Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals

Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals **7 December 2021**

Fortieth session

Geneva, 8-10 December 2021

Item 2 (c) of the provisional agenda

Work on the Globally Harmonized System (GHS): use of non-animal testing methods for classification of health hazards

Use of non-animal testing methods for classification of health hazards: Current issues

Transmitted by the experts from the United Kingdom and the Netherlands on behalf of the informal working group

Introduction

1. This informal document provides an overview on the issues that are currently being discussed by the informal working group on "Use of non-animal testing methods for classification of health hazards" in relation to their work on reviewing the skin sensitization hazard class in Chapter 3.4. These issues are briefly outlined as follows:

(a) The development of a schematic to aid classification and the current points which the NATM have been discussing within the IWG

(b) The initial discussion on the first draft of Chapter 3.4

(c) How much criteria and/or guidance should be provided within the GHS criteria in the case of conflicting results from different tests?

(d) How much can the NATM IWG change the existing criteria when introducing criteria for new types of information?

(e) How to handle technical issues with wider implications for other chapters in the GHS - should this be considered by an alternative/new working group?

2. To assist the discussion of these issues at the forty-first session, the project leads of this group will provide a presentation, a copy of which is attached in Annex 1 of this document. In addition, the OECD will give a presentation on defined approaches for skin sensitisation which is provided in Annex II of this document to support the discussions.

3. The Sub-Committee is invited to note and provide views on the issues provided in paragraph 1 above and Annex 1 of this document.

Annex I

Current issues in the review of skin sensitization hazard class in Chapter 3.4

Agenda item 2(c) Use of Non-Animal Testing Methods (NATM) for classification of Health Hazards: Current issues

Transmitted by the experts from the United Kingdom and the Netherlands on behalf of the informal working group on the use of NATM for classification of health hazards

NATM IWG Update

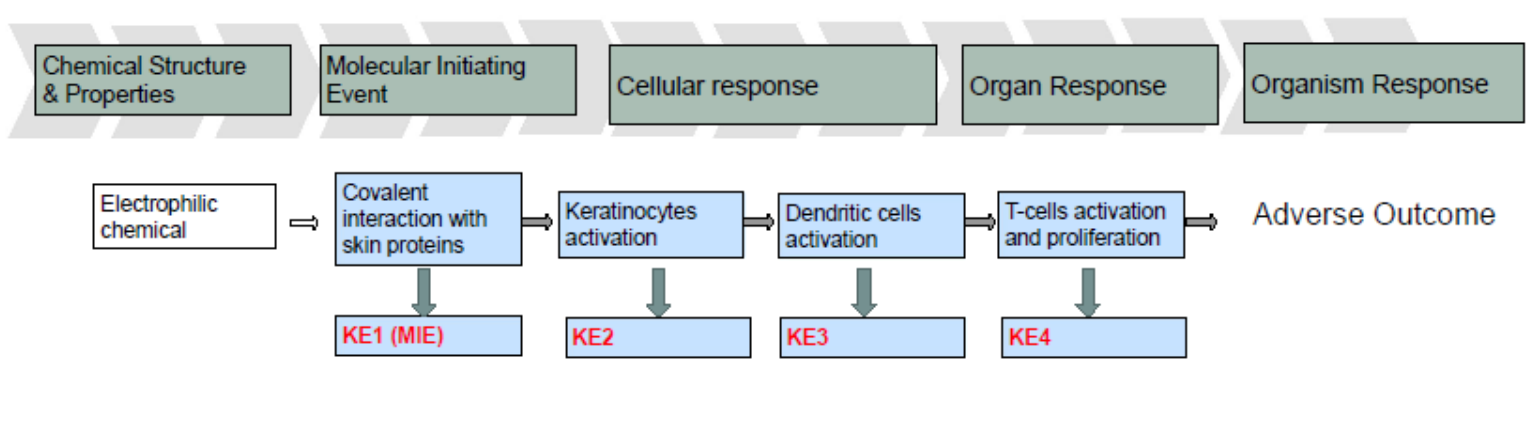
- OECD presentation on Defined Approaches
- How defined approaches have been integrated by the NATM so far – Chapter 3.3 and discussions so far in Chapter 3.4
- Chapter 3.4 revision – open issues and challenges

