Séminaire FRANCOPA

Des nouvelles approches méthodologiques (NAM) pour les tests de toxicité réglementaires : actualités et perspectives

30 September 2022

Vers une acceptabilité réglementaire des NAM

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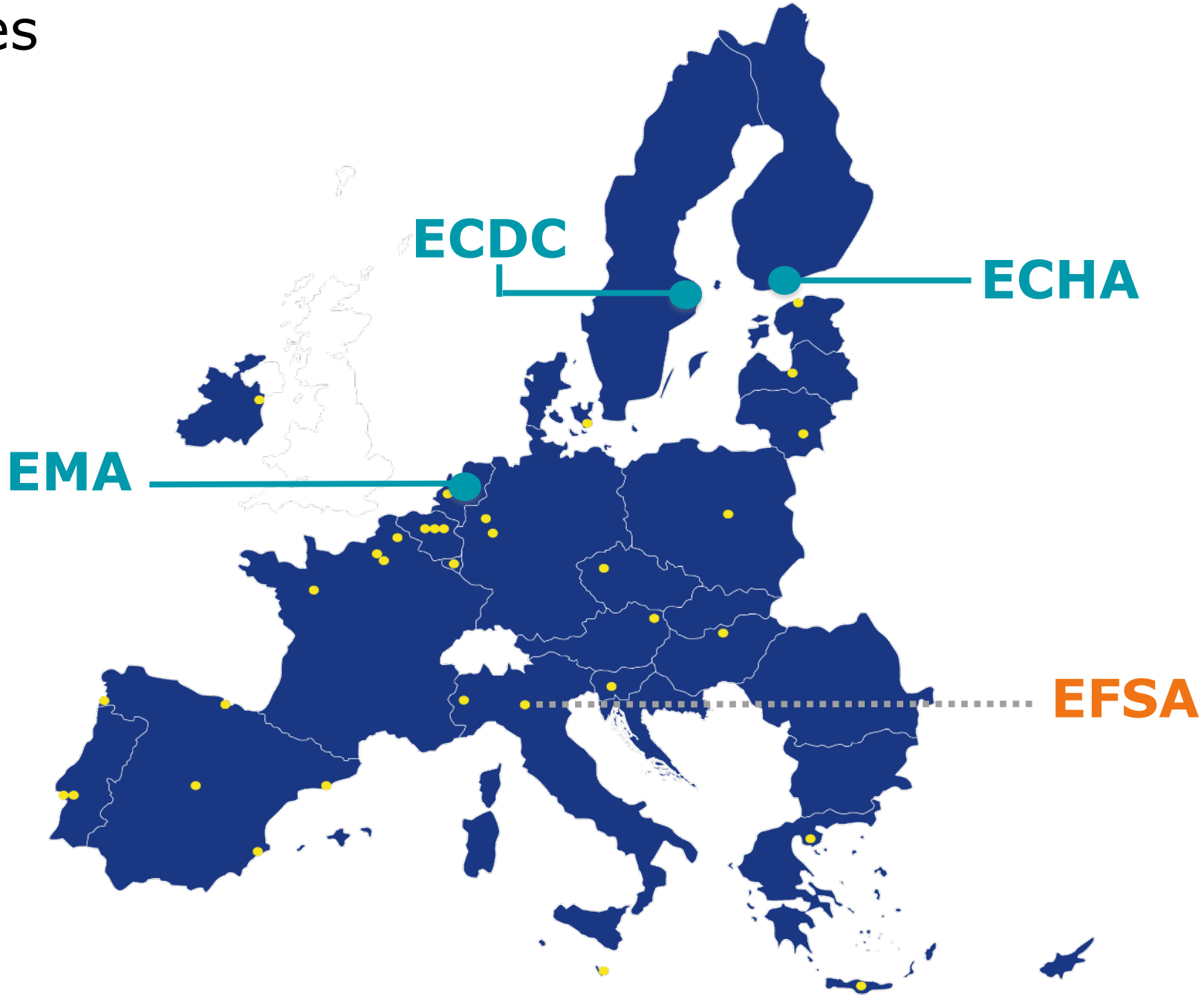
Chief Scientist Office

