

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

What to expect from this presentation

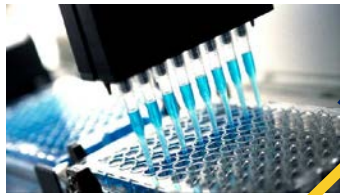
- Standardizing hazard reporting -
The OECD Harmonised Templates for Reporting Chemical Test Summaries (OHTs)
- The odd one out -
OHT 201 - Intermediate Effects – Mechanistic Information
- How it all fits together -
The triangle of chemical safety
- Sanity check -
OHT 201 in real life

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Template? What template?...

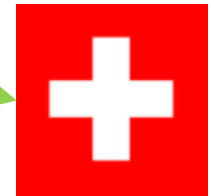
Data producers



Fancy format A

Fancy format B

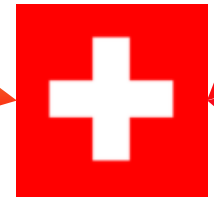
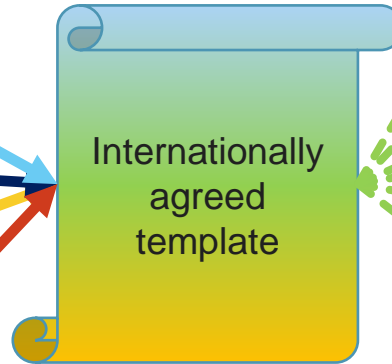
Fancy format C



Authorities

One template to rule them all...

Data producers



Authorities



Apical vs Mechanistic Knowledge

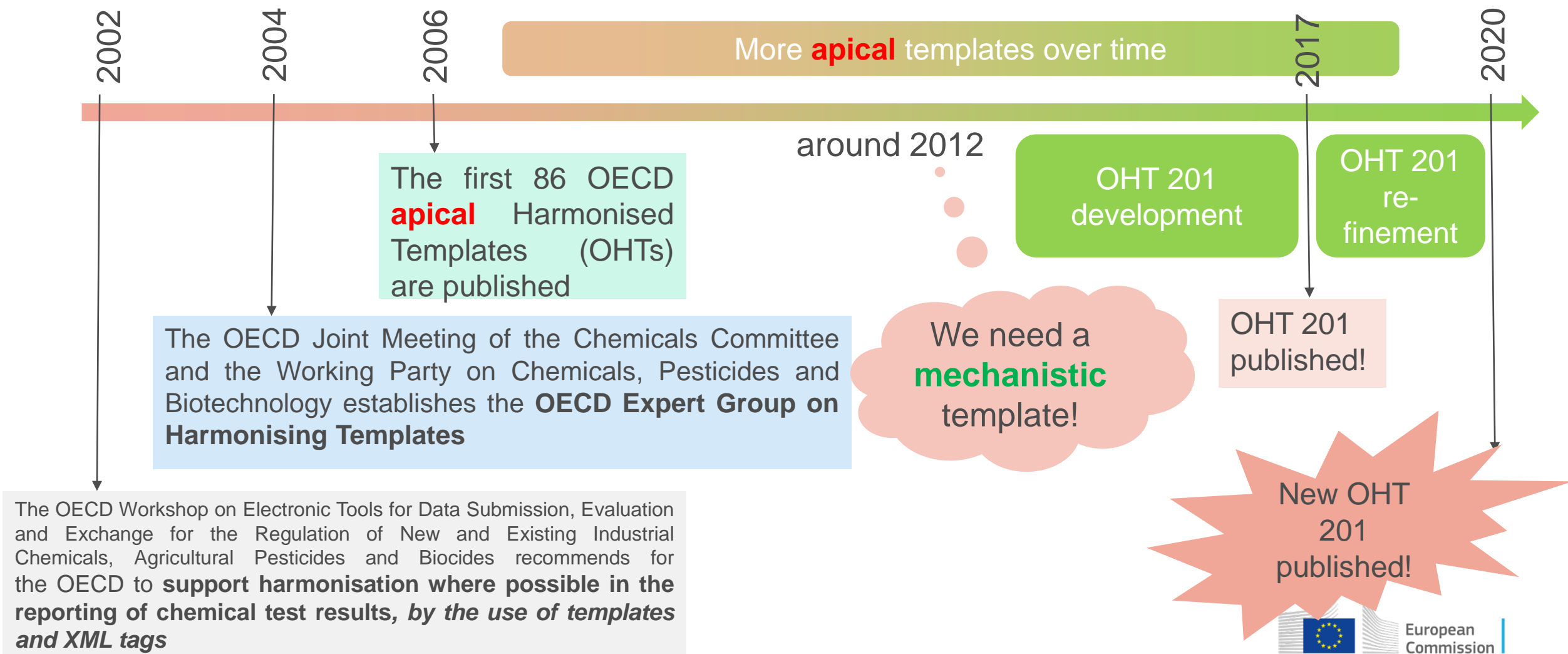
- **Apical Knowledge:** Knowledge about traditional, **directly measured whole-organism outcomes** of exposure in *in-vivo* tests, generally death, reproductive failure, tumour formation, skin/eye irritation, skin/respiratory sensitisation or developmental dysfunction.

