ICCS | INTERNATIONAL COLLABORATION ON COSMETICS SAFETY

OECD Guideline No. 497 – Defined Approaches for Skin Sensitization and Beyond

Presented by: Donna Macmillan, PhD, ICCS

EPIC Webinar: Regulatory tools for assessing the skin sensitization potential of chemicals and a case study using the SARA-ICE model

Overview

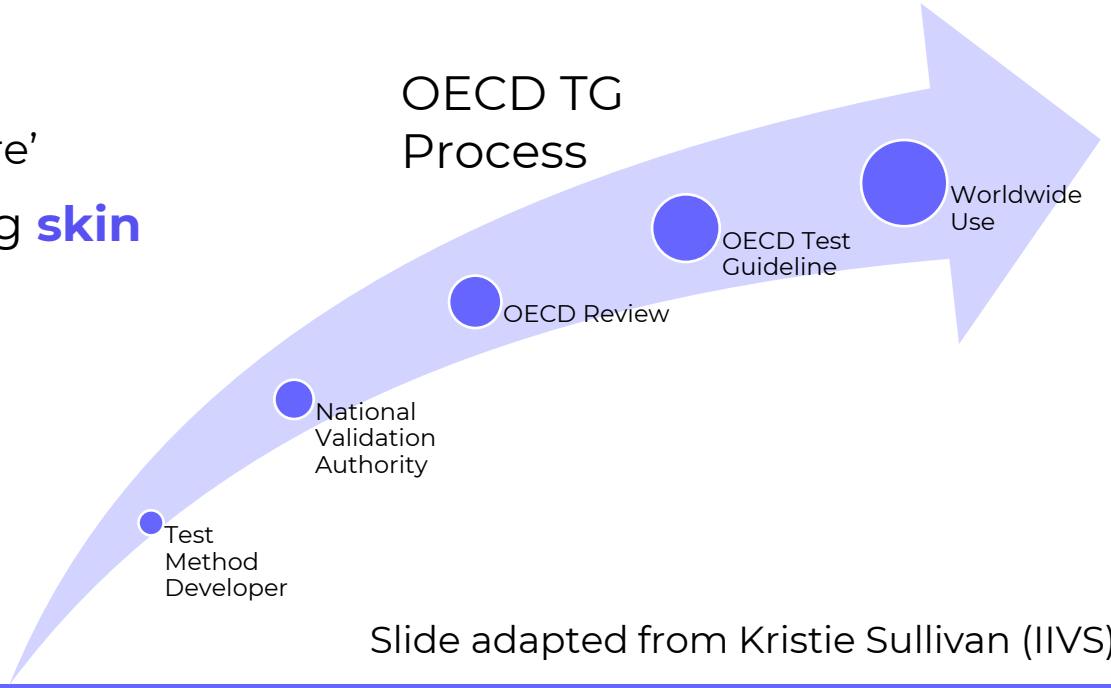
- The Organisation for Economic Co-operation and Development (OECD) Test Guideline Programme
- Introduction to skin sensitization
  - Traditional approaches to assess skin sensitization
  - Non-animal approaches - OECD Key Event-based Test Guidelines
- Defined Approaches for Skin Sensitization
  - Development of Guideline No. 497
  - Publication of Guideline No. 497
  - The 2 out of 3 defined approach (2o3)
  - The Integrated Testing Strategy (ITSv1 and ITSv2)
- Emerging activities
  - Inclusion of alternate methods in OECD GL 497
  - 3D skin models
  - New DAs for quantitative risk assessment
- Conclusions

Disclaimer: The content of this presentation is based on experience in the OECD DASS EG over the past 6-7 years

The Organisation for Economic Co-operation and Development (OECD)

- Established in Paris in 1948 as OEEC
- 38 member countries, who provide an overall ambassador (National Coordinator) and experts to serve on numerous working parties and committees
- Tasked with developing and revising Test Guidelines (TG) for the testing of chemicals for human health and the environment

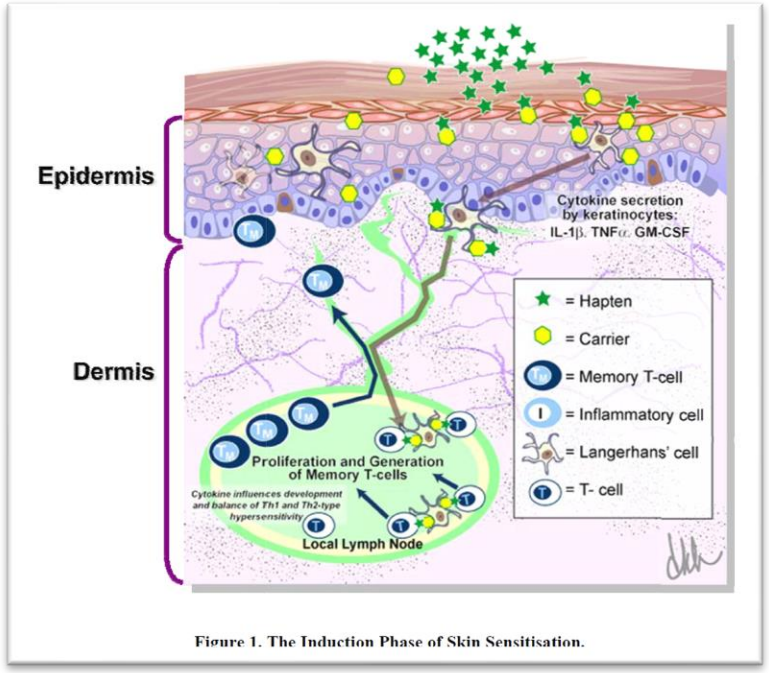
- TG promote Mutual Acceptance of Data (MAD)
  - Avoids duplication of testing
  - Reduces number of lab animals used
  - 'Tested once, accepted for assessment everywhere'
- TG cover many toxicological endpoints including **skin sensitization**



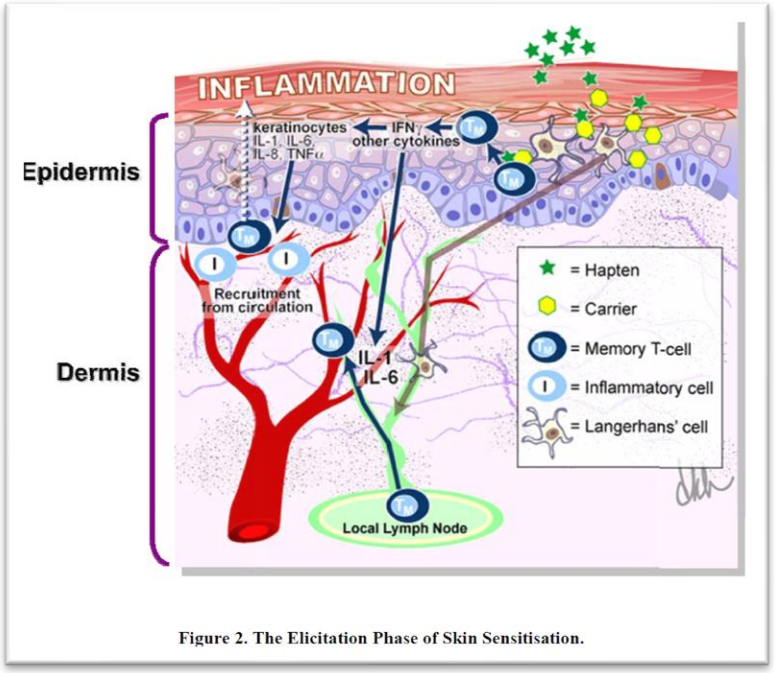
Slide adapted from Kristie Sullivan (IIVS)

Introduction to skin sensitization

- **Skin sensitisation**, also known as **allergic contact dermatitis**, is an important toxicological endpoint evaluated in hazard and risk assessments of chemicals
- Skin sensitisation occurs in two phases:
  - **Induction** – the chemical (hapten) penetrates the outer epidermis of the skin then forms a stable conjugate with carrier proteins. This hapten-protein complex, interacts with keratinocytes and dendritic cells leading to activation of T-cells on the lymph nodes
  - **Elicitation** – following subsequent contact with the same chemical, the hapten-protein conjugate is again formed and after a similar process to that above, an inflammatory response occurs and causes the adverse outcome of **skin sensitization**



Induction phase



Elicitation phase

Figure taken from OECD (2012), The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins. Part 1: Scientific Evidence. Series on Testing and Assessment: No.168.