Trusted science for safe food

efsa
European Food Safety Authority

Disclaimer: The views, thoughts and opinions presented are not necessarily those of EFSA

EU agencies



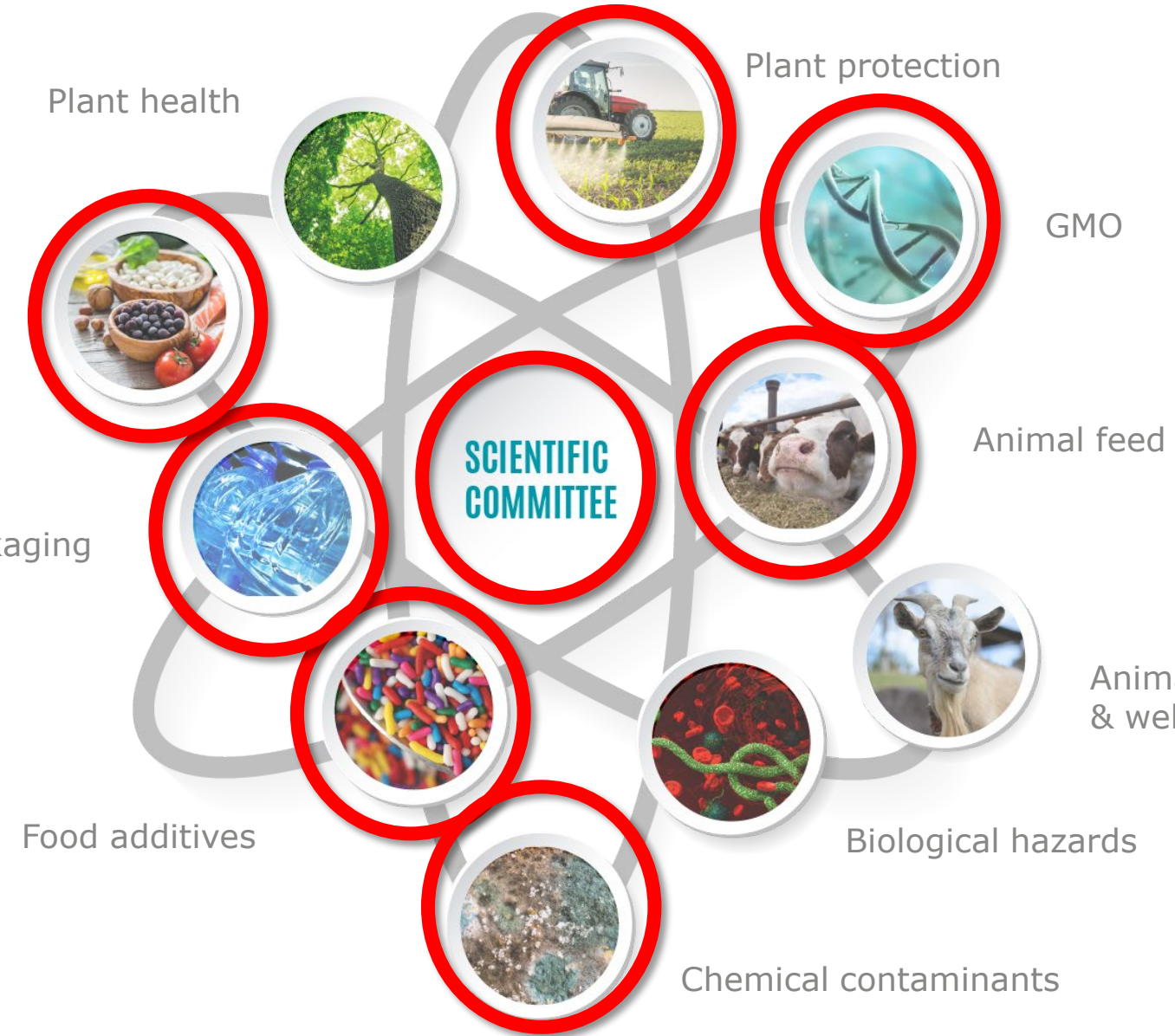
Regulated products

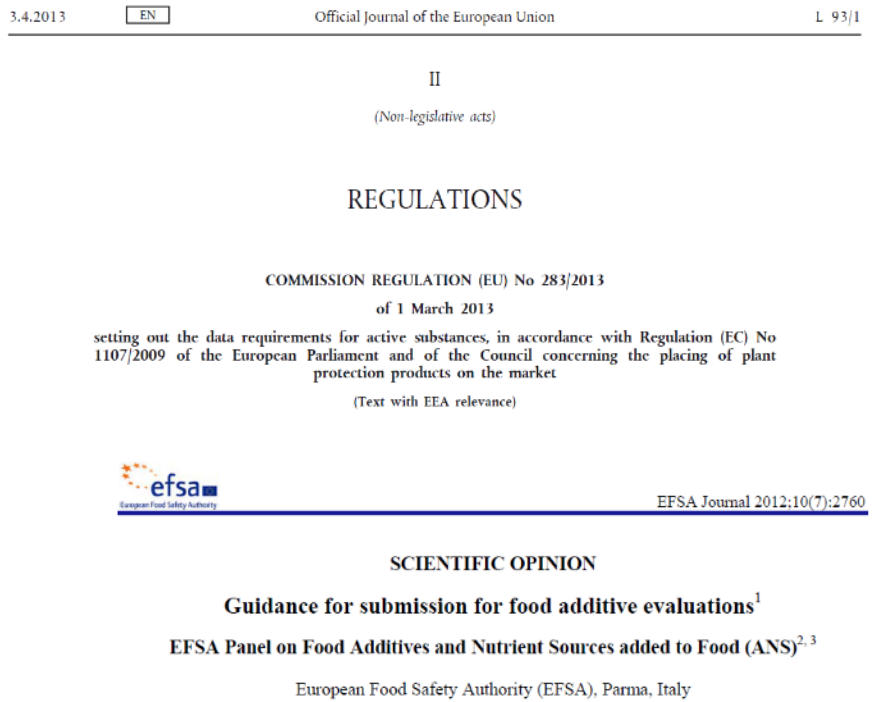
Contaminants

Applicants

No commercial producer

New chemicals or already on market





3.4.2013 EN Official Journal of the European Union L 93/1

II

(Non-legislative acts)

REGULATIONS

COMMISSION REGULATION (EU) No 283/2013

of 1 March 2013

setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

(Text with EEA relevance)

efsa European Food Safety Authority EFSA Journal 2012;10(7):2760

SCIENTIFIC OPINION

Guidance for submission for food additive evaluations[1]

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

Data requirements for food safety: PPPs

REGULATIONS

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INTRODUCTION

Information to be submitted, its generation and its presentation

1. The information submitted shall meet the following requirements.

1.1. The information shall be sufficient to evaluate the foreseeable risks, whether immediate or delayed, which the active substance may entail for humans, including vulnerable groups, animals and the environment and contain at least the information and results of the studies referred to in this Annex.

