region ponders whether it will ever be able to conduct chemical safety assessments with alternative methods

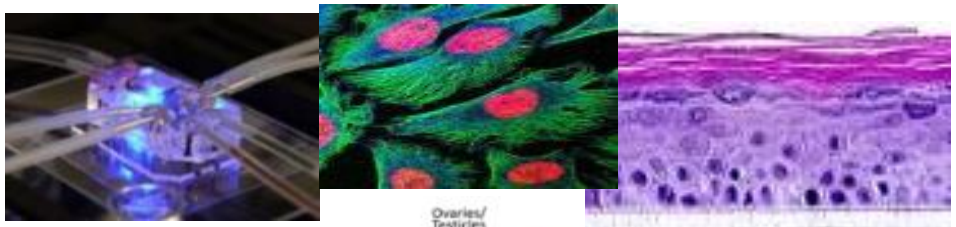
by ***Vanessa Zainzinger, special to C&EN***

August 15, 2022 | A version of this story appeared in **Volume 100, Issue 28**

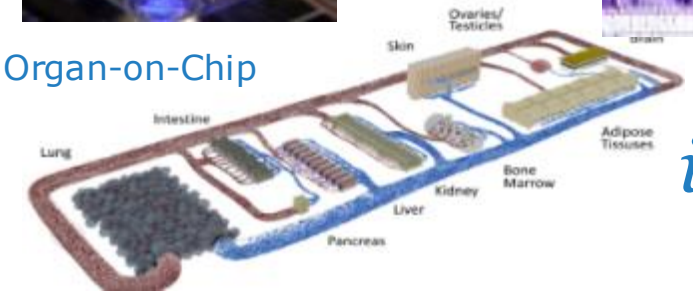


Key elements

Modern safety assessment toolbox

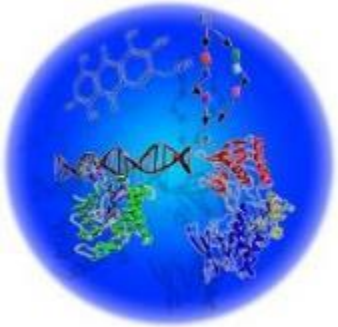


Organ-on-Chip



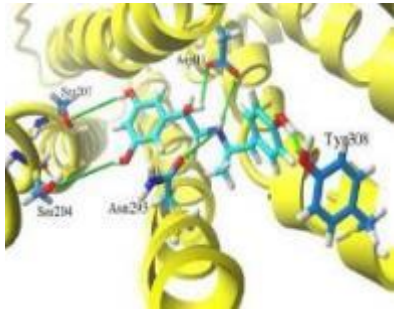
in vitro

QSAR

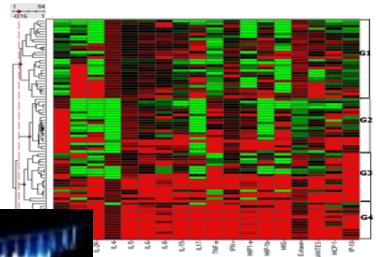


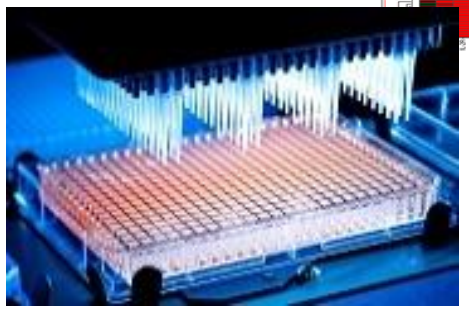
clinical data

docking

