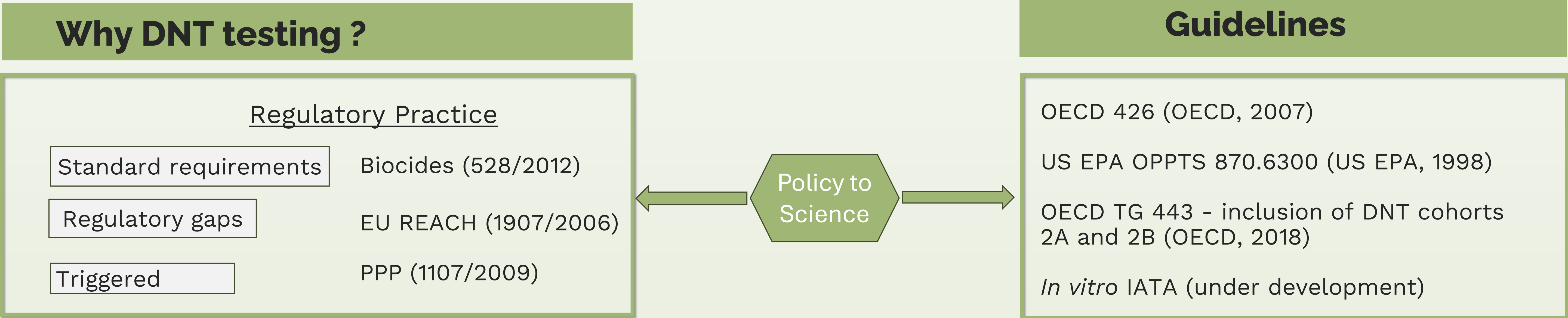
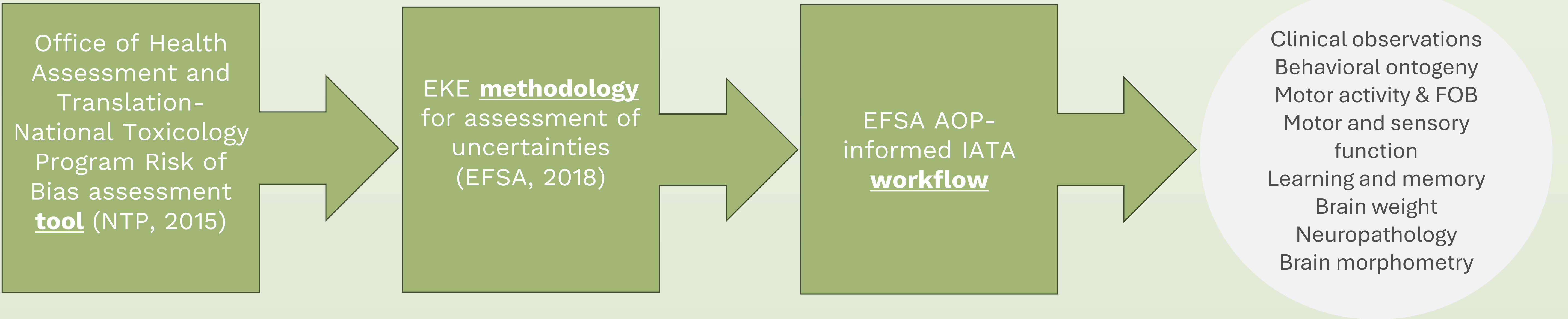


Challenges in the interpretation of DNT endpoints and their regulatory implications

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Tools, methodology and workflow for assessment