Data requirements for food safety: PPPs

SECTION 5. ***Toxicological and metabolism studies***

Introduction

5.1. Studies on absorption, distribution, metabolism and

5.1.1. Absorption, distribution, metabolism and excretion

5.1.2. Absorption, distribution, metabolism and excretion

5.2. Acute toxicity

5.2.1. Oral

5.2.2. Dermal

5.2.3. Inhalation

5.2.4. Skin irritation

5.2.5. Eye irritation

5.2.6. Skin sensitisation

5.2.7. Phototoxicity

5.3. Short-term toxicity

5.3.1. Oral 28-day study

5.3.2. Oral 90-day study

5.3.3. Other routes

5.4. Genotoxicity testing

5.4.1. *In vitro* studies

5.4.2. *In vivo* studies in somatic cells

5.4.3. *In vivo* studies in germ cells

5.5. Long-term toxicity and carcinogenicity

5.6. Reproductive toxicity

5.6.1. Generational studies

5.6.2. Developmental toxicity studies

5.7. Neurotoxicity studies

5.7.1. Neurotoxicity studies in rodents

5.7.2. Delayed polyneuropathy studies

5.8. Other toxicological studies

5.8.1. Toxicity studies of metabolites

Main sources and types of data received by EFSA

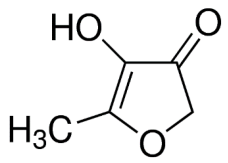
In vivo biological studies	• ADME studies • Following OECD TG and GLP criteria • Traditional TK parameters (Tmax, t1/2, AUC, analytical data, etc...)
In vivo toxicological studies	• Sub-chronic, chronic, repro-dev studies • Following OECD TG and GLP criteria • Traditional Tox parameters (biochemistry, histopathology, weight, food consumption, etc...)
In vitro studies	• Mainly for genotoxicity and metabolism • Following OECD TG and GLP criteria • Traditional parameters (biochemistry, markers for mutagenesis and chromosomal aberrations, etc..)

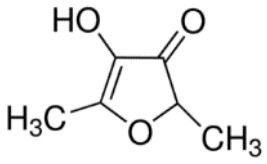
Traditional chemical risk assessment relies mainly on animal bioassays

EFSA’s use of alternative approaches in chemical risk assessment: the past two decades

What if there are no data: Non-testing methods

- (Q)SAR (Structure Activity Relationship test)
  - The basic assumption is that similar molecules have similar activities
  - Regression or classification models
  - Activity = f(physiochemical properties and/or structural properties) + error
  - (Q)SAR can predict certain simple endpoints
- Read-across
  - Non-test approach where endpoint information for one chemical (the source chemical) is used to predict the same endpoint for another chemical (the target chemical)
  - May be non-computational or computational





What if there are no data: Non-testing methods

- Threshold of Toxicological Concern (TTC)
  - Safe exposure levels can be deduced based on structural considerations

Classification	TTC value in µg/person per day	TTC value in µg/kg bw per day
Potential DNA-reactive mutagens and/or carcinogens	0.15	0.0025
OPs and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9.0
Cramer Class I	1800	30

Theophrastus von Hohenheim
'Paracelsus'
1493 (or 1494) - 1541

German: 'Alle Ding sind Gift und nichts ohn' Gift; allein die Dosis macht, das ein Ding kein Gift ist.

English: All things are poison and nothing (is) without poison; only the dose makes that a thing is no poison.

In vitro approaches for genotoxicity testing

- Established battery of in vitro tests
- When clear absence of genotoxicity there is no need for in vivo tests

TTC approach in chemical risk assessment

- Used by EFSA since 2004 for flavourings (EFSA Guidance from 2010 under review)
- For some impurities, metabolites and degradation products
- Pharmacologically active substances present in food of animal origin
- Combined exposure to multiple chemicals
- 2019 Guidance

Read-across in chemical risk assessment

- Flavourings
  - ✓ 1996-2006: Grouping of ~2650 existing flavourings into 34 groups of substances of structurally related compounds expected to show similar metabolic and biological behaviour
  - ✓ Flavouring Group Evaluations (FGEs)
  - ✓ Procedure for evaluation of new flavourings
- Combined exposure to multiple chemicals
  - ✓ Read-across from similar mixtures (sometimes referred to as sufficiently similar mixtures)
  - ✓ Grouping chemicals into assessment groups
- Food contact materials (ad-hoc)

The future of chemical risk assessment in EFSA: New projects, new challenges and new ambitions

Changing the way to do Risk Assessment: EC Policies

EUROPEAN COMMISSION

La stratégie de l'UE pour la durabilité dans le domaine des produits chimiques vers un environnement exempt de substances toxiques

Brussels, 14.10.2020
COM(2020) 667 final

Safety testing and chemical risk assessment need to innovate in order to reduce dependency on animal testing but also to improve the quality, efficiency and speed of chemical hazard and risk assessments.

COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS

Chemicals Strategy for Sustainability
Towards a Toxic-Free Environment

SCIENCE-POLICY INTERFACE

The Commission will:

- foster multidisciplinary research and digital innovations for **advanced tools, methods and models, and data analysis capacities**[102] to also move away from animal testing;

mb210624-a2

Stratégie 2027 de l'EFSA

Science

Sécurité des aliments

Durabilité

Adopté lors de la réunion du conseil d'administration
qui s'est tenue en mode virtuel le 24 juin 2021
Pour le conseil d'administration de l'EFSA
[SIGNÉ]
Raymond O'Rourke
Président du conseil d'administration

efsa
European Food Safety Authority

OBJECTIF STRATÉGIQUE 2

Assurer la préparation de l'EFSA pour faire face aux besoins futurs en matière d'analyse des risques

2.1.3 **Amélioration de la qualité des lignes directrices et des méthodologies scientifiques,** avec les capacités d'évaluation des risques nécessaires, **dans le but de relever les défis futurs.** Dans le cadre de ses approches d'évaluation des risques, l'EFSA développera et intégrera les nouveaux développements scientifiques en mettant l'accent sur les méthodes fondées sur les MNA, la réduction au minimum de l'expérimentation animale et les innovations dans les systèmes, les données et les technologies liées aux denrées alimentaires, et elle s'efforcera de répondre aux besoins de la politique «Une seule santé».

Résultat opérationnel escompté 2.1.3

Amélioration de la qualité des lignes directrices et des méthodologies scientifiques, avec les capacités d'évaluation des risques nécessaires, dans le but de relever les défis futurs

ACTIONS CLÉS

- Développer et intégrer les méthodologies de nouvelles approches (MNA) et les «omiques» pour l'évaluation des risques réglementaires

Read-Across Approaches for Food Safety

- Development for a **horizontal Guidance** on the use of RAx in EFSA and by its Scientific Panels
  - Testing the **regulatory applicability** of RAx to chemicals in remit of food safety
  - Testing opportunities for biological RAx
  - Testing opportunities to underpin RAx with NAM
- Procurement to test RAx using EFSA's database on plant protection products

Recent Sectoral Guidance Documents: Opportunities for NAMs

GUIDANCE

EFSA Journal

ADOPTED: 30 June 2021

doi: 10.2903/j.efsa.2021.6768

Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health

EFSA Scientific Committee,

In vitro studies may provide mechanistic information on the **toxicokinetics and toxicodynamics** of the nanomaterials.