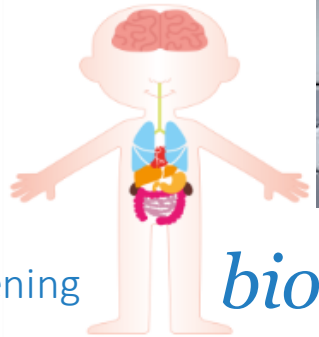


'omics





existing animal data



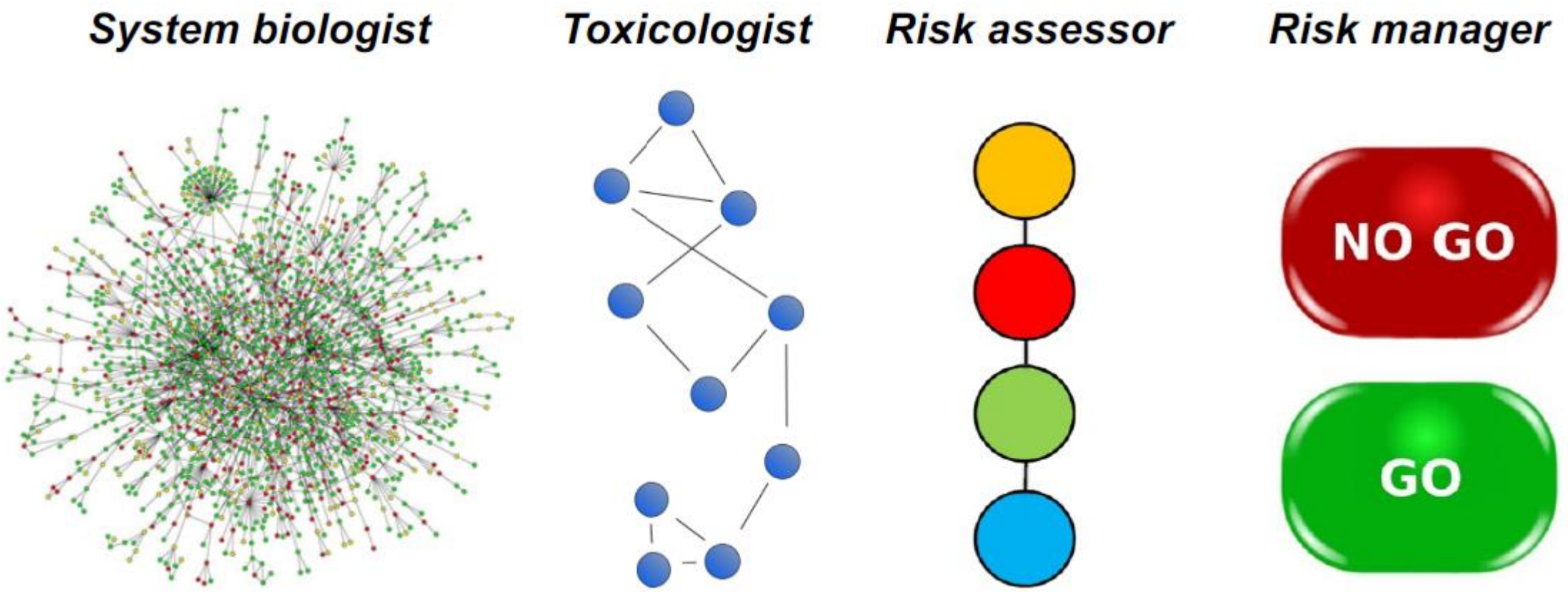
biokinetics

HBM4EU

human biomonitoring

European Commission

Science supporting decisions

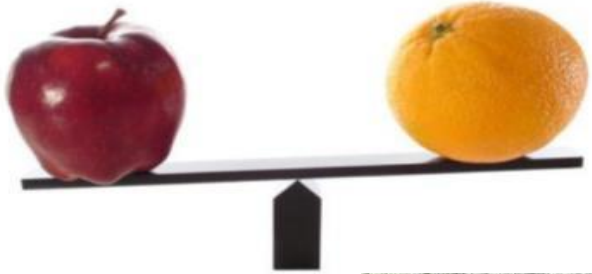


Slide courtesy of Luigi Margiotta-Casaluci

Issues not sufficiently addressed

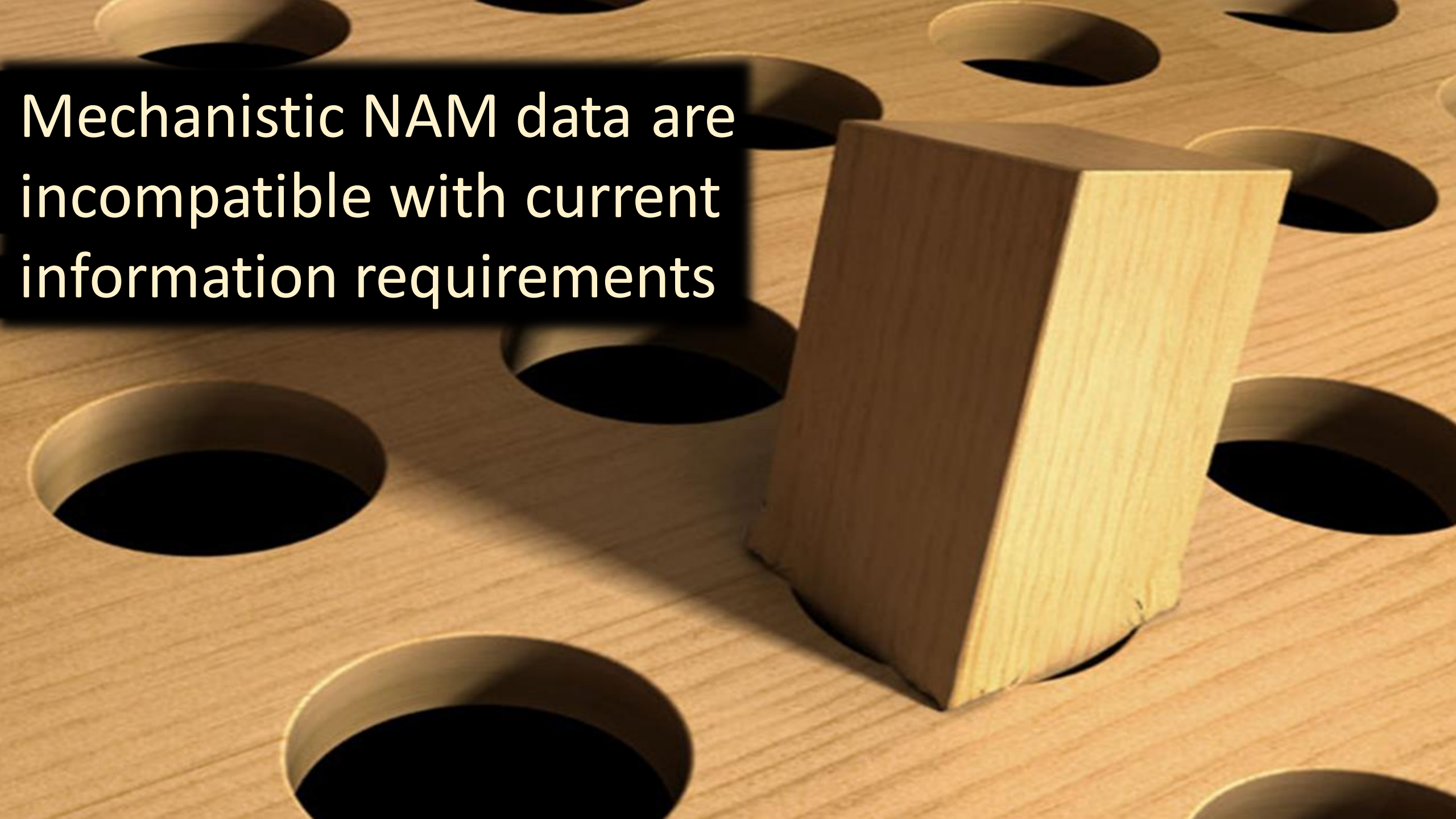
Integration

Benchmarks



Information

European Commission


Mechanistic NAM data are incompatible with current information requirements


Margin
of
Safety

Hazard classification

Generic Risk Assessment

‘One Health …..One Toxicology’

