An OECD Harmonised Template (OHT) to Report NAM Results in Regulatory Environments: Principles and Practical Use

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European Commission – Joint Research Centre (JRC)

EPA NAM Conference 2020: State of the Sciences on Development and Use of NAMs for Chemical Safety Testing

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What to expect from this presentation

- Standardizing hazard reporting -
  The OECD Harmonised Templates for Reporting Chemical Test Summaries (OHTs)
- The odd one out -
  OHT 201 - Intermediate Effects – Mechanistic Information
- How it all fits together -
  The triangle of chemical safety
- Sanity check -
  OHT 201 in real life

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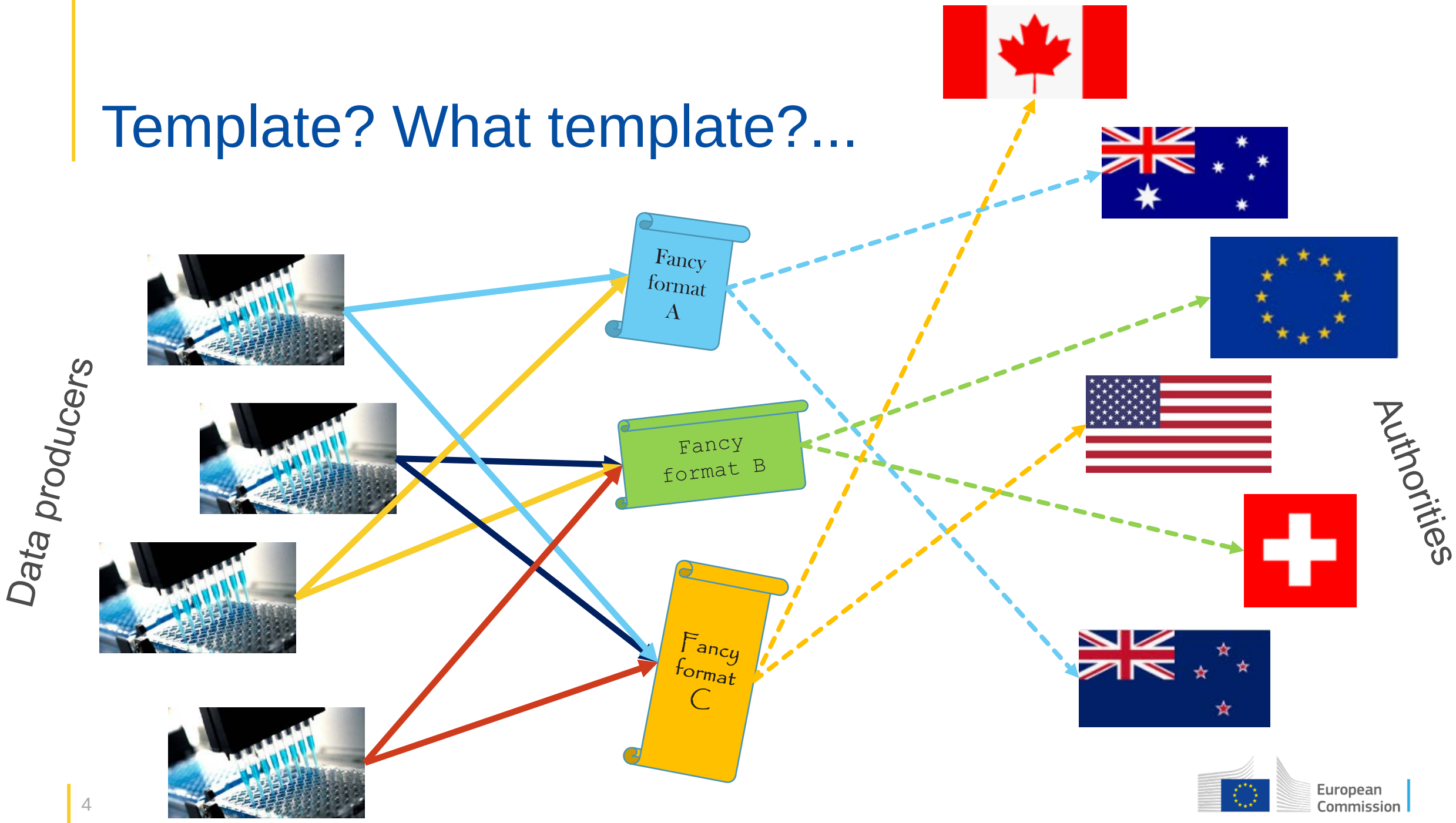
Template? What template?...



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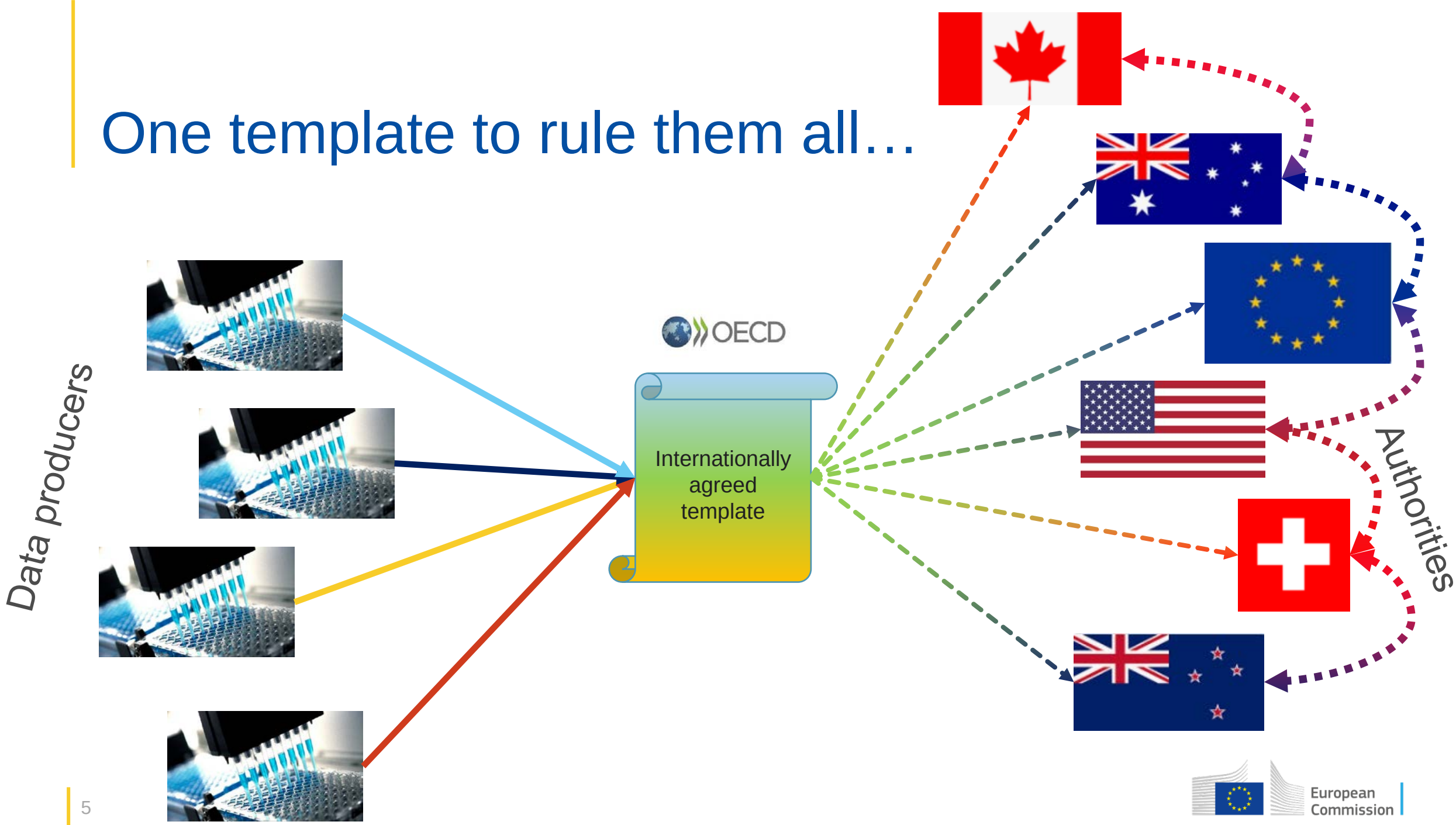
One template to rule them all…



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Apical vs Mechanistic Knowledge

- **Apical Knowledge**: Knowledge about traditional, **directly measured whole-organism outcomes** of exposure in ***in-vivo*** tests, generally death, reproductive failure, tumour formation, skin/eye irritation, skin/respiratory sensitisation or developmental dysfunction.

  One in-vivo test *tells us whether an adverse outcome has been observed or not.*

- **Mechanistic Knowledge**: Knowlegde about the **sequence of events** leading from the exposure to an effective dose of a chemical to the production of a specific biological response in the target organ, in most cases measured in ***non-in-vivo*** tests.

  A series of tests*, mainly non-animal, tells us why an adverse outcome is likely to manifest itself or not.*

Harmonised Templates

2002

The OECD Workshop on Electronic Tools for Data Submission, Evaluation and Exchange for the Regulation of New and Existing Industrial Chemicals, Agricultural Pesticides and Biocides recommends for the OECD to **support harmonisation where possible in the reporting of chemical test results*, by the use of templates and XML tags***

2004

The OECD Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology establishes the **OECD Expert Group on Harmonising Templates**

2006

The first 86 OECD **apical** Harmonised Templates (OHTs) are published

More **apical** templates over time

around 2012

We need a **mechanistic** template!

OHT 201 development

2017

OHT 201 published!

OHT 201 re-finement

2020

New OHT 201 published!

