NAM-derived data in regulatory environments: Templates, AOPs and ontologies

Clemens Wittwehr

European Commission – Joint Research Centre (JRC)

Challenges in Public Health Protection in the 21st Century: New Methods, Omics and Novel Concepts in Toxicology

Berlin, 15-17 November 2021

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

European Commission

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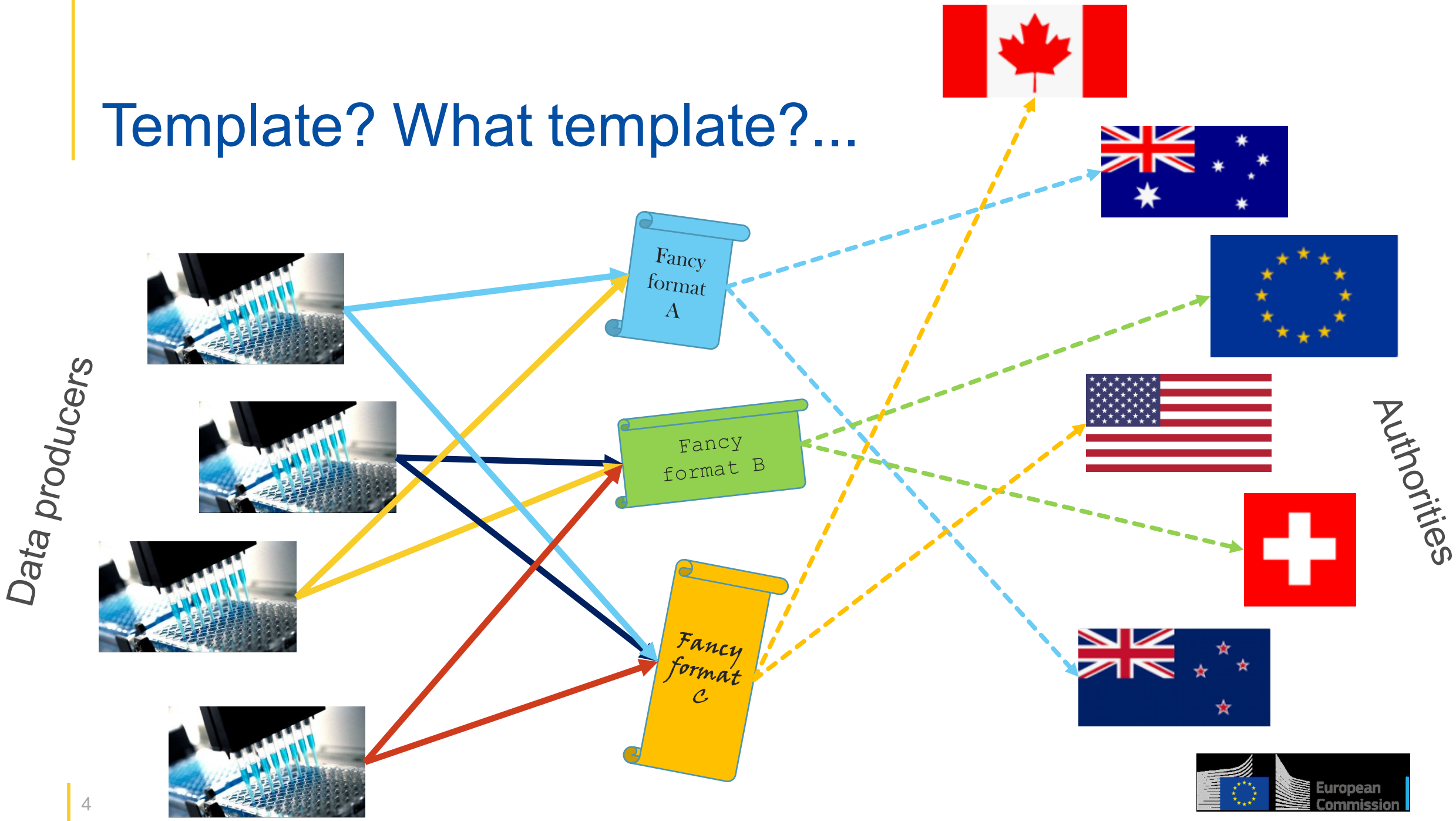
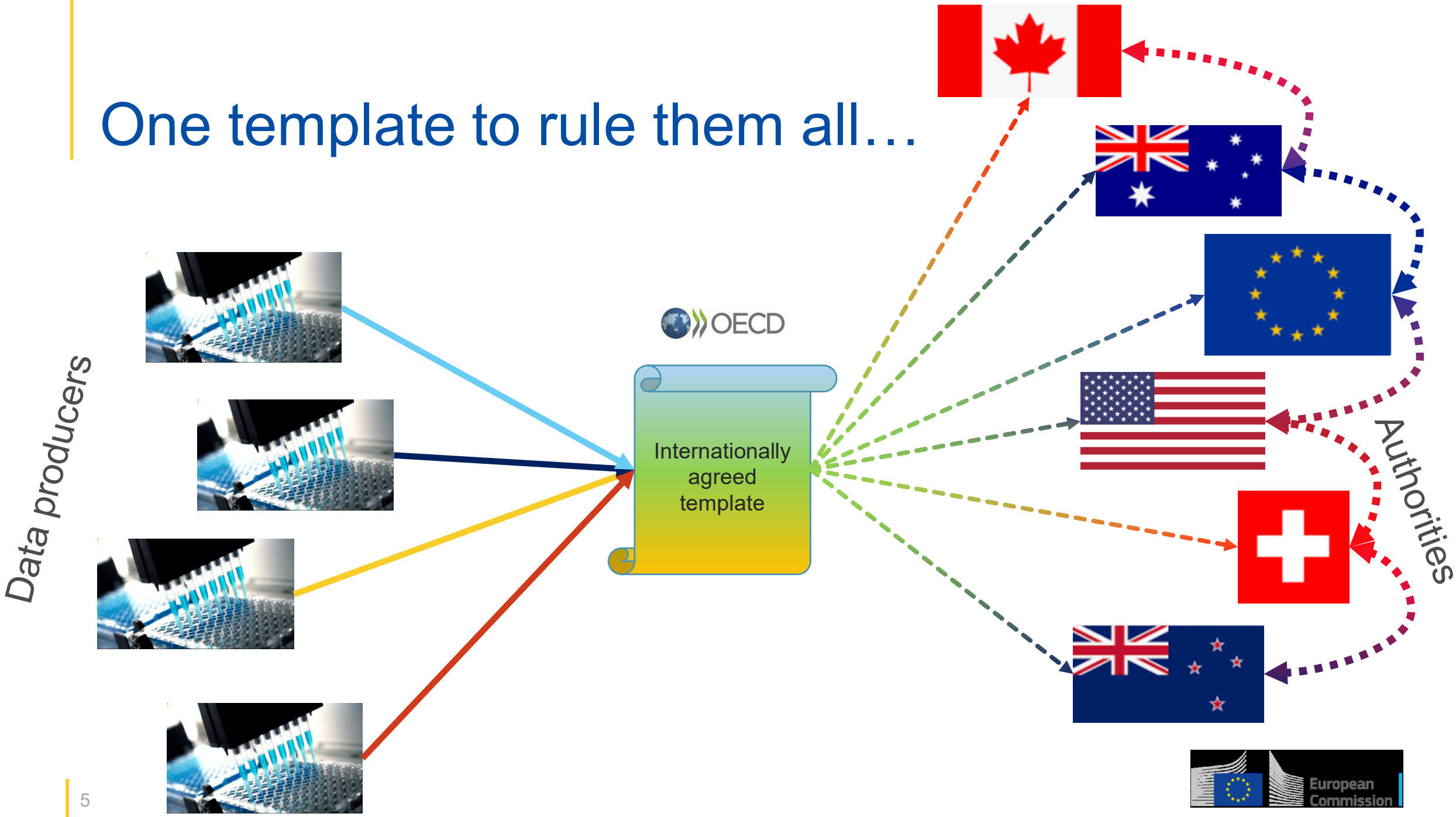
Template? What template?...



One template to rule them all…



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.*

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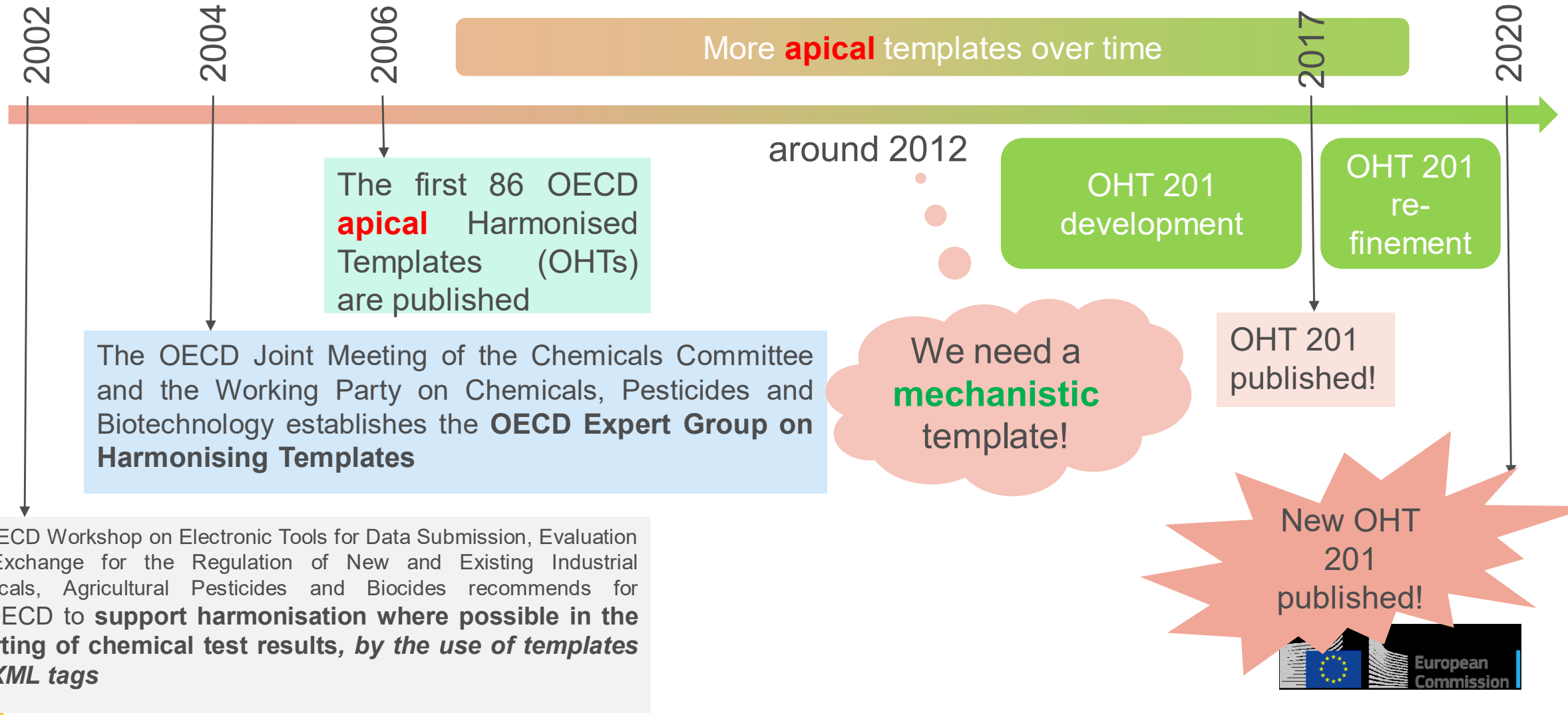
Harmonised Templates