Defined Approaches in Chapter 3.3

- Defined approaches were first included in Chapter 3.3 on Serious eye damage/eye irritation to future-proof the chapter.
- Some DAs have been proposed for serious eye damage/eye irritation but no classification criteria have been yet agreed internationally at the OECD level but are expected soon.
  - New section in chapter 3.3 - Classification based on defined approaches
  - Defined approaches are given the weight and included in the same tier *as in vitro/ex vivo* methods in the tier approach for serious eye damage/eye irritation

Defined Approaches in Chapter 3.4

- In developing Chapter 3.4 aware there were approved and validated methods and criteria at the OECD level – trying to introduce consistency where possible
- Defined approaches are based on the Adverse Outcome Pathway (AOP) for skin sensitisation established by the OECD



Defined Approaches in Chapter 3.4

- Approved and validated defined approaches for skin sensitisation
  - “2 out of 3” Defined Approach
    - UN GHS: Category 1 versus no classification
    - Hazard identification
  - Integrated Testing Strategy (ITS) v1 or v2 Defined Approaches
    - UN GHS category : Sub-category 1A , 1B or no classification
    - Potency categorisation

Chapter 3.4 – Development of schematic to aid classification (1)

Layer 1 – includes classification based on weight of evidence assessment of human data and/or standard animal data and/or Defined Approaches and/or stand-alone *in chemico/in vitro* methods.

- Current points of discussion:
  - Weighting of data within this layer (should human data be weighted higher?)
    - Proposed solution: Work towards completing a matrix listing the data types and possible results to agree a way forward to evaluate this within the WoE approach
  - Ensure that current classifications are not altered using the same data due to this schematic

Chapter 3.4 – Development of schematic to aid classification (2)

Layer 2 – includes classification based on weight of evidence assessment of data from non-standalone in vitro/in chemico methods and/or non-test methods *plus the information from the previous layer*

- Current points of discussion:
  - Need for clear guidance when using negative read-across.
    - Proposed solution: Ensure that it is captured within the text that classification using negative read across data requires robust justification
  - May need to look back at previous chapters to see if there is consistent text required.

Chapter 3.4 – Development of schematic to aid classification (3)

Layer 3 – includes indicators, if two or more of the following are met it may alter the decision on classification. This shall be considered on a case-by-case basis:
(a) Isolated episodes of allergic contact dermatitis;
(b) Epidemiological studies of limited power, e.g. where chance, bias or confounders have not been ruled out fully with reasonable confidence;
(c) Data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in 3.4.2.2.3, but which are sufficiently close to the limit to be considered significant;
(d) Positive data from non-standard methods.

- Current points of discussion:
  - Change into a general weight of evidence but including the use of the existing criteria for indicators.
  - Suggestion that points (a), (b) and (d) could be used in weight of evidence anyway and that (c) may be considered as part of the 1st layer instead.
  - Layer 3 is then the final step in this process and do not need a further weight of evidence

Chapter 3.4 – other issues

- First draft of chapter produced for November IWG Webex
  - No major concerns were raised
  - Consideration of how to include non-test methods and standalone *in chemico/in vitro* methods within the classification criteria
  - Further discussion needed on weight of evidence text
  - Approach to non-validated methods in the guidance

General Issue 1

- An open question is how much criteria and/or guidance should be provided in the GHS criteria in case of conflicting results from different tests.
  - Clear criteria enhances global harmonisation but may sometimes result in erroneous classification
  - Allowing expert judgement on a case-by-case basis may also result in erroneous classification and differences in comparable cases
  - Suggested approach is to be clear where possible and allow expert judgment where not possible but difficult to determine the border. Suggestions?
  - Also, where to put this? In the criteria as part of GHS or in guidance which may not be taken over in national legislation?