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Harmonised Templates

- OHTs as such **are only descriptions**, not an ICT application
- OHTs can be implemented **by anyone** in their local ICT environments
- **Most popular** OHTs implementation 

- IUCLID development is managed by the
- IUCLID **is free** and can be installed in any ICT environment

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OHTs (and IUCLID) are used in **more and more legislations** around the world, among them…

- Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pollution Prevention and Toxics (**OPPT**):
  - **ATAEPI** - *Analysis of TSCA Available, Expected, and Potentially Useful Information*
- **NCCT** and ECHA share data resources from ToxRefDB and IUCLID to provide a comprehensive public resource to estimate anticipated “spread” of repeat dose toxicity POD values.
- US EPA’s Responsible Appliance Disposal (**RAD**)

Key: Areas where IUCLID is used or considered for use	AU (AICIS)	CA (existing chemicals)	CA (new chemicals)	NZ (Hazardous substances)	CH (biocidal products)	CH (new substance notifcation and further obligations for substances)	US (OCSPP)	US (NCCT)	US (RAD)	EU PCN (CLP_ECHA)	EU WFD (ECHA)	EU REACH (ECHA)	EU BPR (ECHA)	EU CLP (ECHA)	EU PPP (EFSA)
Dossier preparation															
Enter data in a structured format	●	●	●	○	●	●			●	●	●	●	●	●	●
Perform presubmission quality checks	●			○	●	●				●	○	●	●	●	○
Reporting generator for dossier preparation	○			○		●				●	○	●	●		○
Previewing publicly disseminated data												●			○
Submission process															
Format check	●				●	●				●	●	●	●	●	
Validation	●			○		●				●	○	●		●	○
IUCLID Extension modules										●	○	●	●	●	
Dissemination															
Filtering												●			○
Aggregation												●			
Provider agent												●			○
Post submission work (analysis/assessment)															
IUCLID for searching dossier contents	●	●		○	●	●	●	●	●			●	●	●	○
IUCLID for entering additional assessment information	●	●		○			●	●	●						
IUCLID reporting engine in assessment/evaluation				○		●						●	●	○	○
IUCLID annotations in assessment/evaluation				○	●	●							●		
IUCLID aggregation engine for assessment/evaluation												●			
IUCLID for data analysis by other, integrated systems		○		○			●	●	●			●	●	●	

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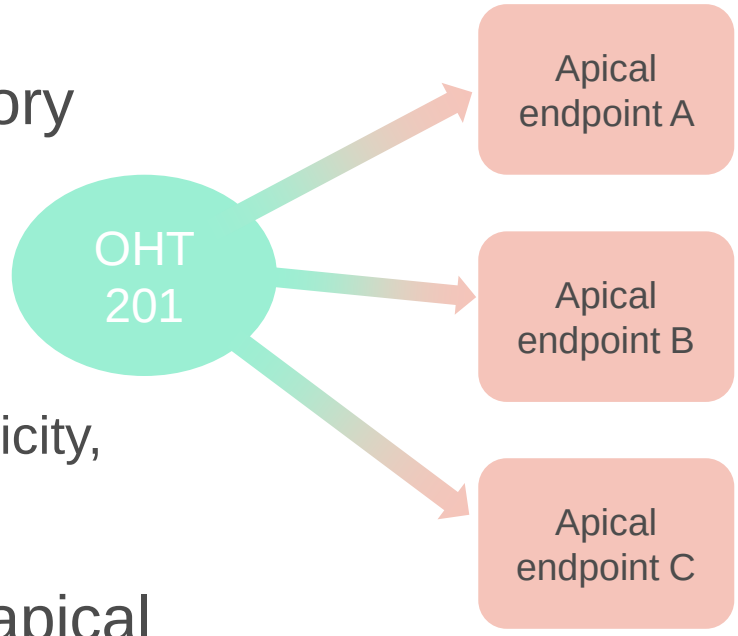
Why OHT 201?

- All other OHTs are **apical**.
- Apical = referring to **one single endpoint** of regulatory concern
  - Ecotox: Fish toxicity, bird toxicity, …
  - Human health: skin sensitisation, carcinogenicity, mutagenicity, reprotocicity, acute toxicity, …
- Mechanistic data are **not intrinsically linked** to an apical endpoint!
- They can be used to **underpin mechanistic explanations** of toxicity – across and beyond apical endpoints



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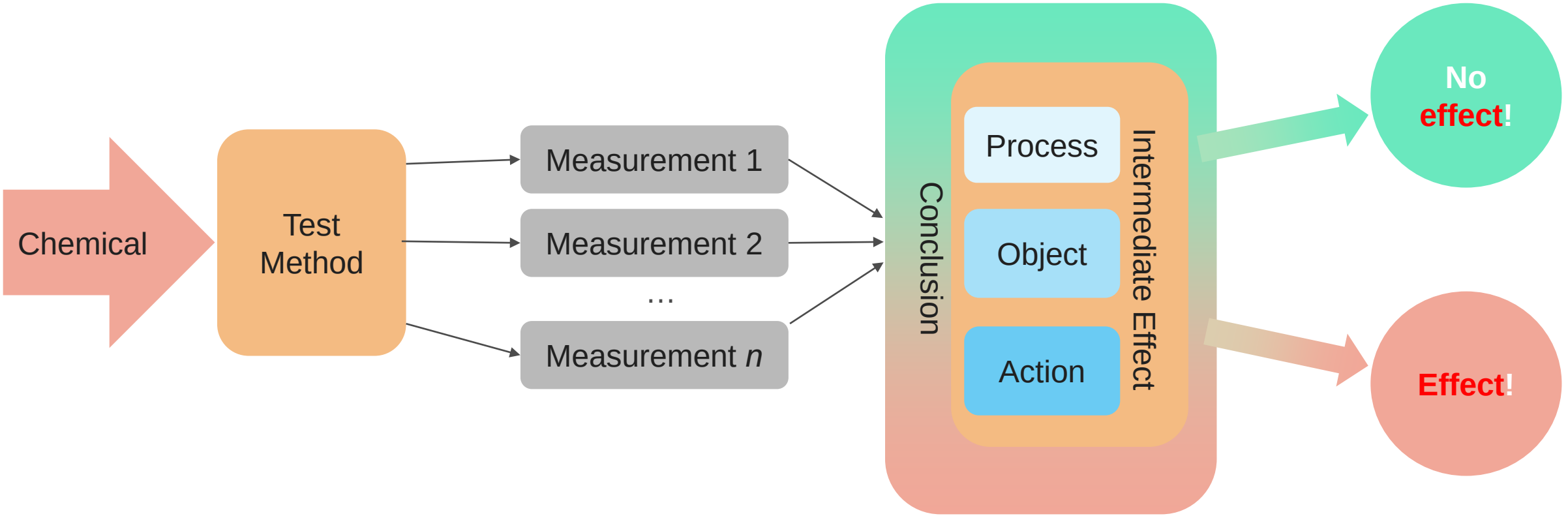
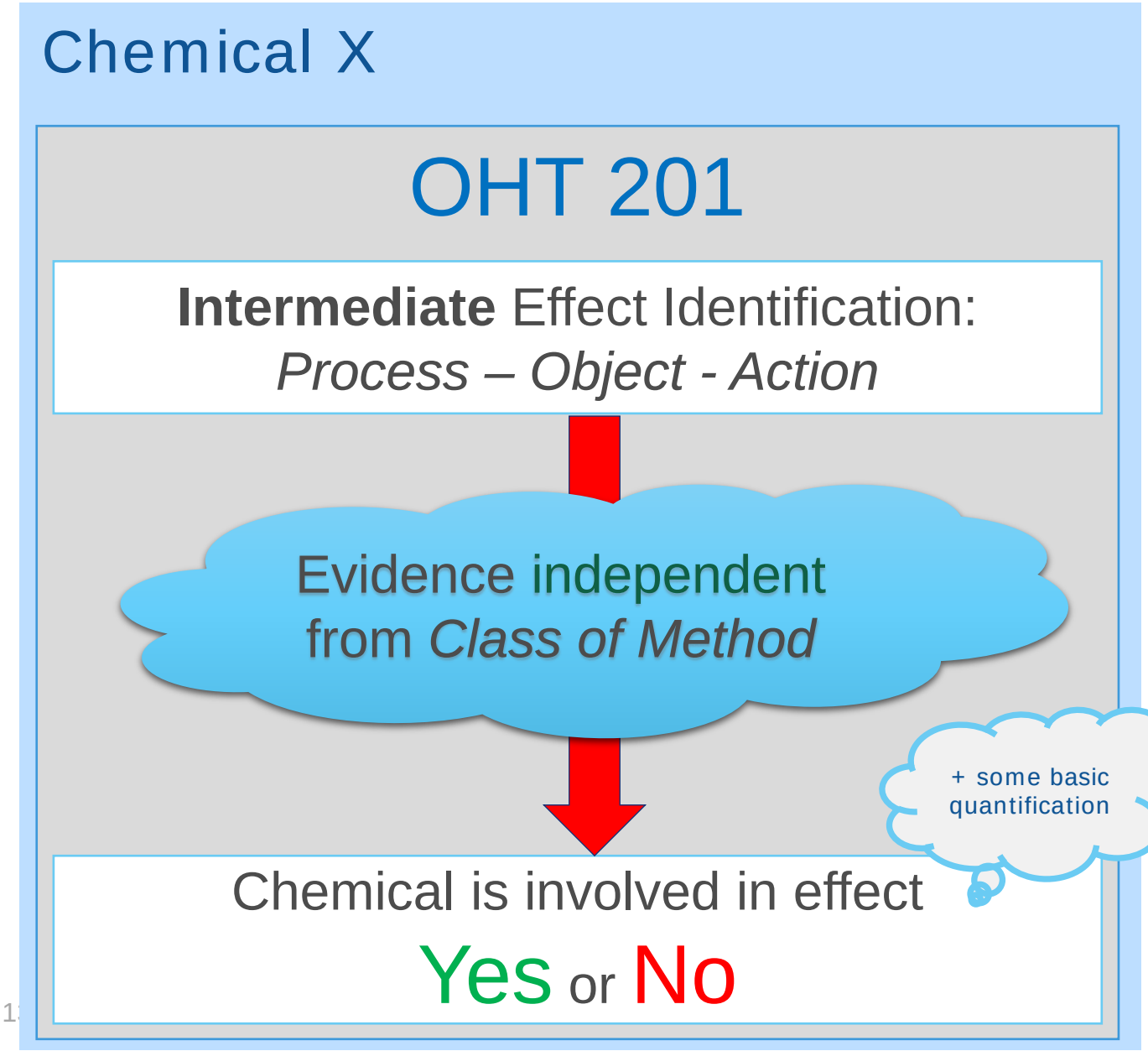
Reporting paradigm using OHT 201