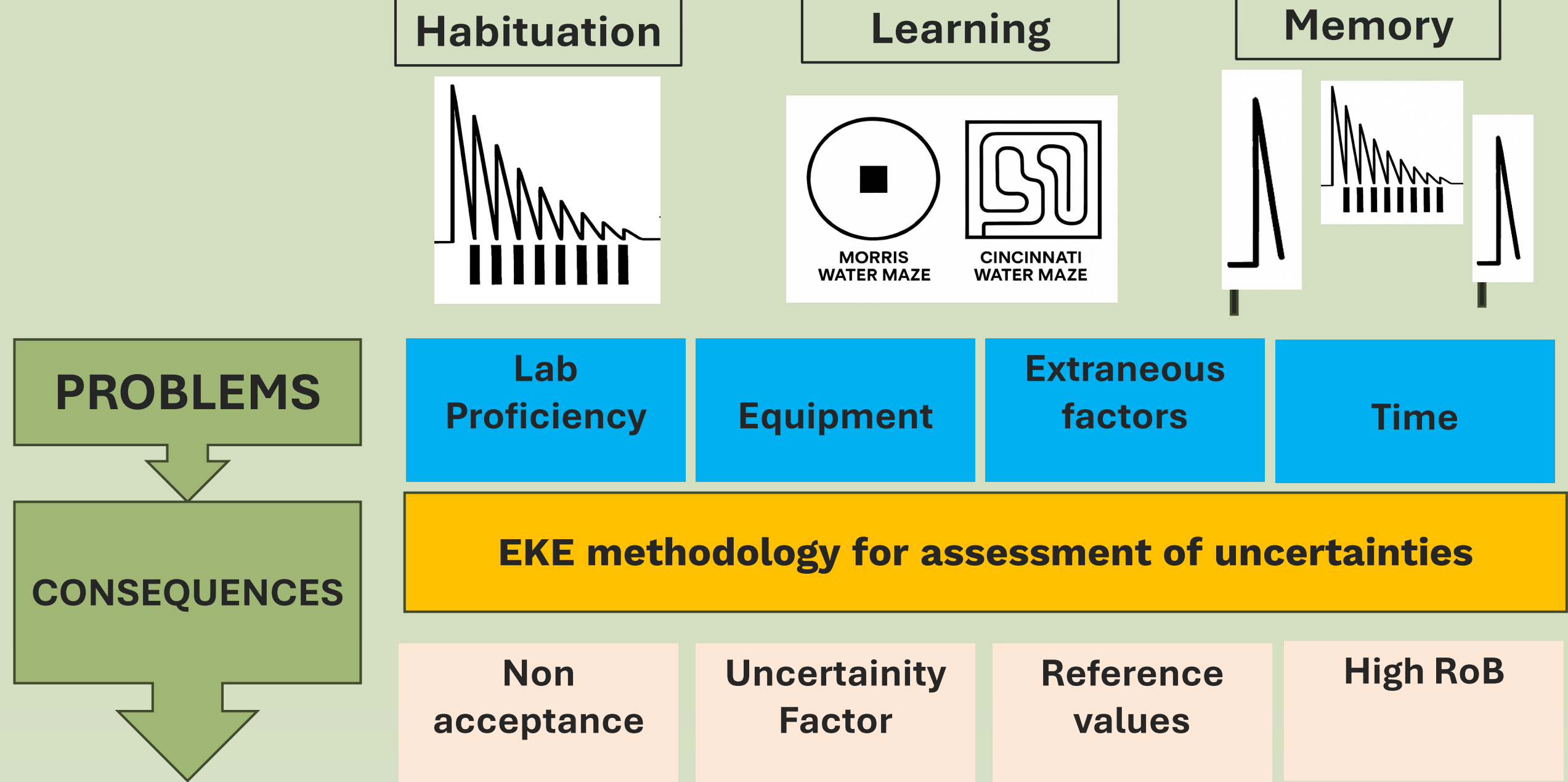


Challenges

- **Goals** – OECD 443 (fertility) versus OECD 426 (neurotoxicity)
- **Exposure duration** - OECD 443 (post weaning) versus OECD 426 (PND 21)
- **3R versus integrity and variability** (MWM - allocentric, CWM – egocentric)
- **Lack of age dependent control responses**

Critical appraisal tool

- Randomization, Allocation concealment, Experiment conditions, Research personnel blinded, Attrition, Exposure characterization, Outcome assessment, Outcome reporting, Systemic or maternal toxicity
- Bias domains (selection, performance, attrition/exclusion, detection, selective reporting and other sources of bias)



Conclusion

- **Important to consider factors for RoB and uncertainties**
- **Integrity of DNT study is imperative for concrete conclusion**

Acetamidrid

Non-acceptance of learning and memory, motor activity and morphometric measurements

Biel Water Maze

- Learning not demonstrated
- Variability in groups
- Inconsistent pattern

Morphometric analysis

- Poor reporting
- Data gap at low and medium doses

HCD - inappropriate

PCD - motor activity

- Habituation not measured

PCD - learning and memory

- No learning curve
- No effect on errors
- Same increase in latencies

Acceptable for the **auditory startle response***. Additional UF of 5 to derive acceptable daily intake (ADI)* and acute reference dose (ARfD)*

Flufenacet

- Low ROB (Tier 1) for Learning and memory

- High ROB (Tier 3) for
- Neurohistopathology - one or two doses were evaluated

Deltamethrin

Missing KEs

- Neuronal network function (KE4)
- Hypomyelination (as a result of KE5)
- Altered behavioural function (AO)

Moderate ROB (Tier 2)

- Lower weight gain
- Low effect size
- Lack of positive and historical control data

Imidacloprid

- LOAEL : ↓ thickness of the caudate/putamen and corpus callosum.
- UF of 10

- Uncertainties in neuropathology

References:
NTP (2015) NTP (National Toxicology Program), OHAT Risk of Bias Rating Tool for Human and Animal Studies.
EFSA (2018) EFSA Guidance on uncertainty analysis (EFSA and EBTC, 2018; EFSA Scientific Committee, 2018a, 2018b).
OECD (2022) Case studies on deltamethrin, flufenacet and imidacloprid for the integration of in vitro data in the developmental neurotoxicity hazard identification and characterization
EFSA (2024) Statement on the toxicological properties and maximum residue levels of acetamidrid and its metabolites

