OVERVIEW OF RECENTLY ADOPTED NAM OECD GUIDELINES AND FUTURE WORKPLAN

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BETTER POLICIES FOR BETTER LIVES

NEW APPROACH METHODS (NAMs)

- What are NAMs?→ all methods that are not based on an animal study
  - Grouping of chemicals and read-across
  - In vitro assays
  - In silico, computational methods, (Q)SARs
  - Integrated approaches that combine any of the above methods
- Some NAMs are amenable to standardisation, others not, because they depend on the chemicals assessed or on the context of use

What is the OECD doing on NAMs?

- For NAMs that are not intended (or not yet) for (method) standardisation:
  - IATA case study project: annual cycle of review of case studies submitted by stakeholders
    - Outcome: lessons learnt and considerations for possible additional guidance, templates, formats

What is the OECD doing on NAMs?

- For methods that are amenable to standardisation:
  - Ex vivo/in vitro/in chemico/in silico methods
  - Combination of the above
    - Defined Approaches
- It is possible to develop Test Guidelines for NAMs
  - NAMs also need validation for data generated to be covered by MAD
  - There can be intermediate steps towards standardisation into TGs
    - e.g. case, studies, standardisation of reporting formats….
      - Each step counts

Achievements in the last 20 years

Primary/permanent tissues/cells from donors (rats, humans, fish)

Organotypic test systems

Reconstructed human tissues/ human-derived test systems

Cell-free test systems

Combination ofmethods

- [Genetic toxicity (many in vitro TGs)]
- Dermal absorption (TG 428 [2004])
- Skin corrosion (TG 430, TG 431, TG 435) [2004]
- Skin irritation (TG 439 [2010])
  - Guidance Document on IATA for skin irritation/corrosion (GD 203)
- Eye irritation (TG437, TG438, TG491, TG 492, TG496) [2009]-ct'd
  - Guidance Document on IATA for skin irritation/corrosion (GD 263)
- Skin sensitisation (TG 442C, TG 442D, TG 442E, TG 497) [2014])
  - AOP and KE-based TGs
  - standardised combinations (e.g. DASS) [2021]
- Fish gill cell line for acute toxicity (TG 249) [2021])

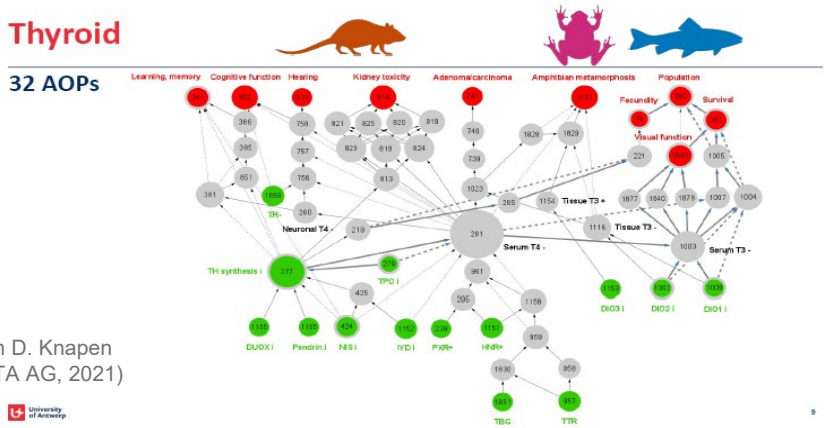
All along, the **OECD Guidance Document 34** has been the guide for getting these NAMs validated and accepted for regulatory use

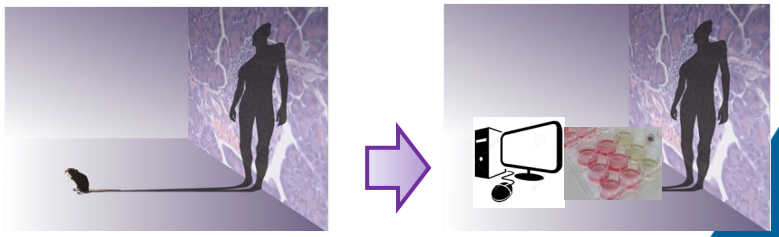
Other evolutions/milestones in the last 20 years