Genomics study finds shared disease pathways for humans and environmental test organisms

NEWS | 29 September 2022

Blurs the line between human toxicology and ecotoxicology

Global | Hazard assessment | Chemical industry | CMRs | Academic studies

Chemicals toxic to humans may be picked up by tests on environmental model species, thanks to shared disease pathways, according to work part-funded by the EU’s PrecisionTox project. The work "blurs the line" between human toxicology and ecotoxicology and paves the way to "species-agnostic" adverse outcome pathways (AOPs), said lead author John Colbourne from the University of Birmingham, UK.

Environmental Advances 9 (2022) 100287

Contents lists available at ScienceDirect

Environmental Advances

journal homepage: www.sciencedirect.com/journal/environmental-advances

Toxicity by descent: A comparative approach for chemical hazard assessment

John K. Colbourne [a,b,*], Joseph R. Shaw [c], Elena Sostare [a], Claudia Rivetti [d], Romain Derelle [b], Rosemary Barnett [a], Bruno Campos [d], Carlie LaLone [e], Mark R. Viant [a,b], Geoff Hodges [d]

PRECISION TOX

Translation

JRC Survey on NAMs*

- Aimed primarily at method users (June ‘21 to March ’22)
- Supporting action to extend REACH info requirements
- Emphasis on regulatory applicability and deployability

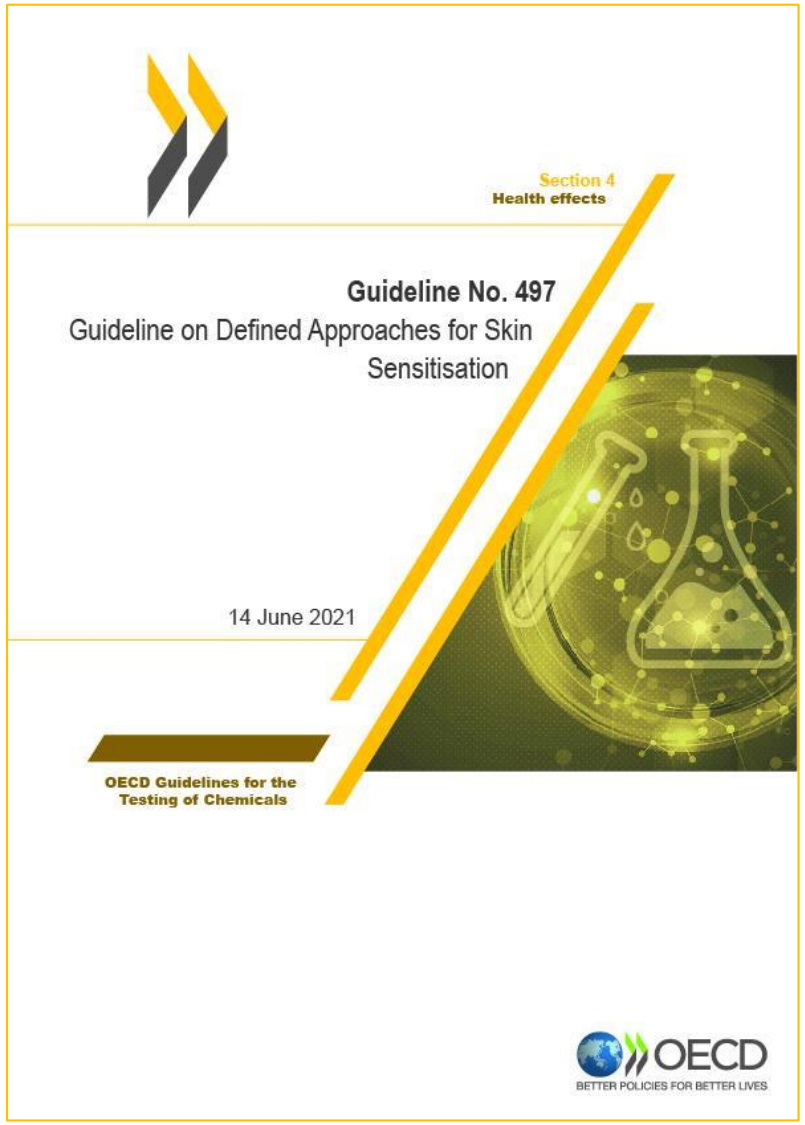
  - **Many methods but few solutions** - impressive range of technologies and tools but without clear purpose
  - **Demonstration rather than validation** - case studies popular for illustrating and communicating concepts
  - **A lot of variety but little standardisation** - multiple ways of generating similar information

*New Approach Methodologies (ECHA 2016)