GUIDANCE

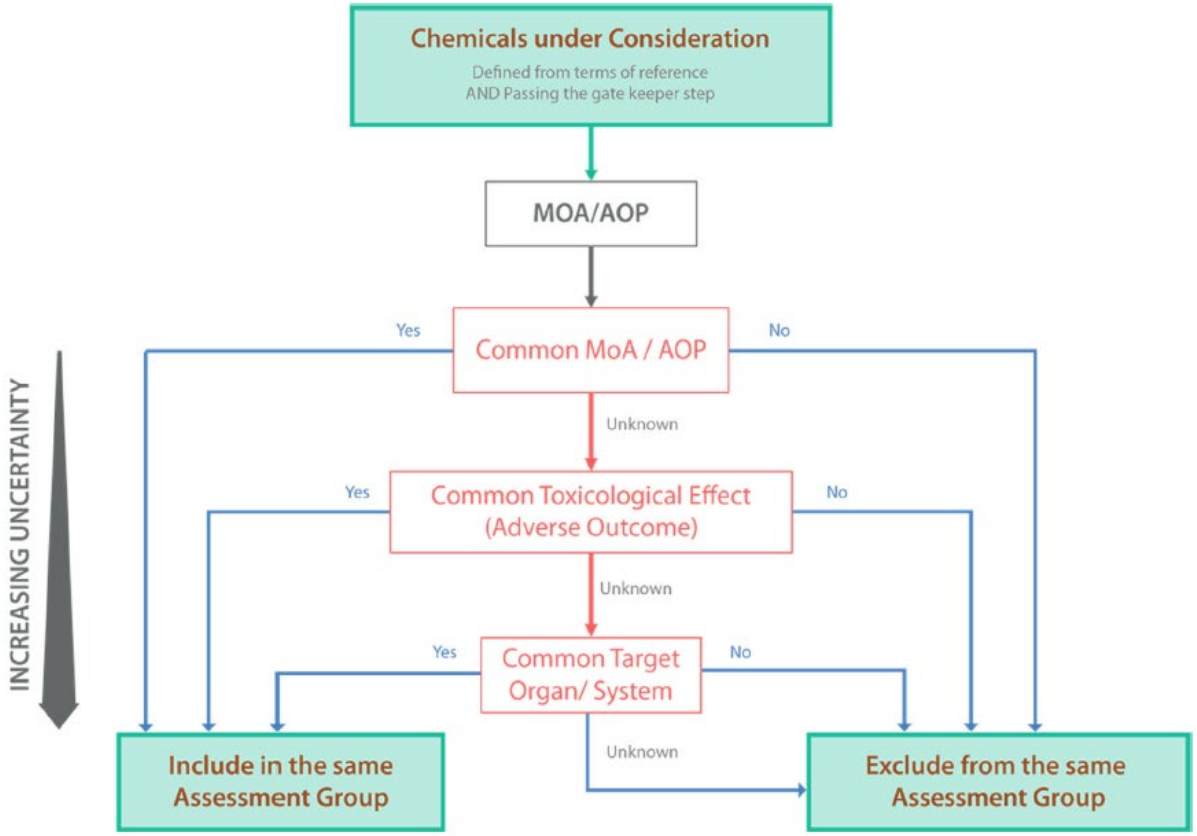
EFSA Journal

ADOPTED: 17 November 2021

doi: 10.2903/j.efsa.2021.7033

Guidance Document on Scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals

EFSA Scientific Committee,



DNT

SCIENTIFIC OPINION

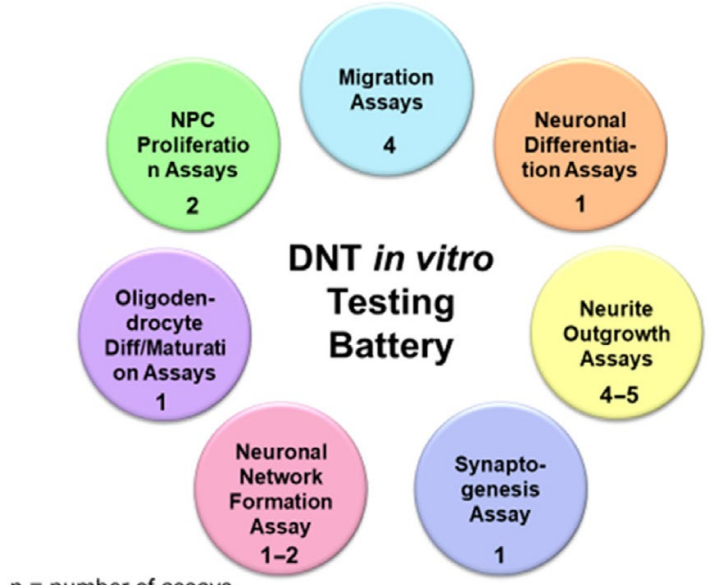
EFSA Journal

ADOPTED: 21 April 2021

doi: 10.2903/j.efsa.2021.6599

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),

