7-8-9 March 20222

Introduction to the european stakeholder workshop on NAMs for DNT and their use in the regulatory risk assessment of chemicals

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INTRODUCTION

- Developmental neurotoxicity refers to “any adverse effects on the normal development of the nervous system structure or function”.
- The current testing paradigm based on ***triggered*** DNT guideline study requires an assessment of motor and sensory function, learning and memory, and neuropathology following maternal exposure.
- A relevant uncertainty of the **traditional approach** is that generally, chemicals for which data are insufficient, are typically treated as not hazardous, that non-tested chemicals are often substituted for hazardous chemicals, and cumulative exposure and risk are often ignored.
- NAMs are offering an opportunity for a fit for purpose testing strategy in the context of an IATA framework.

The challenge

- **Effective regulation of chemicals is crucial for health, the environment and commerce.**
  - How to achieve it is not straightforward.
- **An effective science-policy interface is necessary, and therefore we are here.**
- **The field of regulatory toxicology is challenged by profound changes with respect to methods and approaches for generating evidence.**
- **We should understand the main challenges in chemicals regulation and the main obstacles to the acceptance of New Approach Methodologies (NAMs).**
- **We therefore need a road map for bridging between different scientific methods, approaches and forms of data and evidence to regulatory processes/legislations.**

THE MAIN GOAL

- **The goal is to assess any regulated chemical for DNT using an integrated approach (IATA) and minimize the request of DNT in vivo guideline studies; this throughout an effective science-policy interface**

- **What does this mean for the European chemical regulations (pesticides, biocides, reach)?**
  - What we need in the short term to reach the goal ?
  - What level of uncertainties are we ready to accept by changing paradigm, against the non-testing alternative ?
  - What are the critical scientific and legislative regulatory hurdles to include the DNT-IVB in the regulatory chemical risk assessment ?

Enjoy the workshop

Questions will be Addressed during "DISCUSSION" at the end of the presentations at 17.00.

Please, indicate name and affiliation and to whom the question should be addressed

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Decision tree: A case for pesticides

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Legislative background

- **COMMISSION REGULATION (EU) No 283/2013**
  - When indicated by **observations in other studies** or the **mode of action** of the test substance, *supplementary* studies or information may be required to provide information on the postnatal manifestation of effects such as developmental neurotoxicity.

Legislative background

- **3.6. Impact on human health**
- **3.6.1.** Where relevant, an ADI, AOEL and ARfD shall be established. When establishing such values an appropriate safety margin of at least 100 shall be ensured taking into account the type and **severity** of effects and the **vulnerability of specific groups** of the population. When the critical effect is judged of particular significance, such as **developmental neurotoxic** or immunotoxic effects, an increased margin of safety shall be considered, and applied if necessary.
- **4. Candidate for substitution**
  - there are reasons for concern linked to the nature of the critical effects (**such as developmental neurotoxic** or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones).

ASSUMPTIONS MADE

- The DNT-IVB is a standard data requirement (as part of the MOA information).
- OECD TG DNT studies are considered *in-vivo screening* methods for DNT.
- The level of uncertainties for the DNT-IVB and the *in-vivo* screening test are similar.

- **Problem formulation**:
  - Single chemical hazard assessments when no *in-vivo* DNT data exists.

Available evidence: Tier 1

Chemical structure

Available in-vivo data

- Clinical signs
- Pathology
- Data requirements

Mode of action data

- Pesticide MOA
- *Toxicology MOA ?*

Systematic review

DNT -IVB

- Activity
- Selectivity
- Potency

No hits or inconclusive

Hit specific Tier 2

Perform IATA

- Use metabolically competent methods or test for metabolites.
- Systematic review.
- PB/PK.
- In-vivo DNT screening test can still be necessary based on available evidence and Uncertainty Analysis (UA) e.g. pesticide MOA, endocrine mechanisms.