OHT 201 fits all classes of methods



- OHT 201 **links** a chemical to an intermediate (mechanistic) effect, identified by a **Process-Object-Action** ontology
- OHT 201 is by nature **completely independent** from the **class of method** (*in-vitro*, QSAR, PBK, 'omics, …) used to underpin the link

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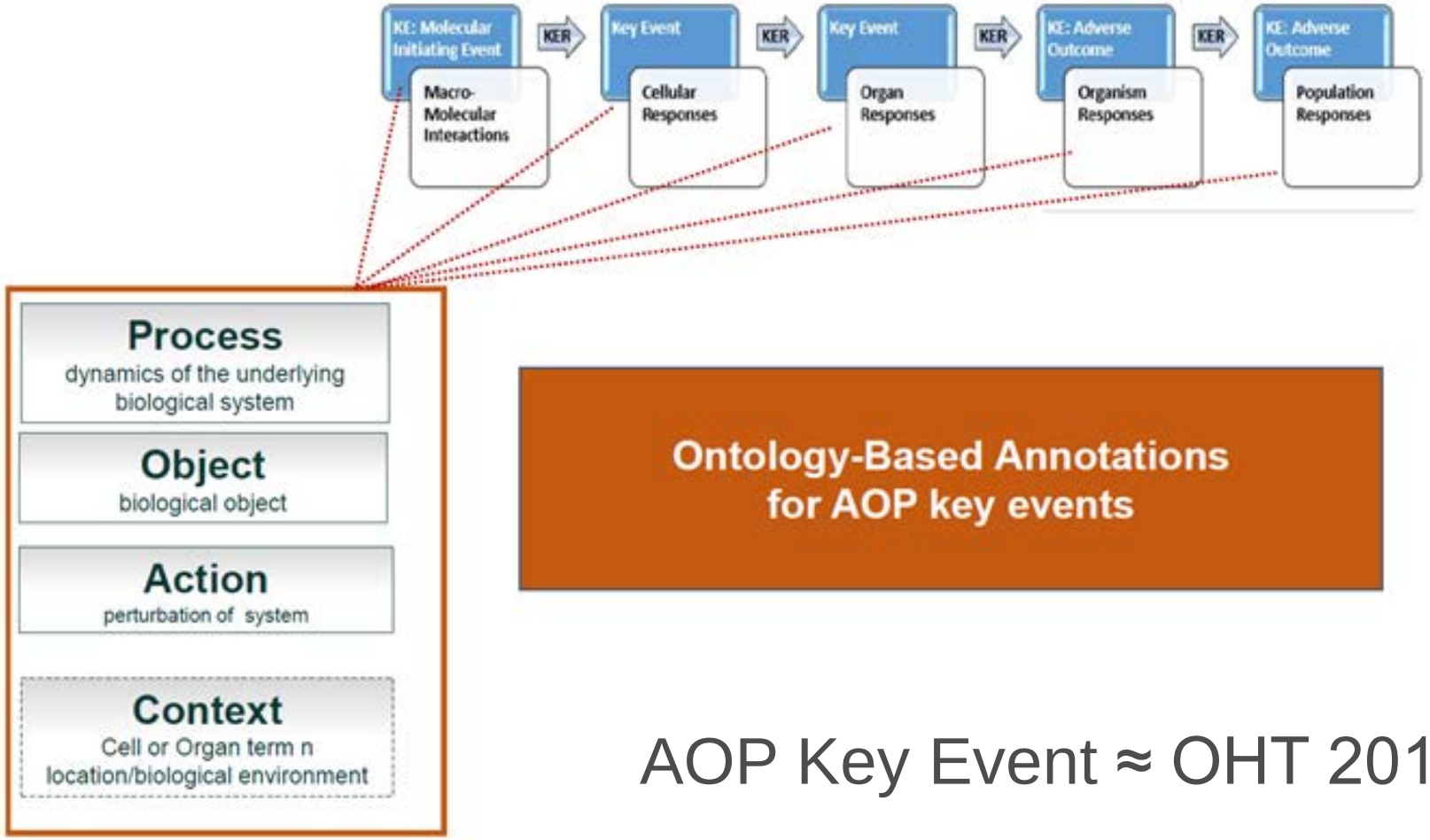
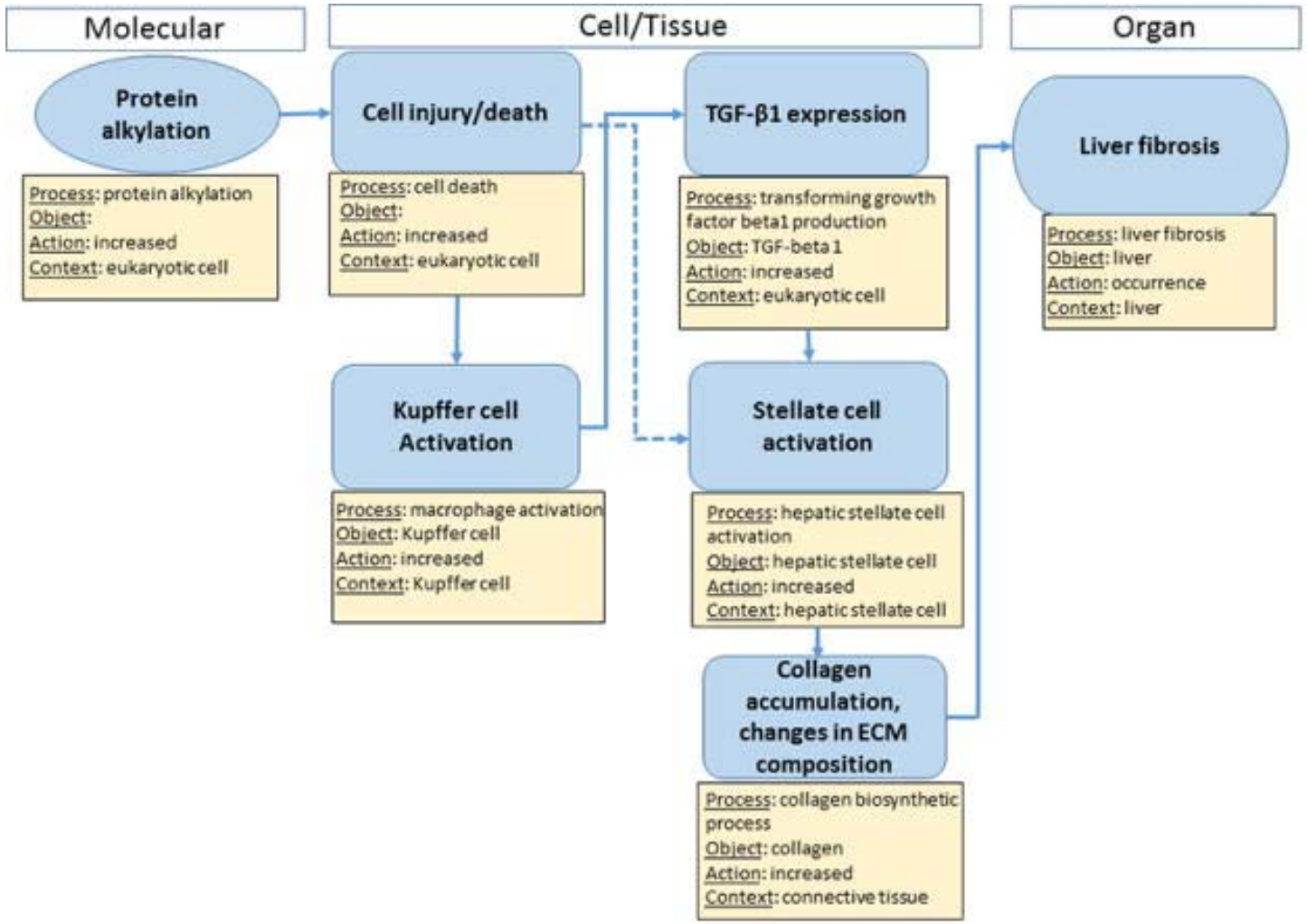
Intermediate Effect Naming



In OHT 201, effects are named **using the same ontology** as the AOP Framework

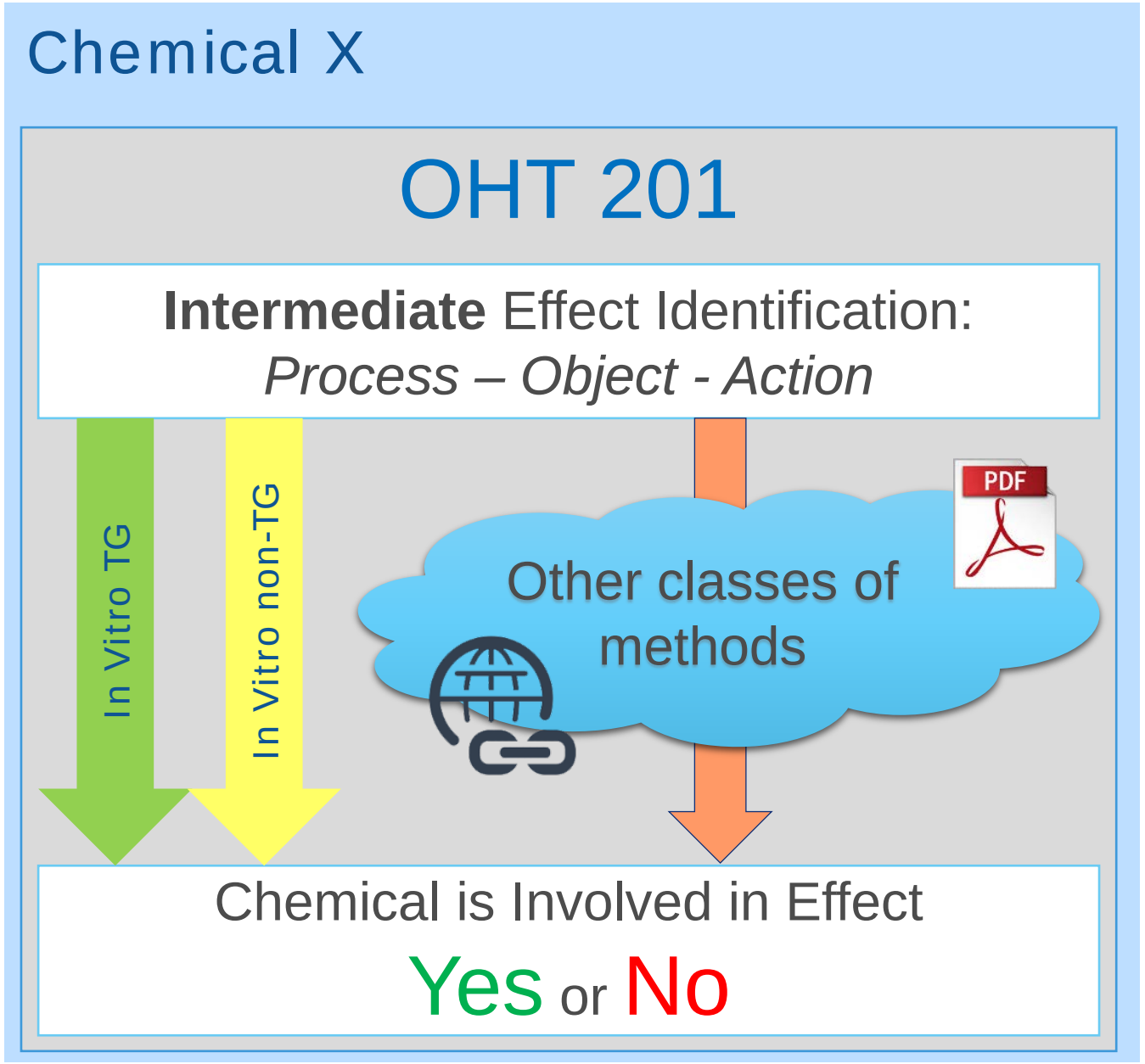
AOP Key Event ≈ OHT 201 Intermediate Effect