General issue 2

- How much can we change the already existing criteria when introducing criteria for new types of information?
  - Stay within the mandate given to the working group (non-animal methods)
  - Prevent that the same data now result in a different classification
  - Suggestions?

General issue 3

- How to handle technical issues with wider implications for other chapters in the GHS should this be considered by alternative or new group?

The GHS Sub-Committee is invited to provide views on the current issues and challenges the NATM IWG is facing and questions outlined in this presention

Finally….

- IWG

- A huge thank you and goodbye to Joao Barroso (JRC), his expertise, drive and enthusiasm will be missed!

Annex II

OECD presentation on defined approaches for skin sensitization

DEFINED APPROACHES AS A NEW TYPE OF OECD GUIDELINES FOR TESTING CHEMICAL SAFETY

Meeting of UN GHS SCE, 8 December 2021

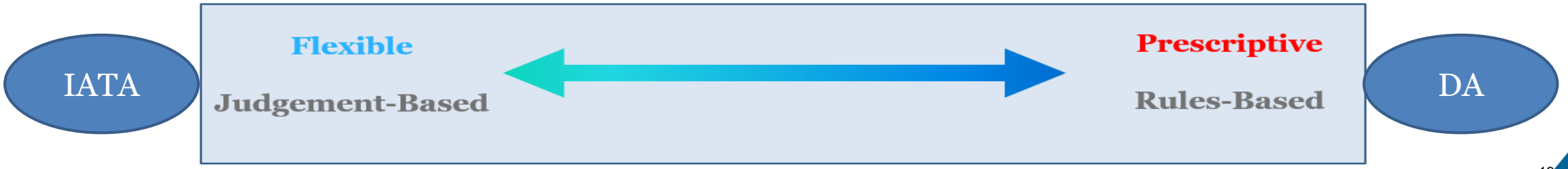
Anne Gourmelon
Principal Administrator- Test Guidelines Programme
OECD Environment Directorate

BETTER POLICIES FOR BETTER LIVES

What is a Defined Approach?

- A defined approach consists of a fixed data interpretation procedure (DIP) applied to data generated with a defined set of information sources to derive a result that can either be used on its own, or together with other information sources to satisfy a s.pecific regulatory need.

- A defined approach is an Integrated Approach to Testing and Assessment that has become stable/fixed



Why is OECD developing Defined Approaches in Test Guidelines?

- OECD Chemical Safety Programme naturally committed to “3Rs” principles to reduce animal suffering and numbers of animals used in testing.

- New Approach Methods have the potential to replace animal testing gradually
  - Biotech revolution
  - Increasing understanding of biological mechanisms leading to adverse health effects
  - Technology becoming affordable, high throughput
  - For complex hazard endpoints:

    → multiple biological mechanisms

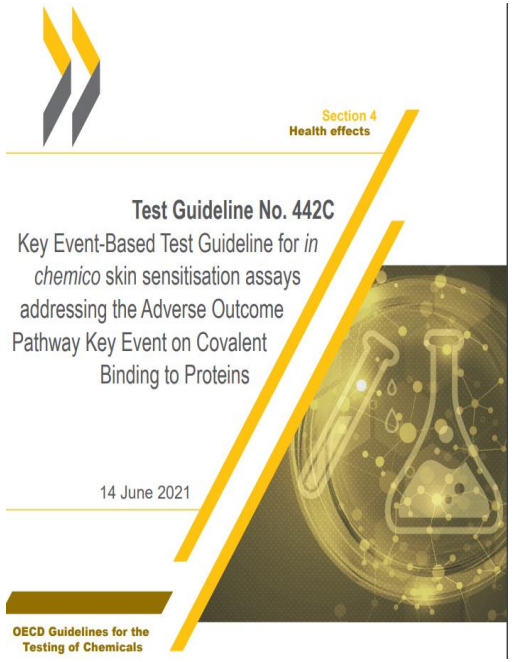
    → multiple information sources

    → combination of data needed to achieve an outcome

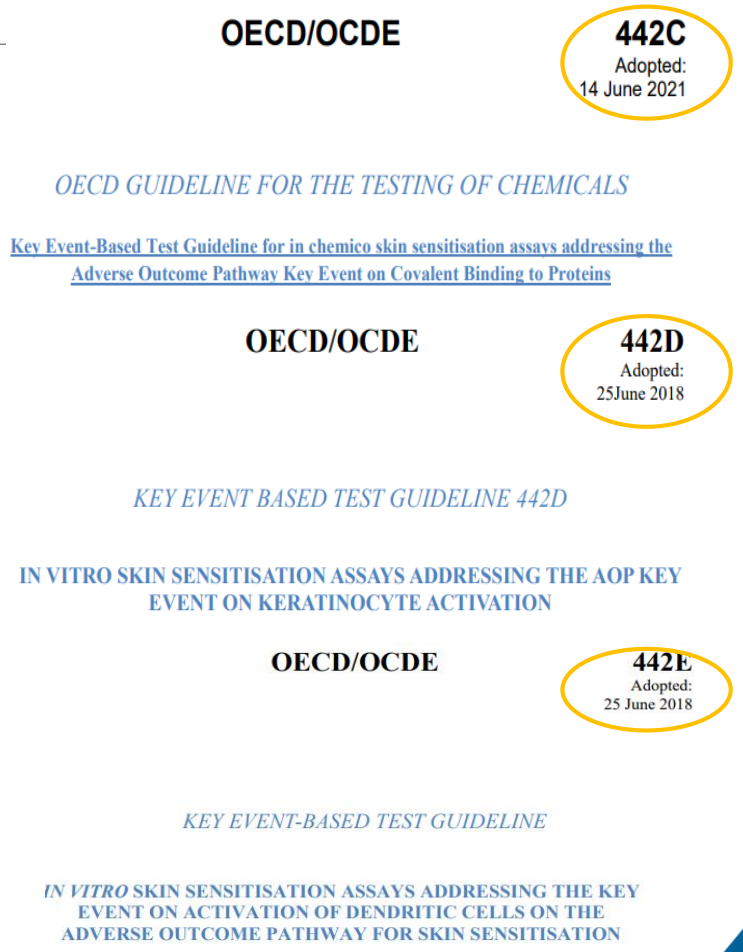
Using the AOP concept to develop novel testing and assessment approaches (2012-2016)