Current OHTs

OHT Series	OHT number
Physico-chemical properties (incl. nanomaterials)	OHTs 1 to 23-5 & 101 to 113
Environmental fate and behaviour	OHTs 24 to 40 & 401
Effects on biotic systems	OHTs 41 to 57
Health effects	OHTs 58 to 84 & 86
Pesticide residue chemistry	OHTs 85-1 to 85-10
Analytical methods	OHT 87
Efficacy	OHTs 88 & 89
Emissions from treated articles	OHT 90
Intermediate effects	OHT 201
Use and exposure information	OHTs 301 to 306

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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

OHTs (and IUCLID) are used in **more and more legislations** around the world

Mother of all IUCLIDs still used for **REACH**

EFSA uses IUCLID for reception, management and dissemination of plant protection product dossiers

More later

Newest kid on the block: JRC Endocrine Active Substances System (**EASIS**)

More later

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 notification 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)	EU EASIS (JRC)	OECD (SIDs)
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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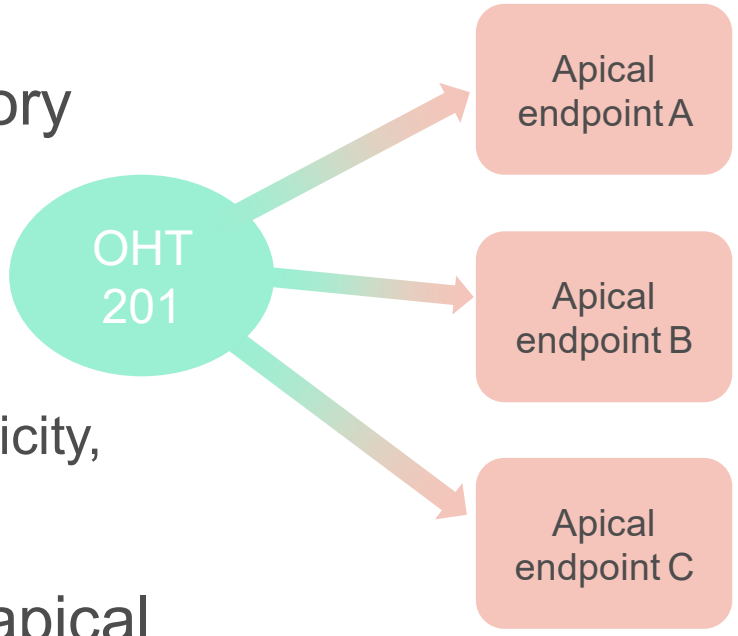
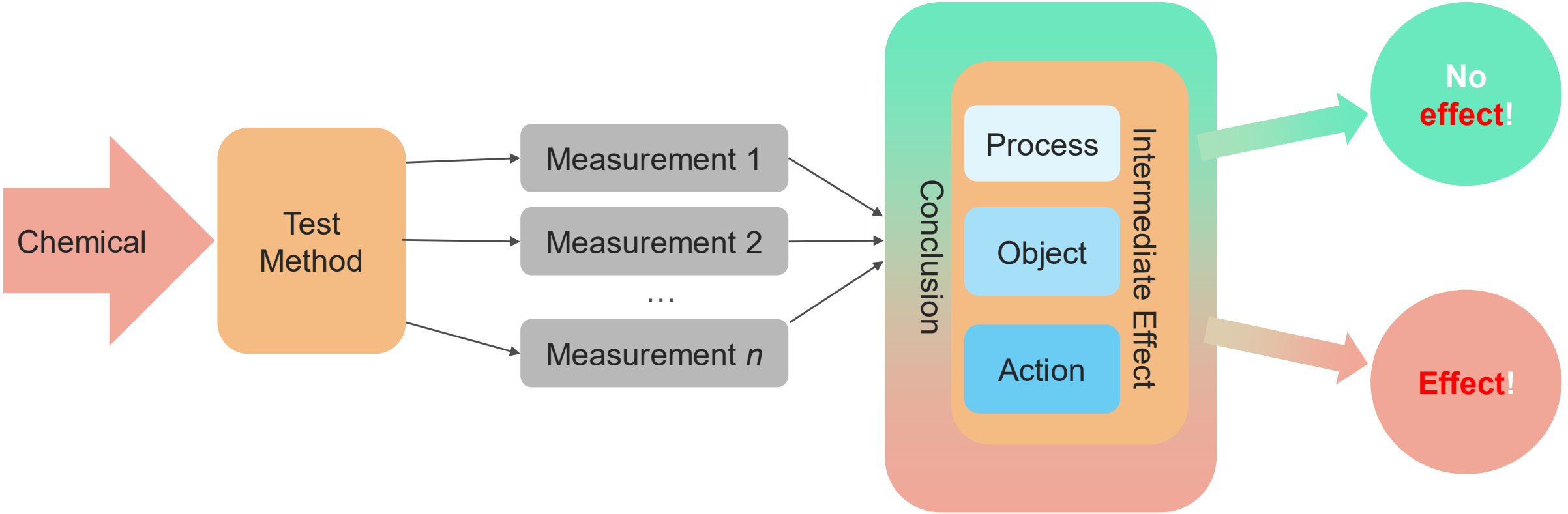
Why OHT 201?

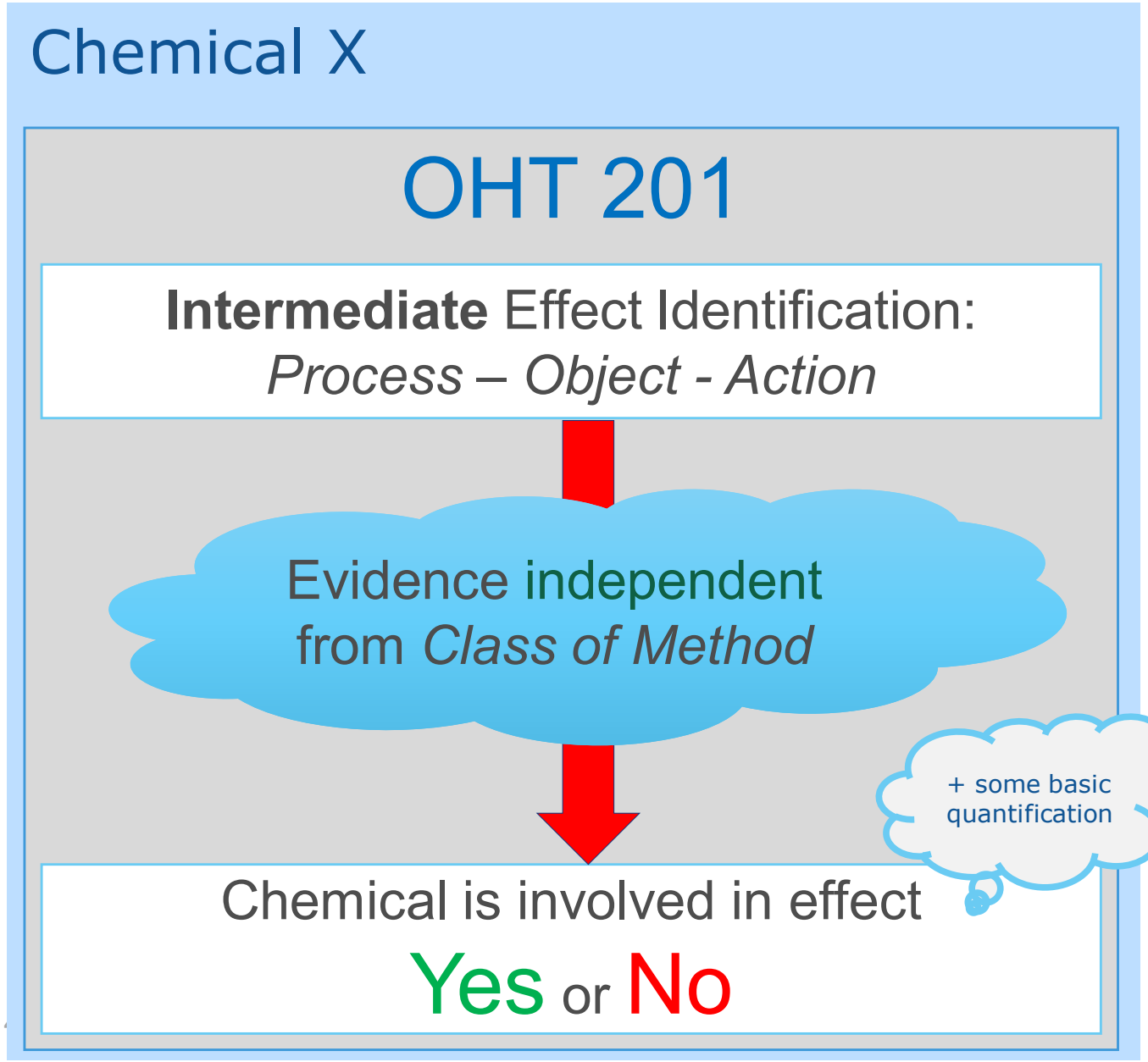
- All other OHTs are **apical**.
- Apical = referring to **one single endpoint** of regulatory concern
  - Ecotox: Fish toxicity, bird toxicity, …
  - Human health: skin sensitisation, carcinogenicity, mutagenicity, reprotocicity, acute toxicity, …
- Mechanistic data are **not intrinsically linked**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