Sample *Process – Object – Action* names



https://aopwiki.org/aops/38

Real life OHT 201 today



- In order to increase its usefulness in *certain* environments, OHT 201 features **structured fields** to accomodate *certain* technologies
- Findings derived from **other technologies** can still be reported!
- Using, weblinks, PDF attachments etc.

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OECD Test Guidelines supported

Guideline	Test Method
TG442C	- DPRA - ADRA
TG442D	- Keratinosens - LuSens
TG442E	- h-CLAT - U-SENS - IL-8 LUC assay
TG455 (including former TG457)	- ERTA STTA - ERTA VM7Luc - ERTA ERα CALUX
TG456	- H295R Steroidogenesis Assay
TG458	- ARTA STTA - ARTA AR-CALUX
TG493	- hrER binding FW assay - hrER binding CERI assay

If NAM **follows an OECD Test Guideline**:
Many fields are pre-filled

If NAM **does not follow an OECD Guideline**:
More manual work needed

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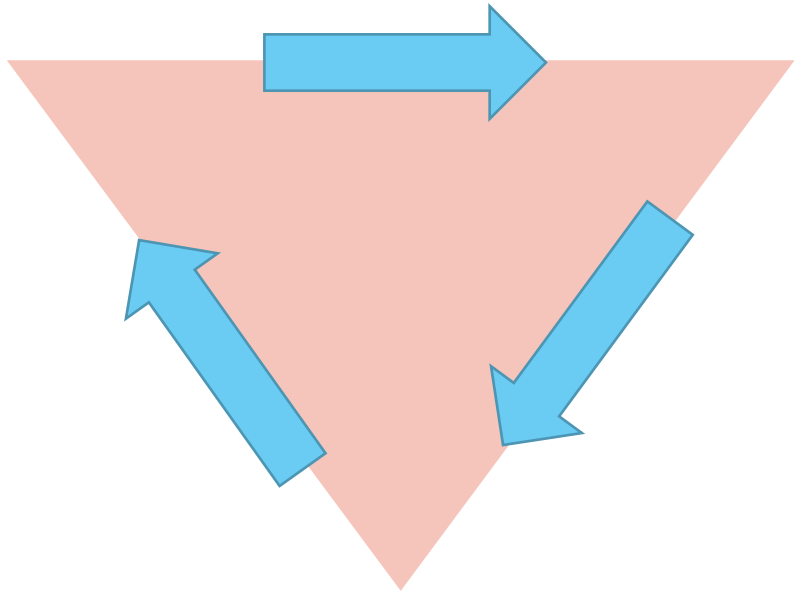
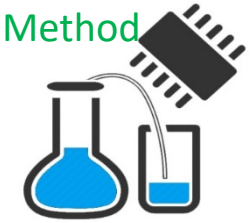
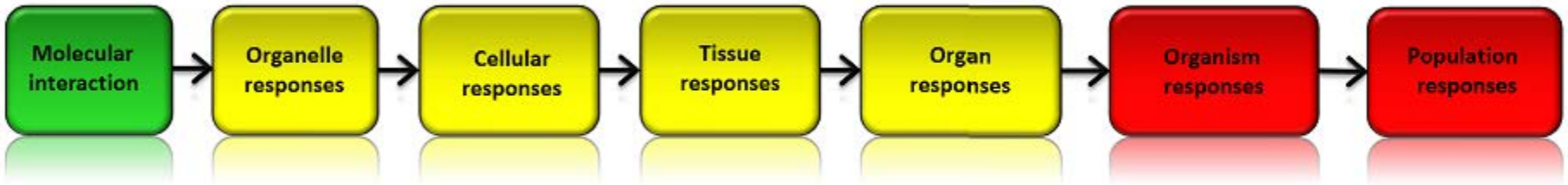
Stressors - Test Methods - AOPs



In-Vivo Test Method

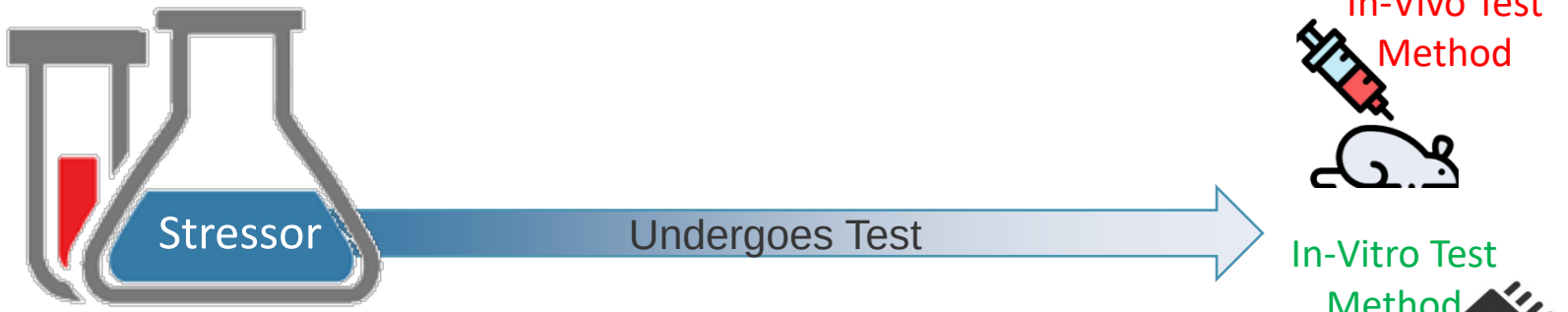
In-Vitro Test Method





Adverse Outcome Pathways

Stressors - Test Methods - AOPs



In-Vivo Test Method

In-Vitro Test Method

IUCLID 6

OHT 201

other OHTs

inconclusive

does not trigger

triggers

does not trigger

triggers

Molecular interaction → Organelle responses → Cellular responses → Tissue responses → Organ responses → Organism responses → Population responses

Adverse Outcome Pathways

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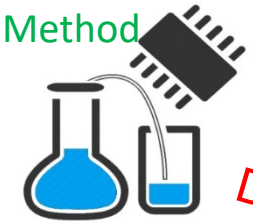
Stressors - Test Methods - AOPs

Undergoes Test

In-Vivo Test Method

In-Vitro Test Method



Methods tagged with **ontology** terms

To be published in late 2020

IUCLID 6

OHT 201

other OHTs

Test Method Dissemination DBs

Inconclusive

does not trigger

triggers

does not trigger

triggers

Effects tagged with **ontology** terms

Molecular interaction

Organelle responses

Cellular responses

Tissue responses

Organ responses

Organism responses

Key Events Tagged with **ontology** terms

Ives C, Campia I, Wang RL, Wittwehr C, Edwards S. Creating a Structured AOP Knowledgebase via Ontology-Based Annotations. Appl In Vitro Toxicol. 2017 Dec 1;3(4):298-311. doi: 10.1089/aivt.2017.0017