Introduction to skin sensitization

- The adverse outcome of skin sensitisation has been well studied and the OECD published the **adverse outcome pathway (AOP) for skin sensitisation initiated by covalent binding to proteins** in 2012, consisting of 4 key events (KE).

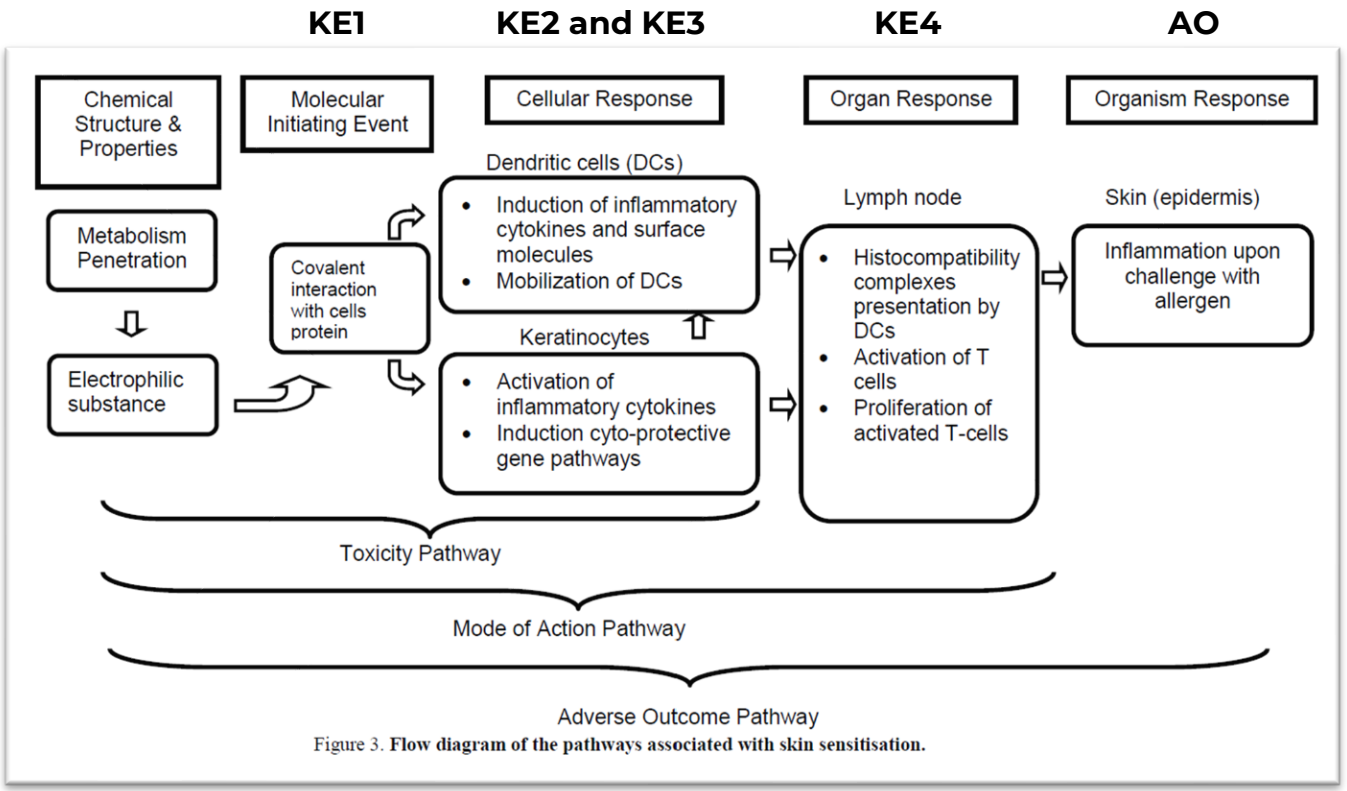


Figure 3. **Flow diagram of the pathways associated with skin sensitisation.**

Flow diagram of the Intermediate Events Associated with the AOP

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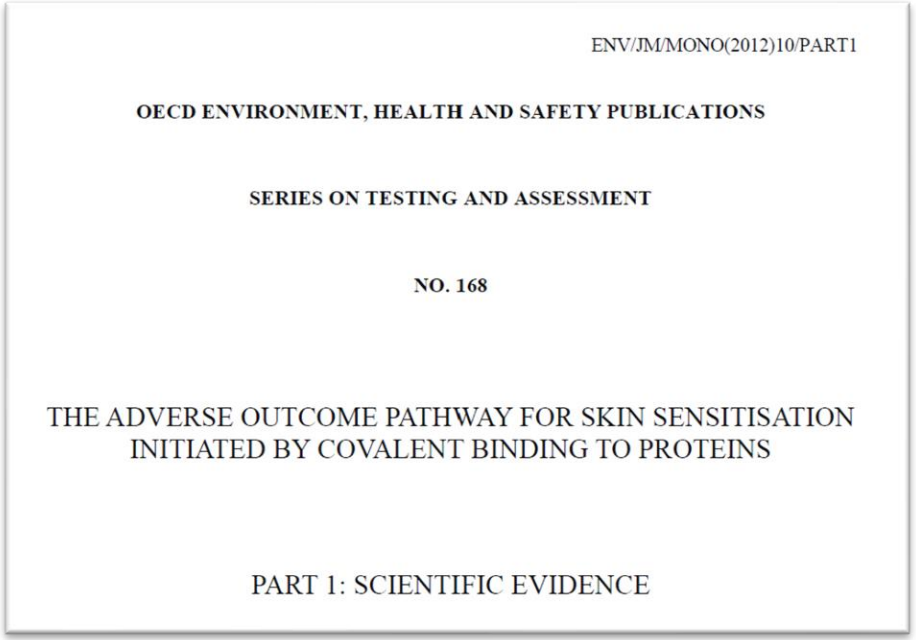
ENV/JM/MONO(2012)10/PART1

OECD ENVIRONMENT, HEALTH AND SAFETY PUBLICATIONS

SERIES ON TESTING AND ASSESSMENT

NO. 168

THE ADVERSE OUTCOME PATHWAY FOR SKIN SENSITISATION INITIATED BY COVALENT BINDING TO PROTEINS

PART 1: SCIENTIFIC EVIDENCE

Figure taken from OECD (2012), The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins. Part 1: Scientific Evidence. Series on Testing and Assessment: No.168.

