New Approach Methodologies as tools for mechanistic understanding of GIT.

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Webinar: Gastrointestinal Tract Toxicity, September 2023

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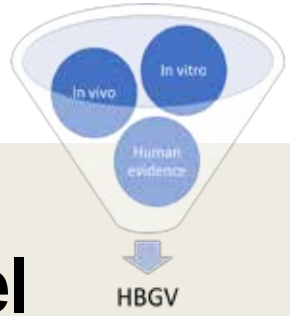
Hazard assessment

20th Century paradigm



Apical endpoints
No Adverse Effect Level
Animal to human extrapolation

21st Century Toxicology

Pathways for adversity

No Adverse Effect Level / 100

≠

Intermediate endpoints
Mechanistic connectors

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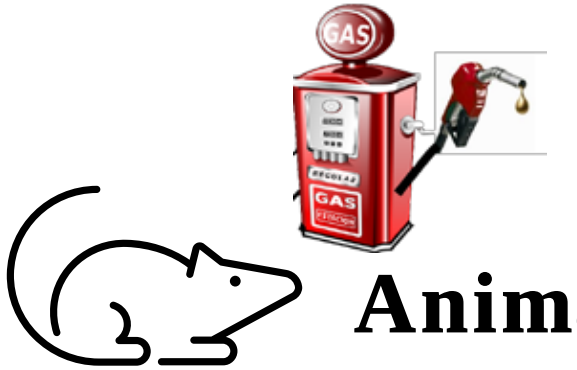
Toxicological models

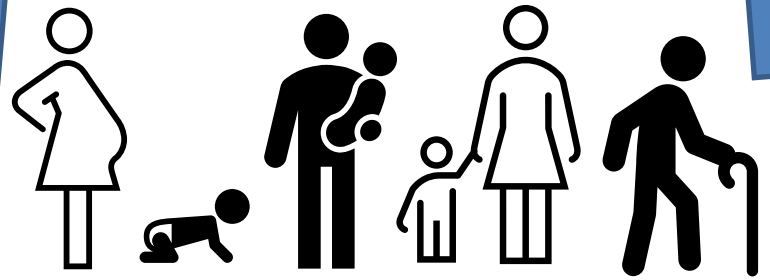


Animal models

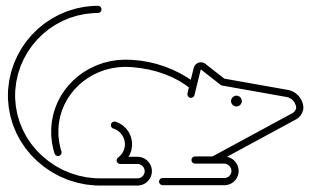
Human *in vitro* models

Inter species extrapolation

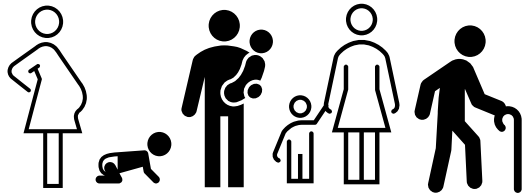
***In vitro* to *in vivo* extrapolation**



Animal models and gut toxicity



Inter species extrapolation



Main assumptions

- Gut processes covered by animal studies
  - No specific considerations regarding interspecies physiological differences
  - Focus on fate and ADME
  - No specific attention on effects on microbiome

Main limitations

- Extrapolation of toxicokinetic properties
  - First step is already the internalization “Absorption” in ADME
    - Focus on quantitative estimation of percentage of absorption
- Focus on dose à gavage administration or animal feed not resembling human food
- Limited consideration of gut local effects
- Lack of information on effects on the microbiome

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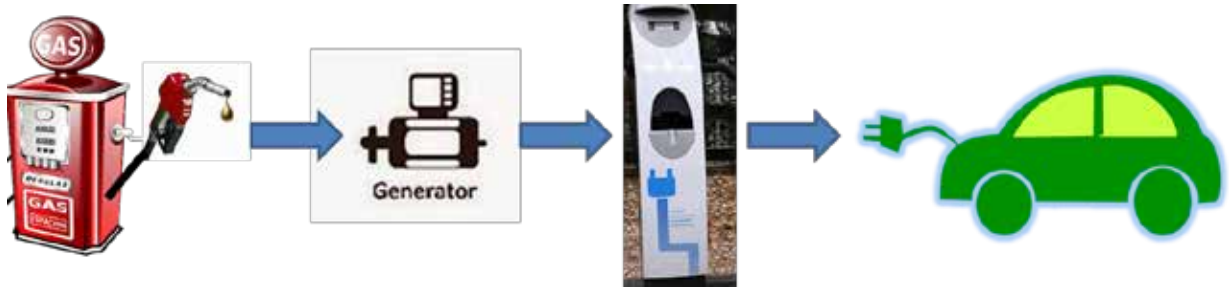
Paradigm evolution

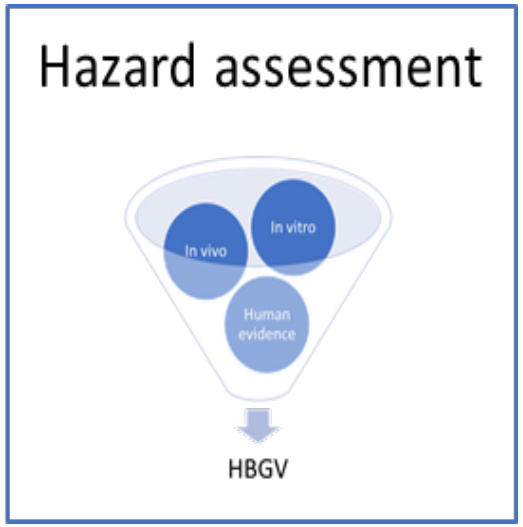


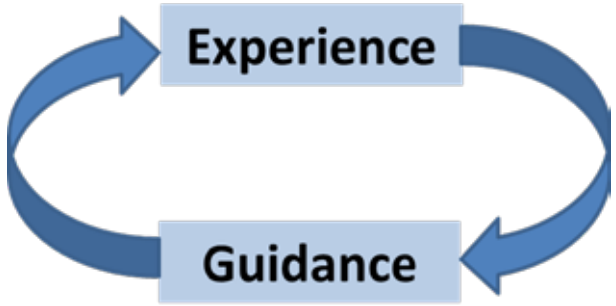
Integrative approaches for setting THE Guidance Value

Existing information → New information → Integration

- *In vitro*
- Read-across

To support/challenge the guidance value





- **Are all NAM effects covered by *in vivo* observations?**
- **Are population groups with expected high susceptibility?**
- **Are interactions of specific concern?**

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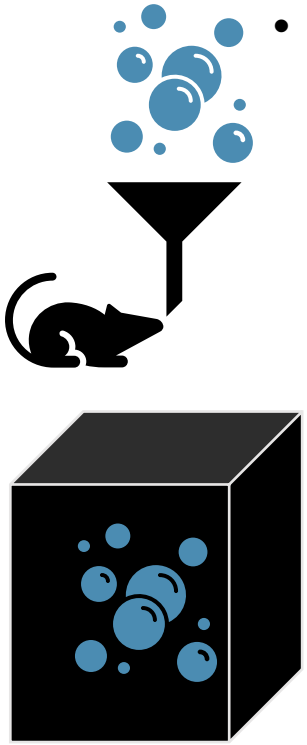
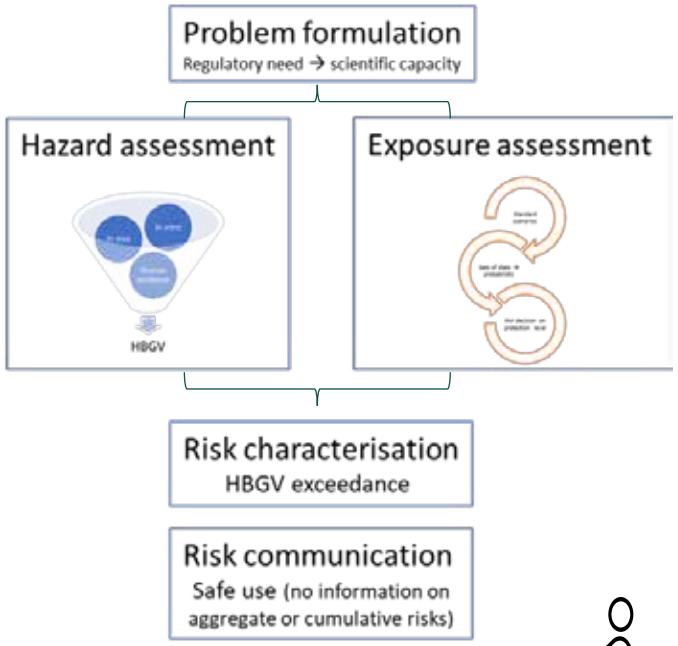
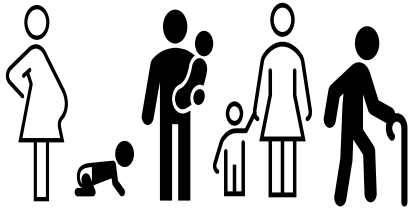
Mechanistic understanding in gut toxicology