Reporting paradigm using OHT 201

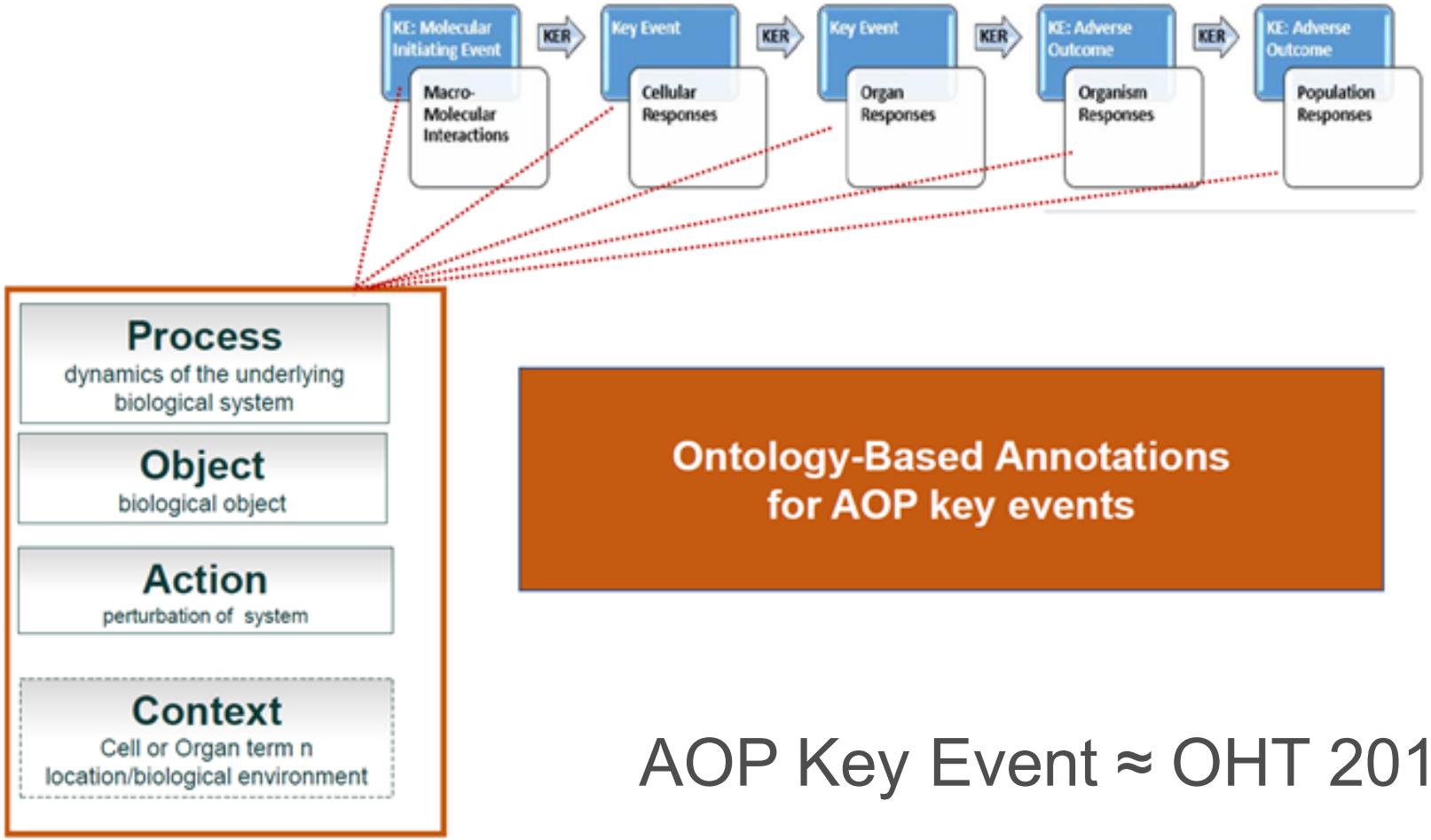


OHT 201 fits all classes of methods



- 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

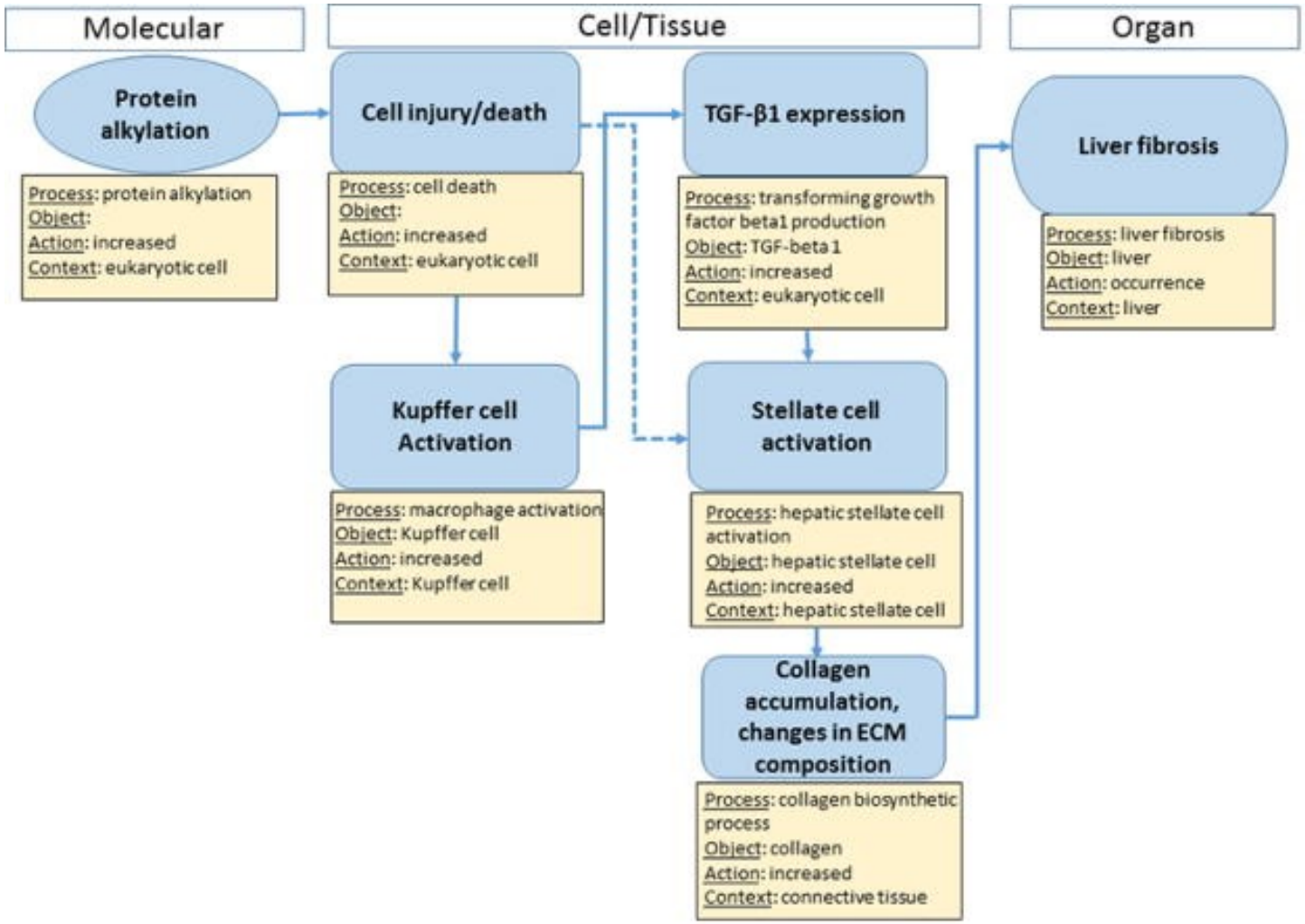
Intermediate Effect Naming



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

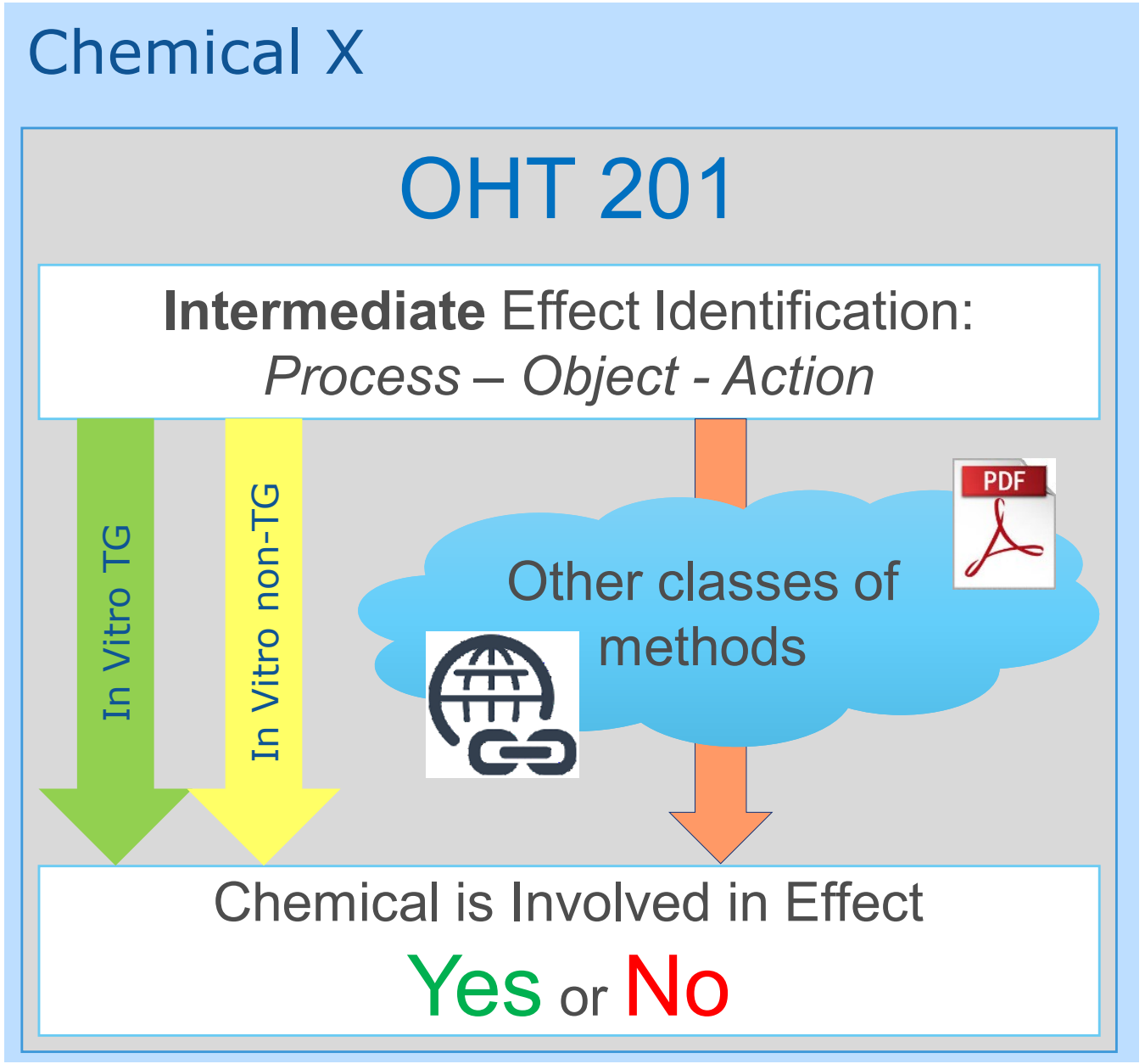
AOP Key Event ≈ OHT 201 Intermediate Effect

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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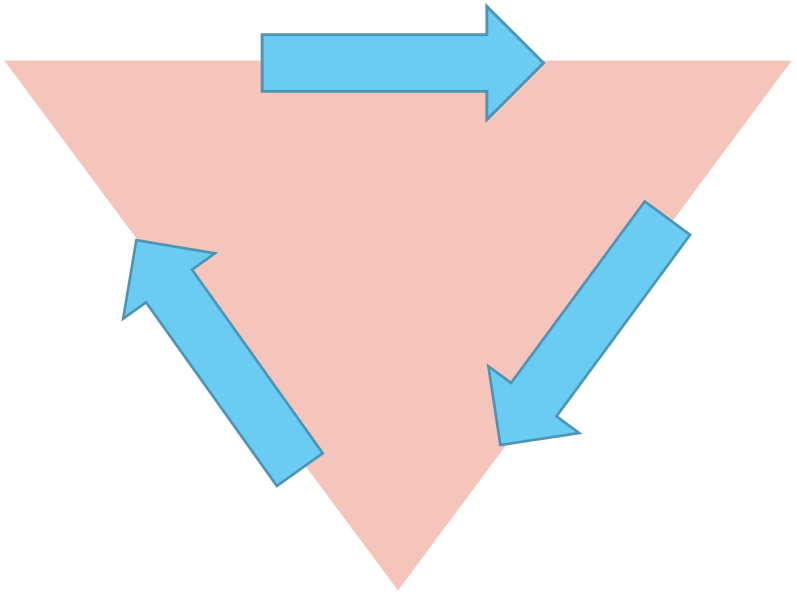
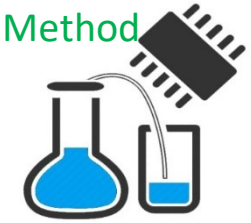
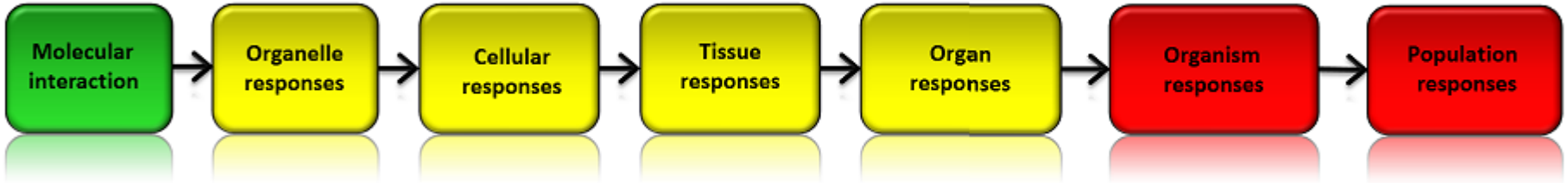
Stressors - Test Methods - AOPs