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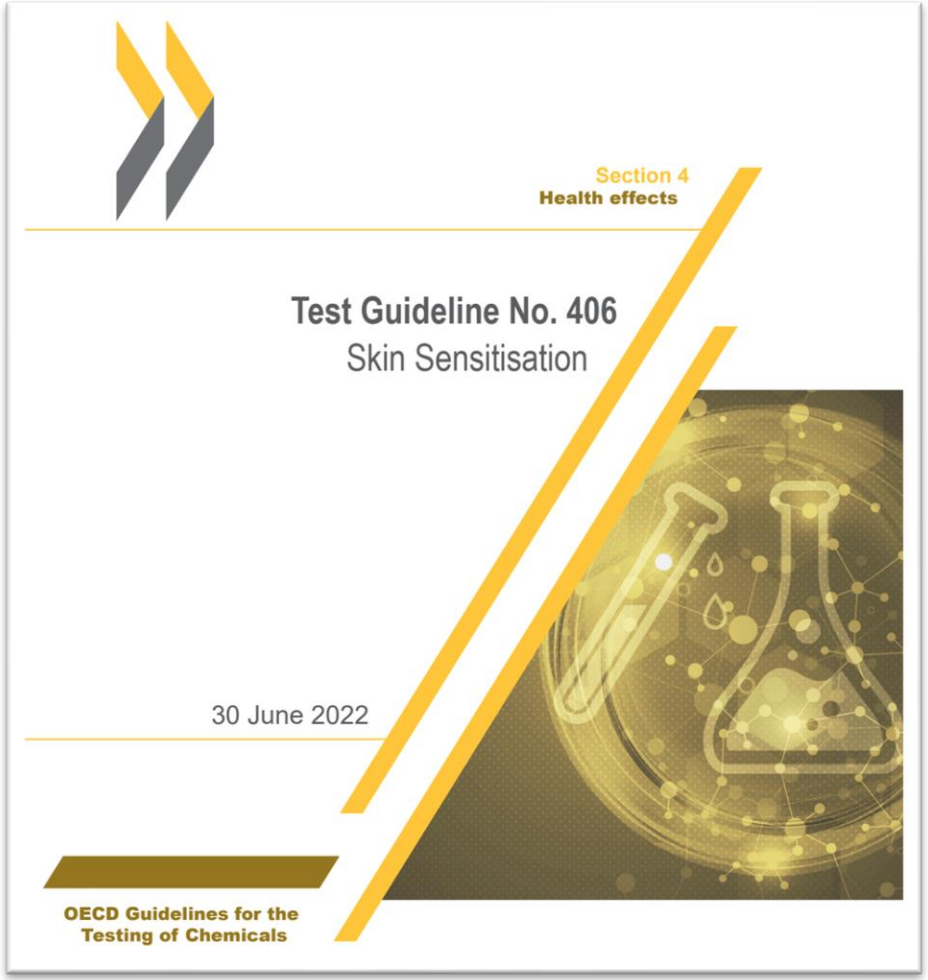
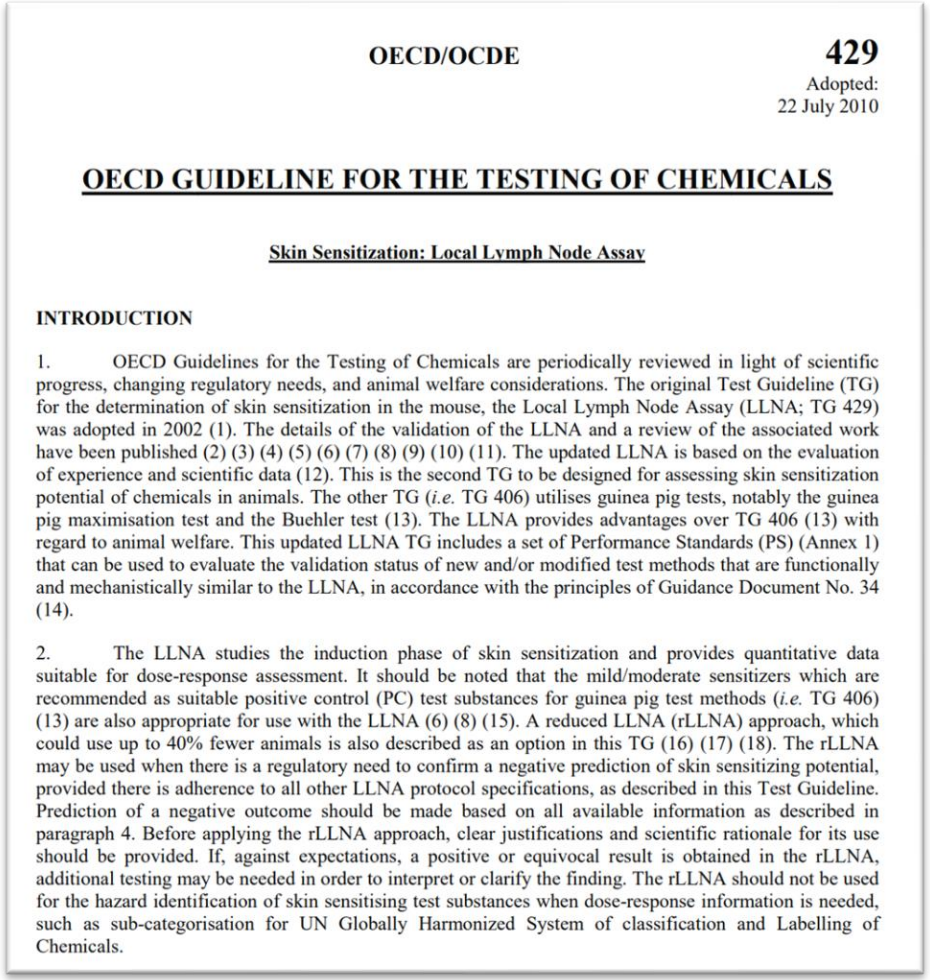
Traditional approaches to assess skin sensitization

- Traditionally, skin sensitization was assessed using the **guinea pig maximisation test** (OECD TG 406) or the **murine local lymph node assay** (LLNA; OECD TG 429) which cover **KE4** and the **AO**, respectively, of the skin sensitization AOP





OECD/OCDE **429**

Adopted:
22 July 2010

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Skin Sensitization: Local Lymph Node Assay

INTRODUCTION

1. OECD Guidelines for the Testing of Chemicals are periodically reviewed in light of scientific progress, changing regulatory needs, and animal welfare considerations. The original Test Guideline (TG) for the determination of skin sensitization in the mouse, the Local Lymph Node Assay (LLNA; TG 429) was adopted in 2002 (1). The details of the validation of the LLNA and a review of the associated work have been published (2) (3) (4) (5) (6) (7) (8) (9) (10) (11). The updated LLNA is based on the evaluation of experience and scientific data (12). This is the second TG to be designed for assessing skin sensitization potential of chemicals in animals. The other TG (*i.e.* TG 406) utilises guinea pig tests, notably the guinea pig maximisation test and the Buehler test (13). The LLNA provides advantages over TG 406 (13) with regard to animal welfare. This updated LLNA TG includes a set of Performance Standards (PS) (Annex 1) that can be used to evaluate the validation status of new and/or modified test methods that are functionally and mechanistically similar to the LLNA, in accordance with the principles of Guidance Document No. 34 (14).

2. The LLNA studies the induction phase of skin sensitization and provides quantitative data suitable for dose-response assessment. It should be noted that the mild/moderate sensitizers which are recommended as suitable positive control (PC) test substances for guinea pig test methods (*i.e.* TG 406) (13) are also appropriate for use with the LLNA (6) (8) (15). A reduced LLNA (rLLNA) approach, which could use up to 40% fewer animals is also described as an option in this TG (16) (17) (18). The rLLNA may be used when there is a regulatory need to confirm a negative prediction of skin sensitizing potential, provided there is adherence to all other LLNA protocol specifications, as described in this Test Guideline. Prediction of a negative outcome should be made based on all available information as described in paragraph 4. Before applying the rLLNA approach, clear justifications and scientific rationale for its use should be provided. If, against expectations, a positive or equivocal result is obtained in the rLLNA, additional testing may be needed in order to interpret or clarify the finding. The rLLNA should not be used for the hazard identification of skin sensitising test substances when dose-response information is needed, such as sub-categorisation for UN Globally Harmonized System of classification and Labelling of Chemicals.