Adverse Outcome Pathways

AOP Wiki

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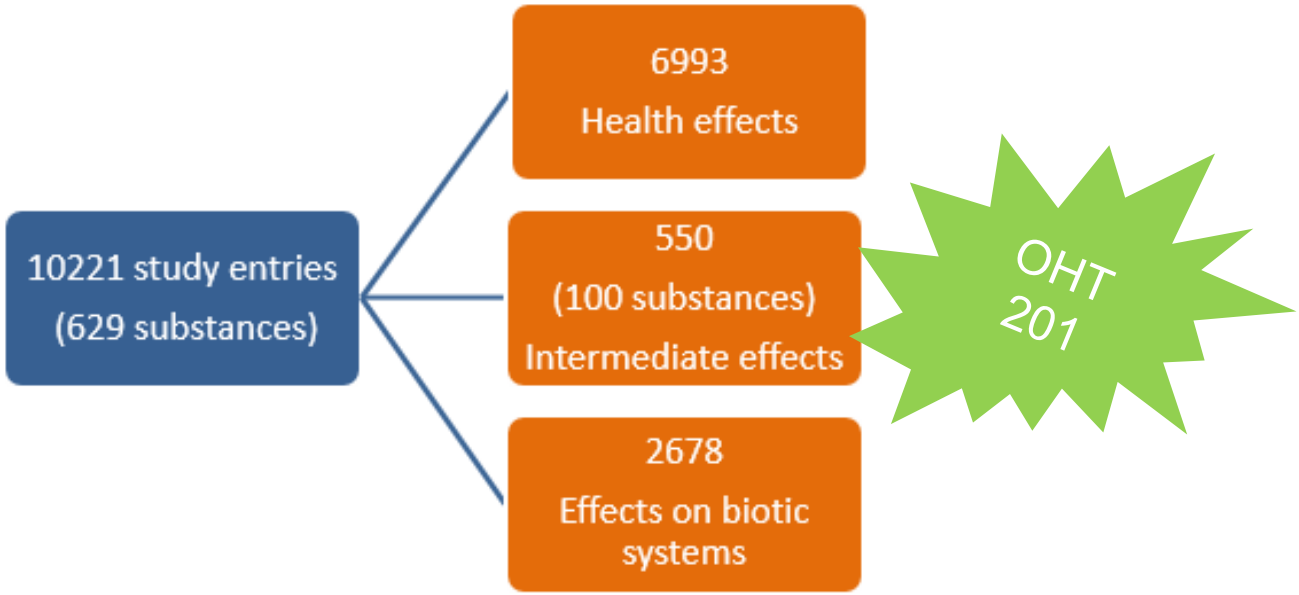
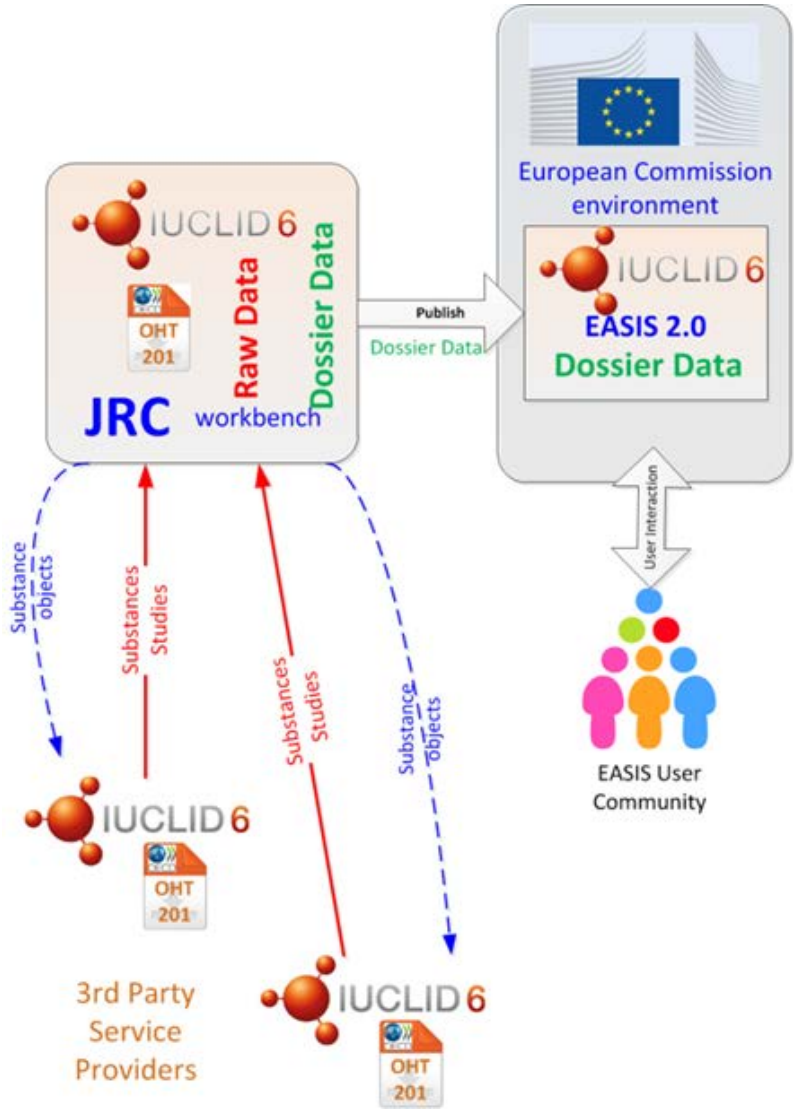
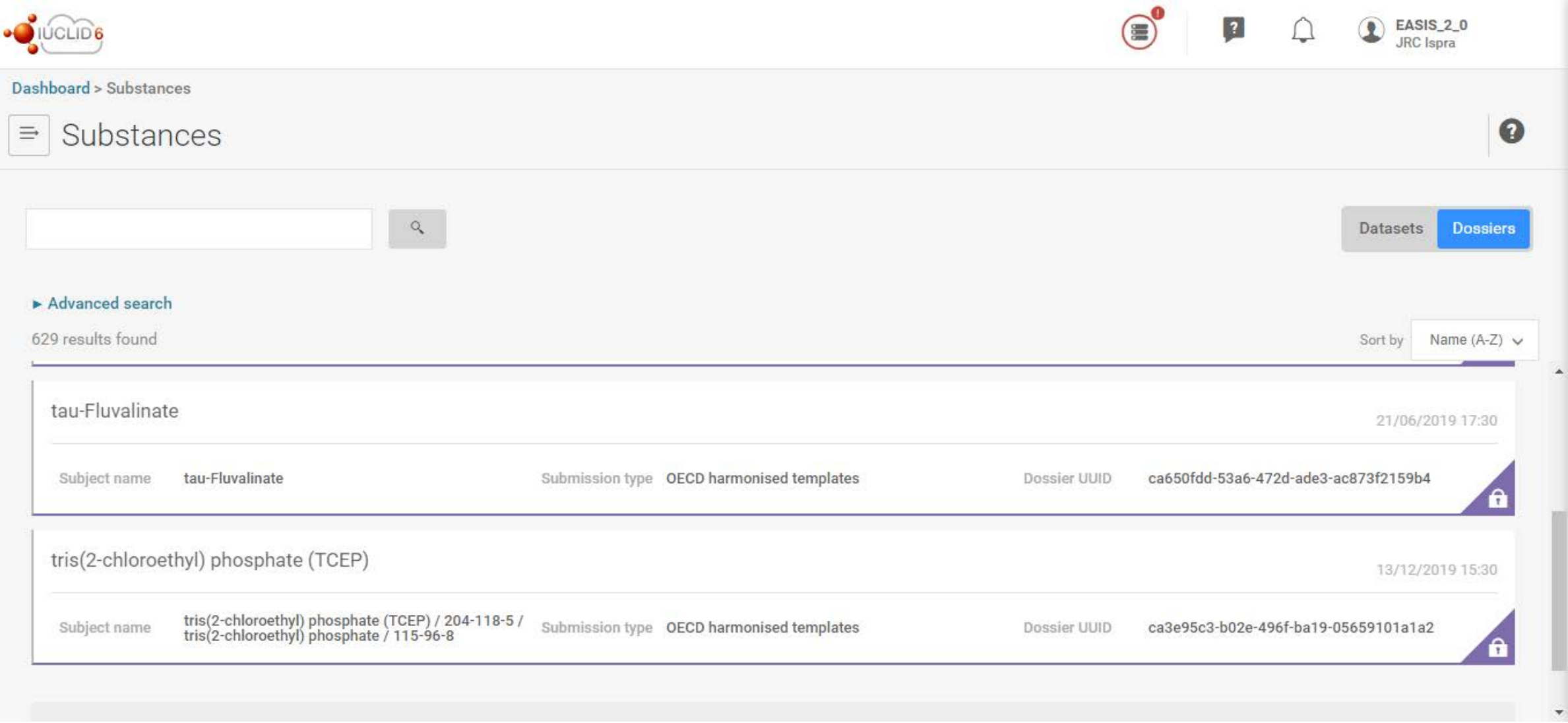
OHT 201 in EASIS

EASIS = **E**ndocrine **A**ctive **S**ubstances **I**nformation **S**ystem





To be published in the coming weeks!



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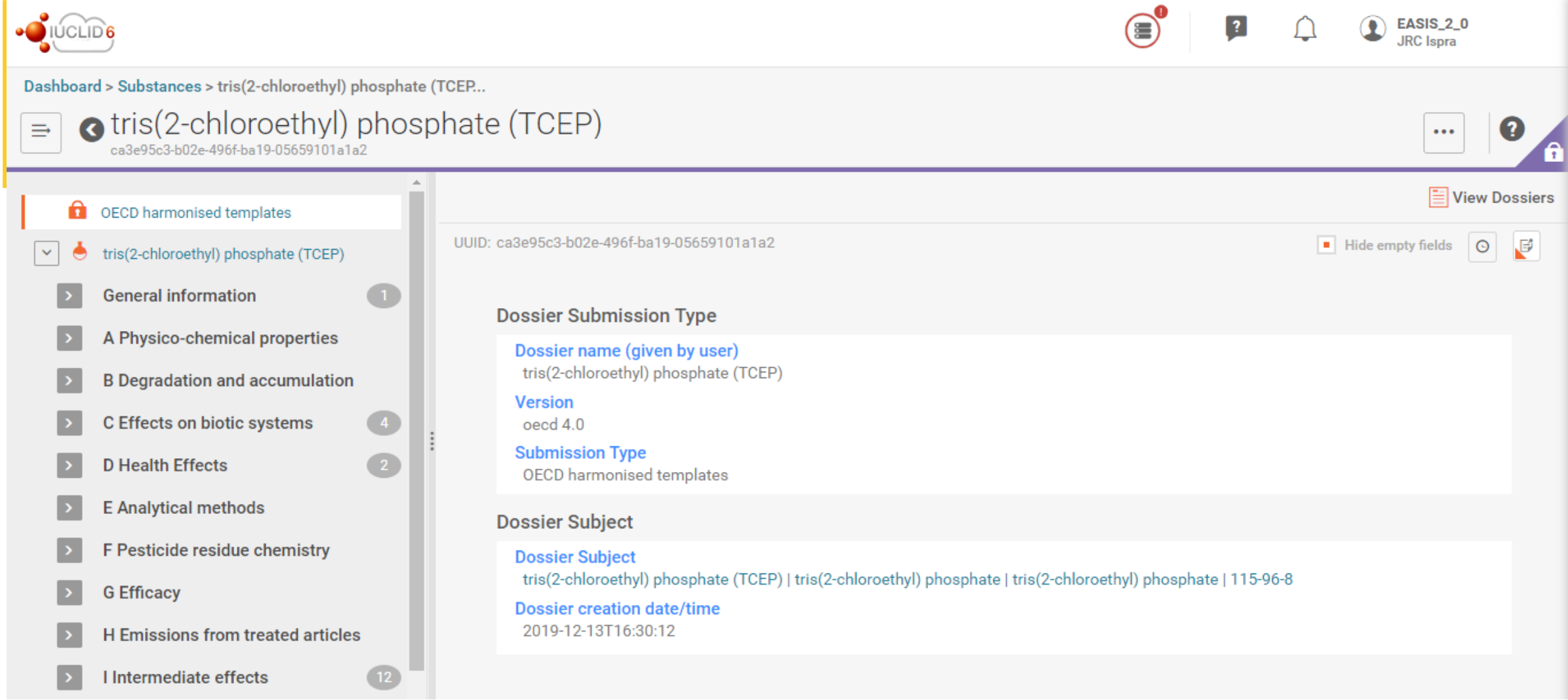