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



- **Mechanistic Knowledge:** Knowledge 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.

OECD Harmonised Templates











































































































OECD 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 6
- IUCLID development is managed by the  OECD
- IUCLID **is free** and can be installed in any ICT environment

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

- Office of Chemical Safety and Pollution Prevention (OCSP), 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**)

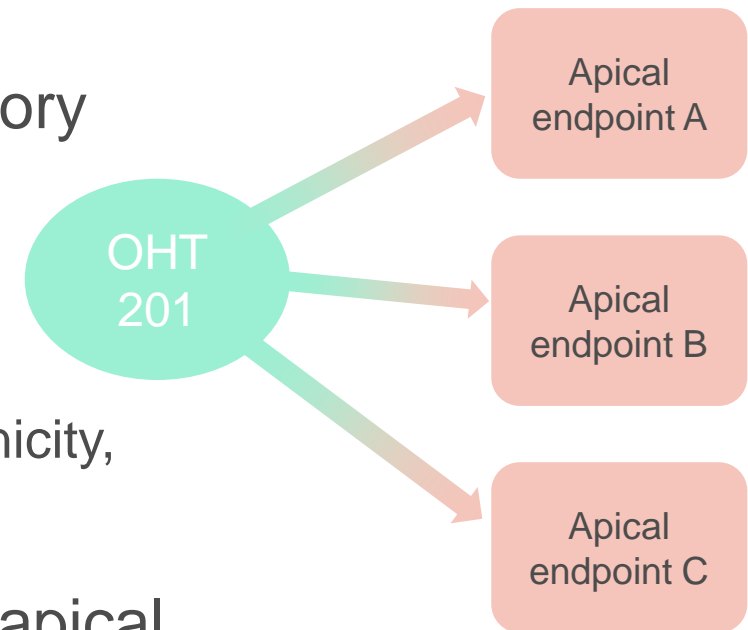
	AU (AICIS)	CA (existing chemicals)	CA (new chemicals)	NZ (Hazardous substances)	CH (biocidal products)	CH (new substance notification and further obligations for substances)	US (OCSP)	US (NCCT)	US (RAD)	EU PCN (CLP_ECHA)	EU WFD (ECHA)	EU REACH (ECHA)	EU BPR (ECHA)	EU CLP (ECHA)	EU PPP (EFSA)
Key: Areas where IUCLID is used or considered for use 															
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															

What to expect from this presentation

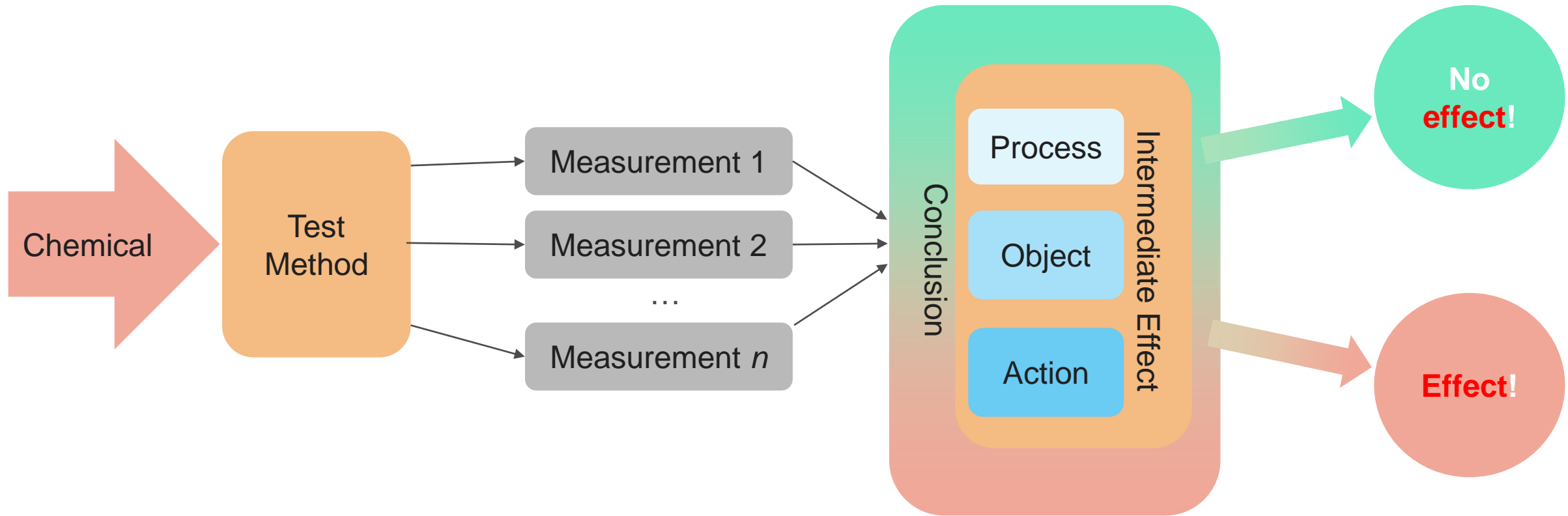
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OHT 201 in real life