Guidance Document Nº 260

http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

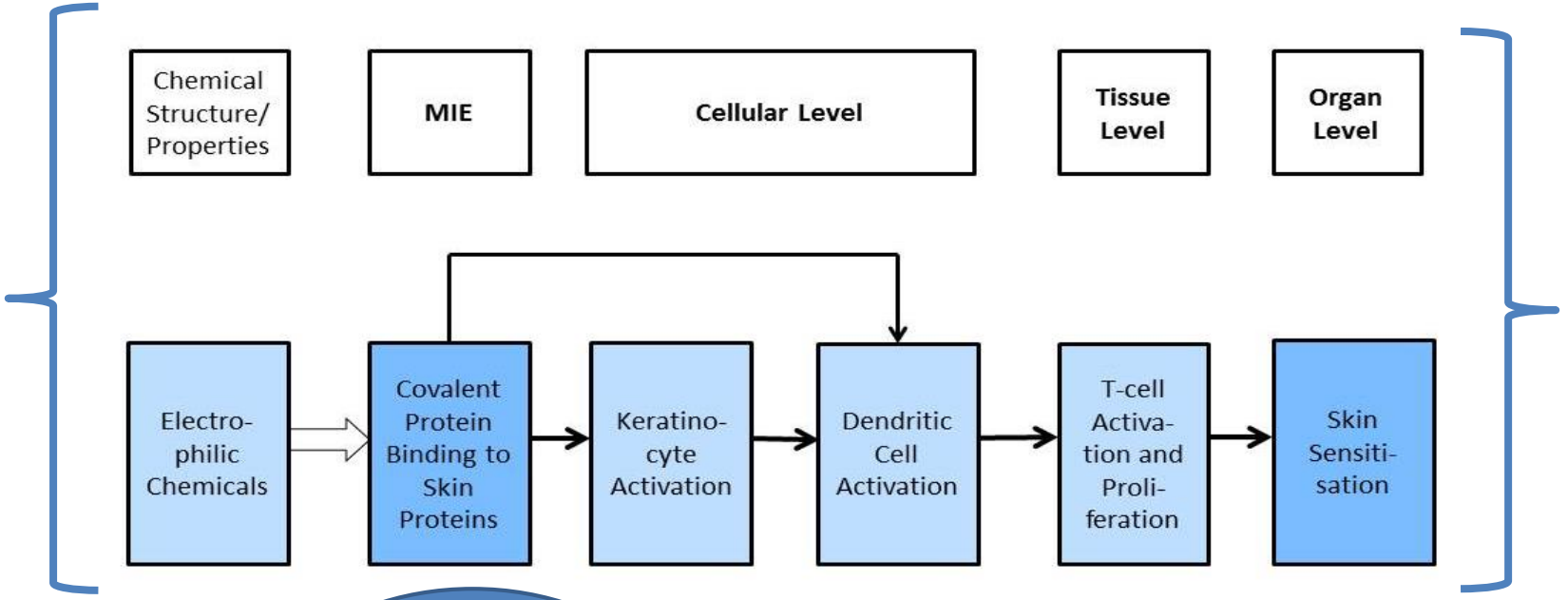


Not stand alone methods, but potential to be used in combination

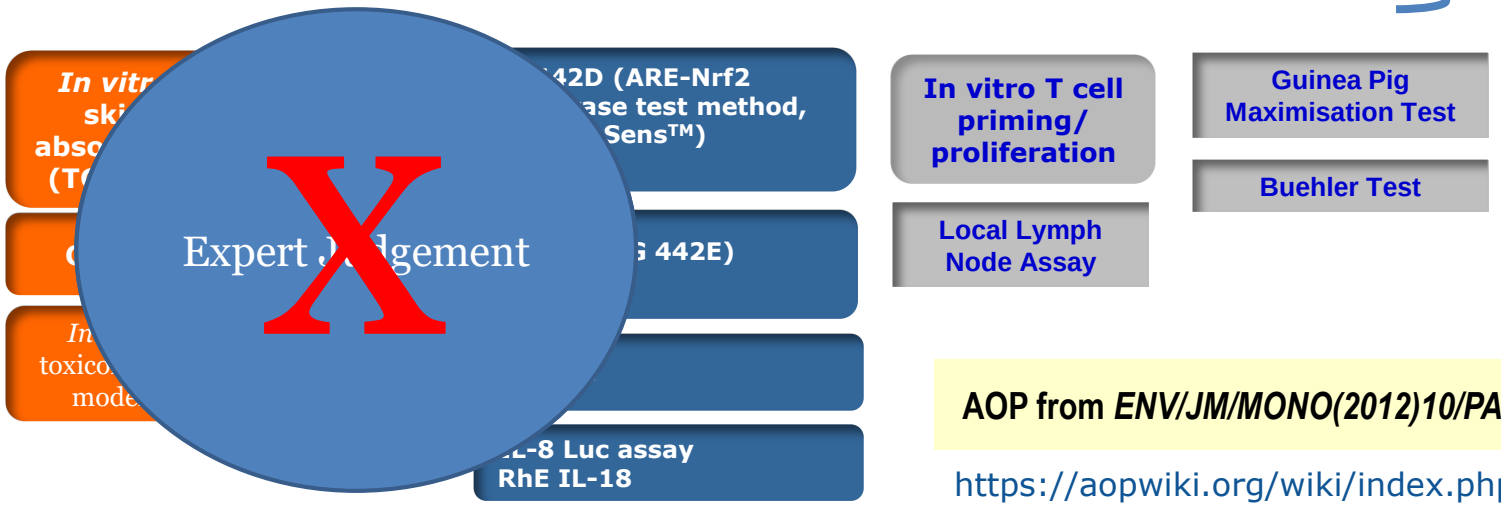


Validated methods, highly reproducible 80-85%