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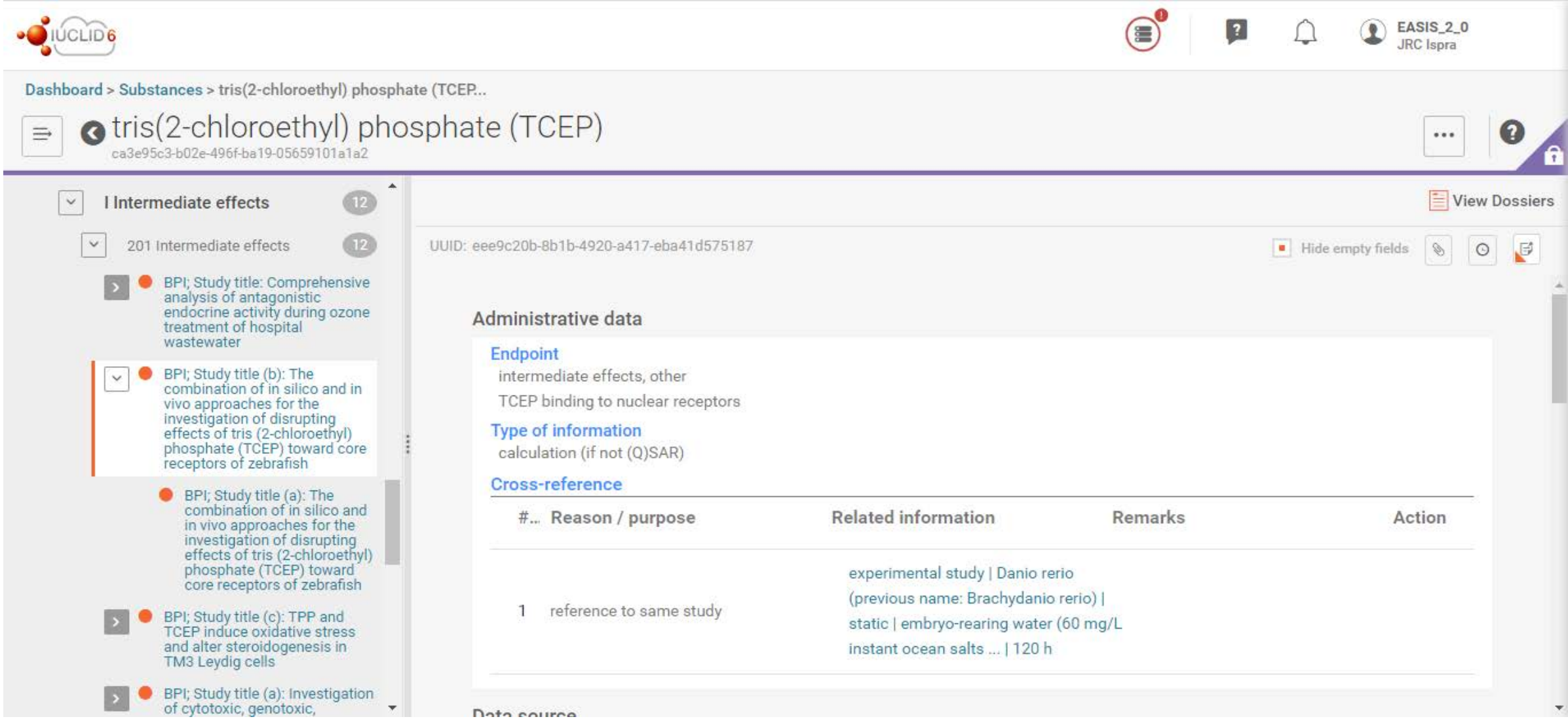

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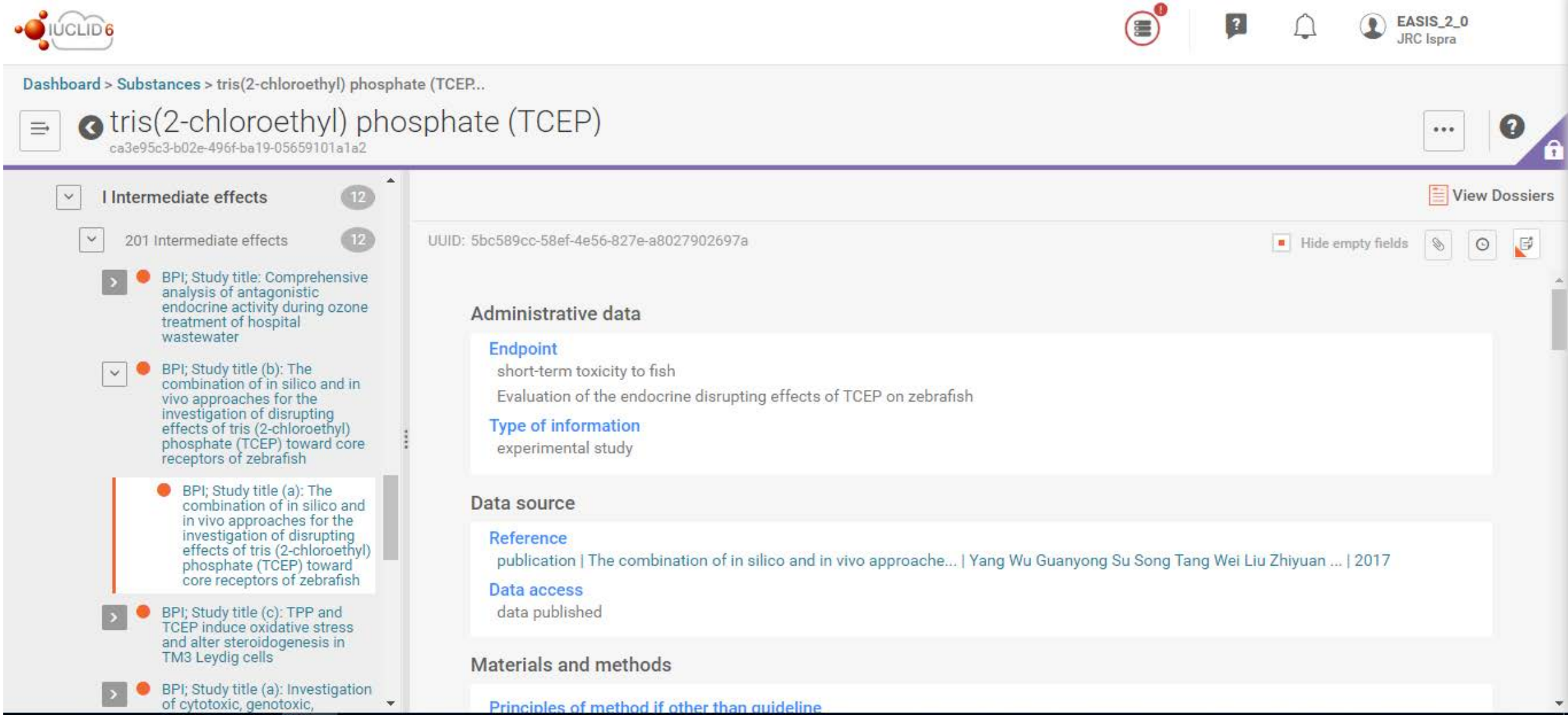

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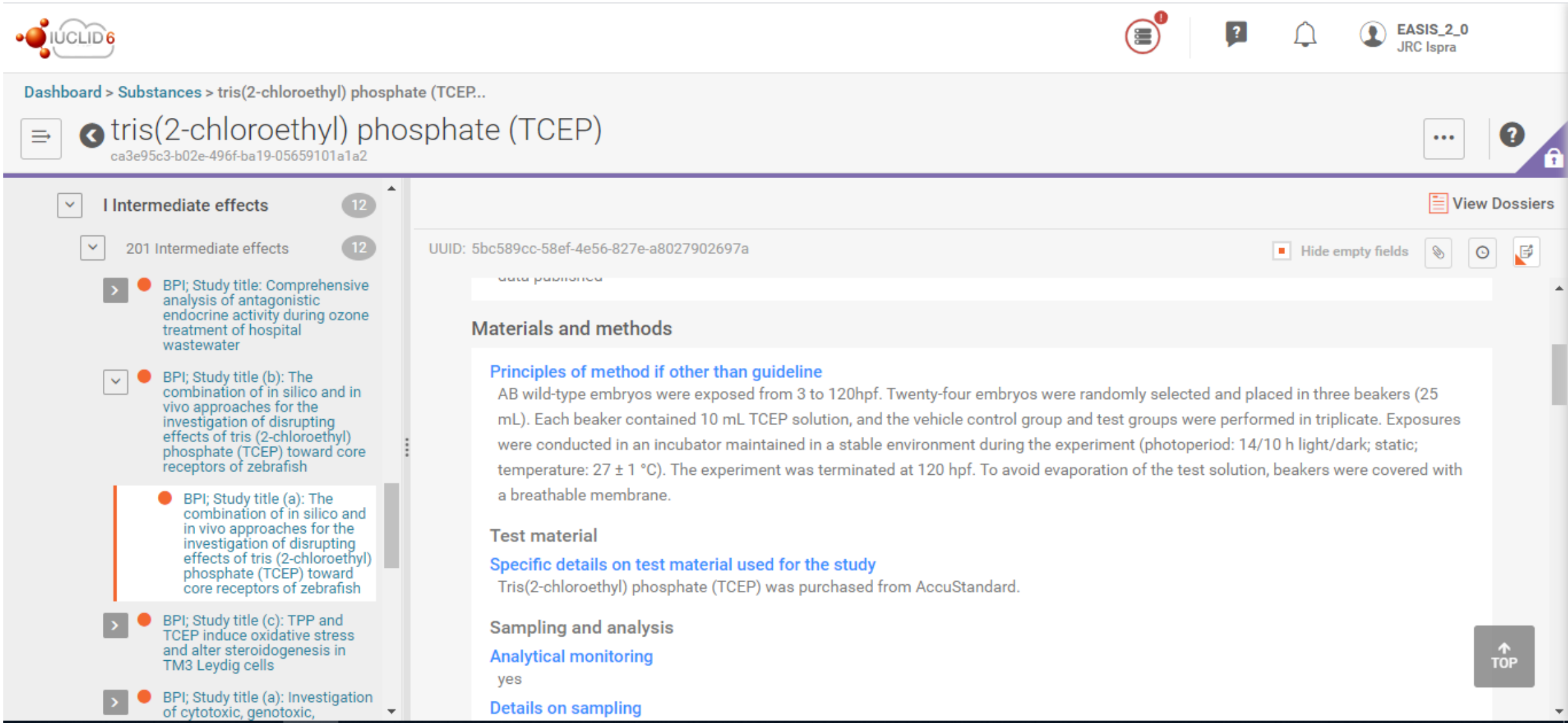