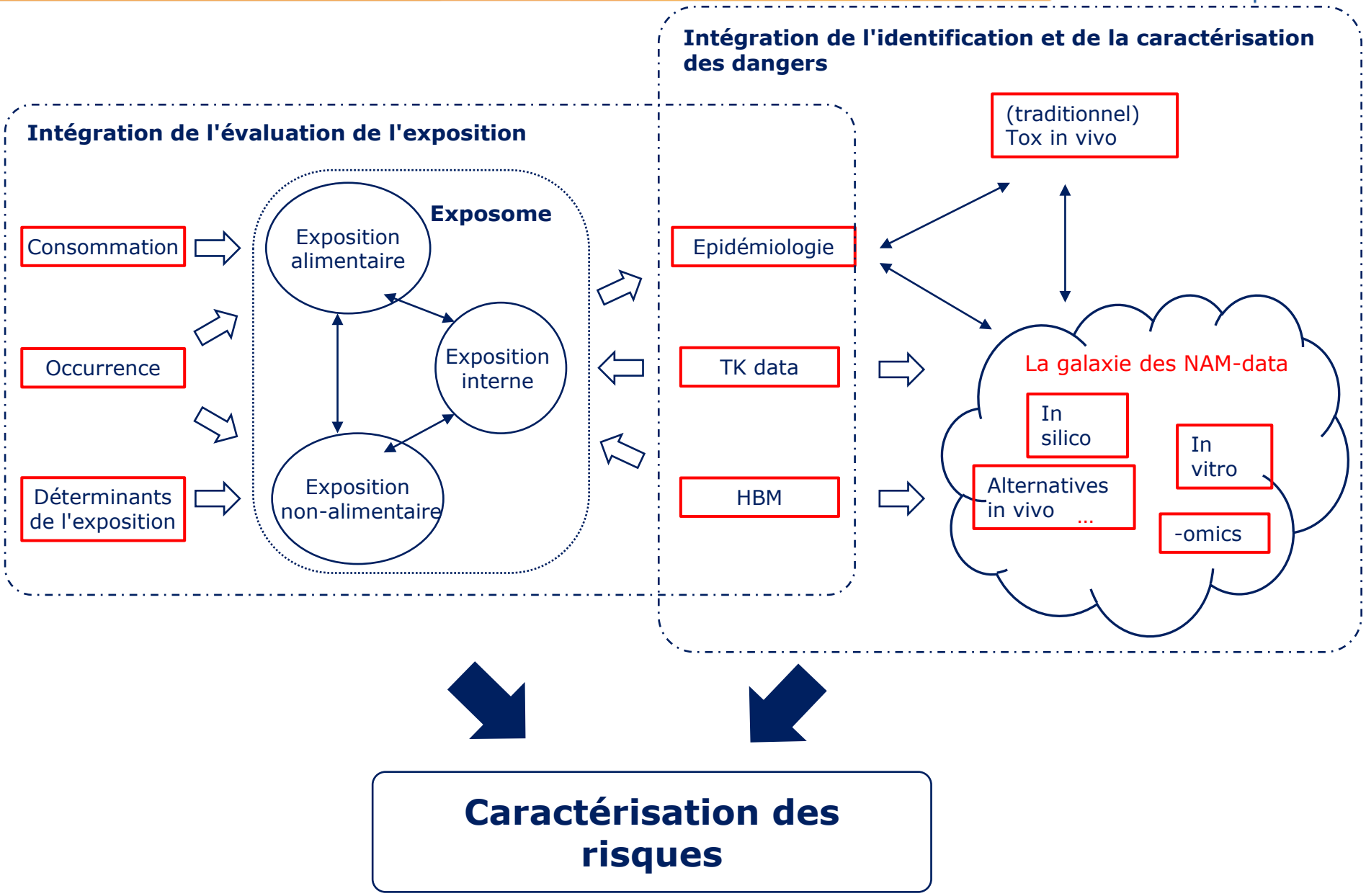


- **The IATA were developed to assess the applicability of the DNT in vitro testing battery (IVB), designed to explore fundamental neuro-developmental processes, in the regulatory risk assessment of pesticides**
- **Case studies** show the applicability of the DNT-IVB for hazard identification and characterisation and illustrate the usefulness of an AOP-informed IATA for regulatory decision making.