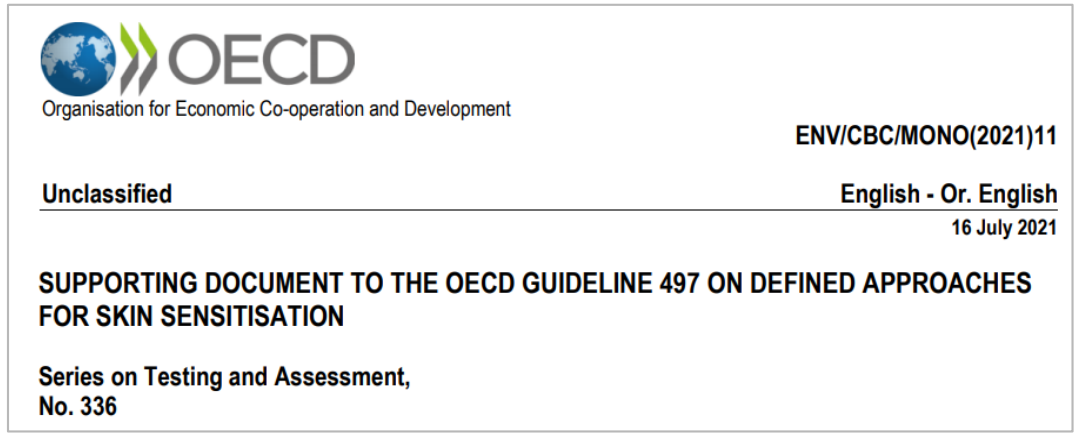
Avenues for uptake of NAM data

International Guidelines	• Mutual Acceptance of Data • Legal certainty & quality assurance • Efficiency and harmonisation
Technical standards	• Multiple uses including validation • Keep pace with NAM development • Important role in innovation
Academic studies	• Bespoke tools and design • Tackle complex problems • Best practices influence quality

OECD Guideline on Defined Approaches



- First OECD Guideline to combine multiple alternative methods in a testing strategy
- First time to include computational methods (structural similarity algorithms) in a Guideline
- DAs for both hazard identification and potency based classification (GHS). The latter also provides a measure of confidence.


OECD
Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2021)11

Unclassified | English - Or. English

16 July 2021

SUPPORTING DOCUMENT TO THE OECD GUIDELINE 497 ON DEFINED APPROACHES FOR SKIN SENSITISATION

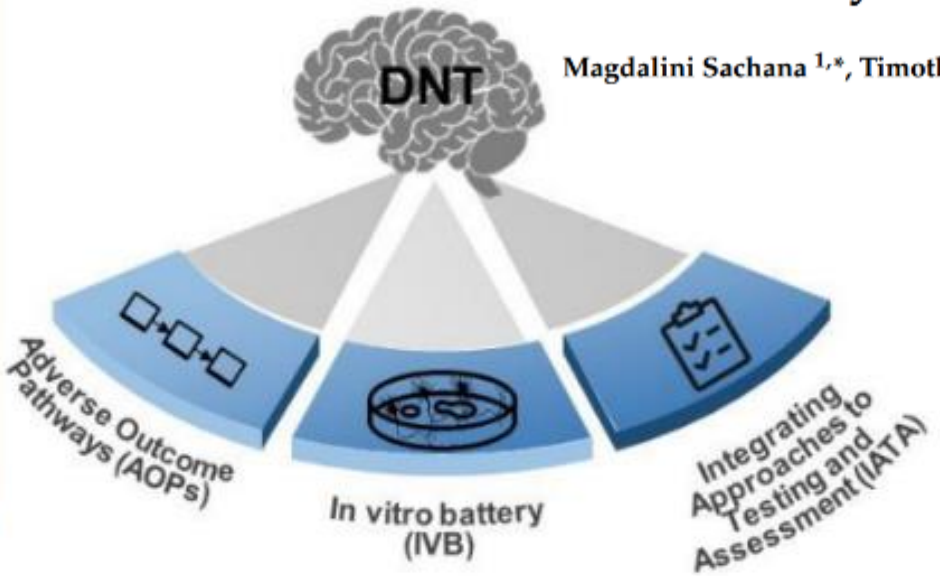
Series on Testing and Assessment, No. 336

European Commission

IATA for Developmental Neurotoxicity (DNT)

Highlights of work

- EFSA/OECD Workshop (Nov 2016)
- Formation of OECD DNT Expert Group (2017)
- Protocol for the implementation and interpretation of DNT in-vitro testing battery (November 2020)
- OECD DNT Guidance (first draft expected mid-2021)



biology

MDPI

Review

Toward a Better Testing Paradigm for Developmental Neurotoxicity: OECD Efforts and Regulatory Considerations

Magdalini Sachana [1,*], Timothy J. Shafer [2] and Andrea Terron [3]

EFSA JOURNAL

Scientific Opinion | Open Access

Development of Integrated Approaches to Testing and Assessment (IATA) case studies on developmental neurotoxicity (DNT) risk assessment

EFSA Panel on Plant Protection Products and their Residues (EFSA PPR Panel), Antonio Hernández-Jerez, Paulien Adriaanse, Annette Aldrich, Philippe Berny, Tamara Coja ... See all authors

First published: 18 June 2021 | https://doi.org/10.2903/j.efsa.2021.6599

Main goals of the OECD DNT project

- Improve DNT testing
- Incorporate mechanistic knowledge
- Provide regulatory relevant examples through case studies
- Accelerate regulatory uptake of the DNT IVB

European Commission

Guideline using ‘omics and machine learning

- Genomic Allergen Rapid Detection (SenzaGen GARD®) methods for **hazard identification and potency classification**
- Cell-based test system combined with **transcriptomics** (~200 genes) and **SVM based algorithm**
- Scientific **peer review by ESAC.** Sets a precedent. Well worth a read!
- OECD resolved **IPR and GLP issues**
- Protocols highly **platform dependant**