Available evidence: Tier 2

Orthogonal analysis

- More replicates, modify concentration range
- Orthogonal assays
- Cytotoxic burst range

In-vitro species differences

- Rat vs. human test systems

Accuracy in concentration estimates

- Chemical partitioning
- Intracellular concentration

Exposure assessment

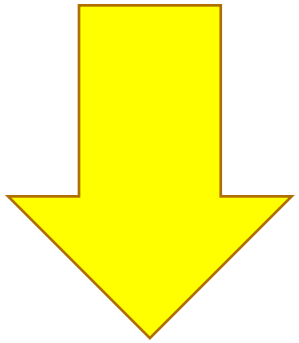
- ADME parametrized IVIVE
- Reverse dosimetry
- in-vivo validation
  - total and free plasma TK
  - total and free brain TK

Regulatory need met
Use as POD

Unacceptable level of uncertainties Tier 3

Available evidence: Tier 3

- **ANIMAL TESTING**
  - Animal model tailored to reduce the uncertainty
    - Ability to measure the adverse outcome or KEs of concern
    - Appropriate dose selection and dose administration scheduling (e.g. use ADME data, placental and milk transfer, brain concentrations)
    - Kinetics that can be modelled and extrapolated to humans



REGULATORY DECISION

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Question 1, slide 1

- **What is necessary for the inclusion of the DNT-IVB as data requirement in different EU legislations (REACH, BPR, pesticides)? Identification of critical gaps, next steps**
  - Important consideration is whether the IVB is part of available information (additional data) or a data requirement.
    - When considering the DNT-IVB as a set of available information, this doesn't need any additional effort and can be considered as ready to use. There is therefore a recognition that the information provided through the different Institutional and Academic organizations has a sufficient level of "Scientific Validation" and associated uncertainties, and can be used as fit for porpoise information in IATA and as part of the WOE in DNT hazard identification and characterization.
    - When considering the DNT-IVB as a data requirement, additional work is necessary for the regulatory application; independently from the legal framework. This is because, using the DNT-IVB as data requirement, implicitly indicates that the data will be used for regulatory decision. The following where the points considered by the group:
      - Inter-laboratory transferability and reproducibility over time
      - Blinded procedures for execution of the testing
      - **There is a recognition that several EU projects are very active in looking after test readiness and scientific validation, but a similar effort should be put in moving towards regulatory application, i.e. laboratory accessibility, transferability and reproducibility**
      - This implicitly indicates that a suitable method description and guidance for the interpretation of the results should be available (OECD TG ?)

Question 1, slide 2

- **What is necessary for the inclusion of the DNT-IVB as data requirement in different EU legislations (REACH, BPR, pesticides)? Identification of critical gaps, next steps**

- The group , considered this step (the inter laboratory transferability and reproducibility) as scientific and formally relevant, but is also considering that the DNT is representing an opportunity to include the outcome from NAMs as a set of information to be used across different legislations, including GHS/CLP.
- The group also discussed how to proceed along this process and who should found this activity.
  - Feedback was given by EC, JRC, EFSA, ECHA, Industry and OECD
  - Private providers of laboratory services should be included in the discussion at an appropriate time
- It was clear to the group that the ownership of the process and the expertise sit in the PARERE/JRC institution
- The interlaboratory transferability/reproducibility, and laboratory accessibility is considered by the group as a relevant step in any road map for the inclusion of the DNT IVB as data requirment

Question 2 slide 1

- **What could be potential option(s) for the use of DNT-IVB in DNT hazard and risk assessment?**
- The group supports the examples and proposals presented at the workshop:
  - read across and WOE (ECHA)
  - IATA case studies
- The group appreciate that the DNT IVB can be used as option in the hazard characterization and RA
  - How to use these data as POD remains a challenge that should be further evaluated and included in the road map as part of the tiered approach
  - ADME parametrized QIVIVE is seen as an opportunity. The group is aware of the challenges and that methodologies and methods description should be implemented for the regulatory implication; though the tandem use of self method validation throughout tailored TK studies could alleviate several of the uncertainties in the application of an ADME parametrized QIVIVE methodology

Question 3

- What would be a suitable tiered approach for using the DNT-IVB in the different regulatory legislations?
  - one approach may not fit to all regulatory frameworks
  - a need to update the current approaches.