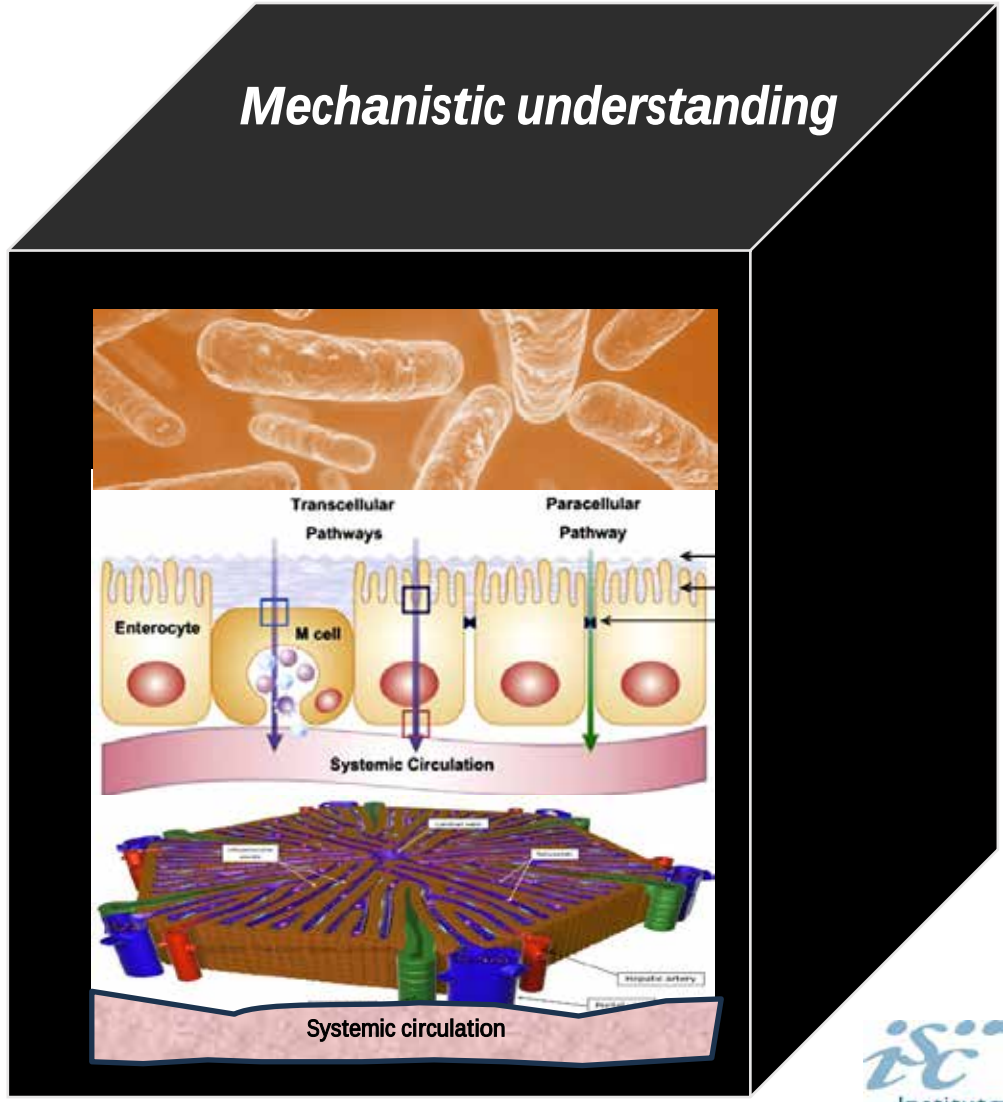
- High doses
- Suspension by gavage







- Apical adverse effects



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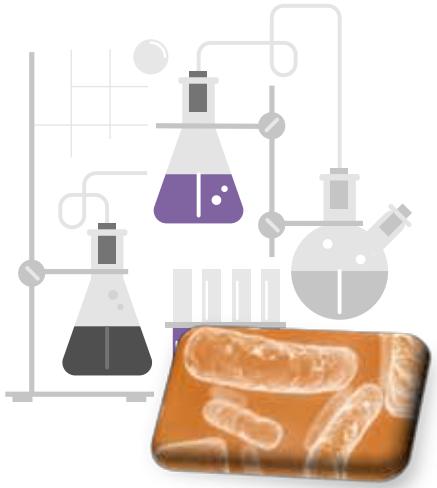

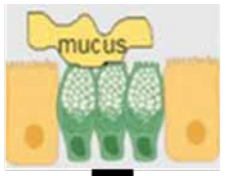

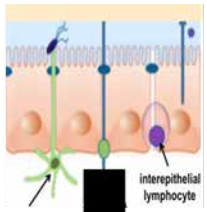

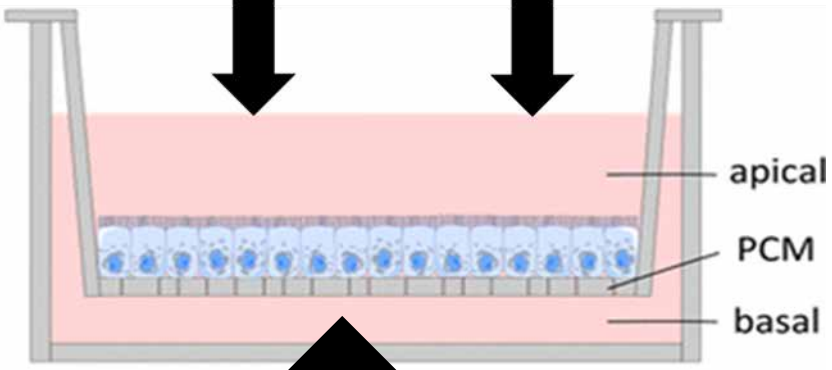

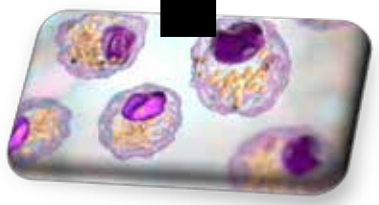

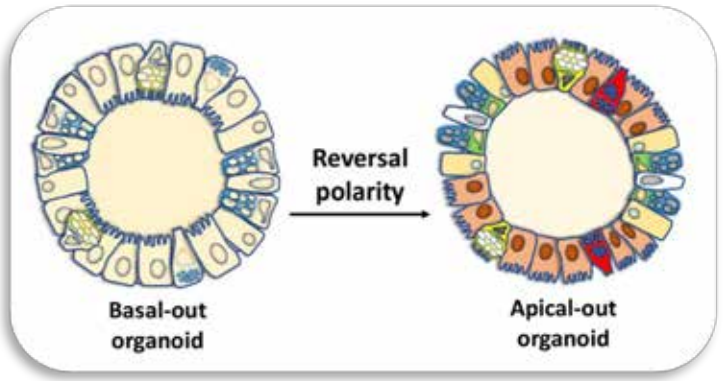

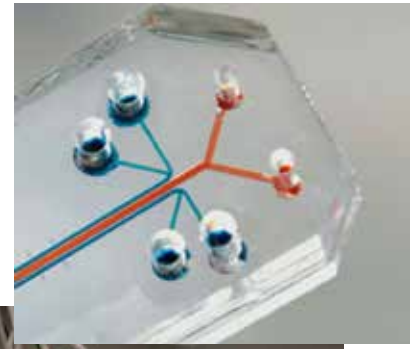

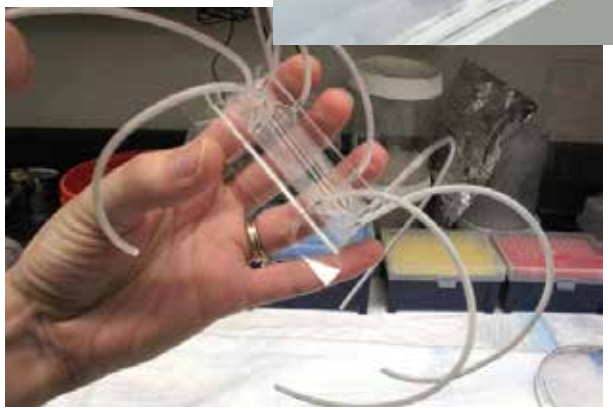

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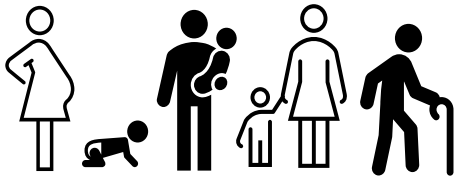
In vitro models and gut toxicology

***In vitro* to *in vivo* extrapolation**



Main assumptions

- Using human cells ensures human physiological relevance
  - *In vitro* conditions may be very different from those physiological
  - Focus on the intestinal epithelia
  - Independent assessments for effects on microbiome
- Use of AOP for extrapolating intermediate effects into adverse outcomes
  - QIVIVE focused on Toxicokinetic considerations

Main limitations

- Different levels of complexity, but even the most complex are oversimplifications
- Mostly with short timeframes
- Only the most complex may integrate microbiome
- Provide mechanistic or quantitative information, but rarely both
  - (Relative) “absorption” for ADME
  - Mechanism of uptake (diffusion, paracellular, transporters, endocytosis, …

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Partnership for the Assessment of Risks from Chemicals