European Commission

28-29 April 2021

Organ-on-chip

Putting Science into Standards

EUROoCS
EUROPEAN ORGAN-ON-CHIP SOCIETY

CEN-CENELEC **Focus Group** on Organ on chip

Stem Cell Reports
Meeting Report
ISSCR
OPEN ACCESS

Putting Science into Standards workshop on standards for organ-on-chip

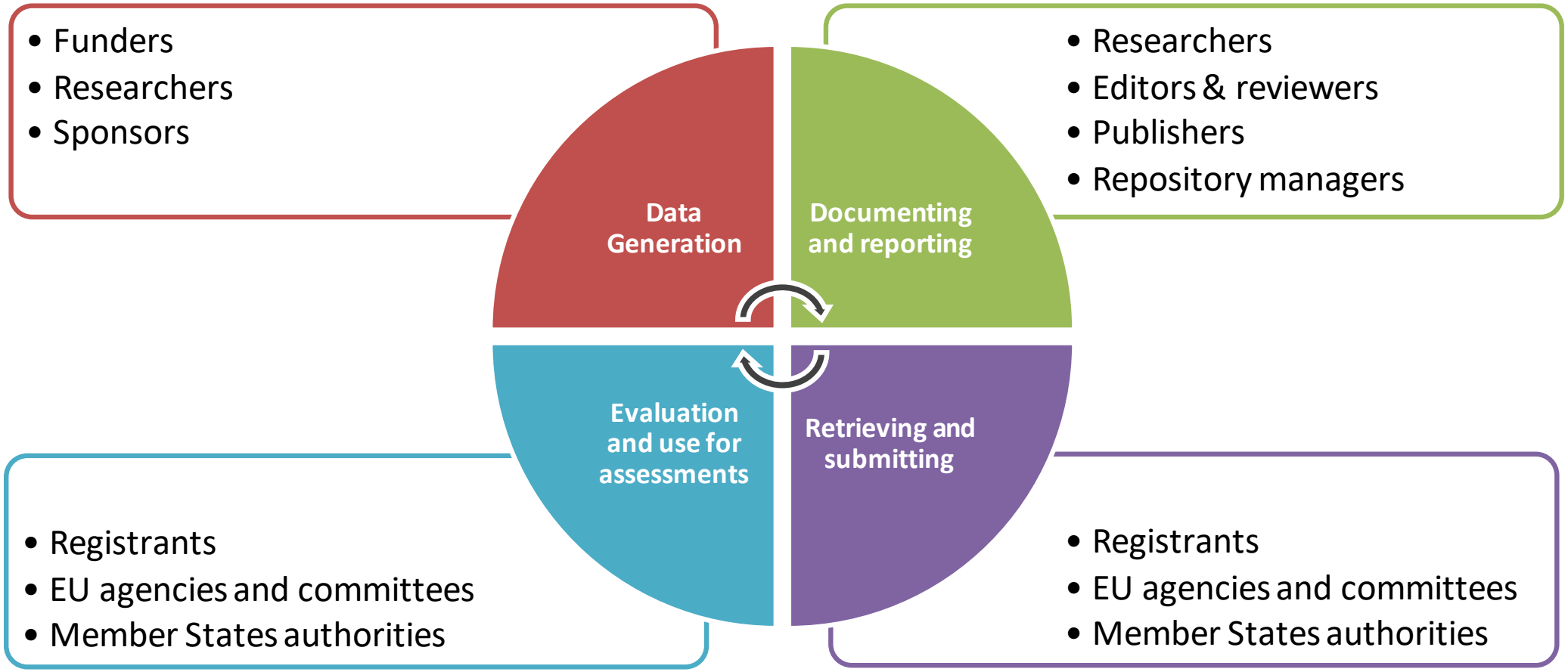
Monica Piergiovanni,[1,*] Ozlem Cangar,[2] Sofia B. Leite,[1] Livia Mian,[3] Andreas Jenet,[4] Raffaella Corvi,[1] Maurice Whelan,[1] Fabio Taucer,[4] and Ashok Ganesh[3]
[1]European Commission, Joint Research Centre (JRC), Ispra, Italy
[2]European Health and Digital Executive Agency (HaDEA), Brussels, Belgium
[3]CEN-CENELEC, Market Perspective and Innovation, Brussels, Belgium
[4]European Commission, Joint Research Centre (JRC), Brussels, Belgium
*Correspondence: monica.piergiovanni@ec.europa.eu
https://doi.org/10.1016/j.stemcr.2021.07.010

The European Commission Joint Research Centre and the European Standardization Organizations CEN and CENELEC organized the "Putting Science into Standards" workshop, focusing on organ-on-chip technologies. The workshop, held online on 28–29 April, 2021, aimed at identifying needs and priorities for standards development and suggesting possible ways forward.

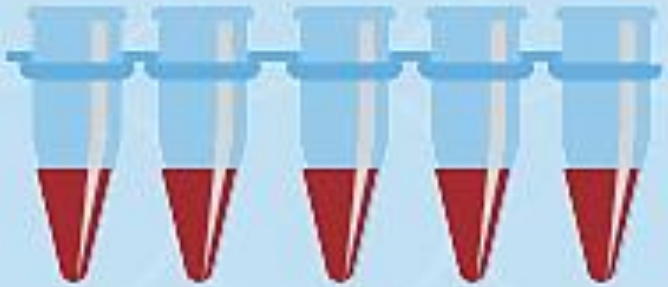
cen CENELEC

European Commission

Better use of academic data



GIVIMP



OECD Guidance Document on Good In Vitro Method Practices

The OECD has published guidance on Good In Vitro Method Practices (GIVIMP) for the development and implementation of in vitro methods for regulatory use in human safety assessement

European Commission

Agenda

Scientific Methods and Protocols:

Roadmap to increase clearness in peer review publications

JRC site

28-29 June 2022

The European Commission's science and knowledge service

Joint Research Centre

Joint Research Centre

European Commission

Agenda

Improving the use of academic data in regulatory assessments

JRC Ispra

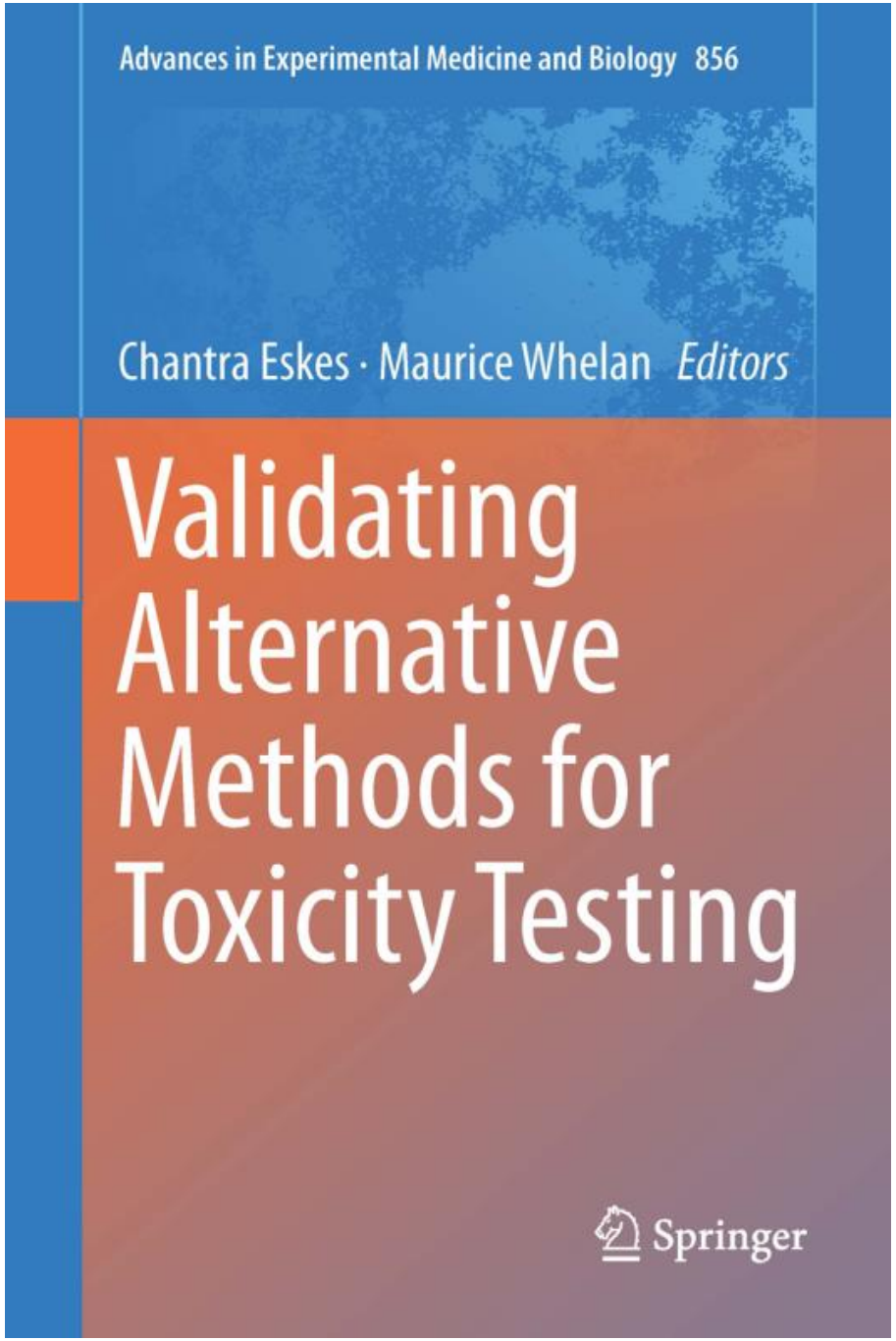
25-26 October 2022

The European Commission's science and knowledge service

Joint Research Centre

Joint Research Centre

Acceptance



This book provides information on **best practices and new thinking** regarding the validation of alternative methods for toxicity testing. It covers the validation of **experimental and computational methods** and **integrated approaches to testing and assessment**. Validation strategies are discussed for **methods employing the latest technologies** such as organ-on-chip systems, stem cells and transcriptomics, and for methods derived from **pathway-based concepts** in toxicology

European Commission

Principles/criteria of different validation frameworks employed within toxicology community