In-Vivo Test
ıod



In-Vitro Test
Method





Adverse Outcome Pathways

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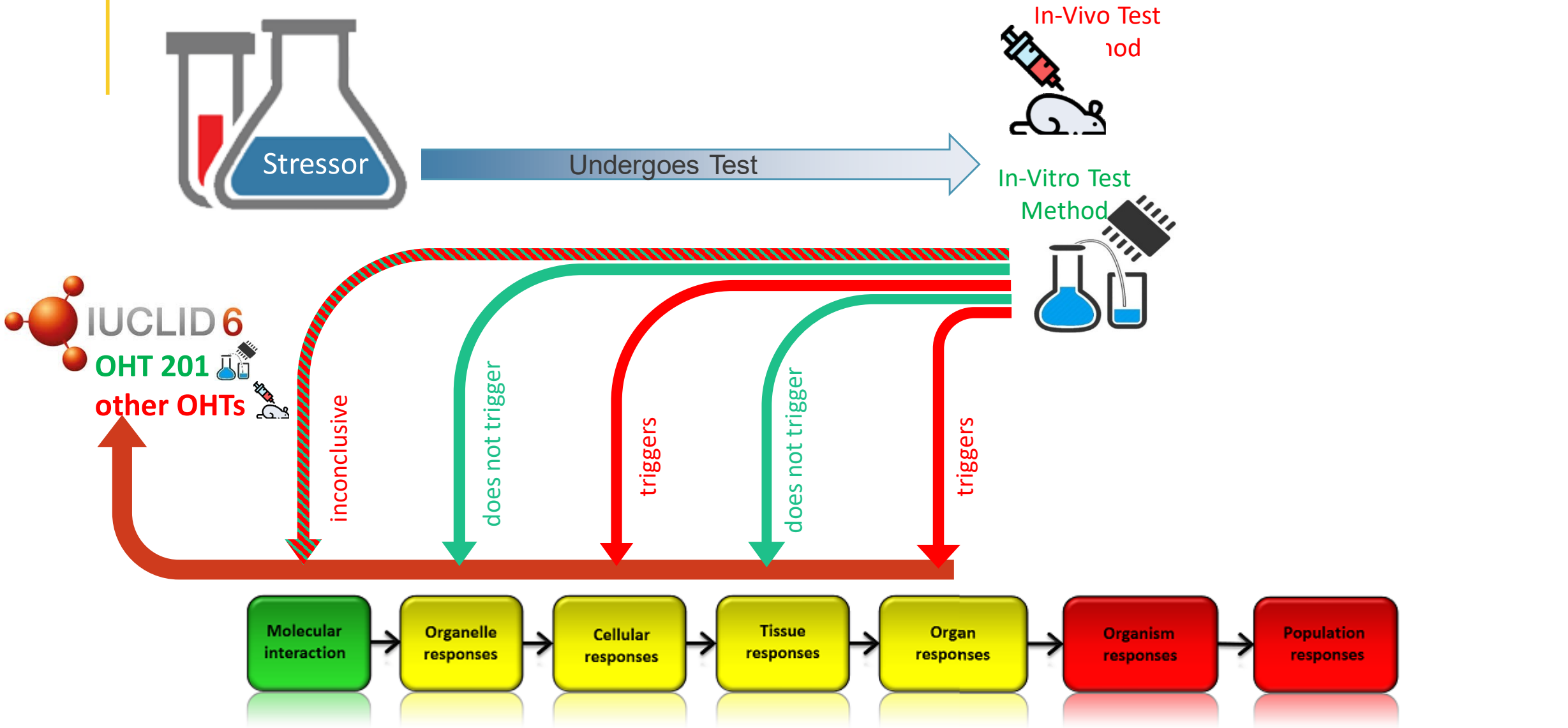
Stressors - Test Methods - AOPs



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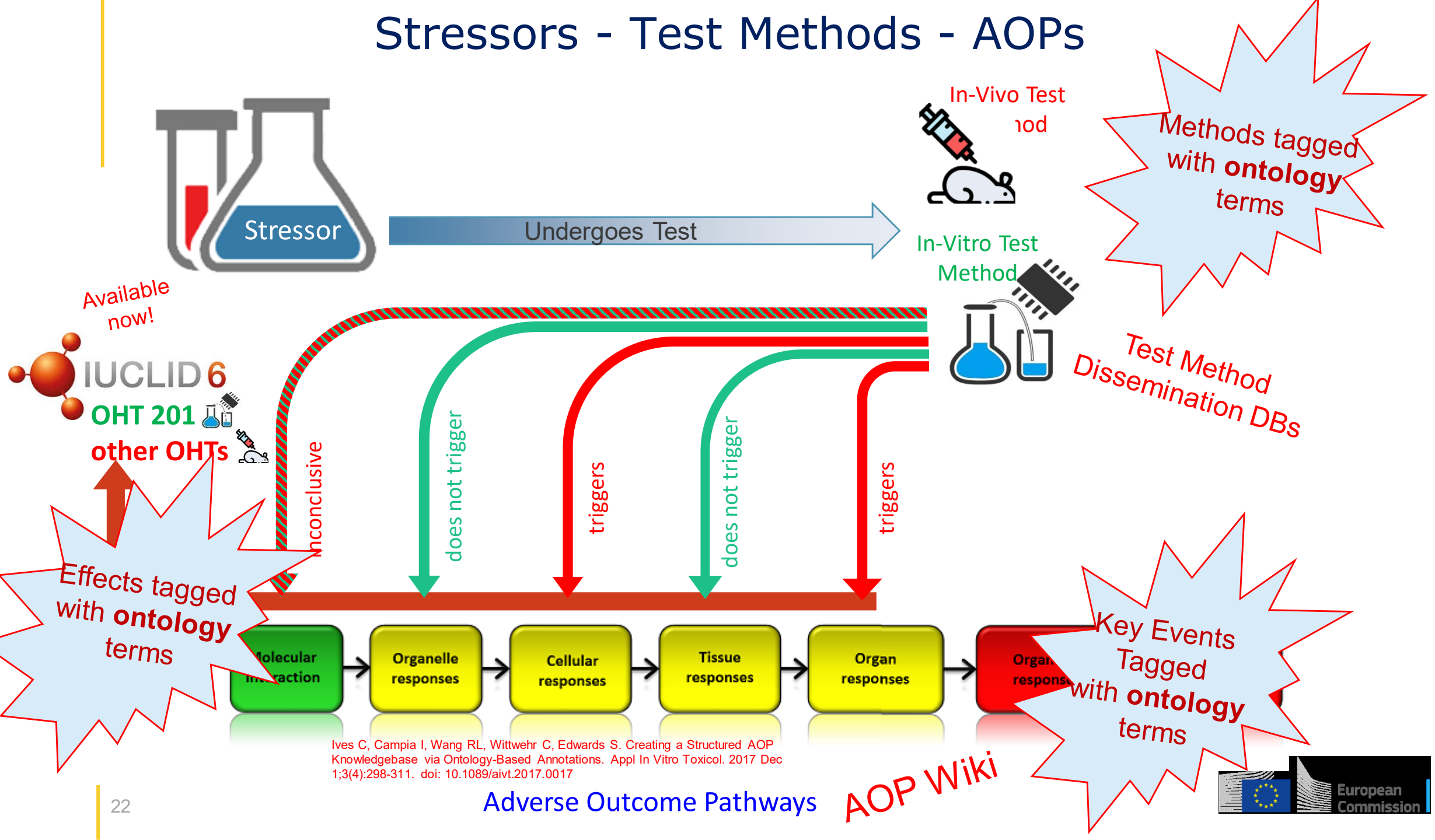

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OHT 201 as receptacle for AI findings

efsa European Food Safety Authority

TENDER SPECIFICATIONS

Reference: OC/EFSA/SCER/2021/08
Subject: Exploring the use of Artificial Intelligence (AI) for extracting and integrating data obtained through New Approach Methodologies (NAMs) for chemical risk assessment

The proposal should also include a minimum of 6 proposals based on endpoints (covering different chemical groups), including proposals covering endocrine activity related endpoints linked to the **JRC Endocrine Active Substances Information System (EASIS)**, and endpoints linked to genotoxicity.

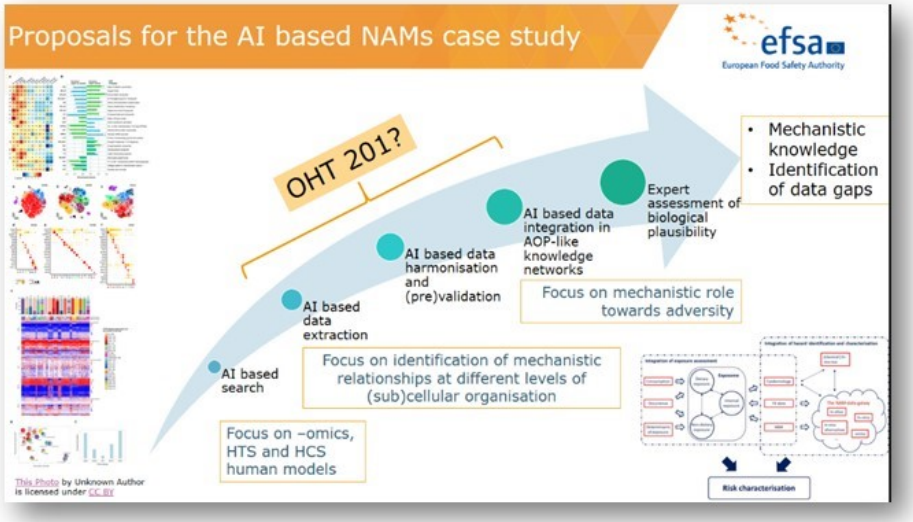
Some quotes…

There is the current need to explore the use of AI for NAM-based chemical risk assessment considering that some NAM-based approaches, e.g. HTS (High Throughput Screening), HCS (High Content Screening) or Omic methods, generate a large amount of data covering initial events of the **Adverse Outcome Pathways (AOP)**.

The **OECD harmonised template OHT 201** facilitates reporting of NAM study results in an internationally agreed format for mechanistic data.