  - For the use in risk assessment a tiered approach should be defined as part of the road map for inclusion of the DNT-IVB in the process
  - The group discussed that for REACH a specific road map may be required considering that the available evidence (data requirements) are very different from other legal frameworks
  - The group briefly commented that it is difficult to understand why, two similar regulations, like PPP and BP, are having a different approach, with BP asking for the in vivo DNT arm as a standard data requirement, while for PPP DNT studies are triggered by evidence /concern in the dataset
  - The group underlined that the DNT IVB is indeed offering an opportunity for using NAMs for CLP; this discussion was very much appreciated.

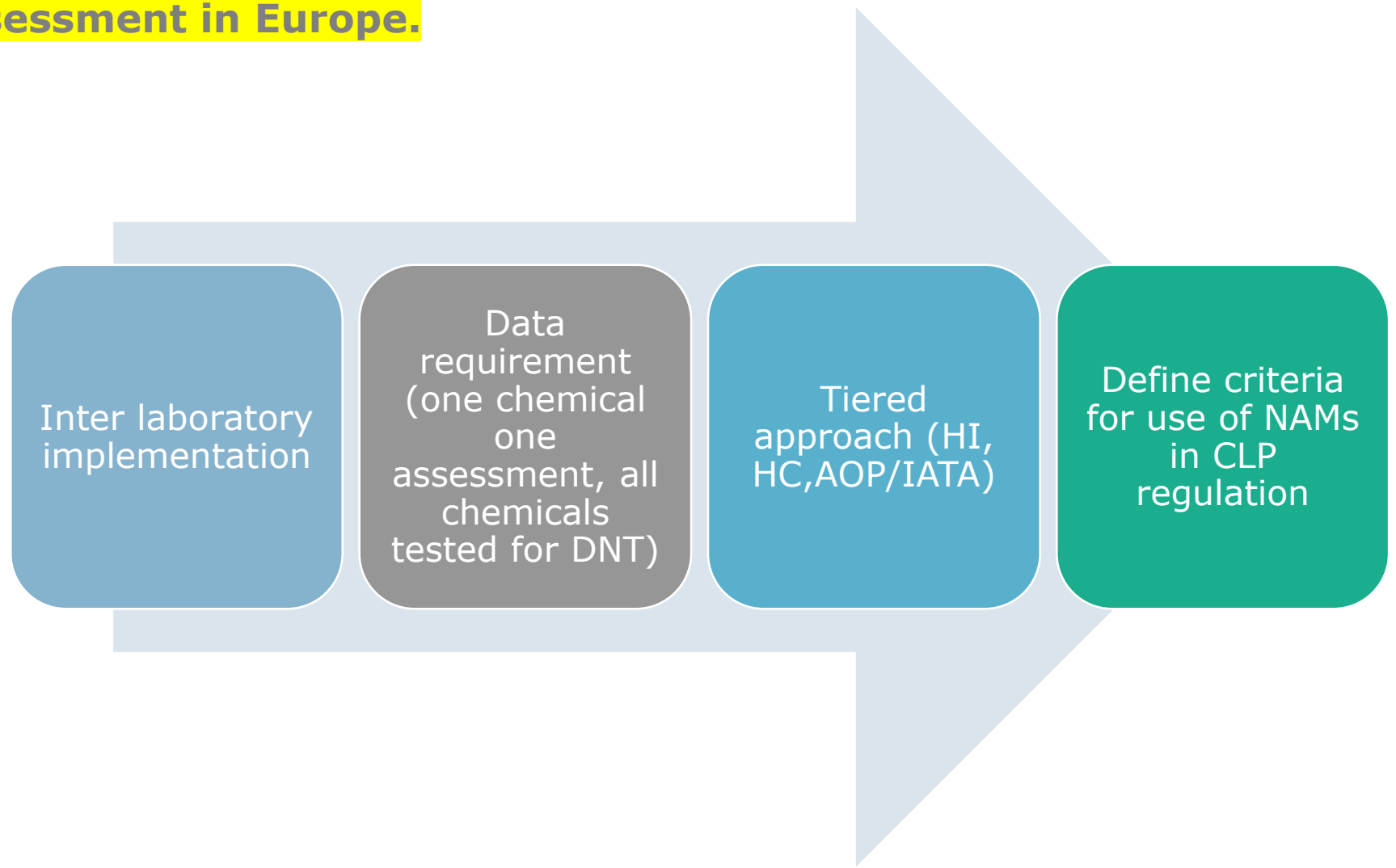
Question 3

- What would be a suitable tiered approach for using the DNT-IVB in the different regulatory legislations?
  - one approach may not fit to all regulatory frameworks
  - a need to update the current approaches.