Defined Approaches can be developed based on AOPs: e.g. Skin sensitisation



Adverse Outcome Pathway for skin sensitisation

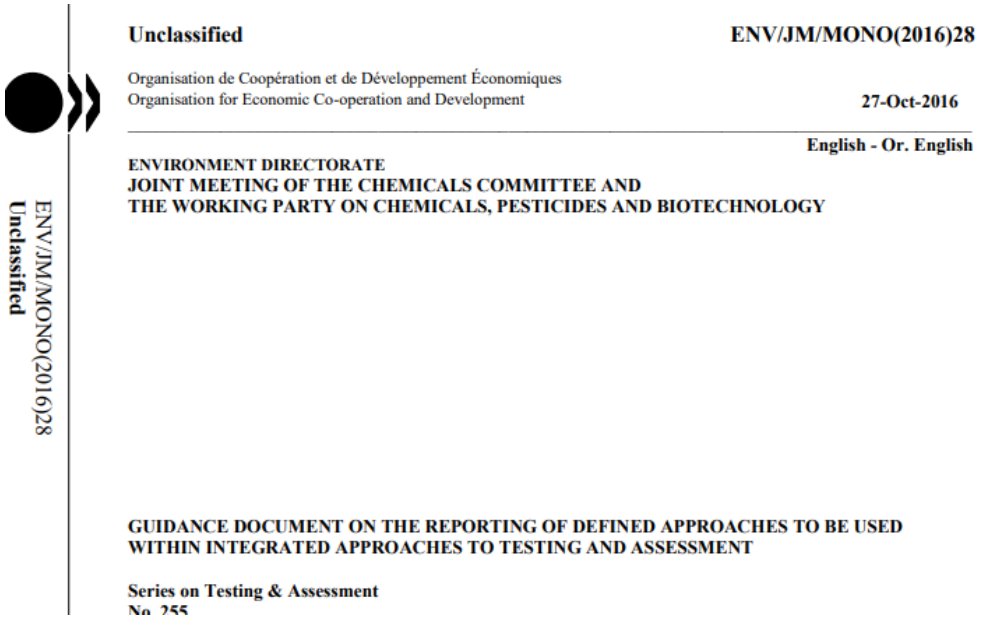


AOP from *ENV/JM/MONO(2012)10/PART1*

https://aopwiki.org/wiki/index.php/Aop:40

Efforts to further standardise IATA into Defined Approaches and apply to case studies (2016)