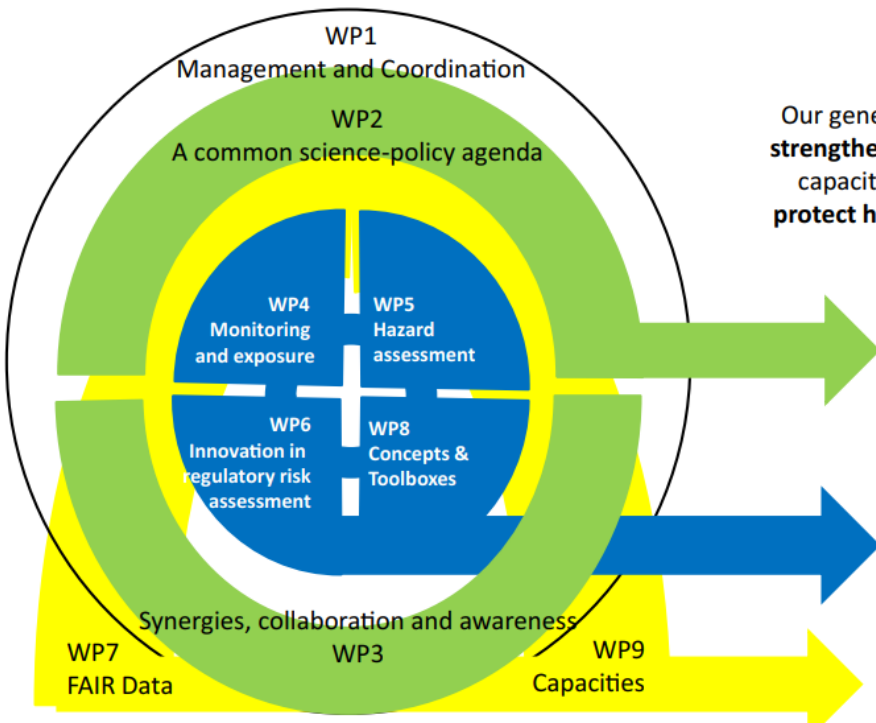
https://www.eu-parc.eu/

Archives of Toxicology (2023) 97:893–908
https://doi.org/10.1007/s00204-022-03435-7

LETTER TO THE EDITOR, NEWS AND VIEWS

A walk in the PARC: developing and implementing 21st century chemical risk assessment in Europe

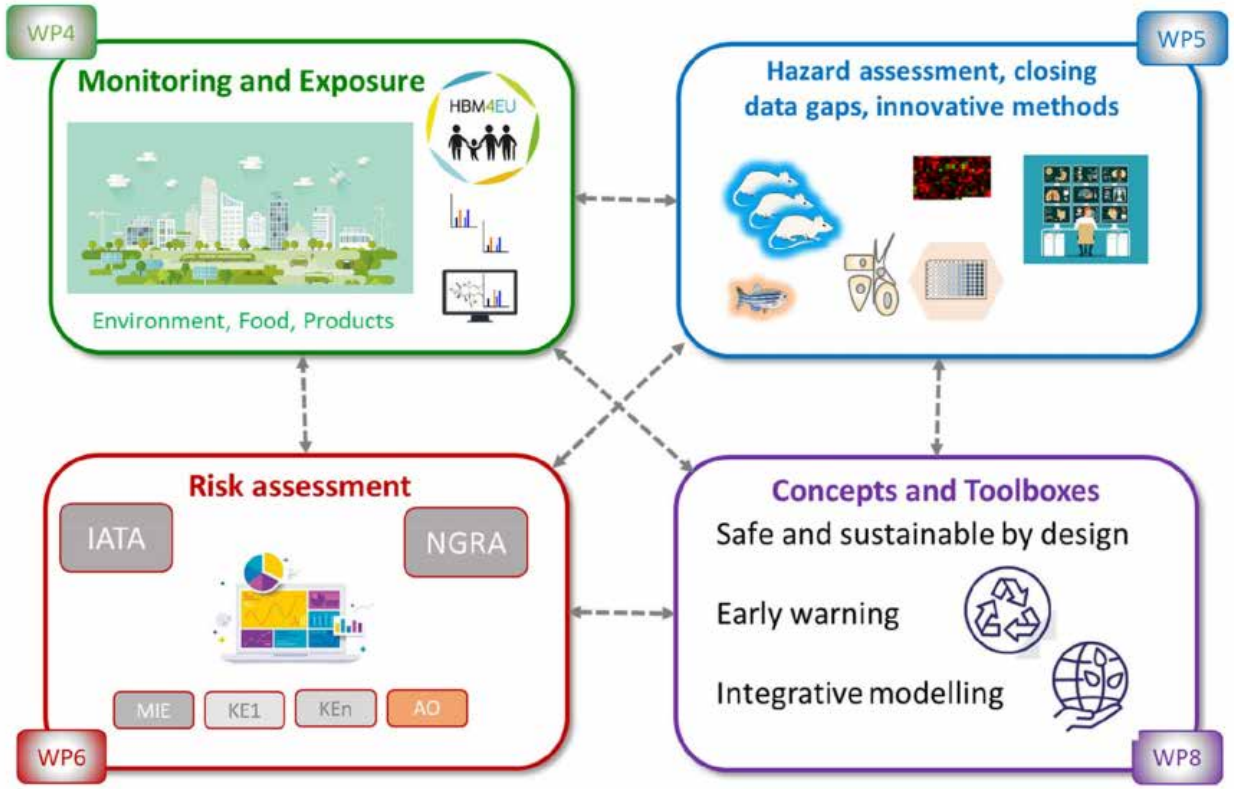
P. Marx-Stoelting[1] · G. Rivière[2] · M. Luijten[3] · K. Aiello-Holden[1] · N. Bandow[4] · K. Baken[15] · A. Cañas[5] · A. Castano[5] · S. Denys[6] · C. Fillol[6] · M. Herzler[1] · I. Iavicoli[7] · S. Karakitsios[8] · J. Klanova[9] · M. Kolossa-Gehring[4] · A. Koutsodimou[10] · J. Lobo Vicente[11] · I. Lynch[12] · S. Namorado[13] · S. Norager[14] · A. Pittman[2] · S. Rotter[1] · D. Sarigiannis[8] · M. J. Silva[13] · J. Theunis[15] · T. Tralau[1] · M. Uhl[16] · J. van Klaveren[3] · L. Wendt-Rasch[17] · E. Westerholm[17] · C. Rousselle[2] · P. Sanders[2]



PARC Objectives

Our general objective is to **consolidate and strengthen** the EU's Research and innovation capacity for chemical risk assessmentto **protect human health and the environment**

1. High level network for regulatory science interface
2. Research & Innovation towards Next Generation Risk Assessment
3. Capacities and Platforms



frontiers | Frontiers in Toxicology

Innovative tools and methods for toxicity testing within PARC work package 5 on hazard assessment

Thalia De Castelbajac[1*], Kiara Aiello[2†], Celia Garcia Arenas[2†], Terje Svingen[3], Louise Ramhøj[3], Daniel Zalko[4], Robert Barouki[5], Tamara Vanhaecke[6], Vera Rogiers[6], Marc Audebert[4], Michael Oelgeschlaeger[2], Albert Braeuning[2], Etienne Blanc[5], Tamara Tal[7], Joëlle Rüegg[8], Ellen Fritsche[9], Philip Marx-Stoelting[21] and Gilles Rivière[11]

TYPE Mini Review
PUBLISHED 19 July 2023
DOI 10.3389/ftox.2023.1216369

WP5 ORGANIGRAM

T5.1 DATA GAPS

- A5.1.1 Human Health: Henriqueta Louro, Maria Joao Silva, Hubert Dirven
- A5.1.2 Environment: Katerina Kyriakopoulou

T5.2 NAMs

- A5.2.1 Human Health: Tamara Vanhaecke, Vera Rogiers, Terje Svingen, Louise Ramhøj
- A5.2.2 Environment: Ludek Blaha, Ondrej Adamovsky

T5.3 NGRA AOPs

Birgit Mertens, Bob van de Water, Sylvia Escher, Robert Barouki

- A5.3.1 NAM-based
- A5.3.2 AOP
- A5.3.3 Human pathophy.
- A5.3.4 PBTK

P5.1.1.a (Myco) Toxins
Doris Marko
Jessica Dietrich

P5.1.1.b HumTox BPA
Kiara Aiello
Sabrina Tait
Catherine Viguié
Sakina Mahouty
Emanuela Corsini
Maria Joao Silva
Daniel Zalko
Emanuela Testai