  - Using a standard Risk Assessment paragdim, the following tiered approach is a possibility:
    - DNT IVB= hazard identification
    - QIVIVE, ADME parametrization, in vivo self-validating TK= hazard characterization
      - This step is indeed a step common to all NAMs and should be clearly described (regulated?)
    - AOP= human relevance

Question 4

- **Road map proposal for the integration of the DNT IV-B in the Chemical Risk Assessment in Europe.**



Concluding remarks

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The initial objective

- **The goal is to assess any regulated chemical for DNT using an integrated approach (IATA) and minimize the request of DNT in vivo guideline studies; this throughout an effective science-policy interface**

- **What does this mean for the European chemical regulations (pesticides, biocides, reach)?**
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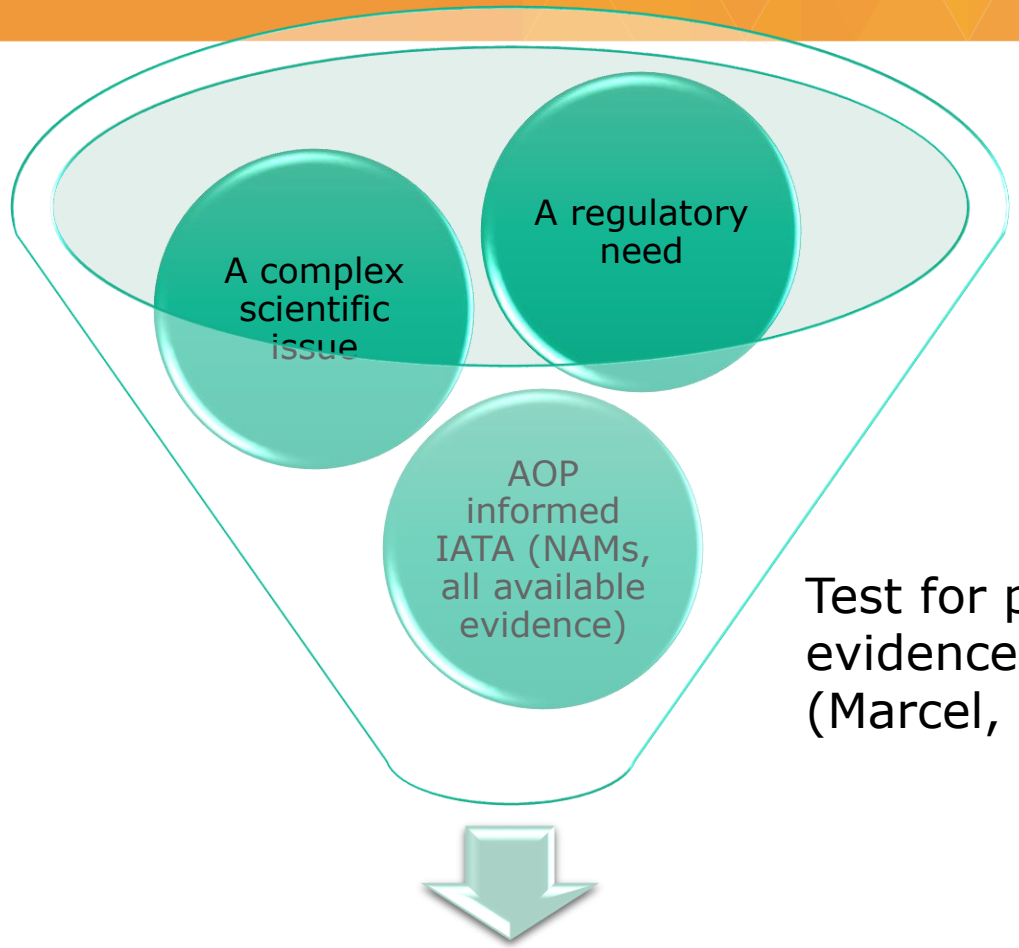
Day 1 High standard presentations, a common ground