The tenderer should demonstrate access and technical capacity for working on all structured databased mentioned in the offer and for constructing new databases with the extracted information and **OECD OHT 201** relevant for contract execution;

Logical and structured step by step explanation of methodology (search tools and protocols**; use of OHT201 for data extraction**; pre-validation and quality assurance; integration in AOP/AON-like approaches) ; **10 points**



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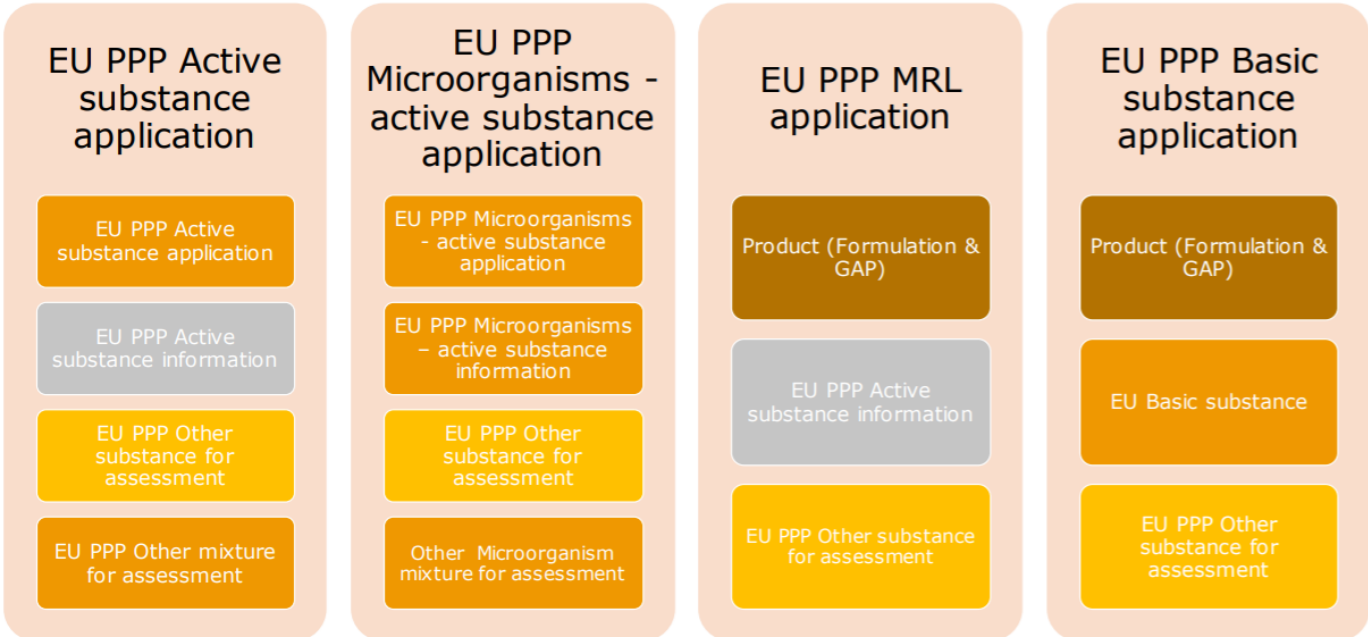
Plant Protection Product (PPP) work

- **EFSA Agency Cloud Service** (i.e. EFSA Agency IUCLID) = platform for the management and submission of pesticides dossiers.
- **Industry** (i.e. applicants) use this tool to prepare their dossiers under Regulation (EC) No 1107/2009 and Regulation (EC) No 396/2005.
- **Rapporteur Member States** (RMS) and **Evaluating Member States** (EMS) can access EFSA Agency IUCLID to view and evaluate submitted dossiers.
- Similarly, interested parties such as **scientists and citizen** can view the submitted dossiers by accessing Public IUCLID through links in **OpenEFSA** portal (https://open.efsa.europa.eu/).
- Ad-hoc webpage ("EFSA Toolkit") with supporting materials and **useful information** on IUCLID are publicly available (https://www.efsa.europa.eu/en/applications/toolkit).

EFSA Agency IUCLID includes four different working contexts which allow users to report PPPs test results according to the data requirement as laid down in each corresponding Regulation:



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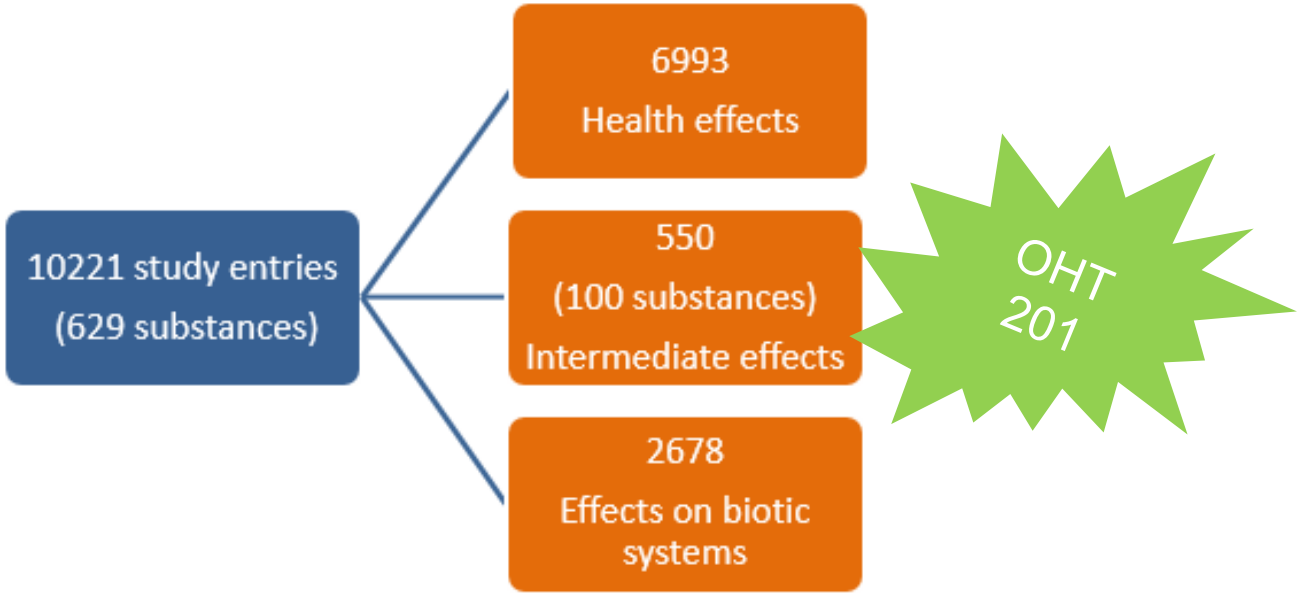
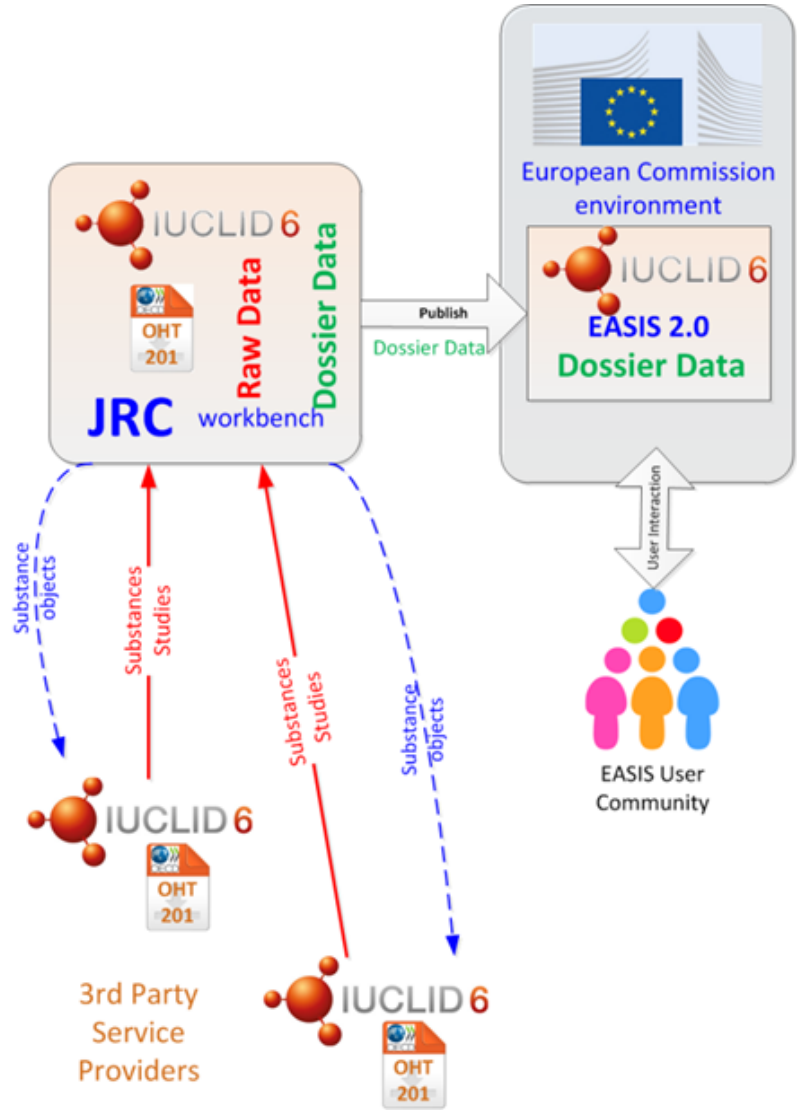
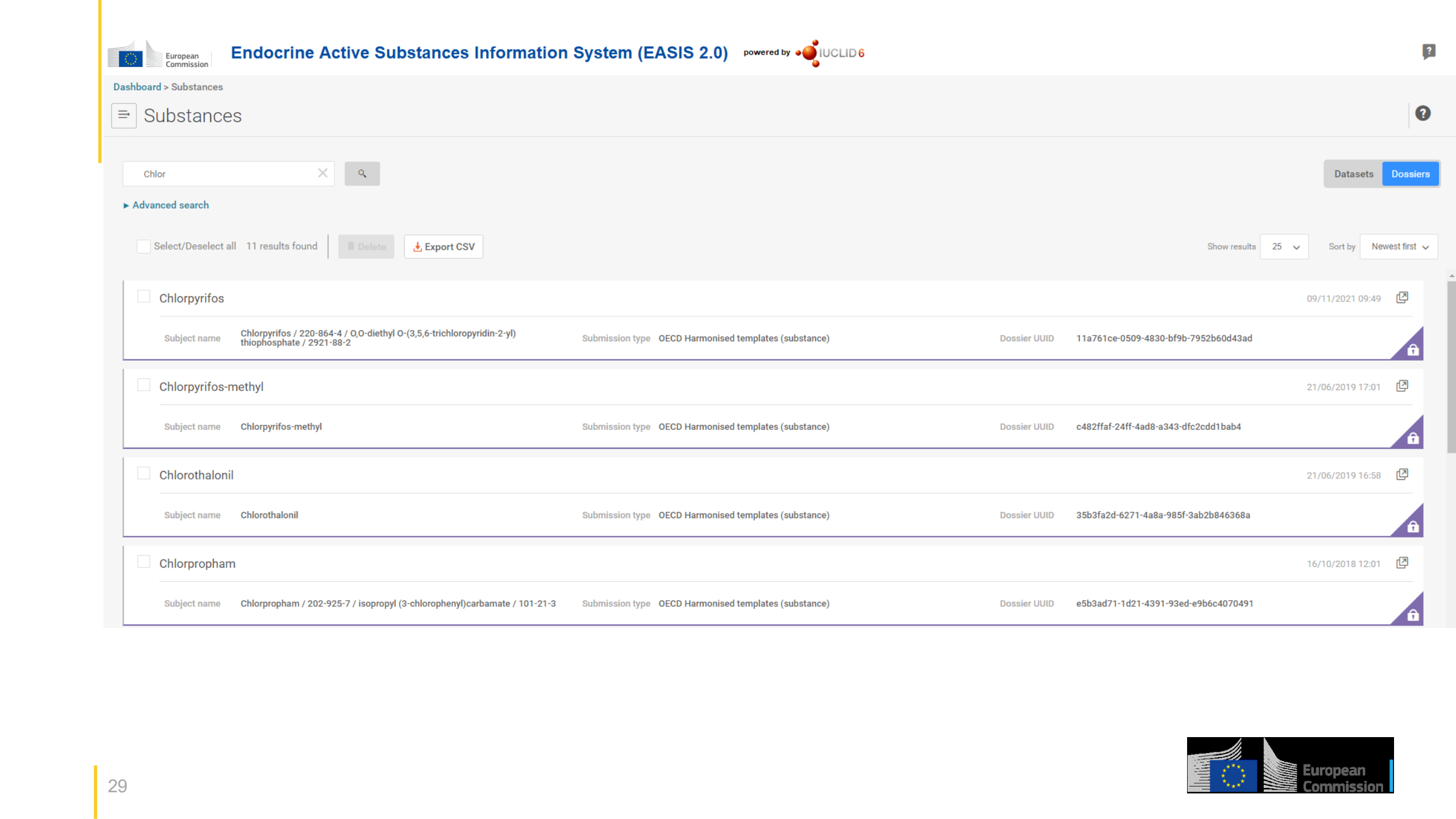
OHT 201 in EASIS

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





To be published in the coming weeks!