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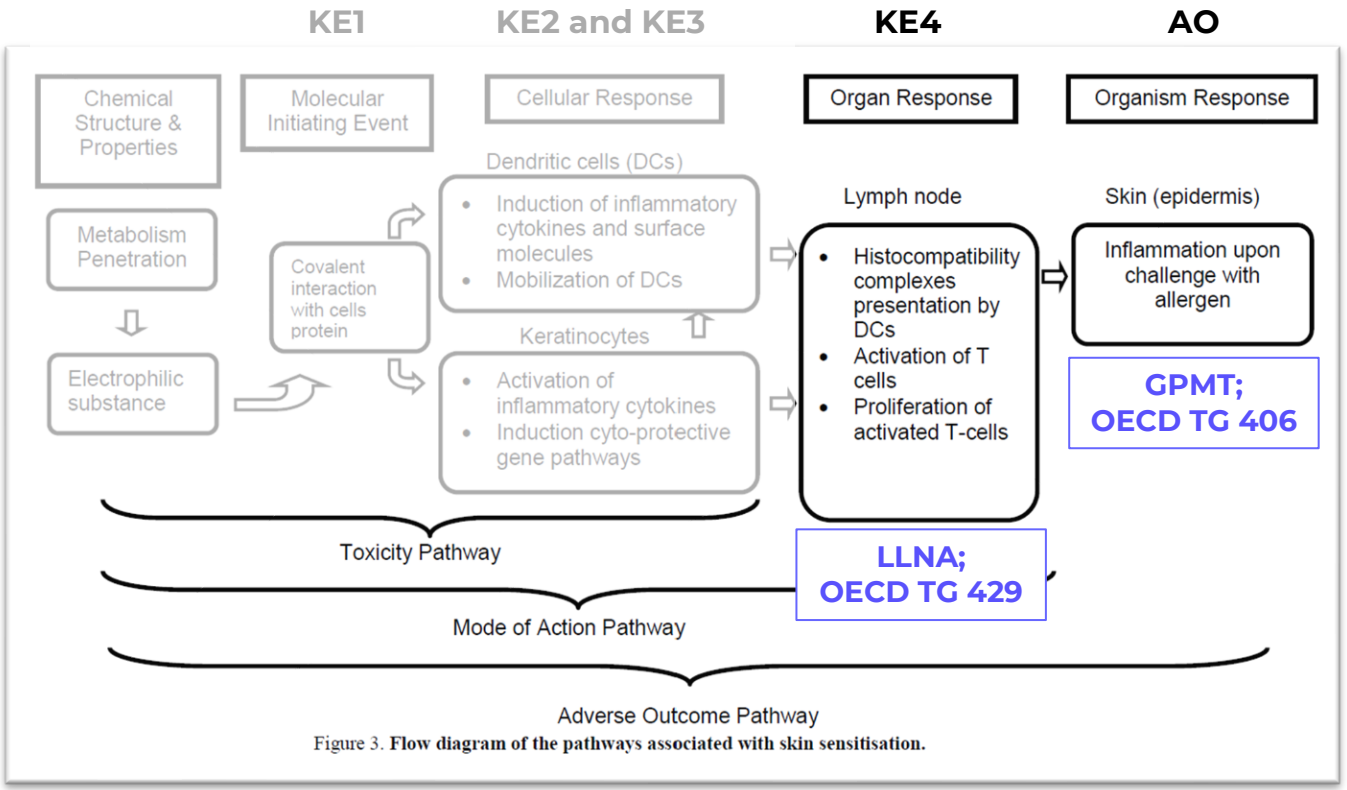

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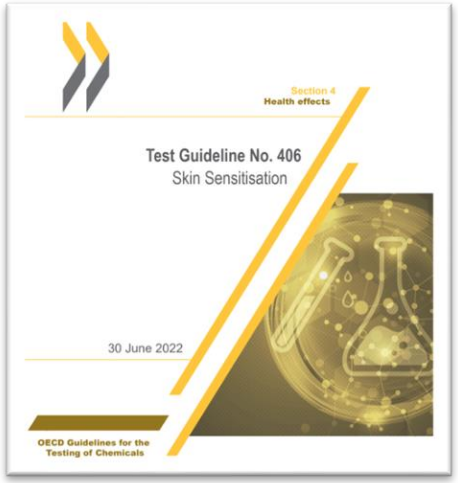

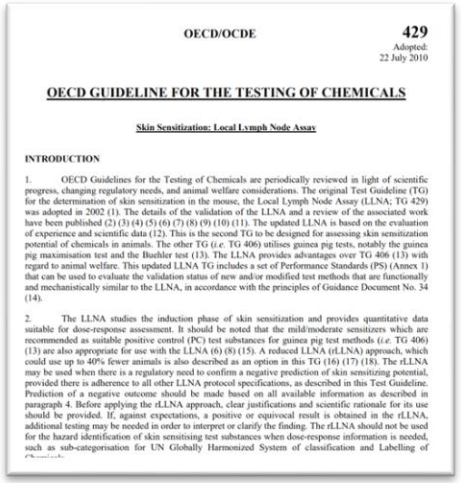
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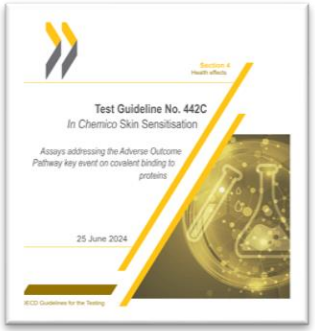
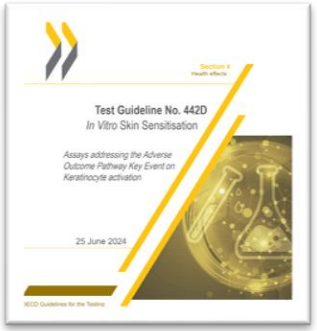
Non-animal approaches - OECD Key Event-based TG

- However, many **non-animal assays** (*in chemico* and *in vitro*) have been developed to assess skin sensitization, each covering a **KE** in the **AOP** and have been published as **OECD TG**



OECD 442C – Assays addressing the Adverse Outcome Pathway key event on covalent binding to proteins

- **Direct Peptide Reactivity Assay (DPRA)**
- Amino Acid Derivative Reactivity Assay (ADRA)
- The kinetic Direct Peptide Reactivity Assay (kDPRA)



OECD 442D – Assays addressing the Adverse Outcome Pathway Key Event on Keratinocyte activation

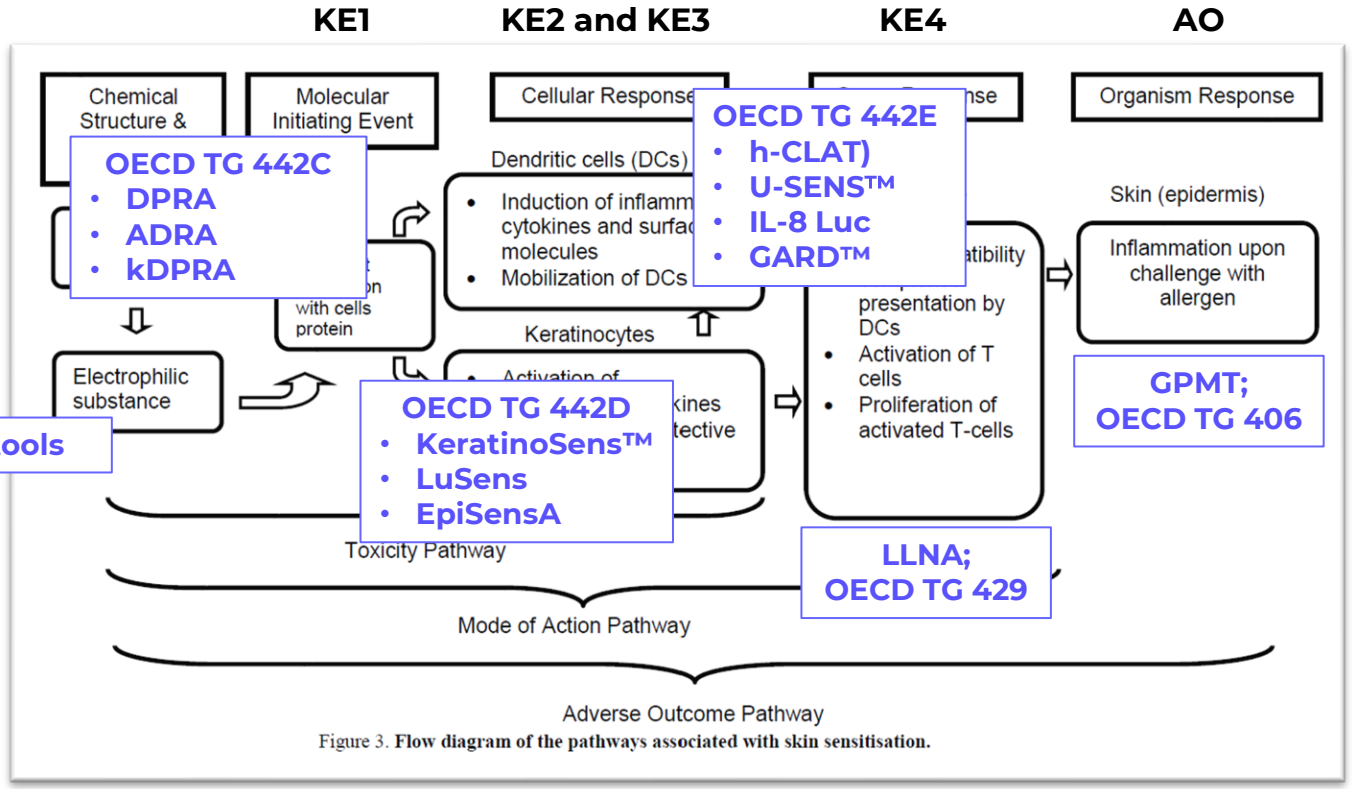
- **The ARE-Nrf2 luciferase KeratinoSens™ test method**
- The ARE-Nrf2 luciferase LuSens test method
- The Epidermal Sensitisation Assay – EpiSensA