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, reprotoxicity, 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

Chemical X

OHT 201

Intermediate Effect Identification:
Process – Object - Action

Evidence independent
from *Class of Method*

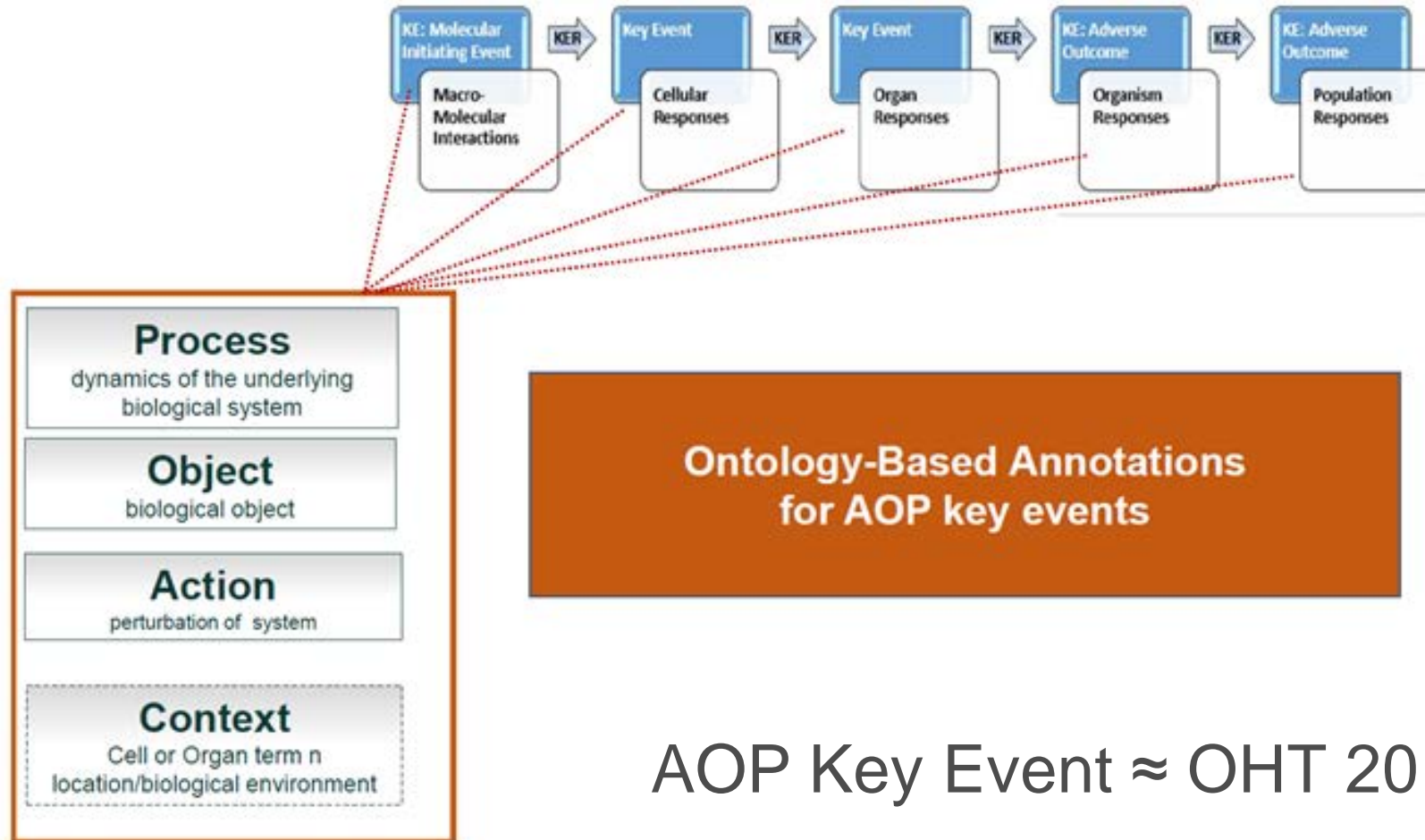
+ some basic
quantification

Chemical is involved in effect

Yes or **No**

- 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

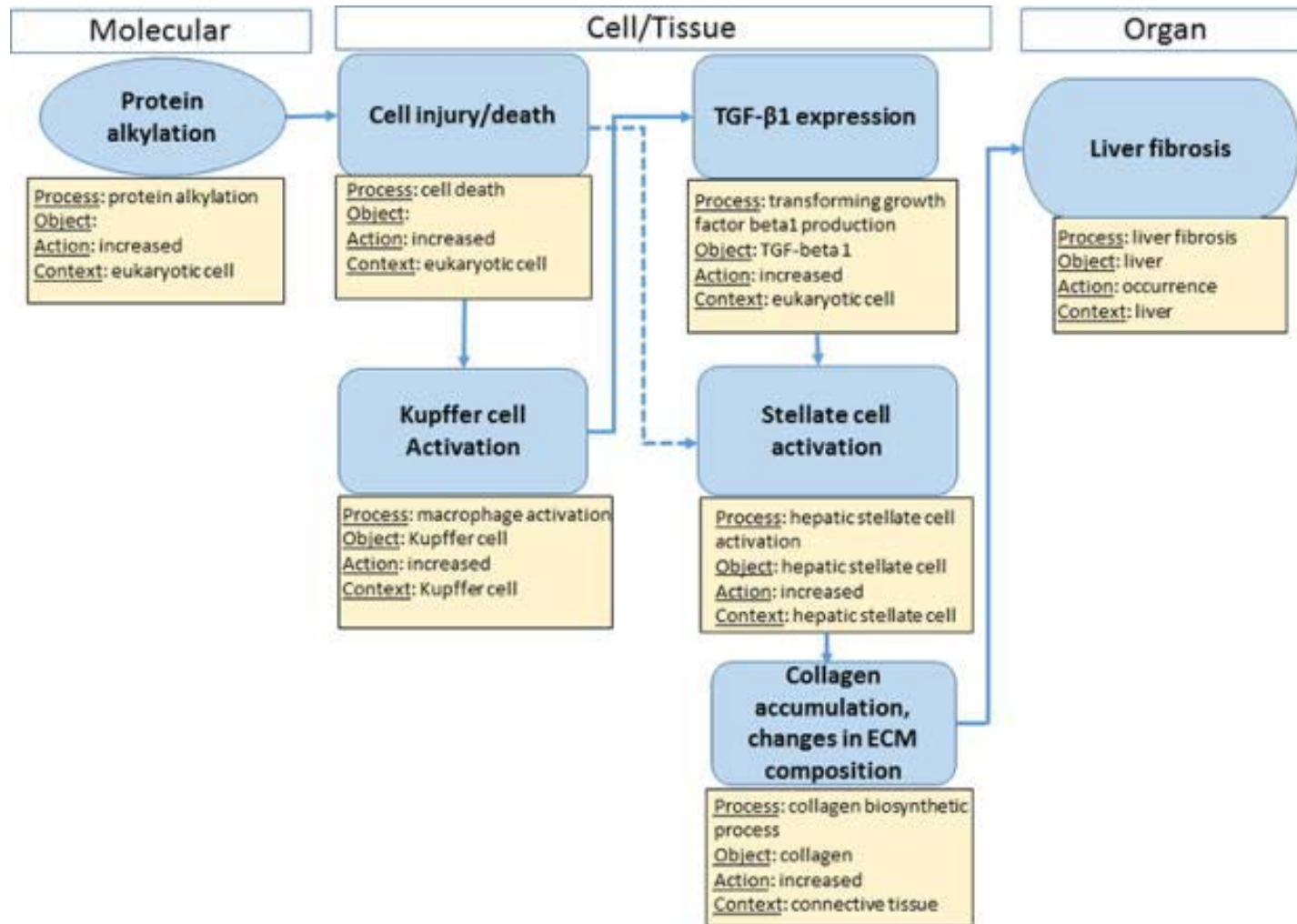
Intermediate Effect Naming



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

AOP Key Event \approx OHT 201 Intermediate Effect

Sample *Process – Object – Action* names



Real life OHT 201 today

Chemical X

OHT 201

Intermediate Effect Identification:
Process – Object - Action

In Vitro TG

In Vitro non-TG

Other classes of
methods

PDF

Chemical is Involved in Effect

Yes or **No**

- 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.