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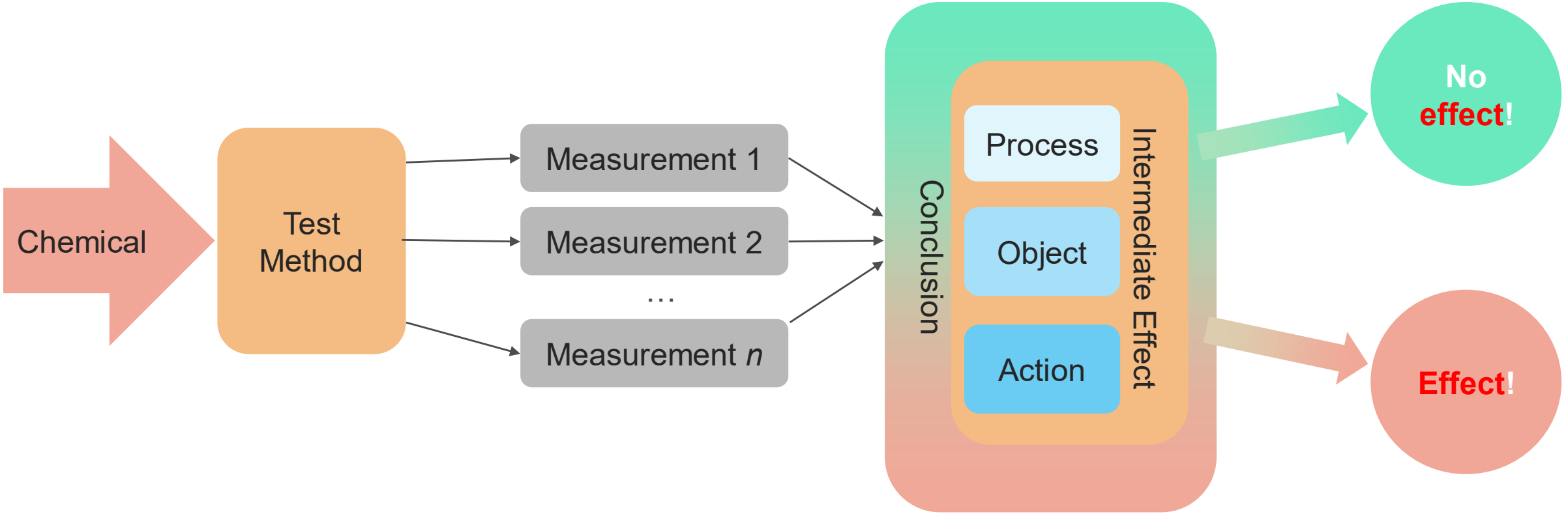
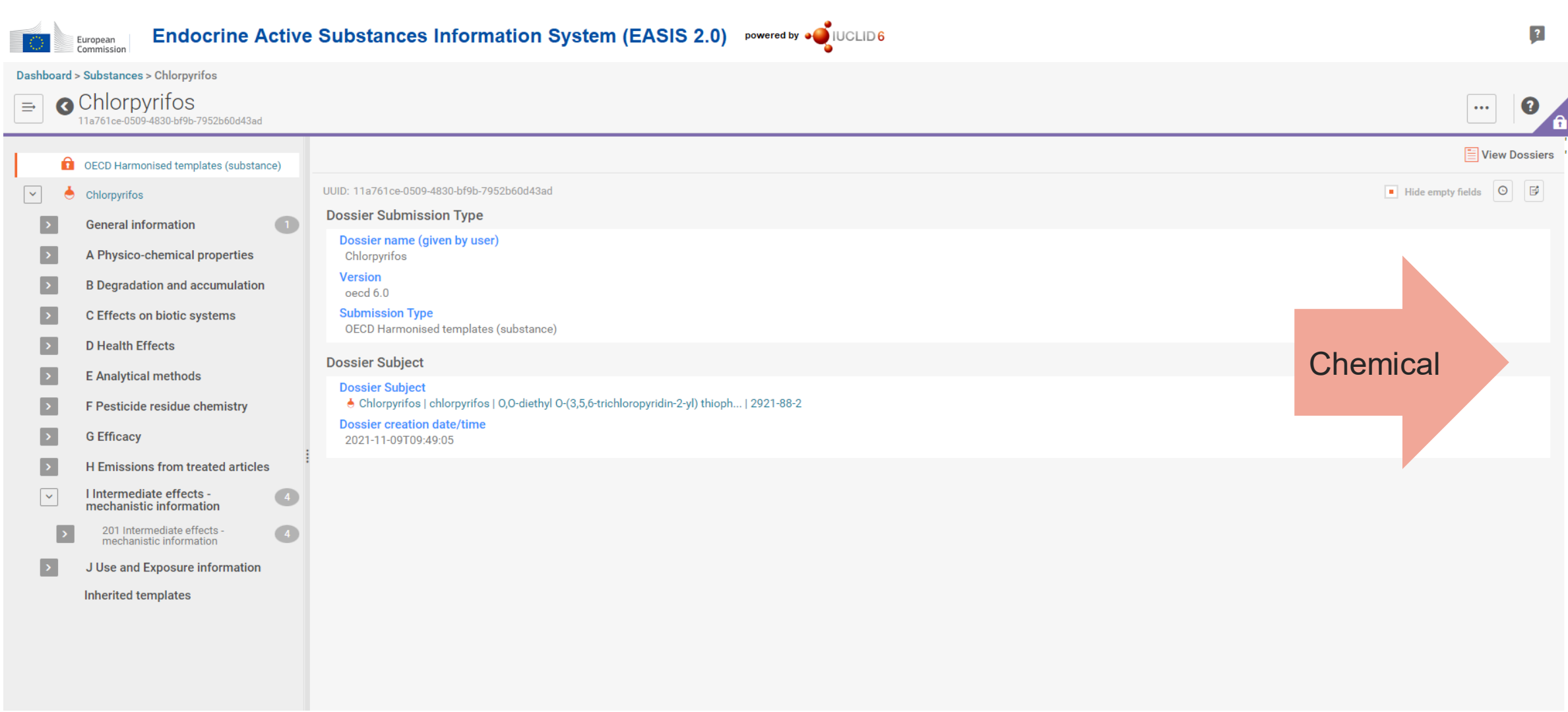
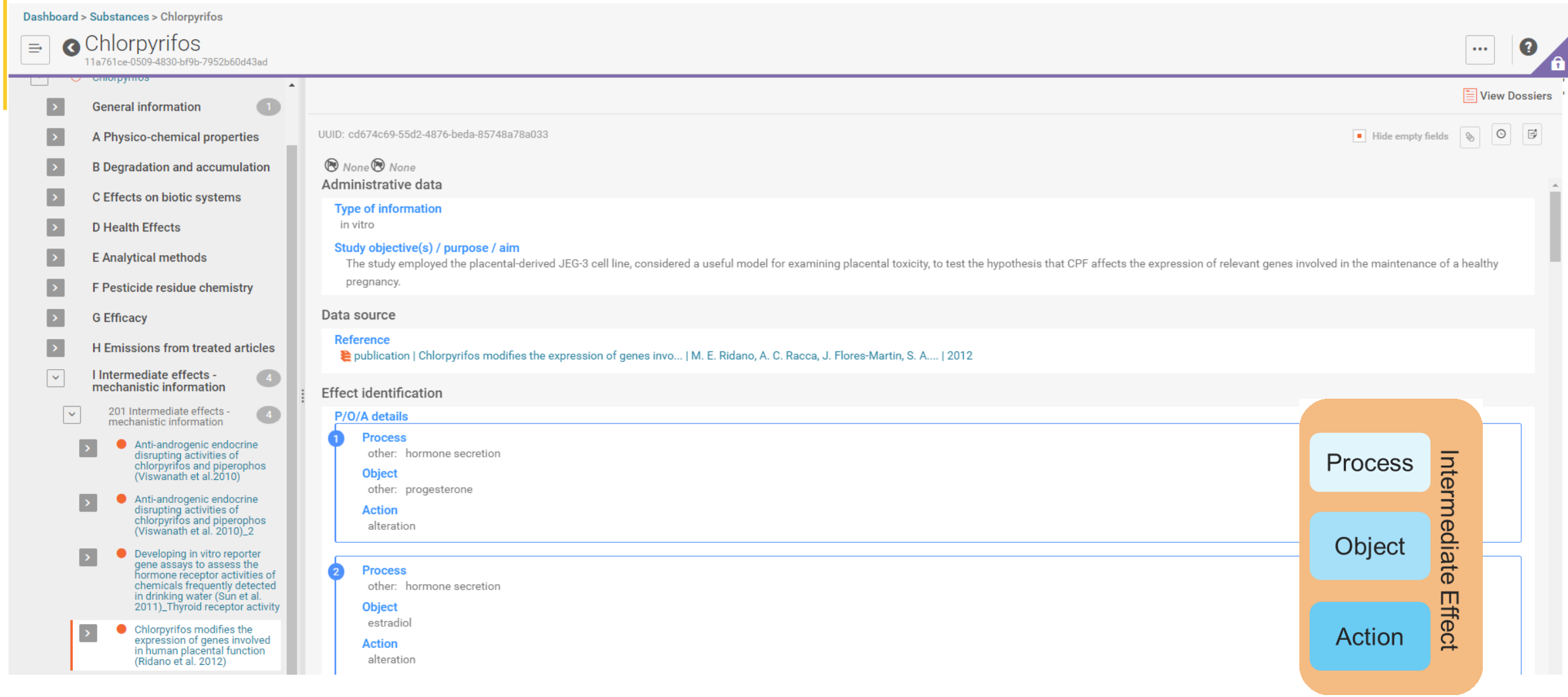
Remember this drawing…