OECD 442E - *In Vitro* Skin Sensitisation assays addressing the Key Event on activation of dendritic cells on the Adverse Outcome Pathway for Skin Sensitisation

- **Human Cell Line Activation test (h-CLAT)**
- U937 cell line activation Test (U-SENS™)
- Interleukin-8 Reporter Gene Assay (IL-8 Luc assay)
- Genomic Allergen Rapid Detection (GARD™) for assessment of skin sensitisers (GARD™skin)

Traditional and non-animal approaches for skin sensitization

- Both the traditional and non-animal approaches can be mapped onto the skin sensitization AOP, in their relative positions according to key event (KE)
- *In silico* tools are also included here



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In silico tools

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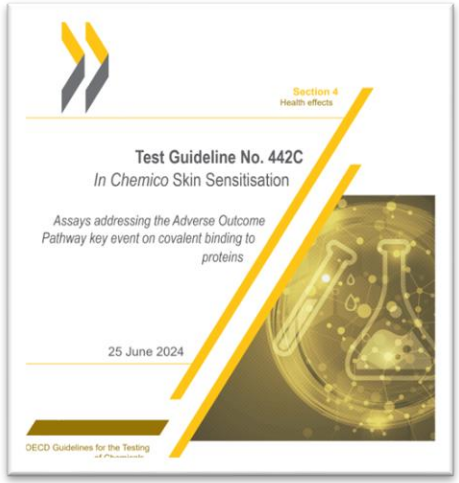
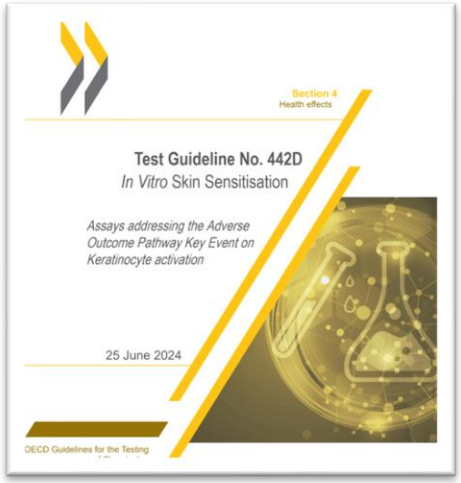
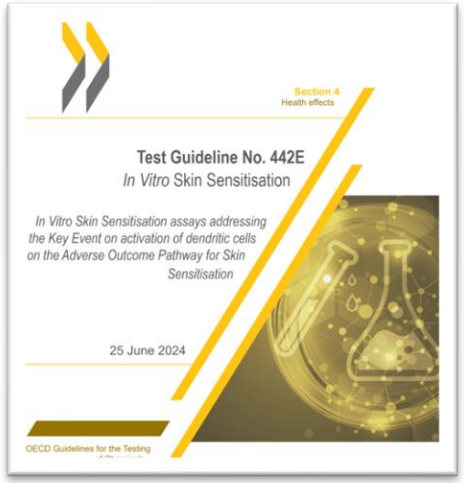






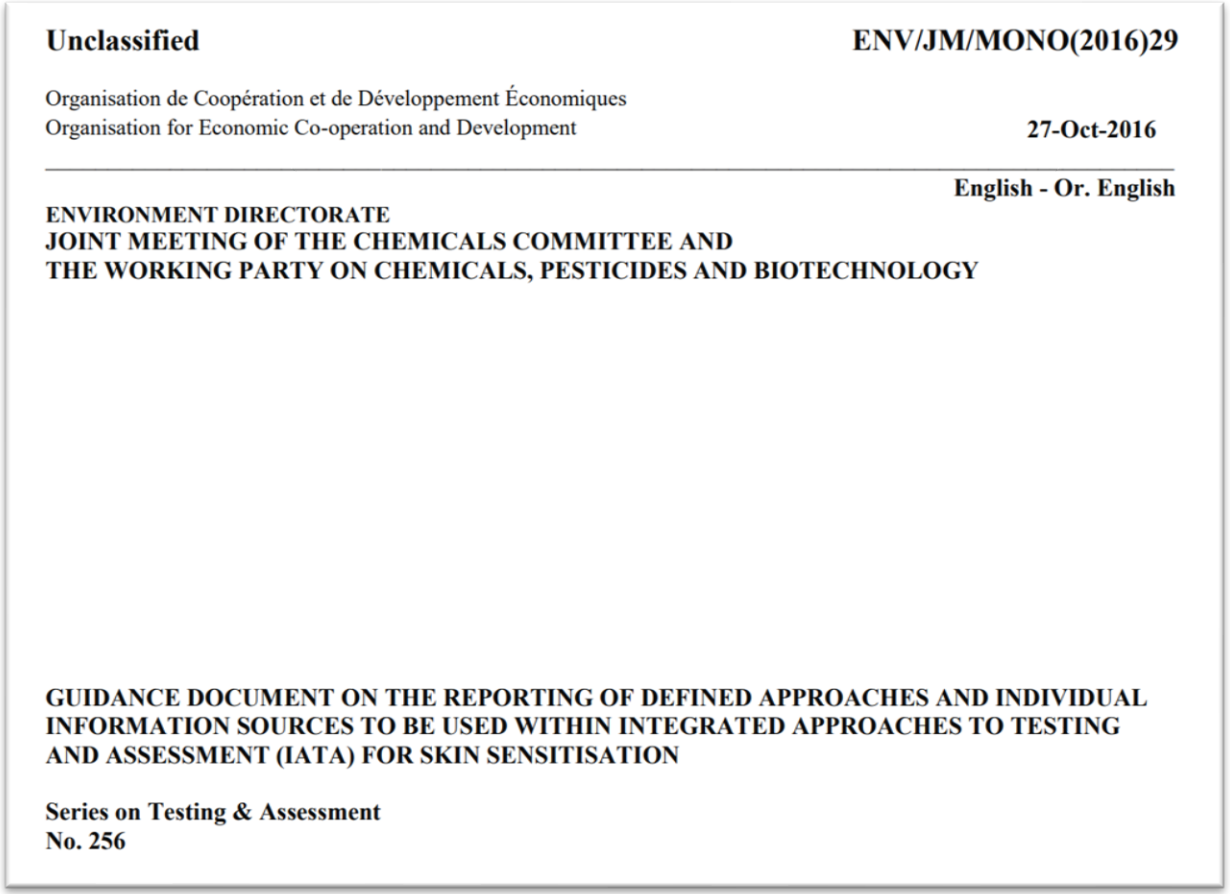
Defined Approaches for Skin Sensitization (DASS)

- Several **non-animal assays** published in OECD TG 442C, 442D and 442E were then used to develop **defined approaches for skin sensitisation** (DASS)
- These **DASS** were published in the scientific literature and then published by the OECD as examples of how to report DASS and Integrated Approaches to Testing and Assessment (OECD (2016), Series on Testing & Assessment No. 256)

Definition

A **defined approach** consists of a fixed data interpretation procedure (DIP) (e.g. a mathematical model, a rule-based approach) applied to data generated with a defined set of information sources (e.g. *in silico* predictions, *in chemico, in vitro* data) to derive a prediction without the need for expert judgment

This removes subjectivity and allows DA predictions to be used under Mutual Acceptance of Data (MAD)