P5.1.2.a Natural Toxins Aqua
Jana Asselman

P5.1.2.b BPA alternatives
Katarina Kyriakopoulou
Ludek Blaha
Ondrej Adamovsky

A5.2.2 Environment

P5.2.1.a NGTxCs
Marc Audebert
Michael Oelgeschlaeger

P5.2.1.b Metabolic ED
Daniel Zalko
Albert Braeuning

P5.2.1.c ED Th Disruption
Terje Svingen
Tamara Vanhaecke

P5.2.1.d Immunotox
Robert Barouki
Etienne Blanc

P5.2.1.e Dev/AcuteNeurotox
Tamara Tal
Joelle Ruegg
Ellen Fritsche

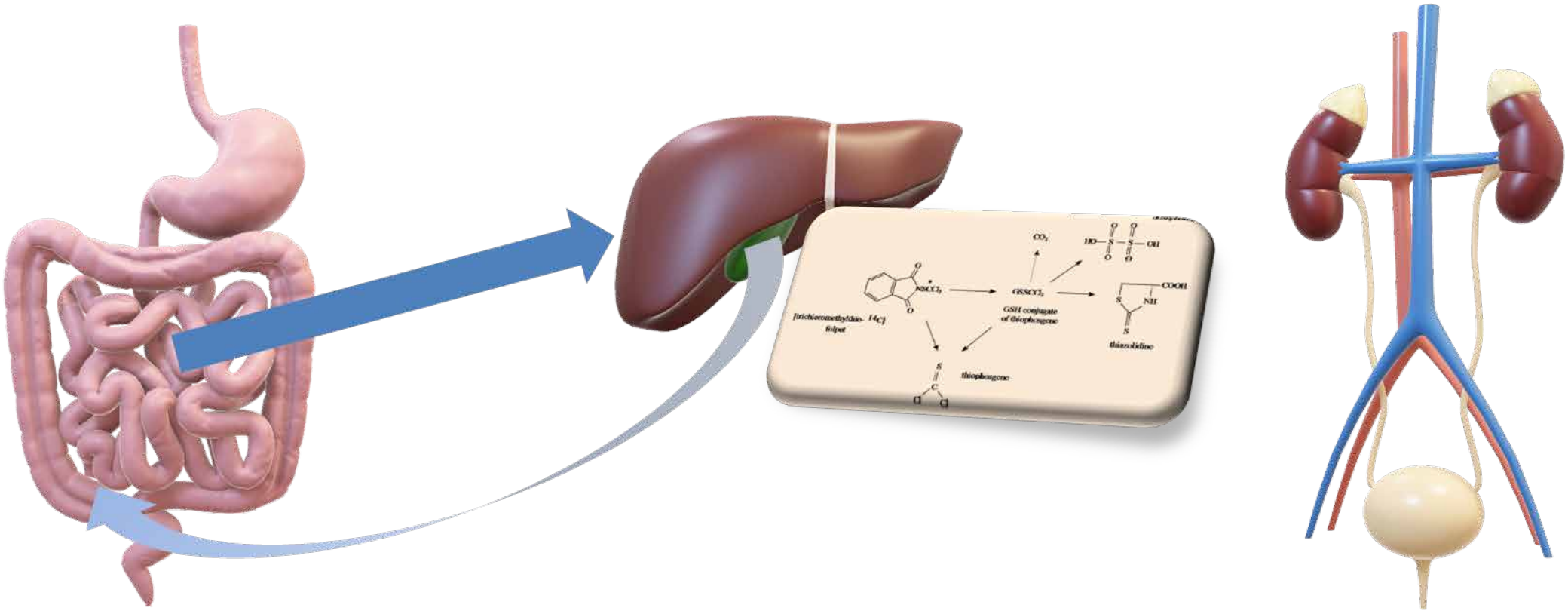
P5.3.1.a Systems Toxicology
Bob van de Water

P5.3.2.a AOP Development
Robert Barouki
Karine Audouze
Birgit Mertens

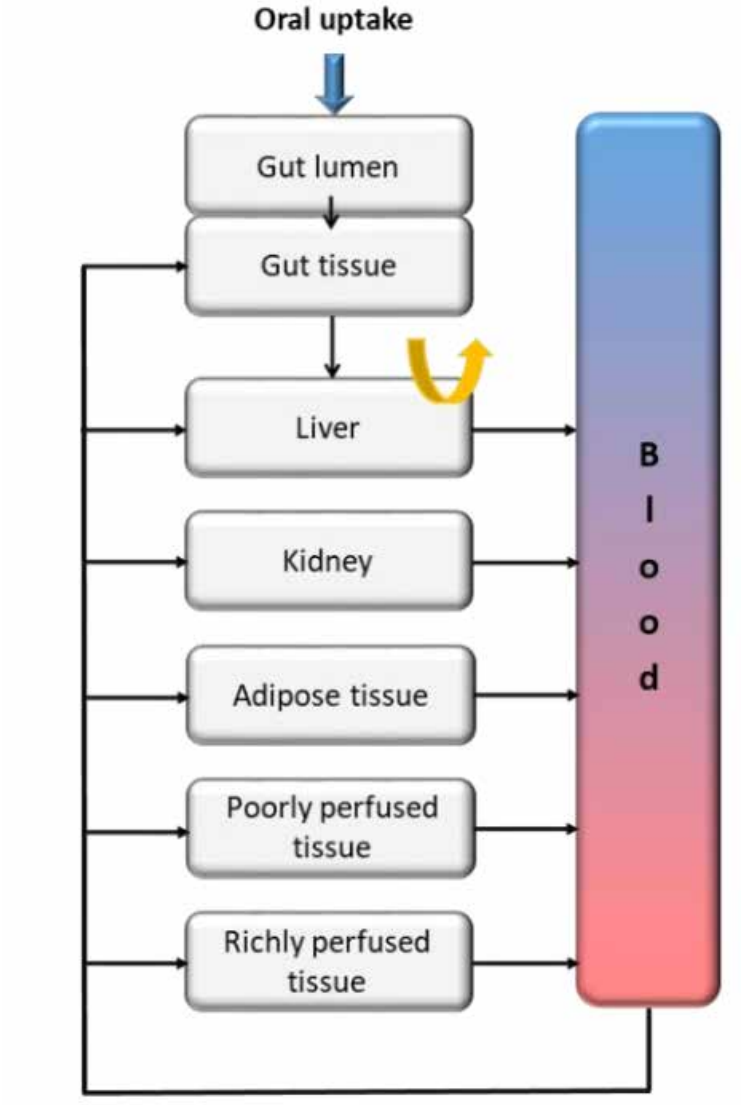
P5.3.4.a PBK Kinetics
Sylvia Escher

PARC
Co-funded by the European Union

Focus on systemic effects and toxicokinetic processes



Absorption **Metabolism** **Elimination**



EXTERNAL SCIENTIFIC REPORT

APPROVED: 22 February 2021

doi:10.2903/sp.efsa.2021.EN-6504

Modelling human variability in toxicokinetic and toxicodynamic processes using Bayesian meta-analysis, physiologically-based modelling and *in vitro* systems

Emanuela Testai, Camille Bechaux, Franca M. Buratti, Keyvin Darney, Emma Di Consiglio, Emma E.J. Kasteel, Nynke I. Kramer, Leonie S. Lautz, Nicoletta Santori, Zoi-Vasiliki Skaperda, Dimitrios Kouretas, Laura Turco, Susanna Vichi

Istituto Superiore di Sanitá (ISS), French Agency for Food, Environmental and Occupational Health & Safety (ANSES), University of Utrecht, University of Thessaly

EXTERNAL SCIENTIFIC REPORT

APPROVED: 29 November 2022

doi:10.2903/sp.efsa.2023.EN-7793

EFSA Pilot Project on New Approach Methodologies (NAMs) for Tebufenpyrad Risk Assessment. Part 1. Development of Physiologically-Based Kinetic (PBK) Model Coupled With Pulmonary and Dermal Exposure

Jérôme HENRI[1], Ludovic LEHEGARAT[1], Adeline CAVELIER[2], Bertrand DESPREZ[2]

French Agency for Food, Environmental and Occupational Health & Safety (ANSES)

[1]ANSES Fougères Laboratory, 10 rue Claude Bourgelat-Javené CS 40608 F-35306 Fougères Cedex

[2]ANSES Directorate of Regulated Products Evaluation, 14 rue Pierre et Marie Curie F-94701 Maisons-Alfort Cedex

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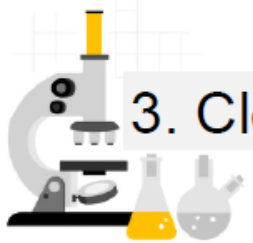
FACILITATING THE REGULATORY USE OF OoC STUDY RESULTS

J.V. Tarazona*, M.C. Astuto, M. Bastaki, Y. Devos, J.-L.C.M. Dorne, G.E.N. Kass and A.K.D. Liem

1. Facilitate replication

2. Describe test substance

CAS No, Batch, …



3. Clear QC for biology viability

4. Report quality assurance

5. Bio-Relevance by design

6. Archive all raw/calibration data

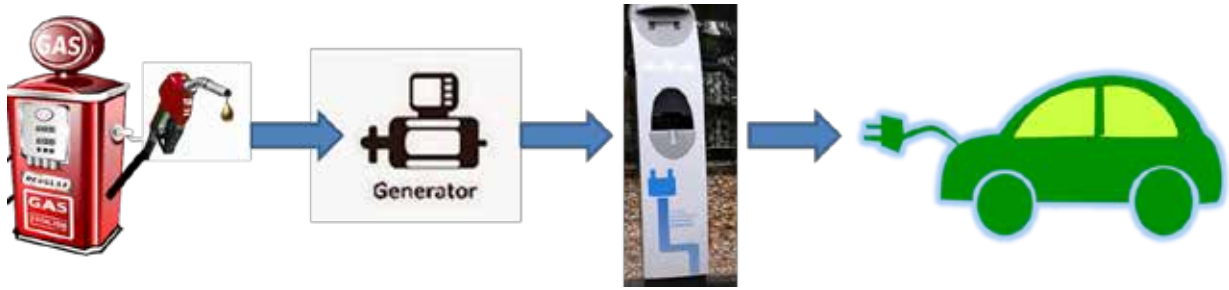
7. Be available for requests

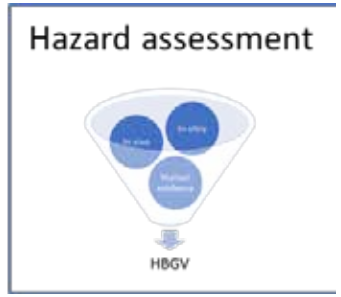
- ✓ **First element**. Description of the OoC tool and methodology sufficiently detailed to allow study **replication and verification** by third parties.
- ✓ **Second element**. All **test substances**, controls and other chemicals (CAS No, purity, source, batch, etc.) should be sufficiently described. For nanomaterials also the characterization of particles, and level of agglomeration [3].
- ✓ **Third element**. OoC elements/tools (commercially) available or indicate suitable alternatives. Describe Quality Criteria for assessing the viability of the **biological components** at the beginning/during/end of the experiment.
- ✓ **Fourth element**. All individual results should come from multiple replicates of the procedure with full **QA/QC information**. The QA/QC should include calibration at inter-laboratory exercise (round robin test); detailed Standard Operating Procedure (SOP); and/or have been replicated in an independent laboratory.
- ✓ **Fifth element.** For toxicokinetic or mechanistic toxicity investigations, appropriate pharmacological **modulators**, **time course,** etc. would need to be included.
- ✓ **Sixth element.** Kept **raw data** if not published, and **records** for all equipment and model **calibrations and quality controls**.
- ✓ **Seventh element.** The authors of the publication are required to make materials, data, code and associated protocols **promptly available** without undue qualifications.