European Commission
Endocrine Active Substances Information System (EASIS 2.0)
powered by IUCLID 6
Dashboard > Substances > Chlorpyrifos
Chlorpyrifos
11a761ce-0509-4830-bf9b-7952b60d43ad
OECD Harmonised templates (substance)
Chlorpyrifos
General information 1
A Physico-chemical properties
B Degradation and accumulation
C Effects on biotic systems
D Health Effects
E Analytical methods
F Pesticide residue chemistry
G Efficacy
H Emissions from treated articles
I Intermediate effects - mechanistic information 4
201 Intermediate effects - mechanistic information 4
J Use and Exposure information
Inherited templates
View Dossiers
UUID: 11a761ce-0509-4830-bf9b-7952b60d43ad
Hide empty fields
Dossier Submission Type
Dossier name (given by user)
Chlorpyrifos
Version
oecd 6.0
Submission Type
OECD Harmonised templates (substance)
Dossier Subject
Dossier Subject
Chlorpyrifos | chlorpyrifos | O,O-diethyl O-(3,5,6-trichloropyridin-2-yl) thioph... | 2921-88-2
Dossier creation date/time
2021-11-09T09:49:05
Chemical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Anti-androgenic endocrine disrupting activities of chlorpyrifos and piperophos (Viswanath et al.2010)
Anti-androgenic endocrine disrupting activities of chlorpyrifos and piperophos (Viswanath et al. 2010)_2
Developing in vitro reporter gene assays to assess the hormone receptor activities of chemicals frequently detected in drinking water (Sun et al. 2011)_Thyroid receptor activity
Chlorpyrifos modifies the expression of genes involved in human placental function (Ridano et al. 2012)
View Dossiers
UUID: cd674c69-55d2-4876-beda-85748a78a033
Hide empty fields
None None
Administrative data
Type of information
in vitro
Study objective(s) / purpose / aim
The study employed the placental-derived JEG-3 cell line, considered a useful model for examining placental toxicity, to test the hypothesis that CPF affects the expression of relevant genes involved in the maintenance of a healthy pregnancy.
Data source
Reference
publication | Chlorpyrifos modifies the expression of genes invo... | M. E. Ridano, A. C. Racca, J. Flores-Martin, S. A.... | 2012
Effect identification
P/O/A details
1 Process
other: hormone secretion
Object
other: progesterone
Action
alteration
2 Process
other: hormone secretion
Object
estradiol
Action
alteration
Process
Object
Action
Intermediate Effect

Chlorpyrifos

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- General information 1
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- E Analytical methods
- F Pesticide residue chemistry
- G Efficacy
- H Emissions from treated articles
- I Intermediate effects - mechanistic information 4
  - 201 Intermediate effects - mechanistic information 4
    - Anti-androgenic endocrine disrupting activities of chlorpyrifos and piperophos (Viswanath et al.2010)
    - Anti-androgenic endocrine disrupting activities of chlorpyrifos and piperophos (Viswanath et al. 2010)_2
    - Developing in vitro reporter gene assays to assess the hormone receptor activities of chemicals frequently detected in drinking water (Sun et al. 2011)_Thyroid receptor activity
    - Chlorpyrifos modifies the expression of genes involved in human placental function (Ridano et al. 2012)

View Dossiers

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None None

Context

#...	System	Organ	Remarks	Action
1	female reproductive system	✓ placenta		

Materials and methods

Method used

Qualifier
no guideline followed

Principle of the method
-Hormone secretion
- name: ELISA
- short description: Culture supernatants of cells incubated with CPF (50, 100 µM) or with vehicle alone were collected and stored at −80 °C. Secreted hCG was quantified through an automated immunochemiluminometric assay (Immulite 2000 HCG, Siemens) according to the manufacture protocol. Electrochemiluminescence immunoassays (ECLIA, Roche) were used for quantification of total progesterone and estradiol concentrations.
parameters: quantification of total hCG, progesterone and estradiol concentrations.

GLP compliance
not specified

Other quality systems, standards or guidance followed
not specified

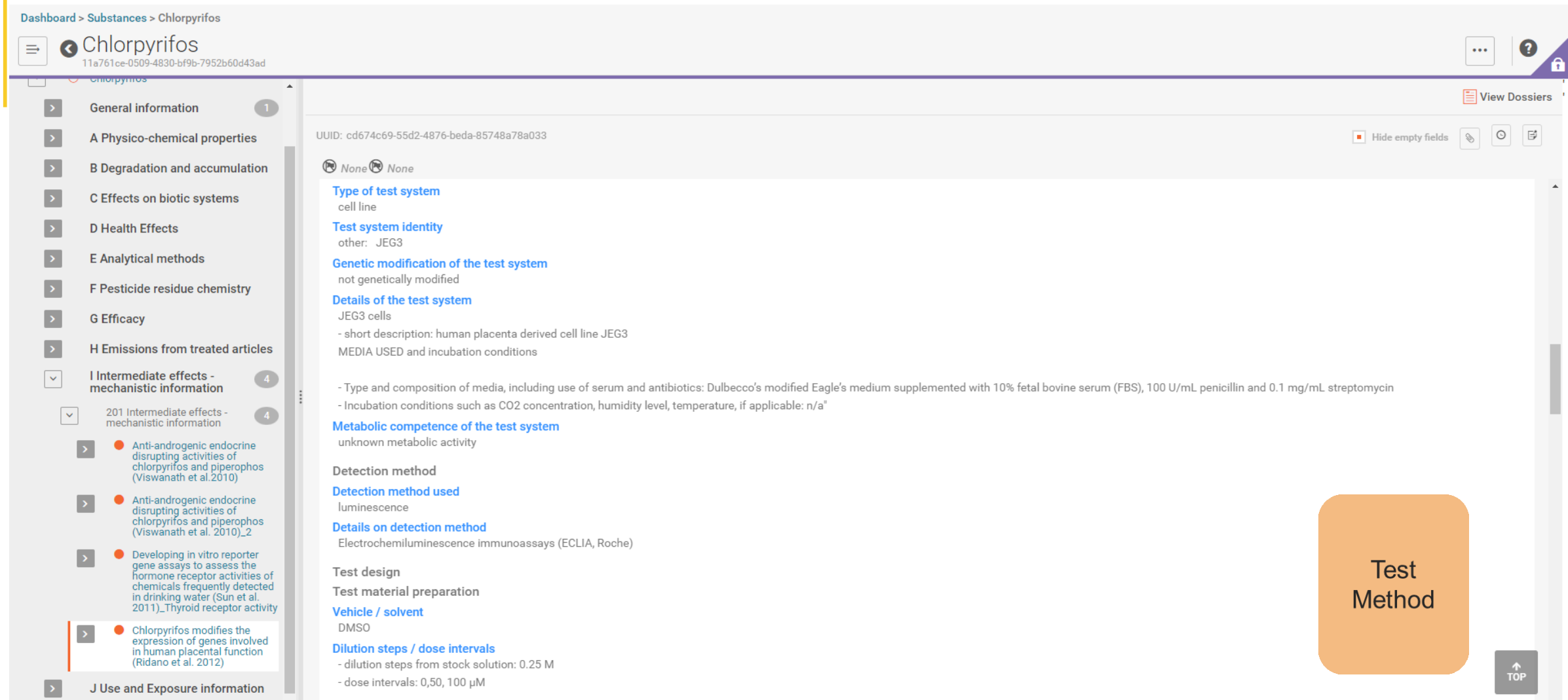
Test material

Test material information
Chlorpyrifos

Specific details on test material used for the study
- CAS: 2921-88-2
- purity: 99.5%