Collaborative (outsourced) NAM case studies

- Pesticides: neurodegenerative diseases
- Nanomaterials: GI uptake and genotoxicity
- Artificial intelligence for NAMs
- PFAS immunotoxicity
- ADME4NGRA
- NAMS4NANO: Integration of New Approach Methodologies results in chemical risk assessments: Case studies addressing nanoscale considerations
- Human variability in toxicodynamics (qAOPs)
- TKplate 2.0 (Open-Source Platform integrating PBTK Models and Machine Learning Models)

Notre vision



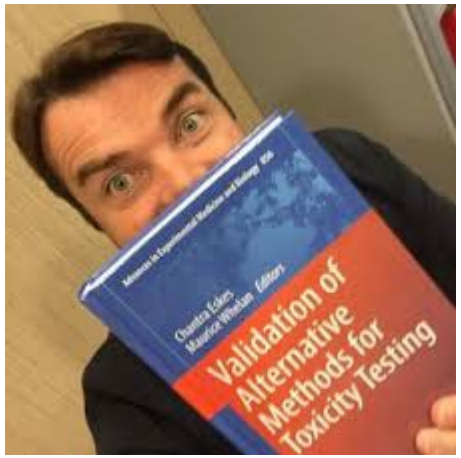
EFSA's Engagement: EU Landscape

Draft proposal for a European Partnership under Horizon Europe

Partnership for the Assessment of Risk from Chemicals (PARC)

Version 03/06/2020

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing



ASPIS Consortium (RISK-HUNT3R, ONTOX and PrecisionTOX)

efsa
European Food Safety Authority

epaa
The European Partnership for Alternative Approaches to Animal Testing

EUTOXRISK

EFSA's Engagement: International Landscape

OECD

efsa
European Food Safety Authority

World Health Organization

Food safety agencies

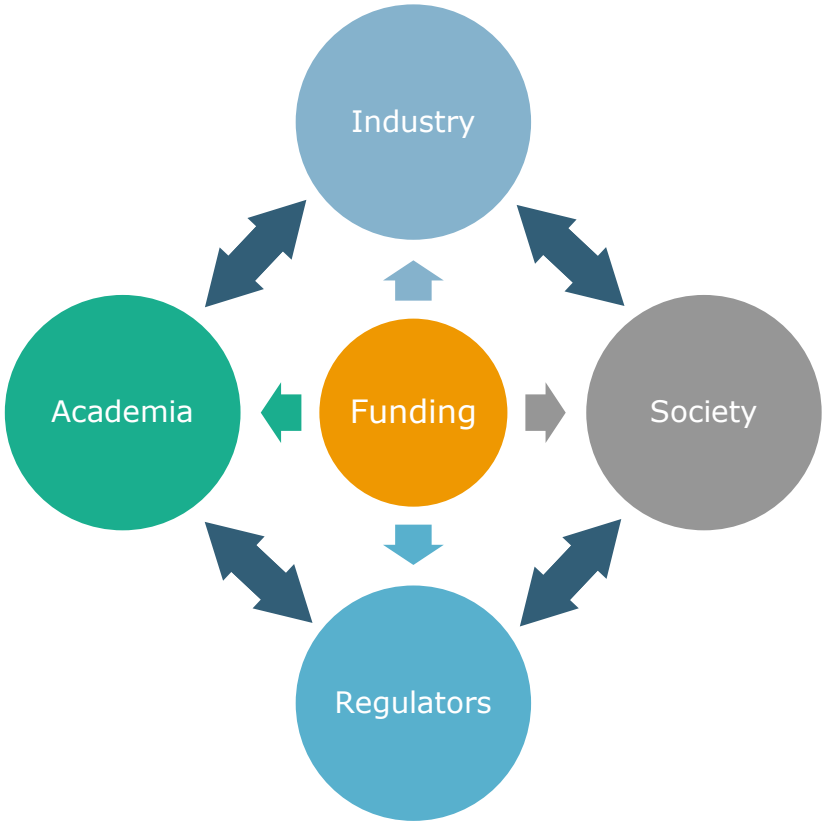
ILMERAC

Global Coalition for Regulatory Science Research

Some final thoughts – how to move to NGRA?

Vision, expectations and opportunities

Collaboration, acceptability and sustainability



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