- Biotech revolution and innovative solutions
  - Recreating the biology, increasing throughput level
  - Adding computational elements, increasing capacity with machine learning, algorithms
  - Economic costs becoming affordable
- Animal testing bans for cosmetics spreading across countries
- 2012: AOP framework developed
  - Increased mechanistic understanding of chemical interactions with the biology leading to adverse effects
  - Anchoring in vitro assays in human-relevant biological processes
  - From data management to knowledge in action

How to build confidence NAMs are as protective as animal tests?

- Global datasphere
  - 90% of the data in the world was generated in the last 2 years
  - Increased usage of human biomonitoring/clinical data
  - Large database of chemical safety information has allowed analyses of information leading to
    - Better understanding of structure-function relationships
    - Better understanding of exposure-outcome relationships and taxonomic applicability
    - Better predictive models





From D. Knapen (EDTA AG, 2021)

What regulators say about acceptance of NAMs?

- Regulators say robust systems/methods are needed to make decisions that relate to public health and environmental protection
  - Reproducibility/reliability are essential
  - Transferability remains very important, but principles may need to/could be adapted for sophisticated systems
  - Regulatory relevance is important, but represent different realities (see GD 34)
    - Quantifiable aspect: accuracy/predictive capacity (%spec, %sens) for target species
    - Non quantifiable aspect: "*whether the test method is meaningful and useful for a defined purpose*" → fit-for-purpose, context-dependent

Where can we gain efficiency?

- Forget about NAM one-to-one replacement:
  - Predictive capacity alone may no longer be a good measure of relevance
  - Increase weight of mechanistic (human)relevance (e.g. key event in AOP)
    - Mechanistic relevance of measurements, biomarkers
  - Think about combinations of robust information sources:
    - Different combinations;
    - Apply combinations in case studies to show value;
    - Define applicability (and known limitations) and document performance;
    - Increase standardisation and transparency: description (non)test and data interpretation procedures, use of reporting formats.
  - Start thinking of defining adversity in NAMs
    - Use case studies as a vehicle

Validation essential to show reproducibility

- Plan validation (incl. funding) to show information sources are robust and reliable:
  - Build and curate reference chemicals datasets;
  - Demonstrate transferability and reproducibility of experimental results between labs using reference chemicals;
    - Longer term thinking needed to enable method developers to show robustness and reliability of methods and technologies with more limited transferability, using the concept of standard

Current activities- Test Guidelines and Hazard Assessment Programmes

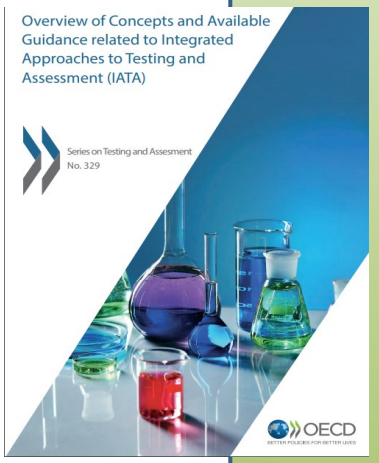
- Promotion and support of AOP development and associated knowledge base
  - Identification of testable key events

- Promotion of good practices to integrate innovation in regulatory standards
- Promotion of Good in vitro Methods Practice (GD 286)

- Identification of alternative methods for complex endpoints
  - Case studies applications, IATA (GD 329)

- Development and promotion of standard reporting templates
  - OHT 201, Omics reporting templates

- Standardisation of non-animal methods (skin sensitisation, ED DNT,...)
- Combination of methods in IATA and Defined Approaches towards integration in Test Guidelines covered by MAD