How? Evolution *versus* revolution

Paradigm evolution

Using alternative methods for setting THE Guidance Value





Paradigm revolution

Developing new paradigms for safety assessments based on mechanistic understanding

Assess
SAFETY
... like for genotoxicity

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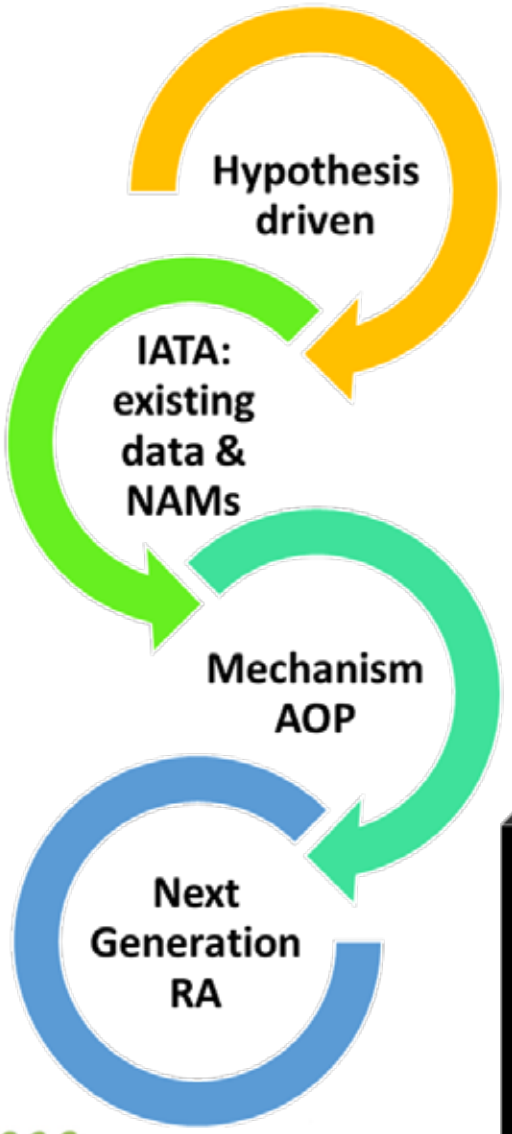
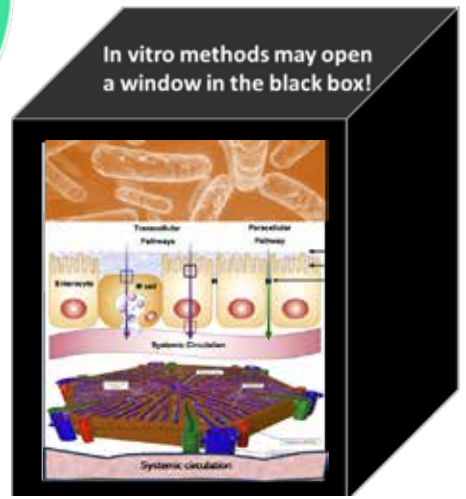
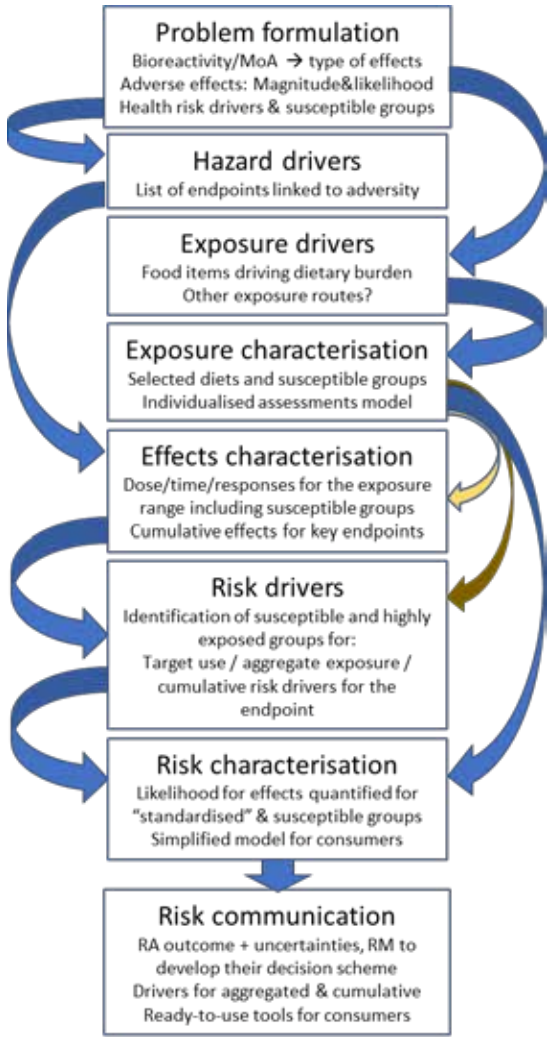
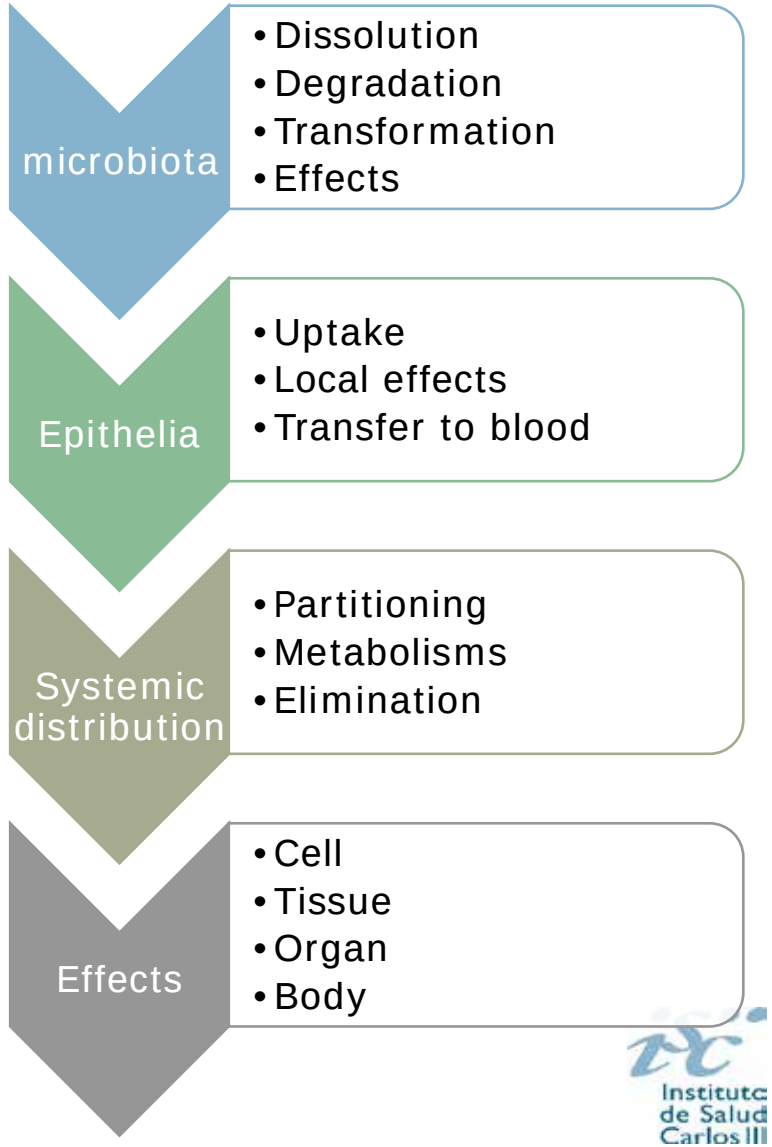
Revolution of the risk assessment paradigm









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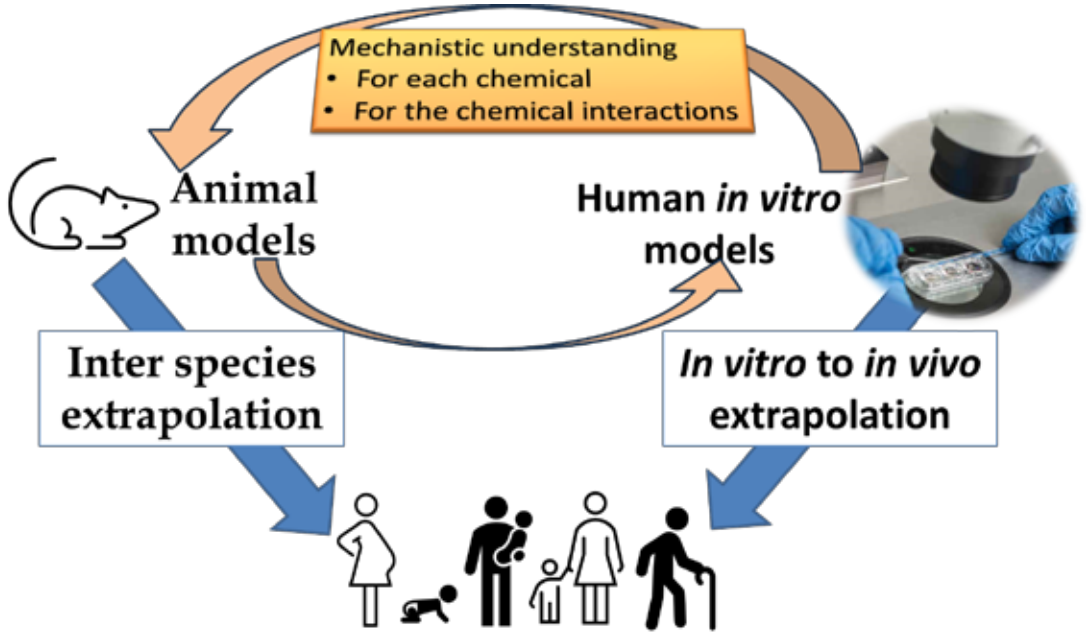
Adverse Outcome Pathways