Unclassified **ENV/JM/MONO(2016)29**

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

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

Development of OECD GL No. 497

- Next, a project was submitted to the OECD by the **European Commission, the US and Canada** to develop a **Guideline** on **DASS**
- The OECD added this to its workplan, and the project began in **2017**

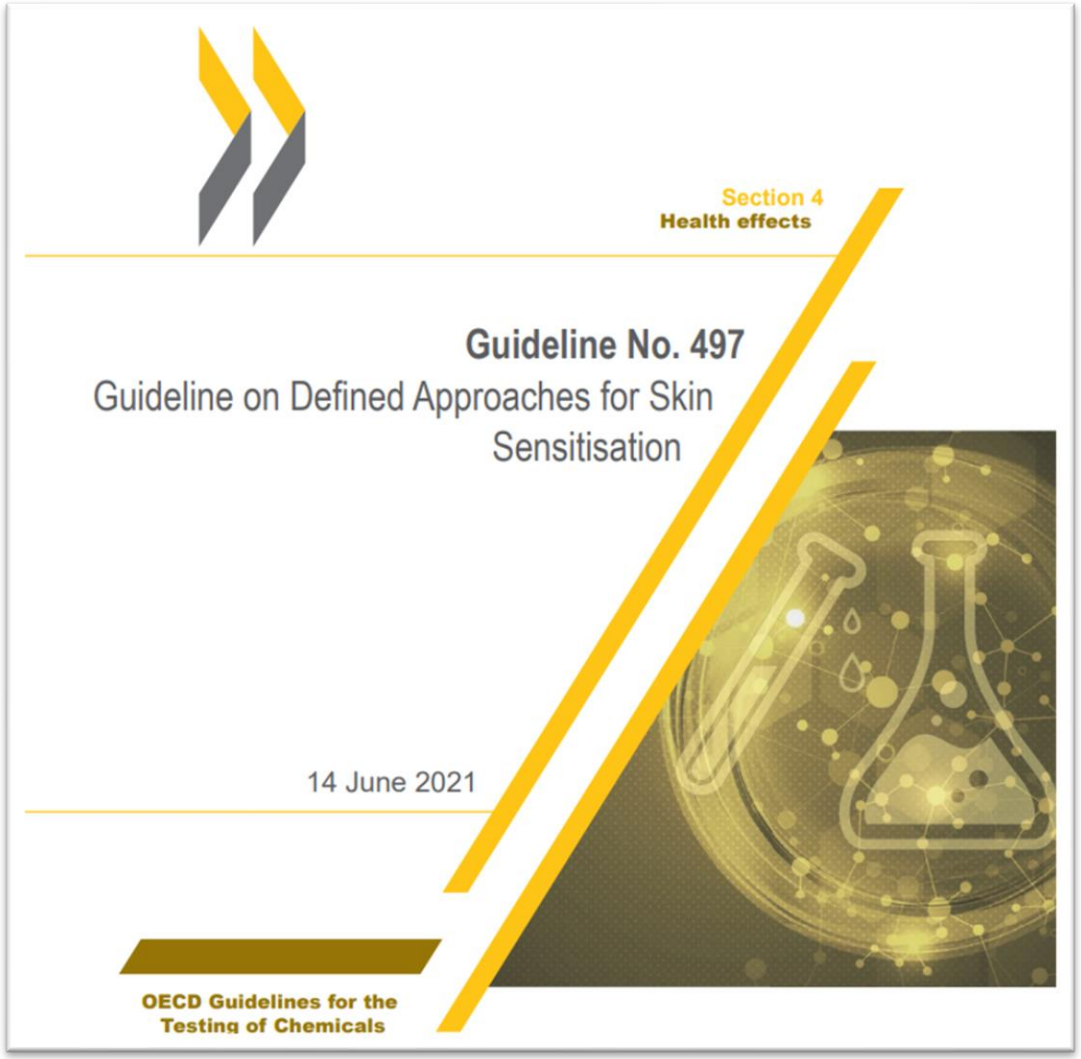
Project 4.116: PBTG on Defined Approach(es) for Skin Sensitisation	
Lead: Inclusion in work plan: Project status and milestones:	EC/US/Canada 2017

Key milestones:

- Whitepaper characterising international regulatory requirements for skin sensitisation testing, by region (completed);
- Whitepaper communicating ICATM workshop outcomes and recommendations (completed);
- Carry out analysis of current animal test (LLNA) data to determine performance thresholds for acceptance based on i) reproducibility of the animal test and ii) concordance with human data, where available (presented at the Special session of WNT in Dec. 2017).
- Propose general assessment framework (including acceptance criteria) for DAs for skin sensitisation (discussed at the Special session of WNT in Dec. 2017).
- Apply assessment framework to existing DAs that have been documented in Annex 1 of the OECD Guidance Document on the reporting of Defined Approaches to testing and assessment for skin sensitisation (OECD GD 256) and other candidate approaches and individual test methods (underway, Q1-Q2 2018).
- Evaluate the feasibility of incorporating DAs (and individual test methods) in the PBTG on the basis of the defined acceptance criteria (Q3 2018).
- Draft PBTG with DAs (and individual test methods) that have proven to be adequate for inclusion (Q4 2018).
- Dedicated Expert Group established, face-to-face meeting scheduled for 6-7 December 2018 at OECD.

Publication of OECD Guideline No. 497

- The **OECD Guideline on Defined Approaches for Skin Sensitisation** was **published in June 2021**
- This guideline formalises the combination of several *in chemico/in vitro* and *in silico* information sources in a **defined approach** (DA)
- The DAs covered in this groundbreaking guideline provide information on the hazard and/or potency of potential skin sensitizer and have **equivalent or better accuracy** than the *in vivo* LLNA
- The DAs included in the Guideline were:
  - The 2 out of 3 defined approach (2o3)
  - The Integrated Testing Strategy (v1 and v2)



The 2 out of 3 defined approach (2o3)

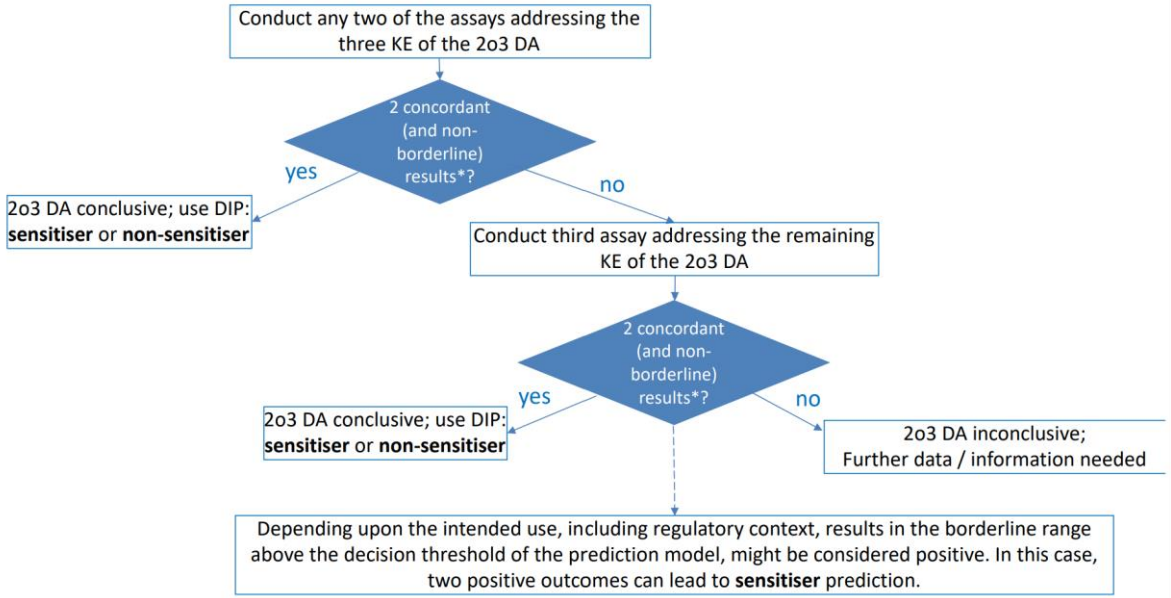
How to conduct DA

- This DA provides a **hazard-based prediction** (sensitiser/non-sensitiser) based on concordant results from up to three assays from the DPRA, KeratinoSens™ and h-CLAT