Test Method

European Commission


Dashboard > Substances > Chlorpyrifos
Chlorpyrifos
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General information 1
A Physico-chemical properties
B Degradation and accumulation
C Effects on biotic systems
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J Use and Exposure information
View Dossiers
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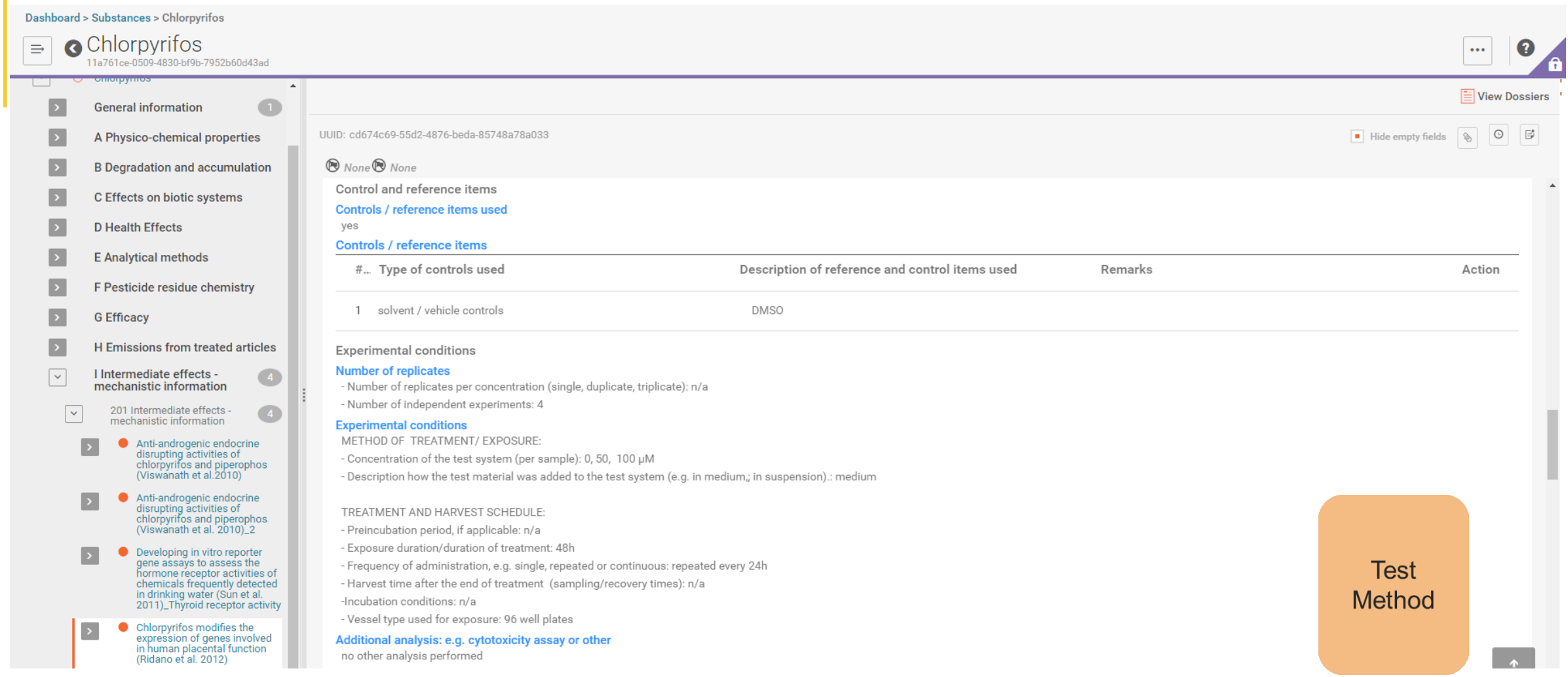
None None
Type of test system
cell line
Test system identity
other: JEG3
Genetic modification of the test system
not genetically modified
Details of the test system
JEG3 cells
- short description: human placenta derived cell line JEG3
MEDIA USED and incubation conditions
- Type and composition of media, including use of serum and antibiotics: Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin and 0.1 mg/mL streptomycin
- Incubation conditions such as CO2 concentration, humidity level, temperature, if applicable: n/a"
Metabolic competence of the test system
unknown metabolic activity
Detection method
Detection method used
luminescence
Details on detection method
Electrochemiluminescence immunoassays (ECLIA, Roche)
Test design
Test material preparation
Vehicle / solvent
DMSO
Dilution steps / dose intervals
- dilution steps from stock solution: 0.25 M
- dose intervals: 0,50, 100 µM
Test Method
TOP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View Dossiers
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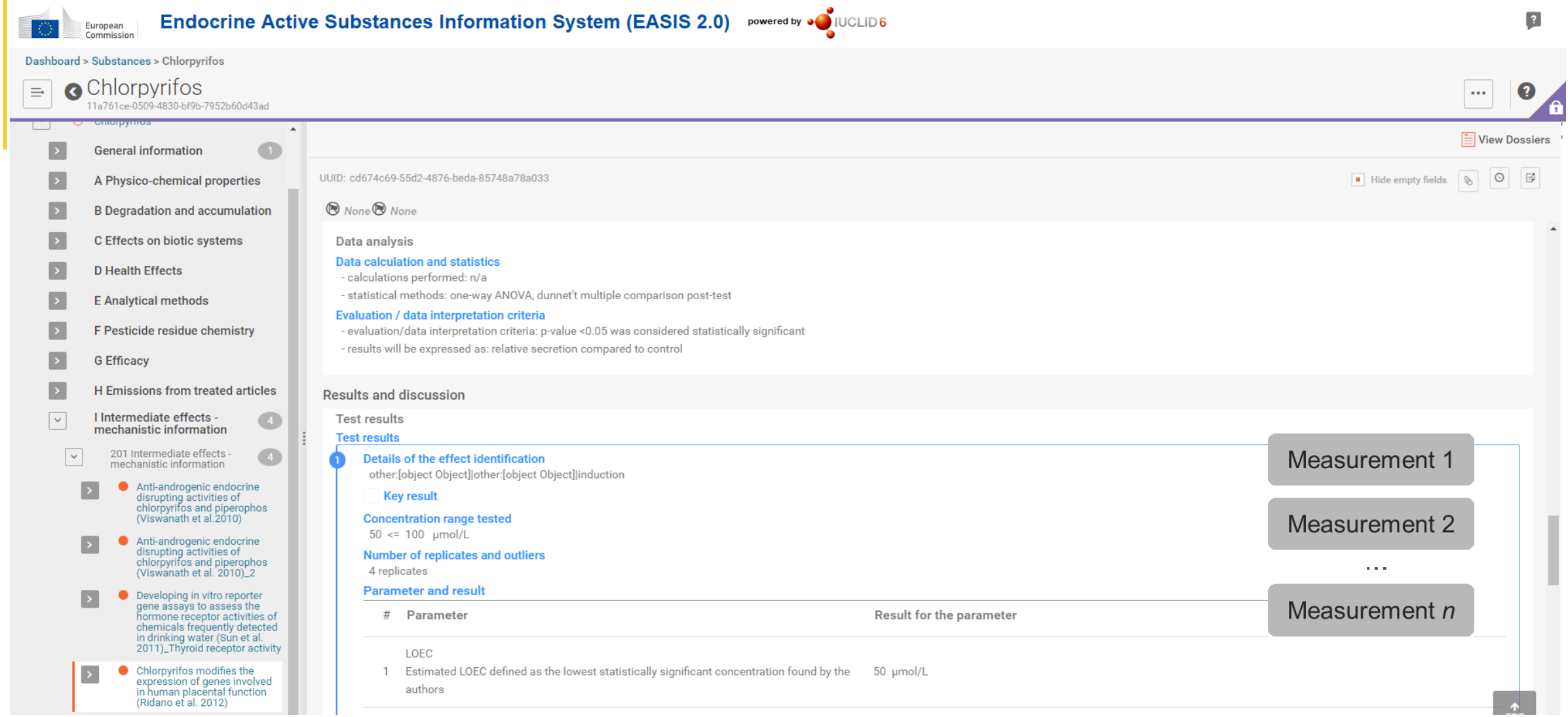
None None
Control and reference items
Controls / reference items used
yes
Controls / reference items
#... Type of controls used
Description of reference and control items used
Remarks
Action
1 solvent / vehicle controls
DMSO
Experimental conditions
Number of replicates
- Number of replicates per concentration (single, duplicate, triplicate): n/a
- Number of independent experiments: 4
Experimental conditions
METHOD OF TREATMENT/ EXPOSURE:
- Concentration of the test system (per sample): 0, 50, 100 µM
- Description how the test material was added to the test system (e.g. in medium,; in suspension).: medium
TREATMENT AND HARVEST SCHEDULE:
- Preincubation period, if applicable: n/a
- Exposure duration/duration of treatment: 48h
- Frequency of administration, e.g. single, repeated or continuous: repeated every 24h
- Harvest time after the end of treatment (sampling/recovery times): n/a
-Incubation conditions: n/a
- Vessel type used for exposure: 96 well plates
Additional analysis: e.g. cytotoxicity assay or other
no other analysis performed

Test Method



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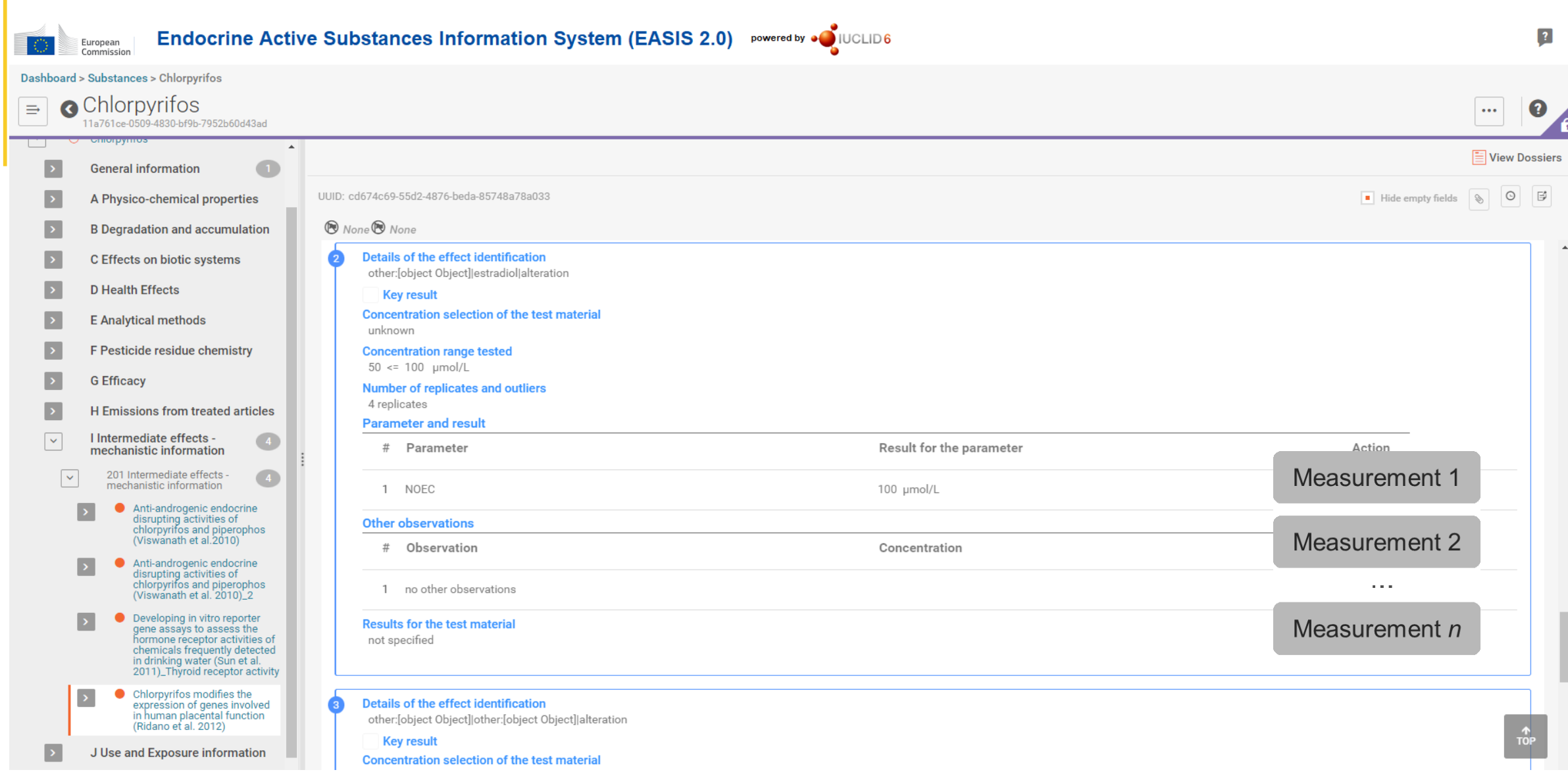

European Commission

Chlorpyrifos

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View Dossiers

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None None

Concentration selection of the test material
unknown

Concentration range tested
50 <= 100 µmol/L

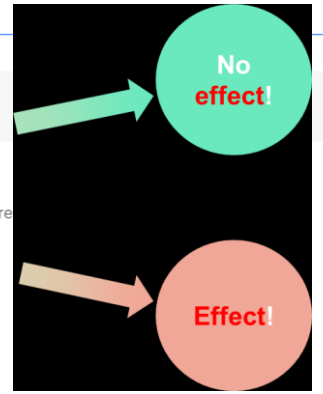
Number of replicates and outliers
4 replicates

Parameter and result

#	Parameter	Result for the parameter	Action
1	NOEC Estimated NOEC based on the highest test concentration when no statistically significant effect was observed by the authors	100 µmol/L	

Other observations

#	Observation	Concentration	Action
1	no other observations		



Applicant's summary and conclusion

Interpretation of results / observations

Overall results and conclusion
Clorpyrifos did not alter the secretion of estradiol and progesterone of JEG3 cells after 48h exposure to concentrations up to 100µmol/l. ßhCG secretion was increased after exposure

Type of result
quantitative

Remarks
Progesterone and estradiol secretion: NOEC = 100µmol/L ßhCG secretion: LOEC = 50µmol/L

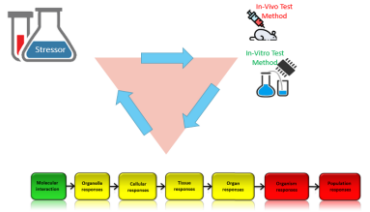
Executive summary

The effects of organophosphate pesticides on human placenta remain poorly investigated although an increased risk of pregnancy alterations has been reported in women chronically exposed to these pesticides. Here, we have addressed whether chlorpyrifos (CPF) modifies the expression of genes relevant for placental function. Human placental JEG-3 cells were exposed to increasing CPF concns. up to 100 µM for 24 and 48 h and cell viability, mRNA, protein and hormone levels were analyzed. Quant. RT-PCR assays revealed that CPF increased the expression of ABCG2, GCM1 and, even more significantly, βhCG mRNAs in conditions where cell viability and morphol. were not compromised. In addn., βhCG protein synthesis and secretion were time-dependently augmented. Present results may reflect a CPF nocive effect on placenta cells or a placental-defense mechanism to preserve its function. These novel CPF trophoblast target genes should be considered in future studies of pregnancy outcomes assocd. with in vivo exposures. [on SciFinder(R)]

Take-home messages

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

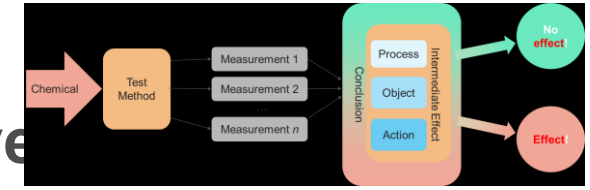
- OHT 201 supports the chemical angle of the "**Stressor – Method – AOP**" triangle



- 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**



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

European Commission

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