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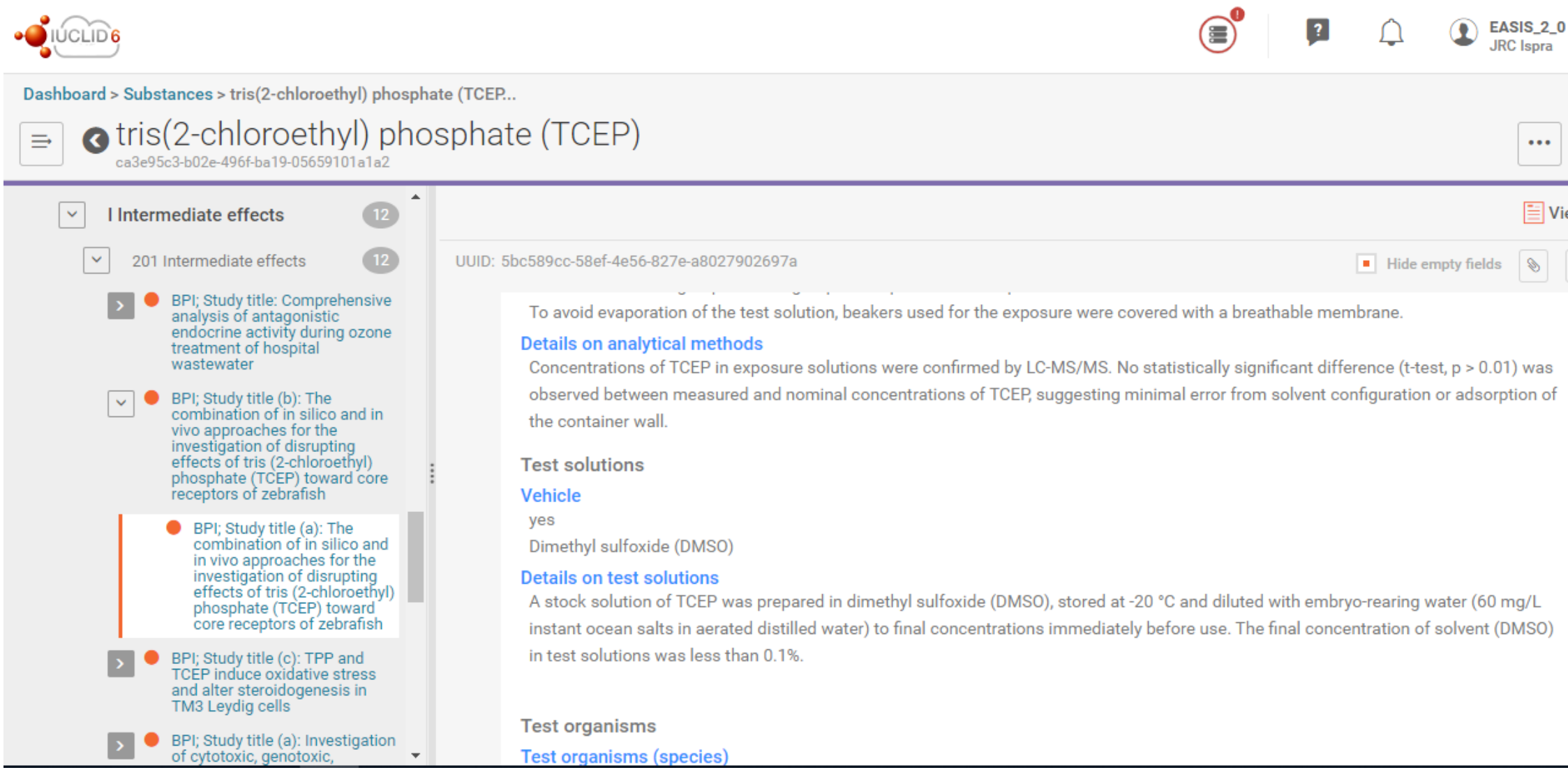

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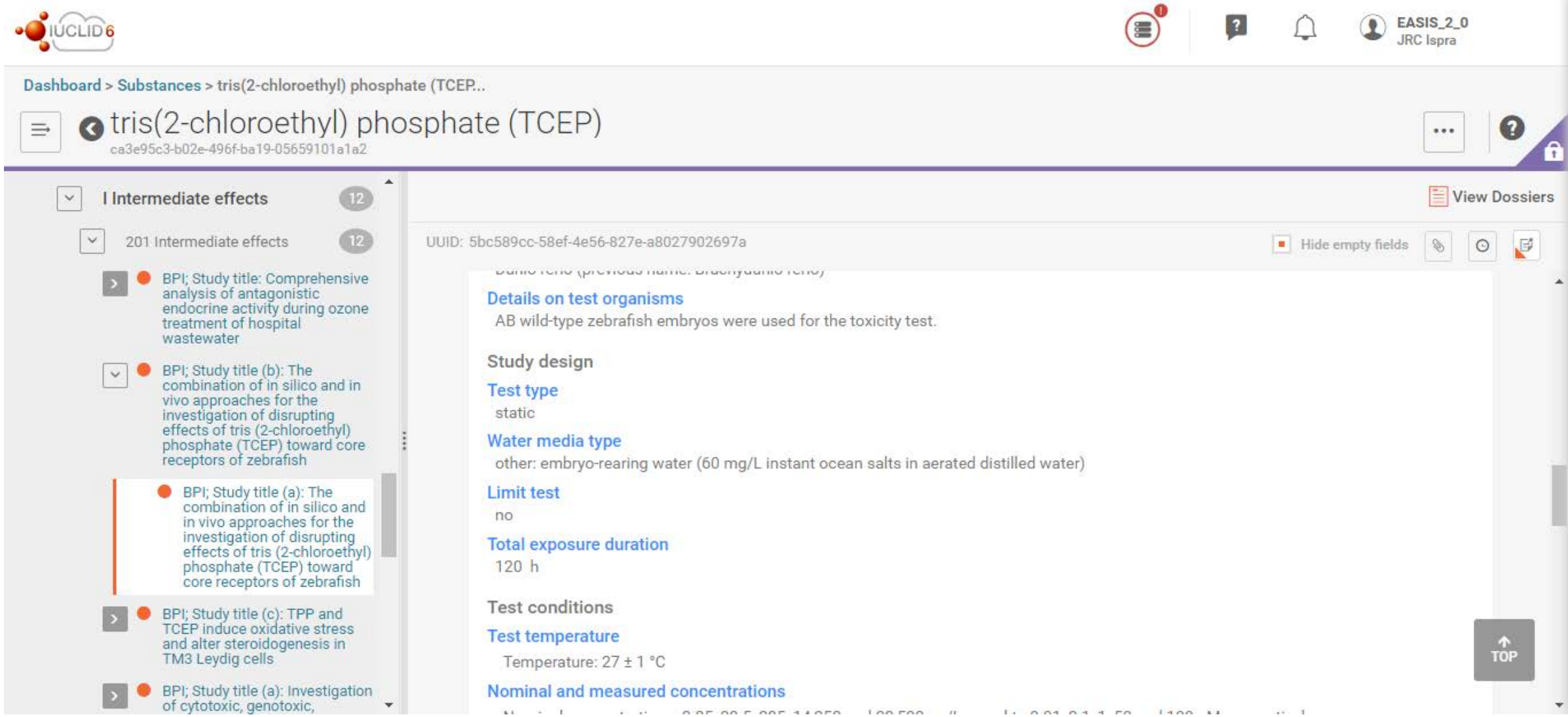