ALTEX, accepted manuscript published March 1, 2022 doi:10.14573/altex.2202141

t⁴ workshop report*

Application of Evidence-Based Methods to Construct Mechanism-Driven Chemical Assessment Frameworks

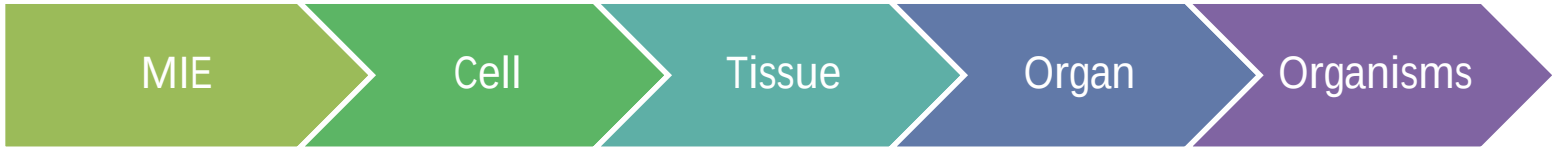
Sebastian Hoffmann[1], Elisa Aiassa[2], Michelle Angrish[3], Claire Beausoleil[4], Frederic Y. Bois[5], Laura Ciccolallo[2], Peter S. Craig[6], Rob B. M. de Vries[1], Jean Lou C. M. Dorne[2], Ingrid L. Druwe[3], Stephen W. Edwards[7], Chantra Eskes[8,9], Marios Georgiadis[2], Thomas Hartung[1,10], Aude Kienzler[9,11], Elisabeth A. Kristjansson[12], Juleen Lam[13], Laura Martino[2], Bette Meek[12], Rebecca L. Morgan[14], Irene Munoz-Guajardo[2], Pamela D. Noyes[3], Elena Parmelli[11], Aldert Piersma[15], Andrew Rooney[16], Emily Sena[17], Kristie Sullivan[18], José Tarazona[2], Andrea Terron[2], Kris Thayer[3], Jan Turner[19], Jos Verbeek[20], Didier Verloo[2], Mathieu Vinken[21], Sean Watford[22], Paul Whaley[1,23], Daniele Wikoff[24], Kate Willett[25] and Katya Tsaioun[1]

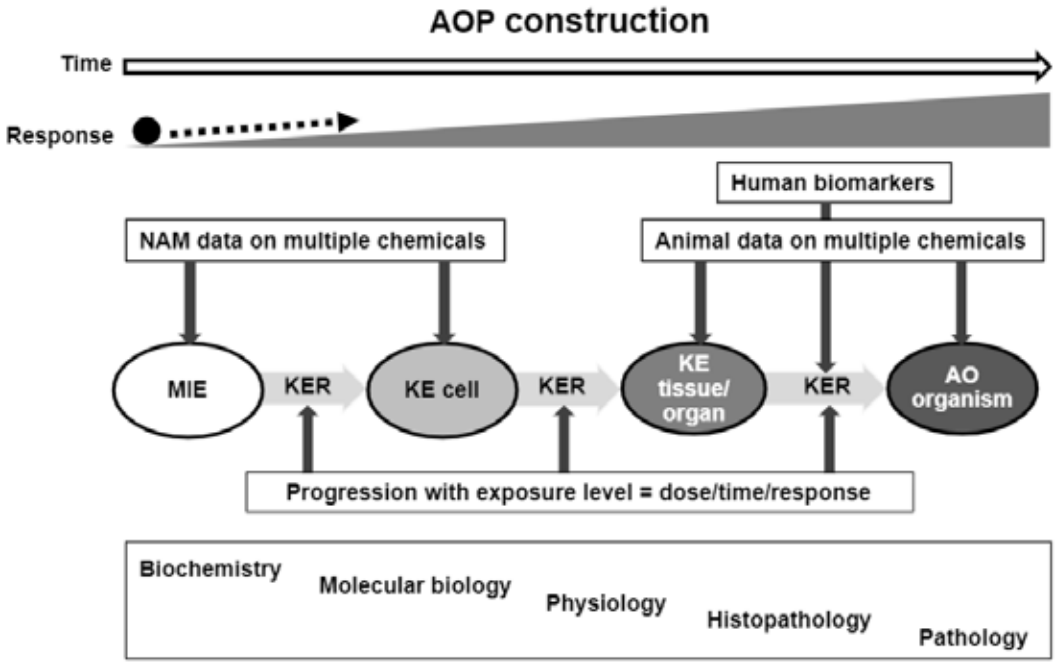
- Constructing an AOP and <u>using the AOP for risk assessment</u> require different approaches
- We need a more pragmatic approach, and more important:

AOP-based approaches should be connected to health impacts

Adverse Outcome Pathway

Toxicology-based risk assessments

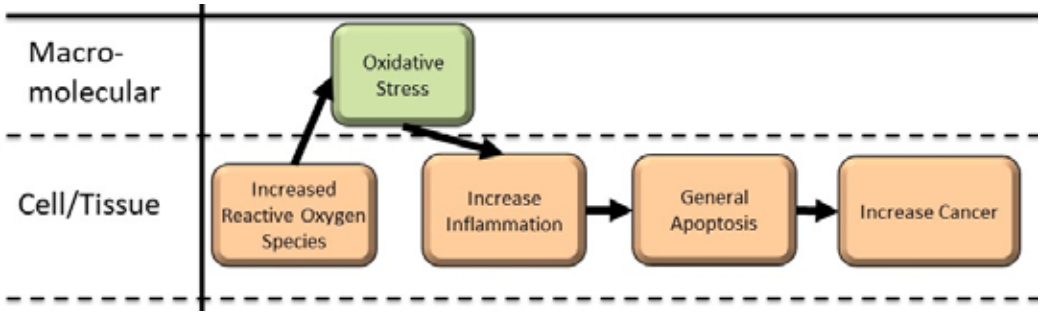




Hoffman et al., 2022. ALTEX

AOP 505 https://aopwiki.org/aops/505

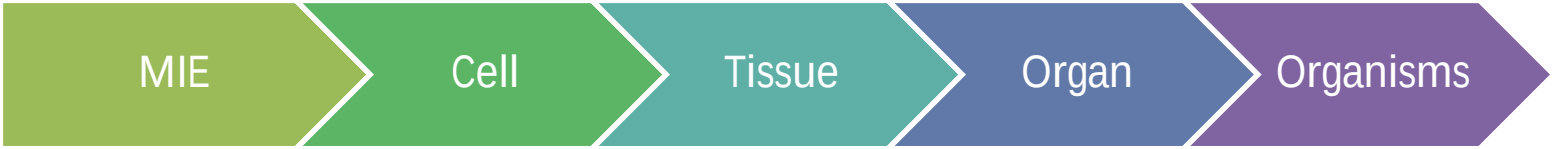
Reactive Oxygen Species (ROS) formation leads to cancer via inflammation pathway