Understanding key brain developmental processes (Marcel & Ellen)

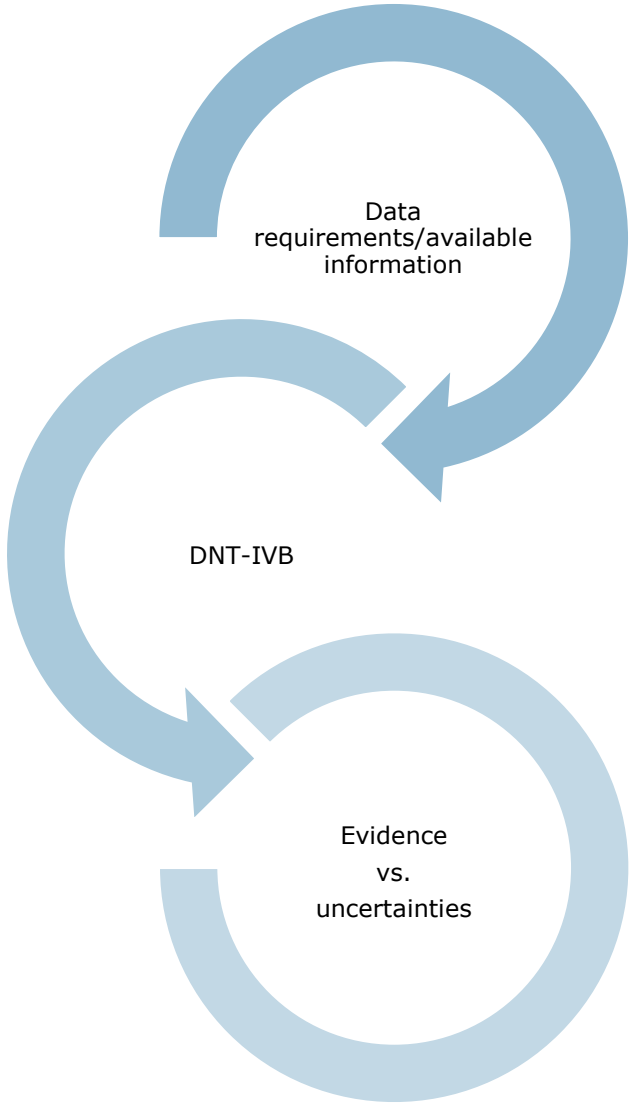


European chemical strategy (Karin)

Test for processes and contextualise evidence vs. uncertainties (Marcel, Martin, Ellen, Kevin, Iris)

Regulatory decision (stakeholders)

DAY 1 An iterative process (outcome of the discussion)