- Standardise reporting format of DAs
- Standardised information sources



Unclassified ENV/JM/MONO(2016)28

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

27-Oct-2016

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2016)28
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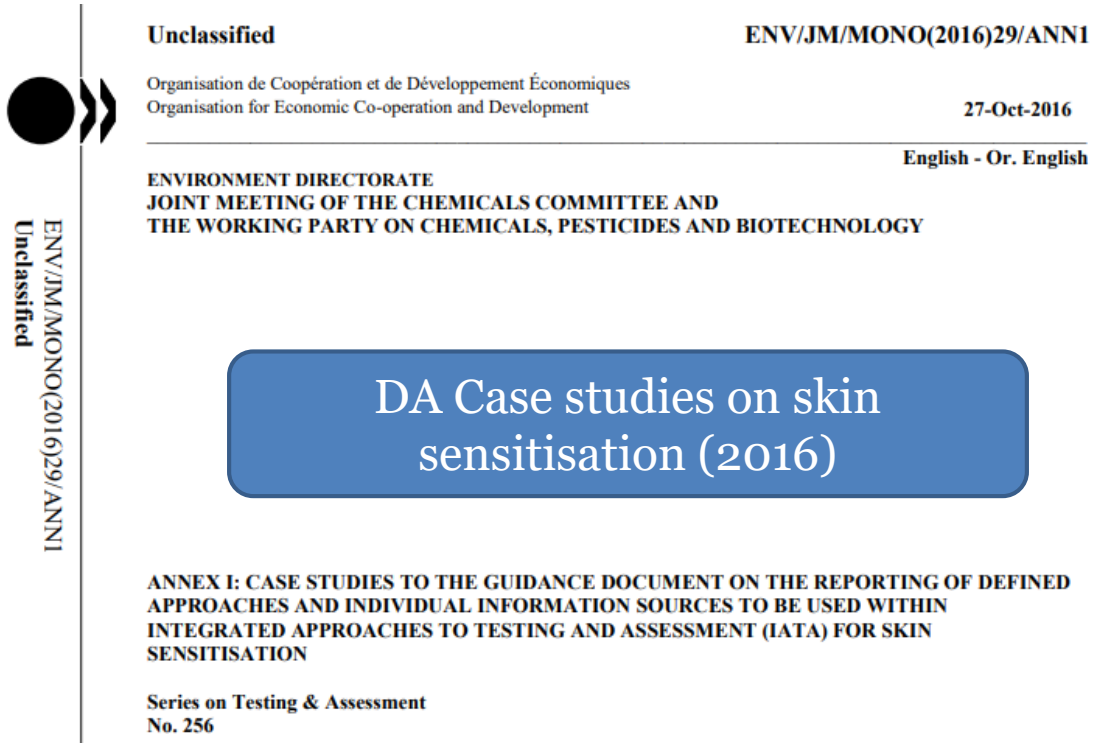
GUIDANCE DOCUMENT ON THE REPORTING OF DEFINED APPROACHES TO BE USED WITHIN INTEGRATED APPROACHES TO TESTING AND ASSESSMENT

Series on Testing & Assessment
No. 255



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DA Case studies on skin sensitisation (2016)

ANNEX I: CASE STUDIES TO THE GUIDANCE DOCUMENT ON THE REPORTING OF DEFINED APPROACHES AND INDIVIDUAL INFORMATION SOURCES TO BE USED WITHIN INTEGRATED APPROACHES TO TESTING AND ASSESSMENT (IATA) FOR SKIN SENSITISATION

Series on Testing & Assessment
No. 256

Proposal to develop a Guideline on DA on skin sensitisation (2017)

- October 2016: ICATM workshop→ starting point for collaboration
- OECD Project led by US- EC JRC-CAN, started in 2017
- OECD Expert Group on DASS established in May 2017
  - Experts in skin sensitisation, test developers, data scientists, regulators
  - Charged with the review of DA case studies in GD 256 annex1
  - Stepwise approach to select 3 simple cases first:
    - **2 out of 3**: 2 concordant results from the 3 assays in TG 442C-D-E
    - **ITS v1**: testing strategy DPRA (TG 442C, KE1)+h-CLAT(TG442E)+ DEREK software
    - **ITS v2**: testing strategy DPRA (TG 442C, KE1)+h-CLAT(TG442E)+ OECD QSAR Toolbox

Work of EG DASS: a major commitment (2017-2021)