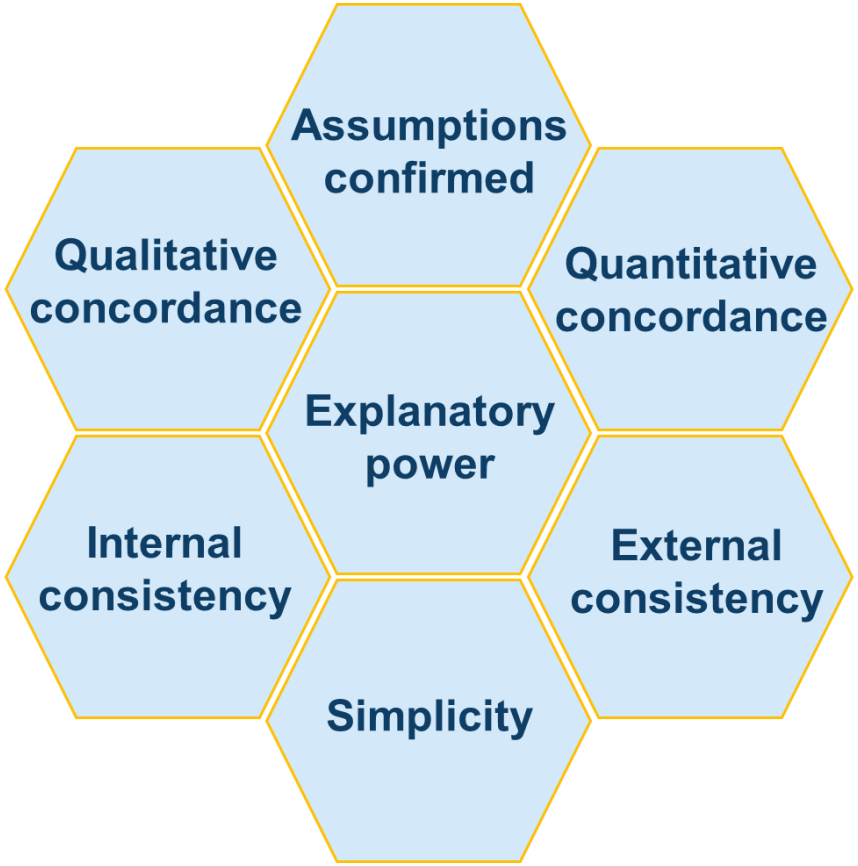
Minimum criteria for a valid test	ECVAM principles on test validity	QSAR validation principles	Defined Approaches	In vitro Developmental Neurotoxicity methods	Physiologically based kinetic models
OECD, 2005 [4]	Hartung et al, 2004 [5]	OECD, 2007 [6]	OECD 2016, 2017 [8,14,20]	Bal-Price et al, 2018 [22]	OECD Guidance Document
Rationale available for scientific need and regulatory purpose **Relevance**: relationship of test endpoint to in vivo biological effect **Protocol available**: subjected to independent peer-review **Repeatability and reproducibility shown**: intra-test, intra and inter-lab variability defined **Reference performance demonstrated** using reference chemicals **Toxicity performance** evaluated against existing relevant toxicity data **Validation available**: all data supporting assessment of validity available for review **Good Laboratory Practice** used to obtain data	**Test method definition**: endpoint, training set, prediction model (PM), applicability and mechanism **Within-laboratory variability:** assessment of reproducibility of data **Transferability**: confirmation by second operator (facility) **Between-laboratory variability**: assessment of reproducibility in 2 to 4 laboratories **Predictive capacity**: ability to predict beyond training set based on comparisons **Applicability domain**: definition of chemical classes and/or ranges for which predictions are reliable **Performance standards**: reference chemicals defined for equivalence between original and new (similar) tests	**A defined endpoint:** transparency of effect being predicted **An unambiguous algorithm:** transparency of description of an unambiguous model **A defined applicability domain:** recognising QSARs are reductionist and inevitably limited to subsets of chemical space **Appropriate measures of goodness-of-fit, robustness & predictivity:** performance when using training set or test set **A mechanistic interpretation:** an assessment of mechanistic associations between descriptors and end-points	**Structure:** elements of defined approach, information provided: **Relevance:** mechanistic basis **Predictive Capacity:** performance compared to reference data **Reliability:** reproducibility **Applicability domain:** technical limitations and chemical space **Complexity** of the Data Interpretation Procedure **Transparency:** availability of elements	**Test system:** definition, stability and biological relevance of cell-based system **Exposure scheme:** details of chemical treatment and incubation conditions **Documentation / SOP:** transparency in method protocol **Endpoint(s):** transparency of effect(s) being measured **Test method controls:** chemicals used to determine whether effects are positive or negative, and endpoint-specific **Data evaluation:** statistical analysis of concentration–response data **Testing strategy:** role in test battery **Robustness:** reproducibility within and between labs and over time **Test benchmarks:** sensitivity and specificity, data acceptance criteria **Prediction model:** how to extrapolate the in vitro data **Applicability domain:** chemistry and biological pathways **Screening hits:** definition of positive vs negative response	**Biological basis:** physiologically relevant model structure and parameters **Theoretical basis of model equations:** established mathematical basis such as Michaelis-Menten kinetics **Reliability of input parameters:** reproducibility **Sensitivity of output to input parameters:** relative importance of input parameters in determining simulation outcome **Goodness-of-fit and predictivity:** performance when using training set or test set

E.A. Patterson, M.P. Whelan, A.P. Worth (2021) The role of validation in establishing the scientific credibility of predictive toxicology approaches intended for regulatory application, *Comp. Tox*, 17, 100144.

Scientific credibility and validation

Scientific Credibility* is the **willingness of others to use the method/data to inform their decisions**.

Requires a process of **social epistemology** to develop a ***shared knowledge and understanding*** between developers, users, and decision-makers.