Jurisdiction specific

Scientifically validated

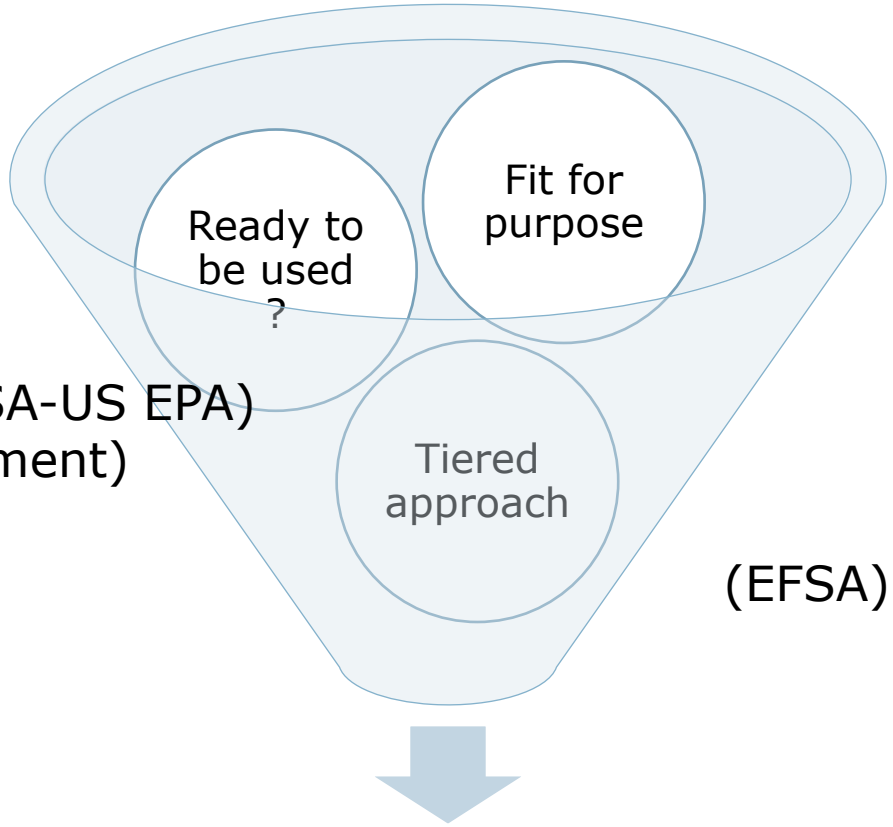
IATA (tiered approach)

DAY 1 conclusive remarks, a common starting point

- All chemicals should be assessed for DNT.
- We can conceptually indicate that the in-vivo DNT test guideline studies and the current DNT-IVB have a similar level of uncertainties.
- The DNT-IVB has a fit for purpose level of scientific validation.
- The use of the DNT-IVB, across different jurisdictional scenario, would benefit of an OECD guidance.

Day 2 The complexity of the real world; opening a new door

Read cross & WOE (ECHA)
IATA case studies (EFSA)
US EPA (case studies, approach similar to EFSA(PPPs))
HC-PMR (approach similar to EFSA-US EPA)
Industry (validation as a key element)



Limitations in the use of NAMs in the current regulatory framework (ECHA)

(EFSA)