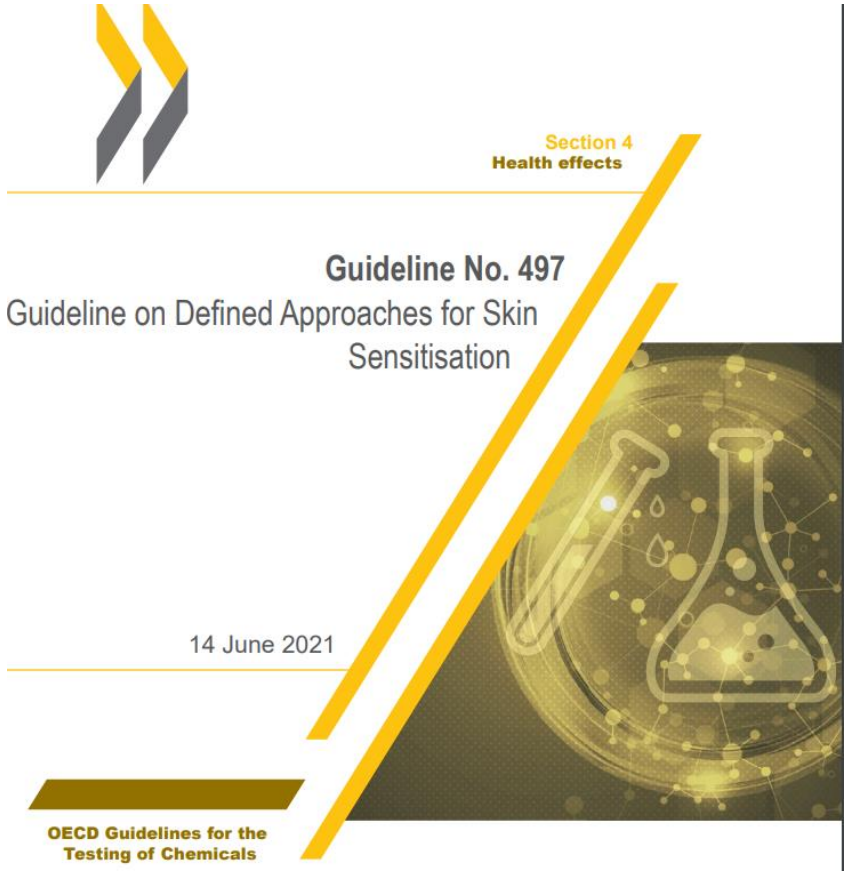
- Extensive review and curation of data Curation of LLNA database
  - Curation of human clinical data
  - Reference chemicals database augmented
- Analysis of uncertainty for borderline chemicals falling between two adjacent UN GHS sub-categories
  - Solutions found e.g. to express of borderline ranges and confidence intervals in individual methods
- Adjustment to the ITS v2 DA for scoring in silico prediction
  - No other changes made to the data interpretation procedures in the DAs
- Standardisation of the workflow to apply computational method in a reproducible manner (ITS v2)
  - First time a computation tool is integral part of an OECD Test Guideline

What information does the user get with the DAs?

- Applying the DA “2 out of 3”:
  - predicts sensitisers versus non-sensitisers
  - Hazard identification (part I of OECD GL 497)

- Applying the DA ITS v1 or ITS v2
  - predicts either UN GHS sub-cat. 1A, UN GHS sub-category 1B or Not classified
  - Potency categorisation (Part II of the OECD GL 497)

June 2021: Adoption of the first OECD Guideline on DAs



- It means that DA results are covered by the Mutual Acceptance of Data System, like other Test Guidelines
  - Countries having the same data requirement cannot ask the tests to be repeated (avoid duplicative testing)
- It does not mean that all countries have to accept the DA result if they have different data requirements
- It does not mean that the DA result should be used in isolation of other information in deriving a UN GHS classification

Next steps beyond 2021

- Proposals for further work to introduce other DAs from case studies in GL 497
- Proposals for evaluation similar methods (“me-toos”) as drop-in replacements to existing methods in DAs

- Further work on other methods/technologies for skin sensitisation
  - E.g. methods using 3D skin tissues exposed and analysis of gene transcripts to determine skin sensitisation potential

- DAs also coming for eye irritation potential.