Regulatory research

Regulation

Projects on the TGP work plan

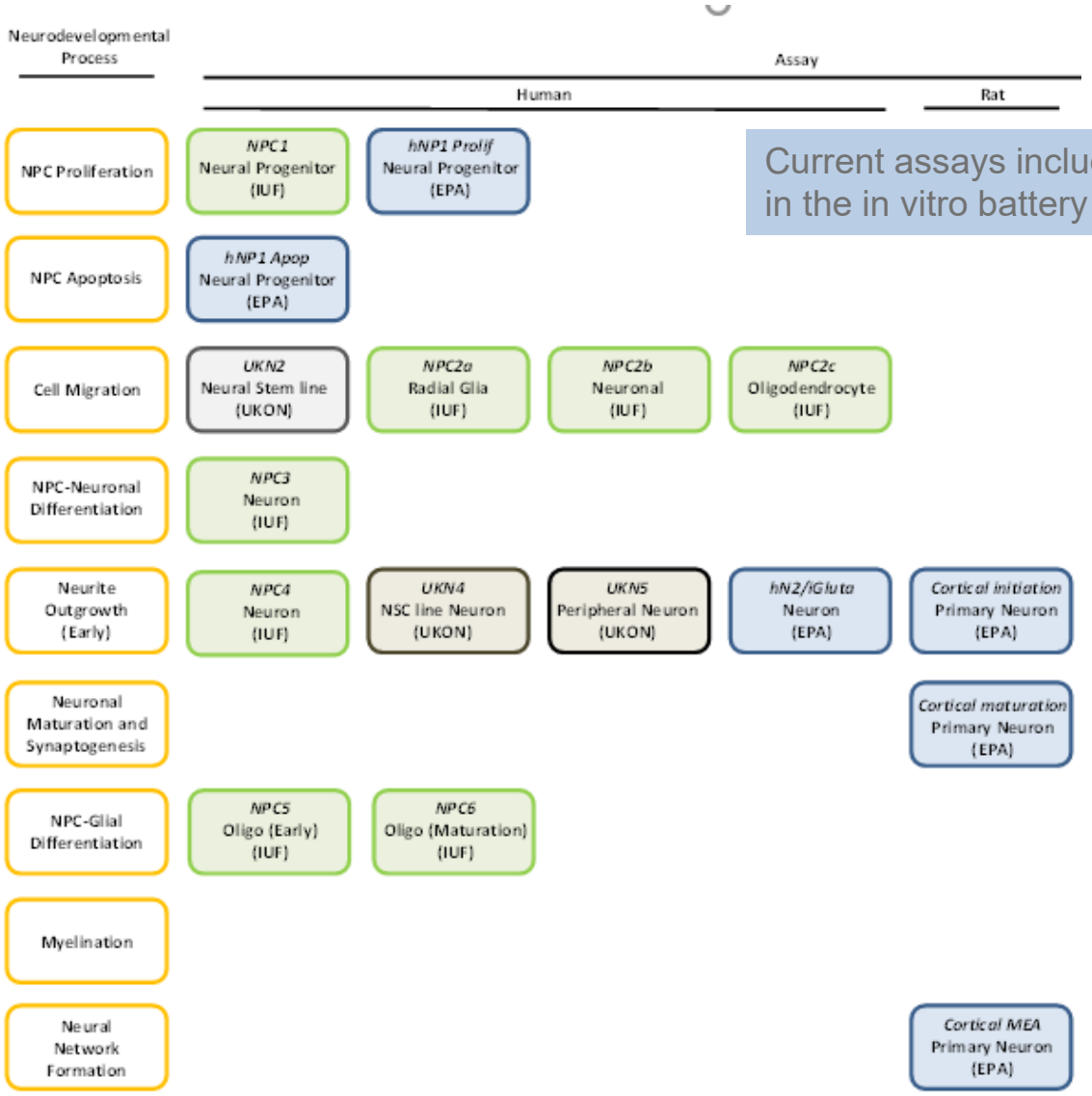
- Projects are led by member countries/regions
  - One or more members can lead a project
  - Input/contribution on a voluntary basis 
  - Projects based on a regulatory need
  - Template (SPSF) for project proposals to document:
    - Rationale for the proposal, intended product/deliverable
    - Regulatory need
    - Resources involved (validation?), timelines, need for an Expert Group
    - Animal welfare considerations
    - Intellectual property rights in methods proposed
      - Commercial availability? Licensing?