Breakout sessions

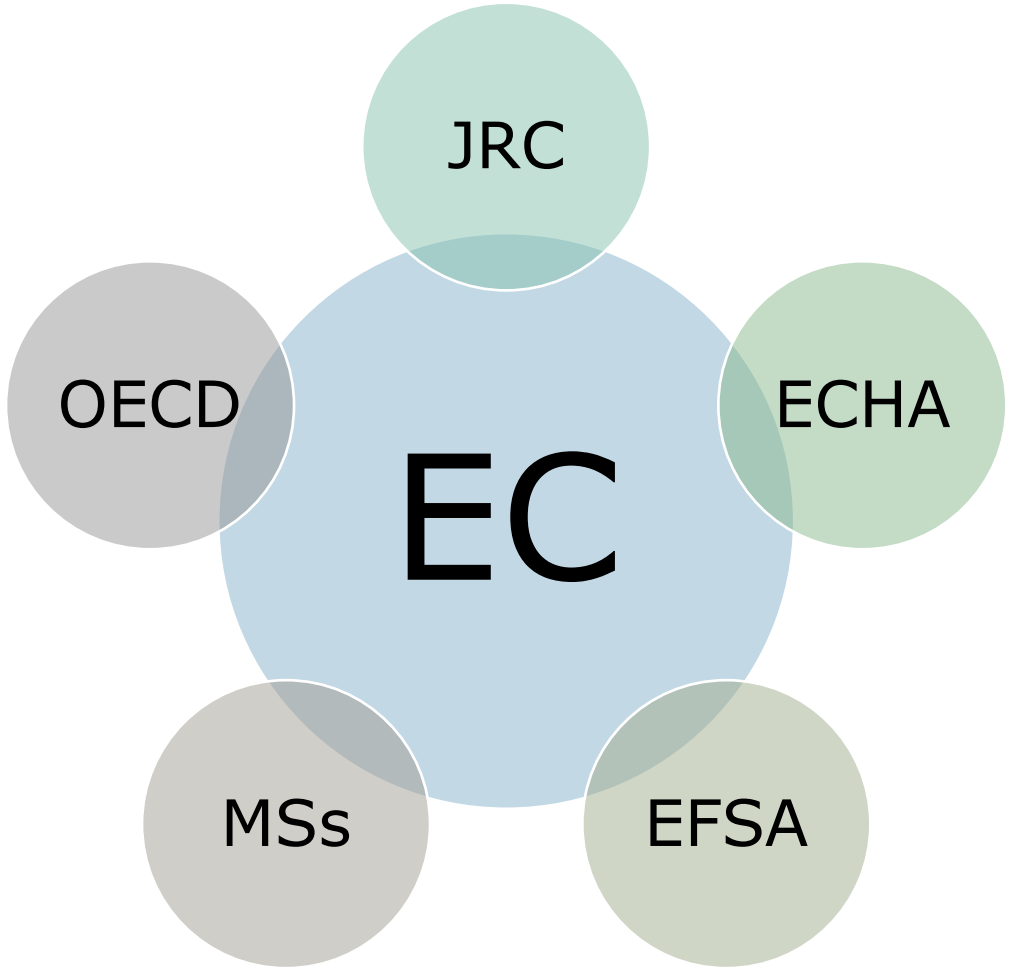
Final discussion and remarks

- The mechanistic (scientific) validation of the DNT IVB is considered sufficient for regulatory applications
- The OECD GD would allow the use of DNT NAMs in the IATA context
- The OECD GD, inspirational for more specific GDs and tiered approach
- **The accessibility to the methods**
  - Intra-laboratory…. OK
  - Inter-laboratory…. TBD
  - TG….TBD
  - **Funding issue to be resolved**

Final discussion and remarks

- Road map
  - OECD in vitro DNT GD √
  - Interlaboratory reproducibility using a selected list of chemicals ?
  - TG ?
  - Tiered approach ?
  - An EFSA ECHA DNT GD ?
  - Update data requirements ?
  - Training of regulators ?
- Continue to work on the in vivo/in vitro database
  - Detailed correlative analysis
  - Detailed uncertainty analysis
  - Understand the limitations of both in vivo and in vitro models to prioritize additional methods to be developed to complement the existing one, filling gaps and reduce uncertainties (e.g. test system, analytical methods, more specific in vivo testing)
  - Do more testing in vitro (this remains always as part of the solution)
  - Do more IATA using all available data

So what ? The need is clear and the DNT IVB is a suitable tool. Fix the next steps; interlaboratory transferability, define a tiered approach …….



Agenda:
Ownership of the process
Timeline
Funding

Discuss alternatives as a contingency plan:
-More testing
-EFSA/ECHA GD

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