Using AOPs for risk assessment – From observations to predictions

Adverse Outcome Pathway

Toxicology-based risk assessments



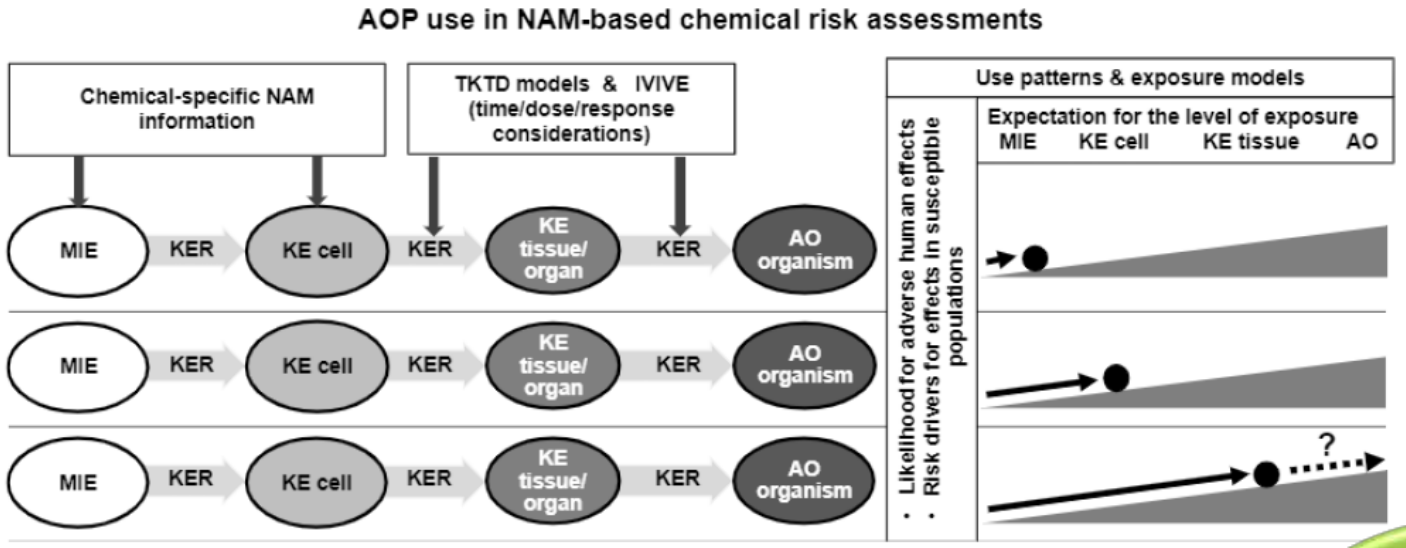
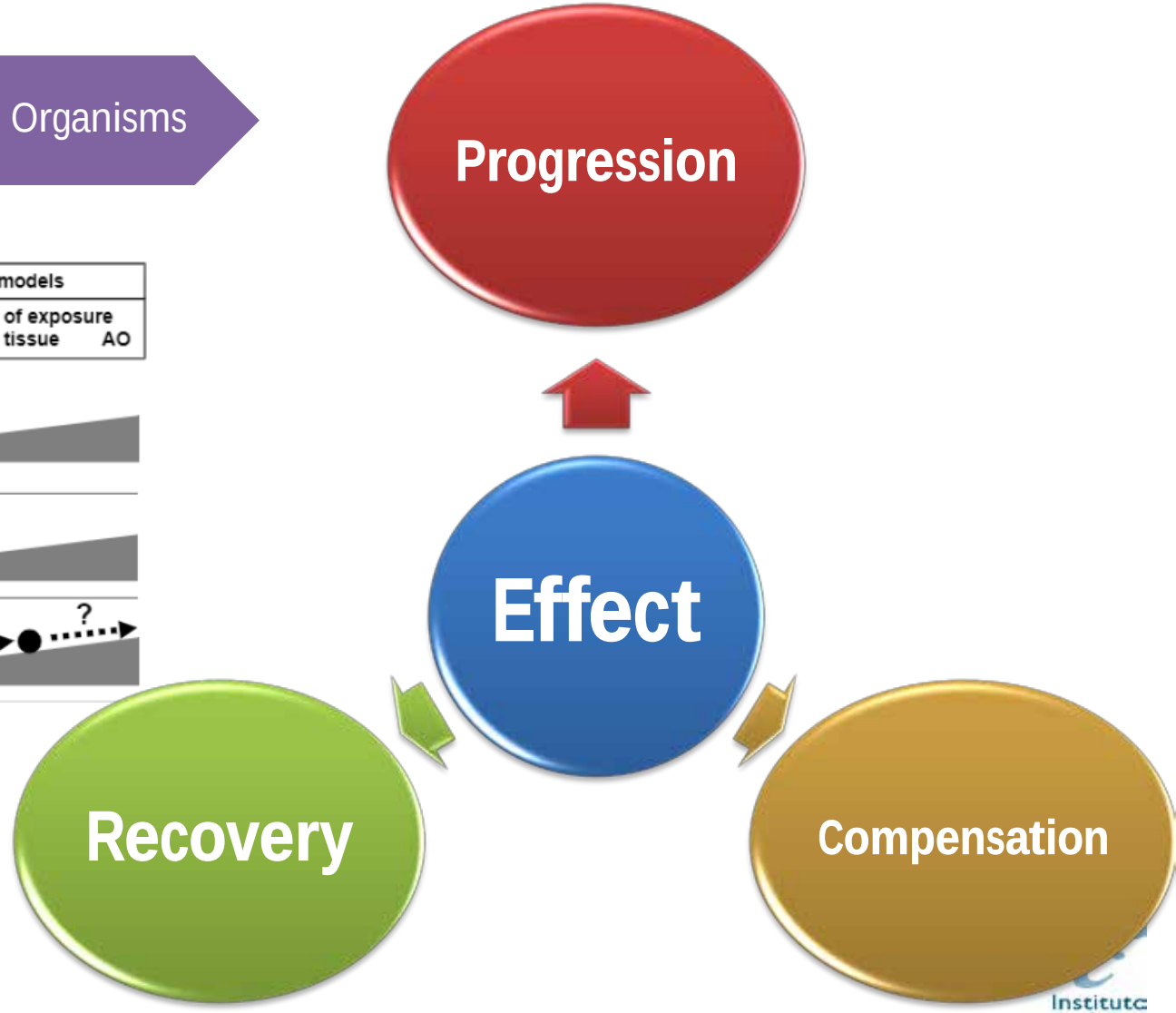


Fig. 5: The use of NAM in AOP-based chemical risk assessment

Hoffman et al., 2022. ALTEX



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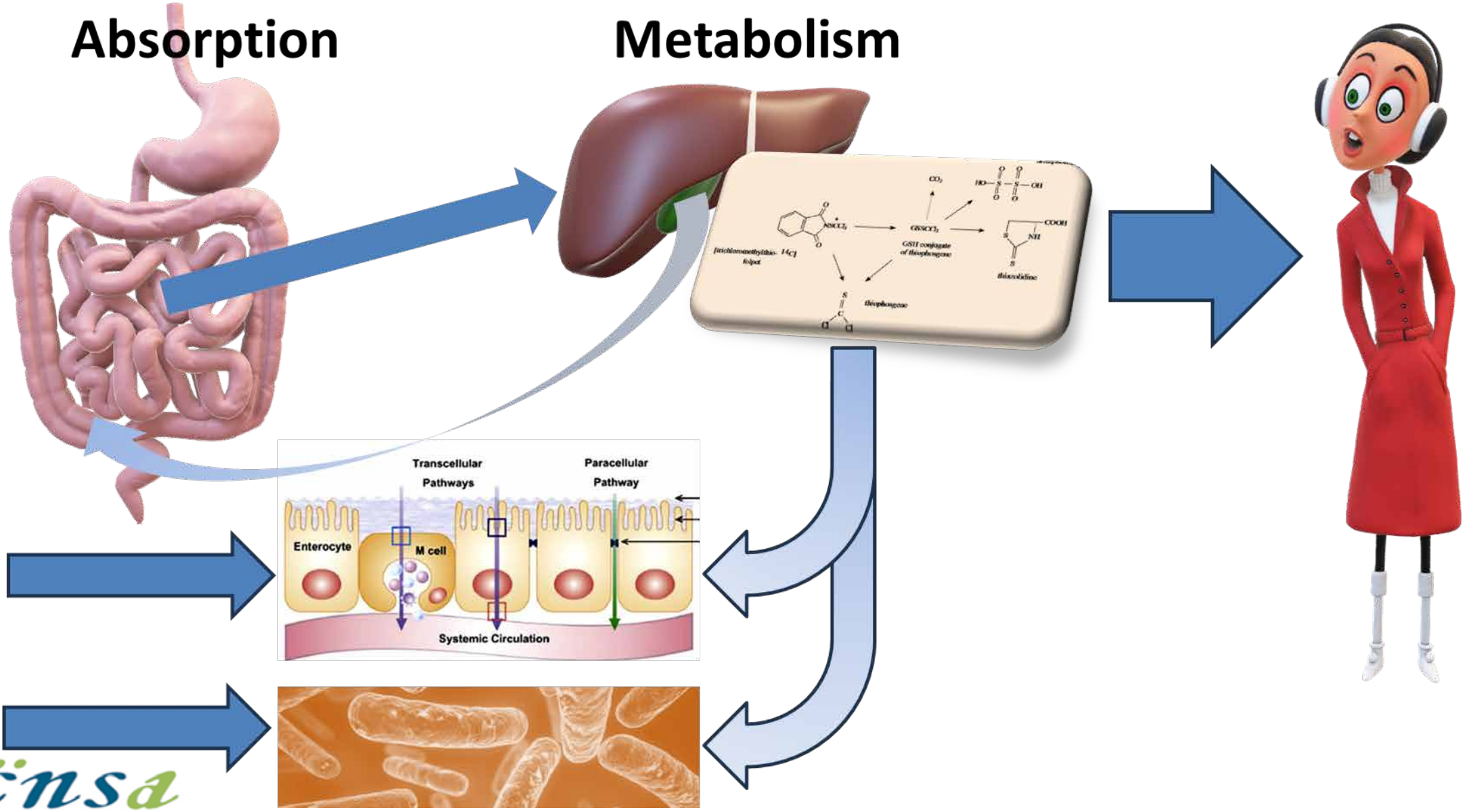
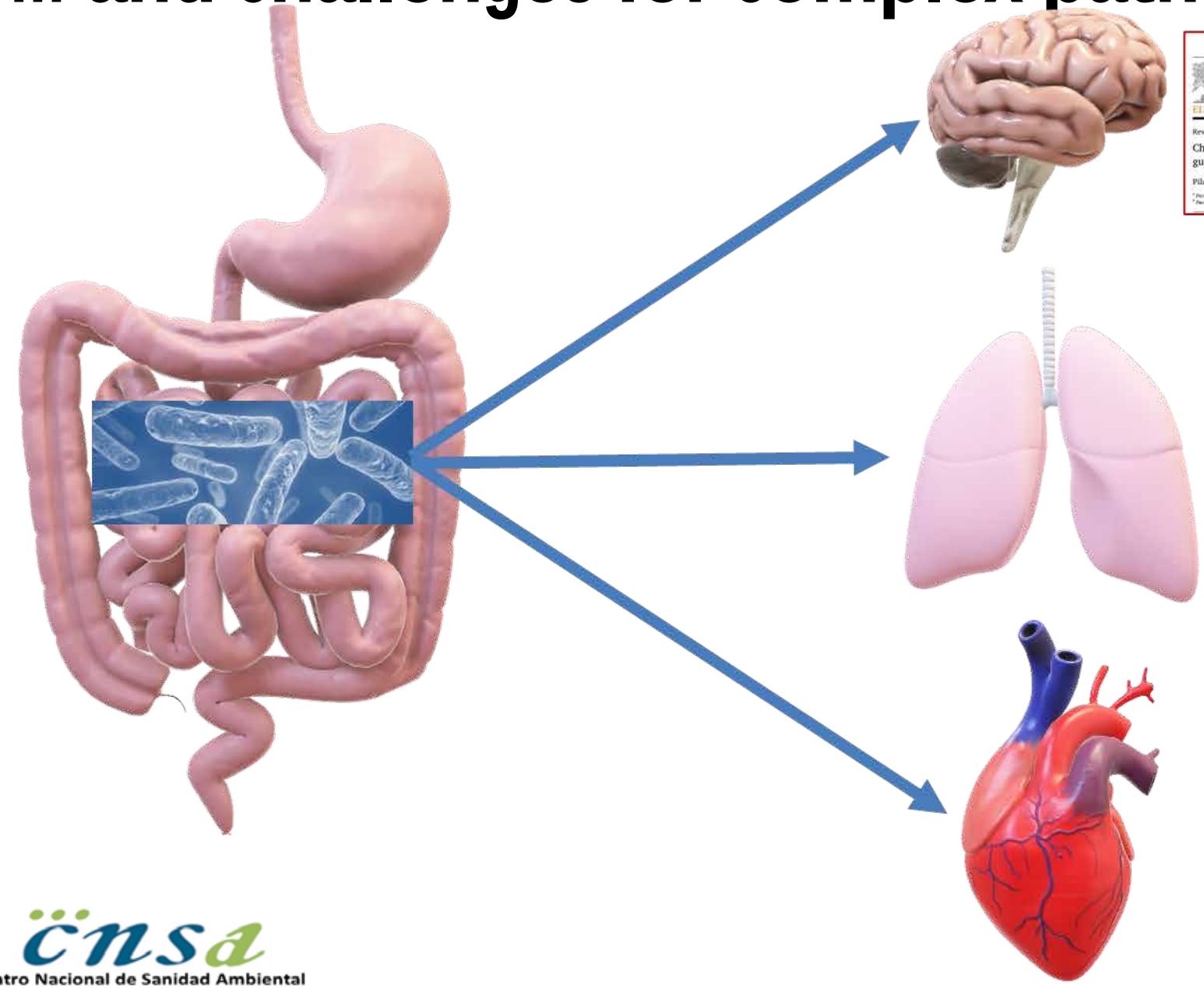
Needs: Proper coverage for local and systemic effects...