  - If two assays **are concordant** and neither have borderline results then the DA prediction is conclusive
    - Positive + Positive + either = Positive (sensitizer)
    - Negative + Negative + either = Negative (non-sensitizer)

  - If the first two assays **are discordant** then the third assay is conducted and a majority 2o3 call is given
    - Positive + Negative + Positive = Positive (sensitizer)
    - Positive + Negative + Negative = Negative (non-sensitizer)

  - If any results are **borderline** (using the thresholds stated in the guideline) then **more information may be needed** before a prediction can be given



The 2 out of 3 defined approach (2o3)

Performance against reference LLNA and human data

2o3 compared to LLNA data

	LLNA	
2o3 DA	Non	Sens
Non	22	19
Sens	4	89
Inconclusive	7	27

DA Performance vs. LLNA Data (N=134)	2o3
Accuracy (%)	83%
Sensitivity (%)	82%
Specificity (%)	85%
Balanced Accuracy (%)	84%

2o3 compared to human data

	Human	
2 of 3 DA	Non	Sens
Non	7	5
Sens	1	42
Inconclusive	3	7

DA Performance vs. Human Data (N=55)	2o3
Accuracy (%)	89%
Sensitivity (%)	89%
Specificity (%)	88%
Balanced Accuracy (%)	88%

LLNA compared to human data

	Human	
LLNA	Non	Sens
Non	2	3
Sens	7	44

LLNA Performance vs. Human Data (N=56)	LLNA
Accuracy (%)	82%
Sensitivity (%)	94%
Specificity (%)	22%
Balanced Accuracy (%)	58%

The Integrated Testing Strategy (ITS) v1 and v2

How to conduct DA - Assignment of scores to information sources

- This DA has two versions, depending on which tool is used as the ***in silico* information source**
  - **ITSv1** - Derek Nexus
  - **ITSv2** - OECD Toolbox
- A score is applied to results from the DPRA, h-CLAT and an *in silico* prediction to provide a **hazard prediction** and **a potency prediction** (based on the UN Globally Harmonized System of Classification and Labeling of Chemical (UN GHS) criteria of 1A and 1B)

ITS scoring system

Score	h-CLAT MIT µg/mL	DPRA mean Cysteine and Lysine% depletion	DPRA Cysteine % depletion*	*In silico* (ITSv1: DEREK; ITSv2: OECD TB)
3	≤10	≥42.47	≥98.24	
2	>10, ≤150	≥22.62, <42.47	≥23.09, <98.24	
1	>150, ≤5000	≥6.38, <22.62	≥13.89, <23.09	Positive
0	not calculated	<6.38	<13.89	Negative

How to apply ITS score:

Potency	Total Battery Score
UN GHS 1A	6-7
UN GHS 1B	2-5
Not classified	0-1

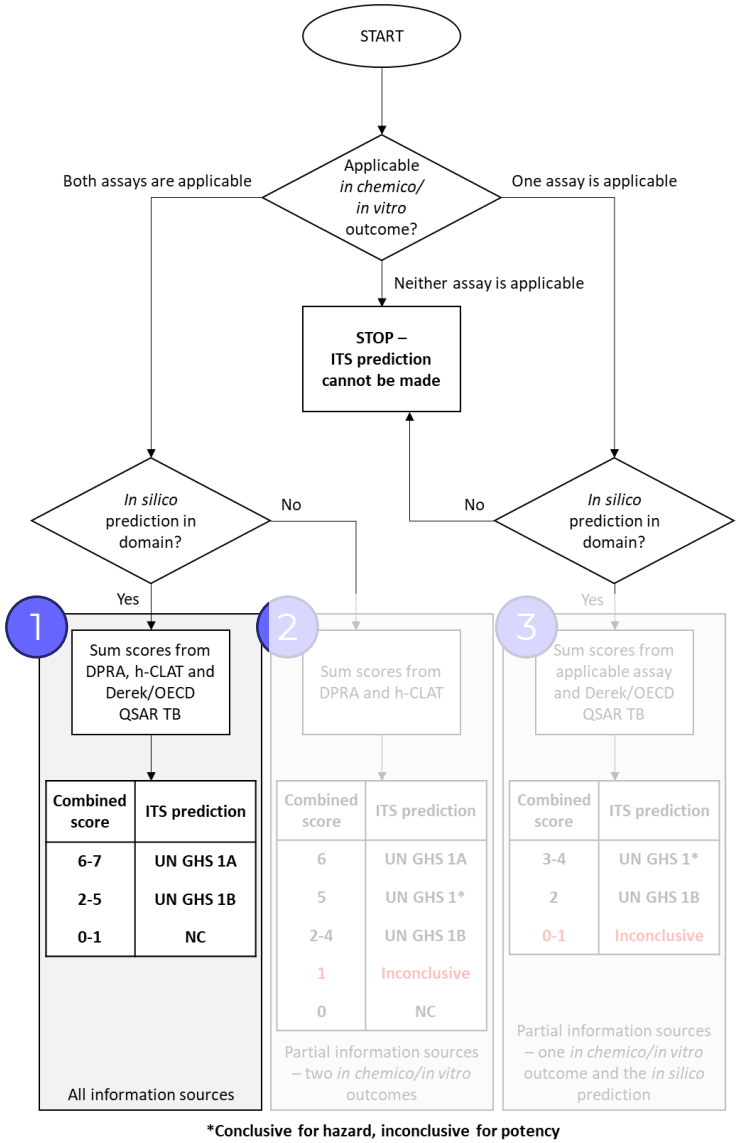
The Integrated Testing Strategy (ITS) v1 and v2

How to conduct DA – Application of score to full and partial information sources

- Scoring is applied using this workflow
  1. Left-hand box is used to provide an ITS prediction when **all information sources are in domain** (*in chemico/in vitro* and *in silico*) - the 'standard' ITS

- Partial information sources
  - When **one component of the ITS is missing**, often an ITS prediction can still be given in cases where the 'missing' component score **would not have an effect on the overall prediction**
    2. Middle box shows how to use the score to provide an ITS prediction **even when the *in silico* prediction is out of domain** (as stated in the applicability domain section in the guideline)
    3. Right-hand box shows how to use the score to provide an ITS prediction when **one of the *in chemico/in vitro* assays is out of domain**

- **Inconclusive predictions** may be considered in a weight-of-evidence approach and/or within the context of an IATA together with other information sources (Macmillan et al., 2022)



The Integrated Testing Strategy (ITS) v1 and v2

Performance against reference LLNA and human data - **hazard**

ITSv1 & v2 compared to LLNA data (hazard)

	LLNA	
ITSv1 DA	Non	Sens
Non	21	11
Sens	9	118
Inconclusive	3	6

	LLNA	
ITSv2 DA	Non	Sens
Non	20	9
Sens	10	117
Inconclusive	3	9

DA Performance vs. LLNA Data (N=159)	ITSv1	ITSv2
Accuracy (%)	87%	88%
Sensitivity (%)	92%	93%
Specificity (%)	70%	67%
Balanced Accuracy (%)	81%	80%

ITSv1 & v2 compared to human data (hazard)

	Human	
ITSv1 DA	Non	Sens
Non	4	4
Sens	5	51
Inconclusive	2	0

	Human	
ITSv2 DA	Non	Sens
Non	4	3
Sens	5	50
Inconclusive	2	2

DA Performance vs. Human Data (N=64)	ITSv1	ITSv2
Accuracy (%)	86%	87%
Sensitivity (%)	93%	94%
Specificity (%)	44%	44%
Balanced Accuracy (%)	69%	69%

LLNA compared to human data (hazard)

	Human	
LLNA	Non	Sens
Non	2	3
Sens	7	44

LLNA Performance vs. Human Data (N=56)	LLNA
Accuracy (%)	82%
Sensitivity (%)	94%
Specificity (%)	22%
Balanced Accuracy (%)	58%

The Integrated Testing Strategy (ITS) v1 and v2

Performance against reference LLNA and human data - **potency**

ITSv1 compared to LLNA data (potency)