7 Credibility Factors

*LW Schruben, *Simulation*, 34:101-105, 1980

European Commission

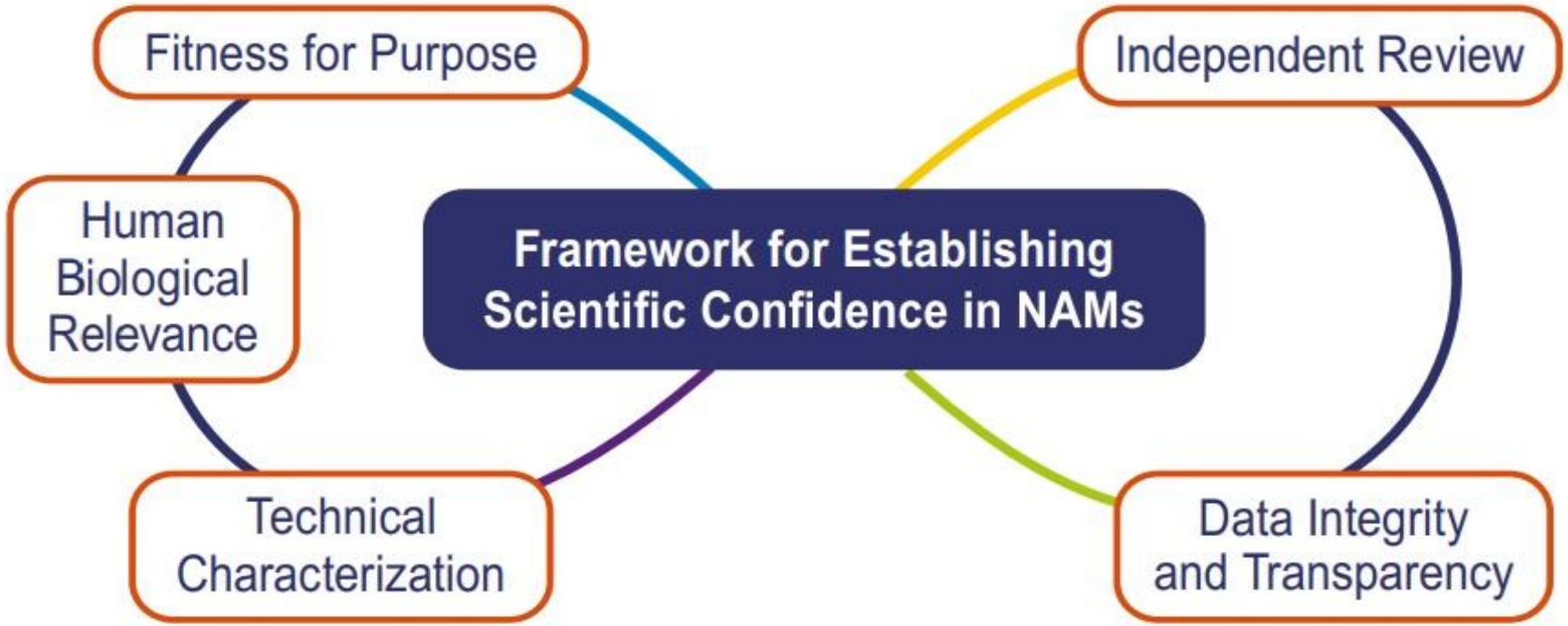
Archives of Toxicology
https://doi.org/10.1007/s00204-022-03365-4

August 2022

REVIEW ARTICLE

A framework for establishing scientific confidence in new approach methodologies

Anna J. van der Zalm[1] · João Barroso[2] · Patience Browne[3] · Warren Casey[4] · John Gordon[5] · Tala R. Henry[6] · Nicole C. Kleinstreuer[7] · Anna B. Lowit[6] · Monique Perron[8] · Amy J. Clippinger[1]



ADDRESSING EVIDENCE NEEDS IN CHEMICALS POLICY AND REGULATION

JRC Science for Policy Report (Feb 2022)

https://publications.jrc.ec.europa.eu/repository/handle/JRC126724

European Commission

Current challenges in regulation of chemicals

- the science directly informing policy and regulatory decision-making often lags behind current science;
- there is a lack of consensus on different methods and approaches in toxicological sciences, exacerbated by difficulty of access to large quantities of dispersed and non-standard data;
- there is mistrust among stakeholders in different sectors;
- there is not a shared understanding of how data is constituted as evidence for regulatory decisions, or for current and future policy regarding chemicals;
- in view of the likely increasingly contentious nature of chemicals and other potential stressors, transparency of the decision-making process in regulation and policy, for all stakeholders, becomes an ever[illegible]allenge.

transparency 'plus' !

JRC Science for Policy Report (Feb 2022)

Bundesinstitut für Risikobewertung

2. BfR-Wissensdialog „Vertrauen in der Krise“

8. November 2022 im Magnus-Haus Berlin
Am Kupfergraben 7, 10117 Berlin

Vertrauen beeinflusst das gesamte soziale Miteinander und ist dennoch so schwer greifbar. Wer vertraut, befindet sich in einem Zustand zwischen Wissen und Nichtwissen und macht sich womöglich verletzbar.

Entgegengebrachtes Vertrauen kann aber auch belohnt werden und zu intensiveren Beziehungen und besseren Erfolgen führen.

Unsere Fachleute diskutieren über Vertrauen – nicht nur in Zeiten von COVID-19, Krieg und Klimawandel. Moderiert wird die Veranstaltung von Eva Wolfangel.

Der BfR-Wissensdialog ist Teil der
Berlin Science Week 2022.

Anmeldefrist:

Bitte melden Sie sich bis zum 06.11.2022 hier an.

Anfahrtsbeschreibung
Bitte beachten Sie, dass der Veranstaltungsort nicht barrierefrei ist.

BERLIN SCIENCE WEEK 1–10 NOV 2022

15:00 – 16:00	**Registrierung**
16:00 – 16:15	**Begrüßung** Prof. Dr. Dr. Andreas Hensel, Präsident des Bundesinstituts für Risikobewertung, Berlin
16:15 – 16:45	**Zum Wissenschaftsvertrauen in Deutschland - Erkenntnisse aus dem (bevölkerungsrepräsentativen) Wissenschaftssurvey *Wissenschaftsbarometer*** Ricarda Ziegler, Wissenschaft im Dialog, Berlin
16:45 – 17:15	**Bedingungen für kritisches Vertrauen** Prof. Dr. Lisbet Fjæran, Universität Stavanger, Norwegen
17:15 – 17:45	**Vertrauen in der digitalen Ökonomie** Prof. Dr. Timm Teubner, TU Berlin
17:45 – 18:15	**Vertrauen: Opium für das Volk oder Schmieröl für die Gesellschaft?** Prof. Dr. Michael Siegrist, ETH Zürich
18:15 – 19:00	**Podiumsdiskussion**
ab 19:00	**Ende der Veranstaltung und Get-together**
Moderation:	Eva Wolfangel

Kontakt: BfR-Akademie | Bundesinstitut für Risikobewertung | Max-Dohrn-Straße 8 – 10 | 10589 Berlin | E-Mail: akademie@bfr.bund.de | Website: www.bfr.bund.de

Thank you

Maurice Whelan

Head of Unit, Chemical Safety and Alternative Methods,

Directorate for Health, Consumers and Reference Materials,

European Commission, Joint Research Centre (JRC).

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European Commission