... and challenges for complex pathways!



ANNUAL REVIEWS

Annual Review of Pharmacology and Toxicology

Microbiota-Gut-Brain Axis: New Therapeutic Opportunities

Caitríona Long-Smith,[1] Kenneth J. O'Riordan,[1] Gerard Clarke,[1,2] Catherine Stanton,[1,3] Timothy G. Dinan,[1,2] and John F. Cryan[1,4]

Toxicology

Review

Chronic consumption of food-additives lead to changes via microbiota gut-brain axis

Pilar Abiega-Franyutti, Veronica Freyre-Fonseca

Current Opinion in Pulmonary Medicine

OBSTRUCTIVE, OCCUPATIONAL AND ENVIRONMENTAL DISEASES: EDITED BY MANISH JOSHI AND BASIL VARKEY

Lung microbiome, gut–lung axis and chronic obstructive pulmonary disease

Gokulan, Kuppan[a]; Joshi, Manish[b,c]; Khare, Sangeeta[a]; Bartter, Thaddeus[b,c]

Author Information

Current Opinion in Pulmonary Medicine 28(2):p 134-138, March 2022. | DOI: 10.1097/MCP.0000000000000853

microbial biotechnology

Open Access

Minireview

The gut microbiota and its interactions with cardiovascular disease

Hui Xu, Xiang Wang, Wenke Feng, Qi Liu, Shanshan Zhou, Quan Liu and Lu Cai

cells

MDPI

Review

The Influence of Gut Dysbiosis in the Pathogenesis and Management of Ischemic Stroke

Saravana Babu Chidambaram, Annan Gopinath Rathipriya, Arehally M. Mahalakshmi, Sonali Sharma, Tousif Ahmed Hediyal, Bipul Ray, Tuladhar Sunanda, Wiramon Rungratanawanich, Rajpal Singh Kashyap, M. Walid Qoronfleh, Musthafa Mohamed Essa, Byoung-Joon Song and Tanya M. Monaghan

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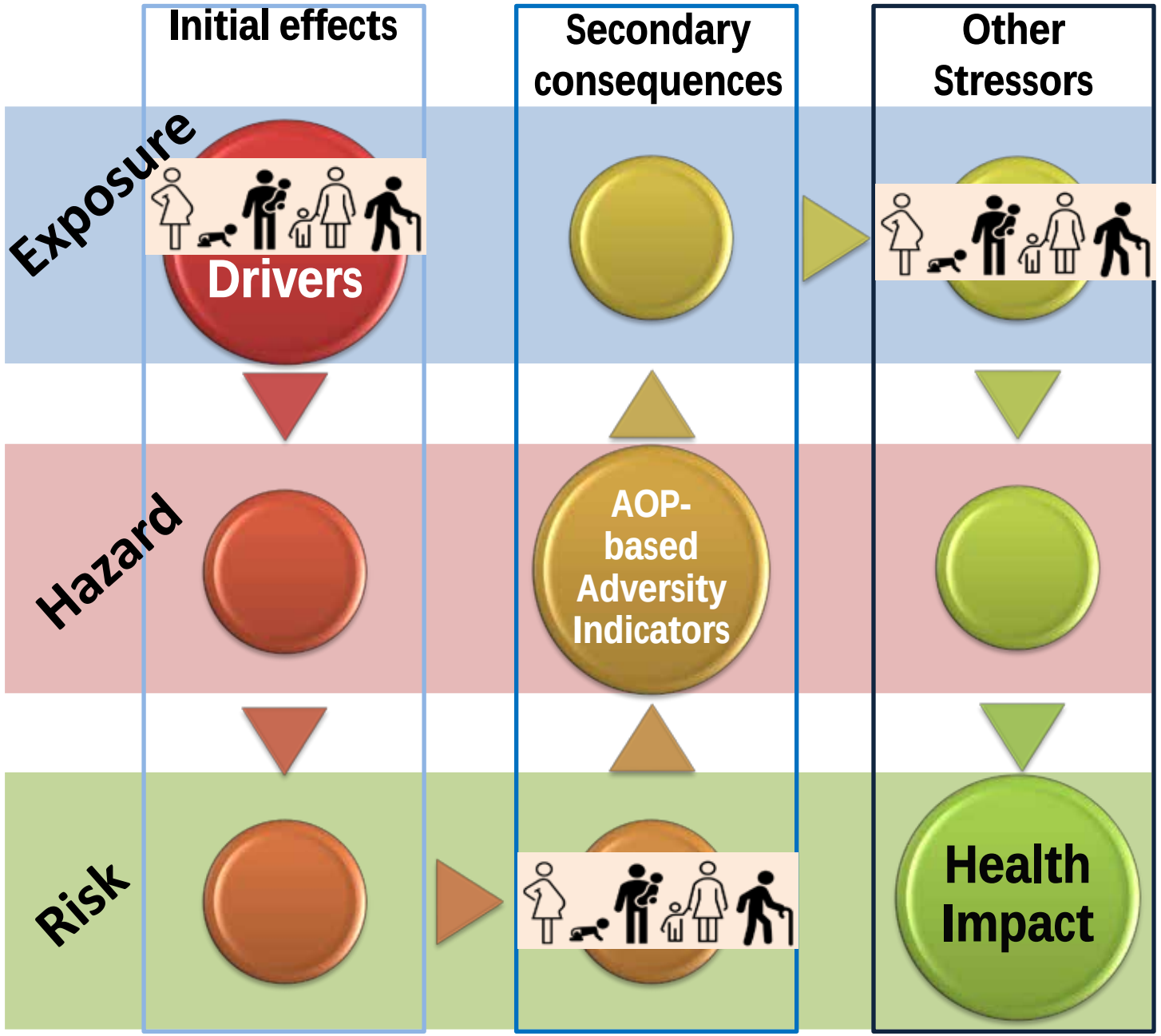
Adversity:

Quantitative estimation of the **likelihood** for and **intermediate effect** to progress towards consequences affecting measurable health indicators



Conclusions

- We should:
  - Consider the assumptions, limitations, and uncertainties for both animal and NAM-based approaches
- We have
  - Significant advances for NAM-based toxicokinetics
  - A relevant number of tools with different levels of complexity, covering different mechanisms
- We need
  - Systems for qualifying their use for regulatory assessments
  - **A new paradigm for Next Generation Risk Assessment, addressing initial effects (microbiome and gut cells) and the identification of associated consequences**

Thank you!!!

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