	LLNA		
ITSv1 DA	NC	1B	1A
NC	21	11	0
1B	9	55	10
1A	0	12	28
Inconclusive	3	7	0

71% correct classification overall

ITSv2 compared to LLNA data (potency)

	LLNA		
ITSv2 DA	NC	1B	1A
NC	20	9	0
1B	10	54	10
1A	0	12	26
Inconclusive	3	10	2

71% correct classification overall

ITSv1 compared to human data (potency)

	Human		
ITSv1 DA	NC	1B	1A
NC	4	4	0
1B	5	24	7
1A	0	3	13
Inconclusive	2	0	1

68% correct classification overall

ITSv2 compared to human data (potency)

	Human		
ITSv2 DA	NC	1B	1A
NC	4	3	0
1B	5	24	6
1A	0	3	12
Inconclusive	2	1	3

70% correct classification overall

LLNA compared to human data (potency)

60% correct classification overall

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Performance of GL 497 DAs - overview

- Each **DA accurately predicts skin sensitisation hazard** (>80%) and **potency** (~70%) when **compared against *in vivo* LLNA data**
- Furthermore, each DA predicts the **human skin sensitisation potential** (hazard and potency (only for ITS)) of substances **better than the LLNA** (in bold red)

	Hazard		Potency	
DA	**LLNA**	**Human**	**LLNA**	**Human**
2o3	84%	88%	-	-
ITSv1	81%	69%	71%	68%
ITSv2	80%	69%	71%	70%
LLNA	-	**58%**	-	**60%**

Emerging methods

Inclusion of alternate methods in OECD GL 497

- Additional projects are underway at the OECD to further improve the **utility** and **applicability domain** of the DASS
- This includes:
  - Use of alternate OECD TG information sources (project 4.153)
- Alternate methods under evaluation:
  - **KE1**
    - ADRA
    - EpiSensA
  - **KE2**
    - LuSens
  - **KE3**
    - U-SENS
    - GARDskin
  - ***In silico***
    - iSafeRat
    - Leadscope Model Applier
    - STopTox

Project 4.153: Defined Approach on Skin Sensitisation for similar methods in TG 442C TG442D and TG 442E	
Lead: Inclusion in work plan: Project status and milestones:	**United States** **2022**
• Identify DAs and "me-too" information sources for assessment – Q1 2022 • Gain EG DASS consensus on application of assessment framework (e.g. reference chemicals, documentation, applicability domain) – Q2 2023 • Generate additional in chemico/in vitro data (as needed) – Q3 2023 • Adapt data interpretation procedure (as needed) – Q4 2023 • Apply assessment framework to DAs with "me-too" information sources – Q1 2024 • Draft additions to GL 497 – Q2 2024.	
Subsidiary body of the JM	WNT
Expert group	EG Defined Approaches on Skin Sensitisation

Emerging methods

3D skin models – **EpiSensA**

- Recently published by the OECD under OECD Test Guideline 442D
- Uses a 3D reconstructed human epidermal tissue model (LabCyte EPI-MODEL24)
- Permits direct application of test material to the tissue surface
- Uses a gravimetric approach
- Predicts hazard and potency

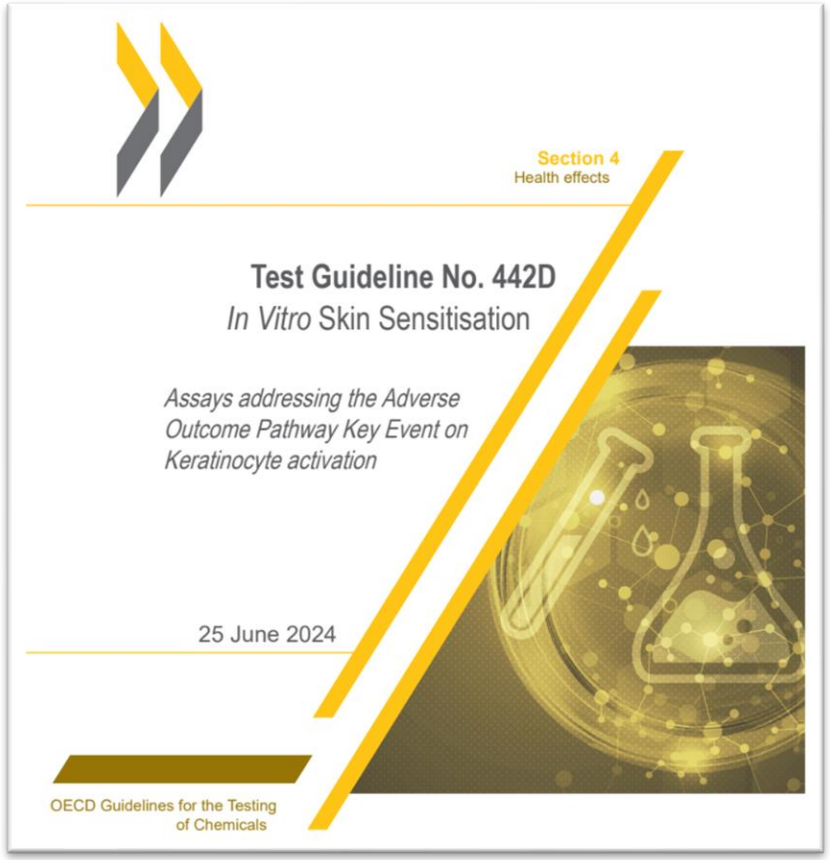
‘Difficult to test’ chemicals

29 lipophilic (logKow≥3.5) chemicals
- Sensitivity, 93%,
- Specificity, 100%
- Accuracy, 93%

43 hydrophilic chemicals (including 11 pre/pro-haptens)
- Sensitivity, 96%,
- Specificity, 75%
- Accuracy, 88%

compared with the LLNA

Saito et al., 2017



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Emerging methods

3D skin models - **SENS-IS**

- Under evaluation at OECD
- Uses a 3D reconstructed human epidermal tissue model (EpiSkin)
- Permits direct application of test material to the tissue surface
- Uses a gravimetric approach
- Predicts hazard and potency

Potency prediction

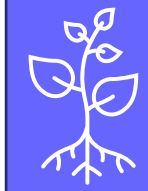
Performance of the SENS-IS assay for potency prediction of 174 materials (150 sensitizers, 24 non-sensitizers)
Potency benchmark was based on a weight of evidence (WoE) approach

- Considers all data, including human, animal, *in chemico*, *in vitro*, *in silico*

Na et al., 2022

Compared to WoE, n = 174	
Specificity	79.0%
Sensitivity	86.7%
Accuracy	85.6%
Balanced Accuracy	82.9%

Botanicals



SENS-IS used initially, if negative, followed by the h-CLAT. KeratinoSens was used to conclude when a discrepancy occurred between the results of the two first models. In case of a positive result with SENS-IS, the chemical was concluded as a skin sensitizer.

Statistical analysis of the results compared to in vivo data showed an accuracy of 96% (24/25), with a sensitivity of 100% (11/11) and a specificity of 93% (13/14).

Puginier M., et al., 2022

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Emerging methods

New DAs for quantitative risk assessment/Point of Departure (PoD)

DA	Input	Output	Open Source	Reference
Shiseido ANN	DPRA, h-CLAT, KeratinoSens/LuSens	EC3	Yes (Kleinstreuer et al., 2018)	Hirota et al., 2015
2of3 Regression	Combination of: kDPRA, h-CLAT, KeratinoSEns, Vapor Pressure	pEC3/EC3	Yes	Natsch and Gerberick, 2022
Skin Allergy Risk Assessment (SARA) model	A combination of: HRIPT, LLNA, DPRA, kDPRA, KeratinoSens, h-CLAT, U-SENS	ED01	Coming in 2024 as SARA-ICE	Reynolds et al., 2019 & 2022, Reinke et al., (accepted)
BN-ITS3	DPRA, h-CLAT, KeratinoSens, TIMES-SS, bioavailability	pEC3	No	Jaworska et al., 2015

Note: Not an exhaustive list

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Emerging methods

New DAs for quantitative risk assessment

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Thank You