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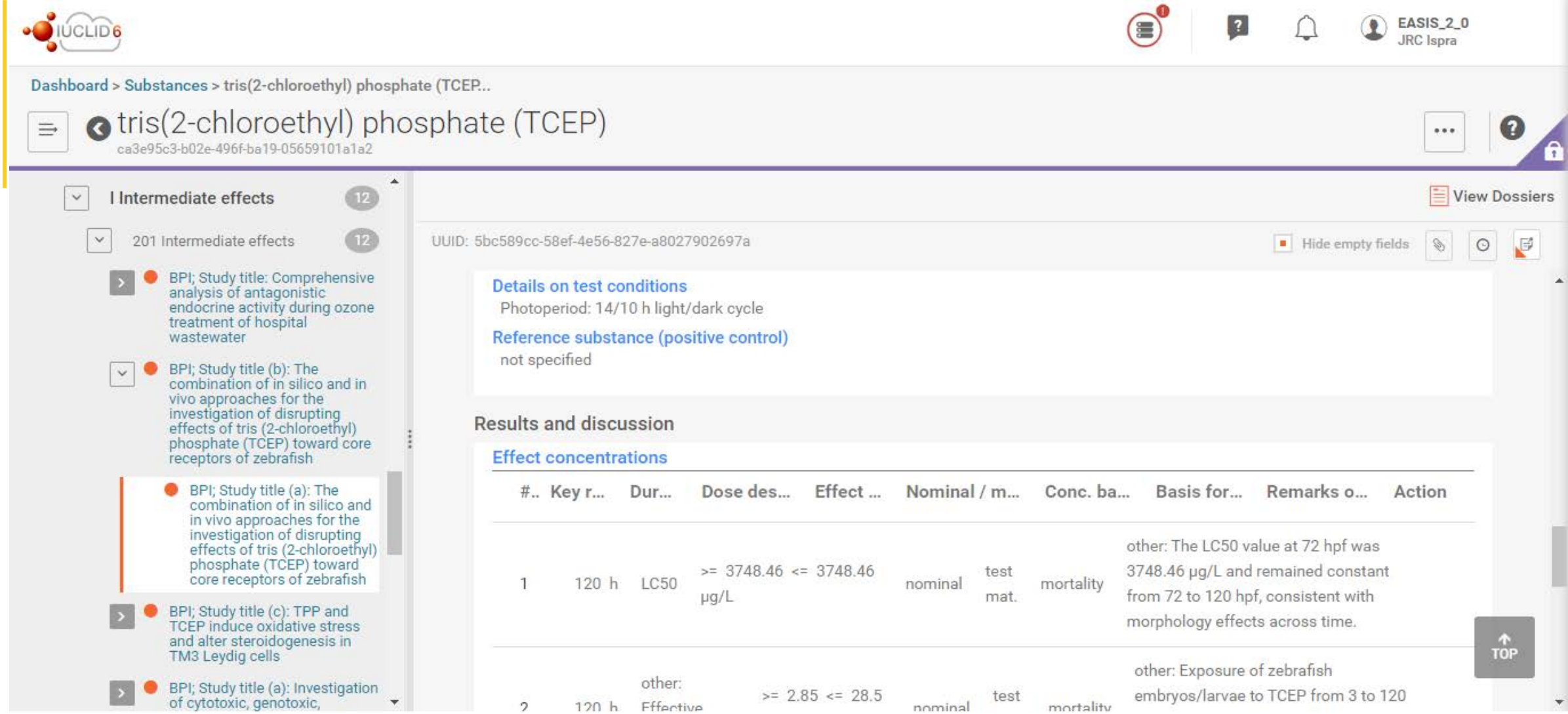

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tris(2-chloroethyl) phosphate (TCEP)

ca3e95c3-b02e-496f-ba19-05659101a1a2

I Intermediate effects 12

201 Intermediate effects 12

- BPI; Study title: Comprehensive analysis of antagonistic endocrine activity during ozone treatment of hospital wastewater
- BPI; Study title (b): The combination of in silico and in vivo approaches for the investigation of disrupting effects of tris (2-chloroethyl) phosphate (TCEP) toward core receptors of zebrafish
  - BPI; Study title (a): The combination of in silico and in vivo approaches for the investigation of disrupting effects of tris (2-chloroethyl) phosphate (TCEP) toward core receptors of zebrafish
- BPI; Study title (c): TPP and TCEP induce oxidative stress and alter steroidogenesis in TM3 Leydig cells
- BPI; Study title (a): Investigation of cytotoxic, genotoxic,

View Dossiers

UUID: 5bc589cc-58ef-4e56-827e-a8027902697a

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4	120 h	other: Effective concentration	>= 2.85 <= 285 µg/L	nominal	test mat.	other: Expression of genes associated with several NR signaling pathways.	other: Exposure to 2.85, 28.5 and 285 µg TCEP/L resulted in changes in the mRNA expression of genes associated with several NR signaling pathways.

Reported statistics and error estimates

The data from MD simulations was analyzed in GROMACS 4. The root-mean-square deviation (RMSD), which is the measure of the average distance between the atoms of superimposed proteins, was calculated. Origin 8 was used to analyze the RMSD fluctuations. GraphPad was primarily used for statistical processing. One-way analysis of variance (ANOVA) and Tukey's test were used to determine significant differences between experimental and control groups. The resulting network genes (nodes) were colored by the Enhanced Graphics application within Cytoscape v3.1.1 according to the significant changes in gene expression in the respective treatments.

TOP

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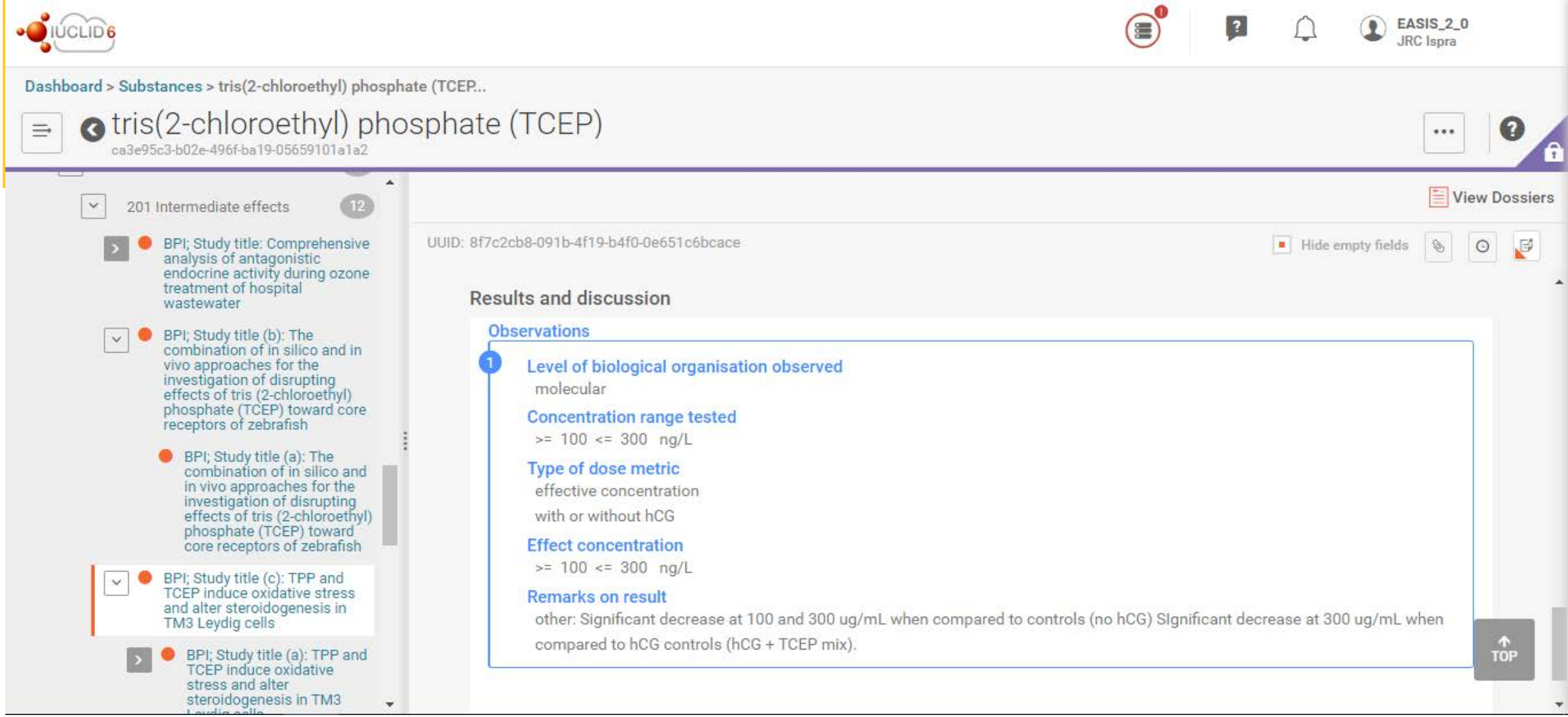

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Take-home messages

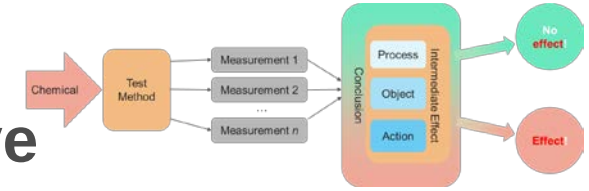
- OHT 201 facilitates **reporting of NAM study results** in an internationally agreed format

- OHT 201 supports the chemical angle of the "**Stressor – Method – AOP**" triangle

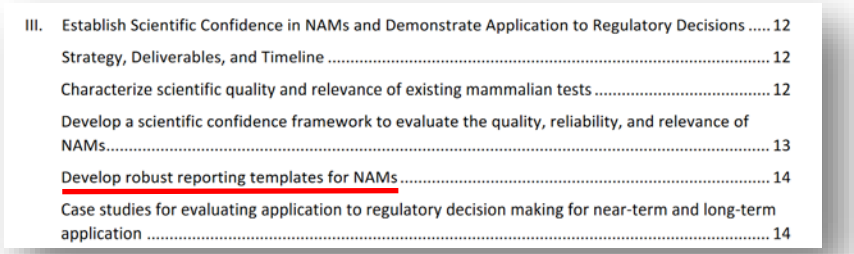
- OHT 201 is available in a **free ICT** application

- OHT 201 supports **all classes of NAMs**, especially *in-vitro* methods

- OHT 201 reports (per chemical and intermediate effect) one or more objective measurements and **one subjective conclusion**



How this fits into the EPA NAMs workplan…



OECD Harmonised Template 201 is **explicitely mentioned** in the EPA NAMs workplan

Develop robust reporting templates for NAMs

Studies are submitted to regulatory programs with specific reporting requirements to aid in evaluation and interpretation. To promote consistency, the OECD has general reporting templates that may be used by different regulatory jurisdictions. The templates include standard elements that should be included in methods descriptions for individual test assays, batteries of assays, and algorithms for evaluating sets of assay results. Although the reporting templates for NAMs are still evolving, the OECD has developed guidance to help standardize *in vitro* methods suitable for regulatory purposes[18] as well as a reporting template for *in vitro* tests describing molecular and cellular observations that can be relevant to the hazard assessment.[19] To accommodate mutual acceptance of data, the EPA will build off these established templates while providing additional templates that capture the range of specific NAMs used for Agency decisions.

Deliverable: *Reporting templates which may be used by EPA and stakeholders that capture the range of specific NAMs used for Agency decisions. The reporting templates will be delivered in the fourth quarter (Q4) of 2022.*

[19] OECD. OECD Harmonised Template 201: Intermediate effects

Links

OECD Harmonised Templates
http://www.oecd.org/ehs/templates/

OHT 201
http://www.oecd.org/ehs/templates/harmonised-templates-intermediate-effects.htm

IUCLID
https://iuclid6.echa.europa.eu/

EASIS
https://ec.europa.eu/jrc/en/scientific-tool/endocrine-active-substances-information-system-easis

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