Currently on TGP work plan or soon to be

Skin and eye

- Guideline for Defined Approaches for eye irritation
  - A solution based on existing methods, to better identify moderate eye irritants
- Augmentation of the Test Guideline on DASS
  - Review of performance and possible inclusion of similar methods addressing same key events on AOP

Guidance Document IATA for Developmental Neurotoxicity (EFSA/US/DK)



EFSA/OECD workshop (2016)

Current assays included in the in vitro battery

Guidance Document covers:

- IATA, assay descriptions
- Establishing WoE for DNT
- Criteria for individual assay interpretation
- Evidence integration
- Uncertainties
- Usage in hazard assessment

Proposed **tiered approach** to testing

Case studies applications of the in vitro battery

Immunotoxicity: emerging NAMs combinations and standardisation

New/complex endpoints

- In vitro immunotoxicity (project led by Japan with a group of OECD experts)
  - Draft Detailed Review Paper for WNT approval in April 2022, including list of reference chemicals
  - On the TGP work plan: IL-2Luc method in combination with other information sources
  - Horizon scanning: what other information sources and methods might be useful and amenable to standardisation
    - Case studies might be helpful to show evidence, relevance of candidate methods

- Identified by the European Chemical Sustainable Strategy as a priority
  - Mentioned in European Partnership PARC

Non genotoxic carcinogenicity: emerging NAMs

New/complex endpoints

- Non-genotoxic carcinogenicity IATA (project led by the UK with a group of OECD experts)
  - Vast and complex project, 13 assay blocks identified representing key processes involved in non-genotoxic carcinogenicity
  - Endeavour to thoroughly describe/review available assays for each assay block
  - On-going discussions on the structure of the IATA
- Several activities on-going in countries (US EPA, NIH,…)
- Identified by the European Chemical Sustainable Strategy as a priority
  - Mentioned in European Partnership PARC

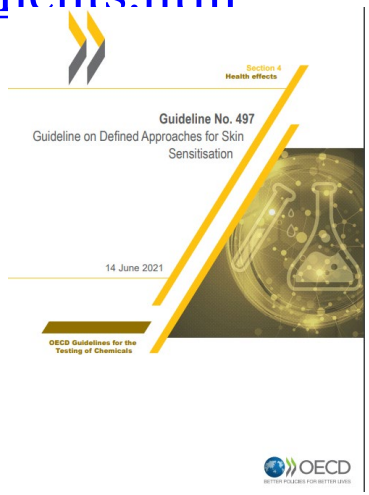
Thyroid disruption: emerging NAMs combinations and standardisation

New/complex endpoints

- 2014: OECD Thyroid Scoping Document (GD 207)
  - Identification of 8 thyroid-related processes
  - Review of relevance and level of readiness for validation
- 2017: EU-NETVAL started work on optimisation and pre-validation of ~17 in vitro methods representing 8 key processes
  - ~30 reference chemicals identified
  - October 2022: completion of activities
- OECD Expert Group on Thyroid disruption methods created:
  - to work on the standardisation of most promising methods and endpoints
  - Human health and environment will be addressed
  - AOP will be used as a framework for organising knowledge
  - Case studies will be needed to show evidence around certain assay combinations

Any question?

- OECD Test Guidelines:
  - https://www.oecd.org/chemicalsafety/testing/oecd-guidelines-testing-chemicals-related-documents.htm



- OECD Chemical Safety website:
  - https://www.oecd.org/chemicalsafety/

- AOPs: www.aopwiki.org