OECD Test Guidelines supported

Guideline	Test Method
TG442C	<ul style="list-style-type: none">- DPRA- ADRA
TG442D	<ul style="list-style-type: none">- Keratinosens- LuSens
TG442E	<ul style="list-style-type: none">- h-CLAT- U-SENS- IL-8 LUC assay
TG455 (including former TG457)	<ul style="list-style-type: none">- ERTA STTA- ERTA VM7Luc- ERTA ERα CALUX
TG456	<ul style="list-style-type: none">- H295R Steroidogenesis Assay
TG458	<ul style="list-style-type: none">- ARTA STTA- ARTA AR-CALUX
TG493	<ul style="list-style-type: none">- hrER binding FW assay- hrER binding CERI assay

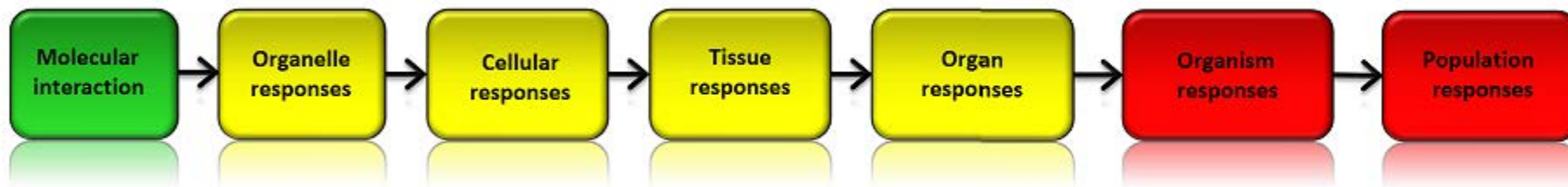
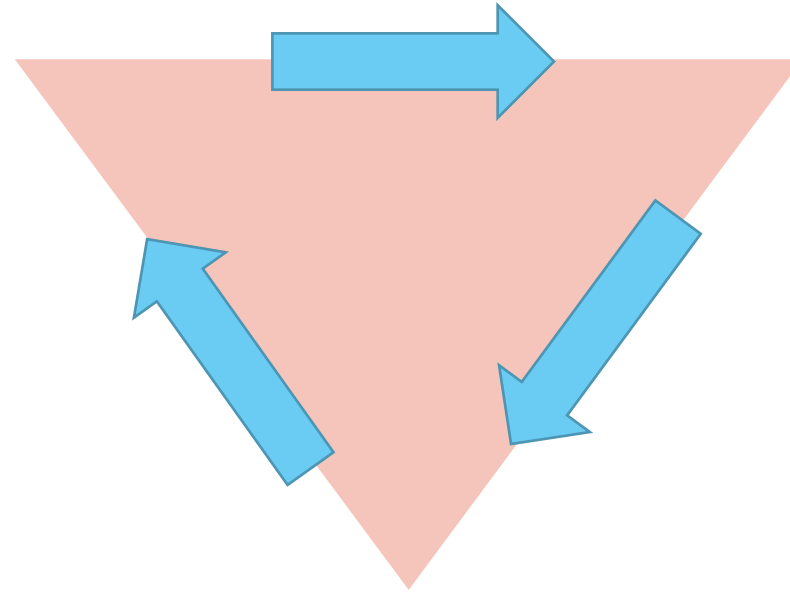
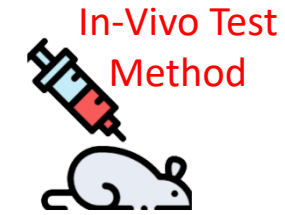
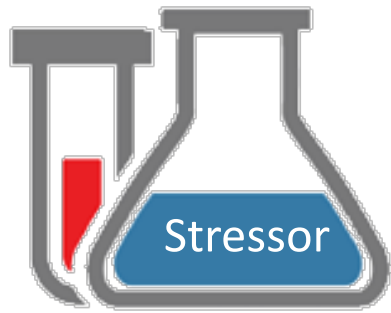
If NAM **follows an OECD Test Guideline:**
Many fields are pre-filled

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

What to expect from this presentation

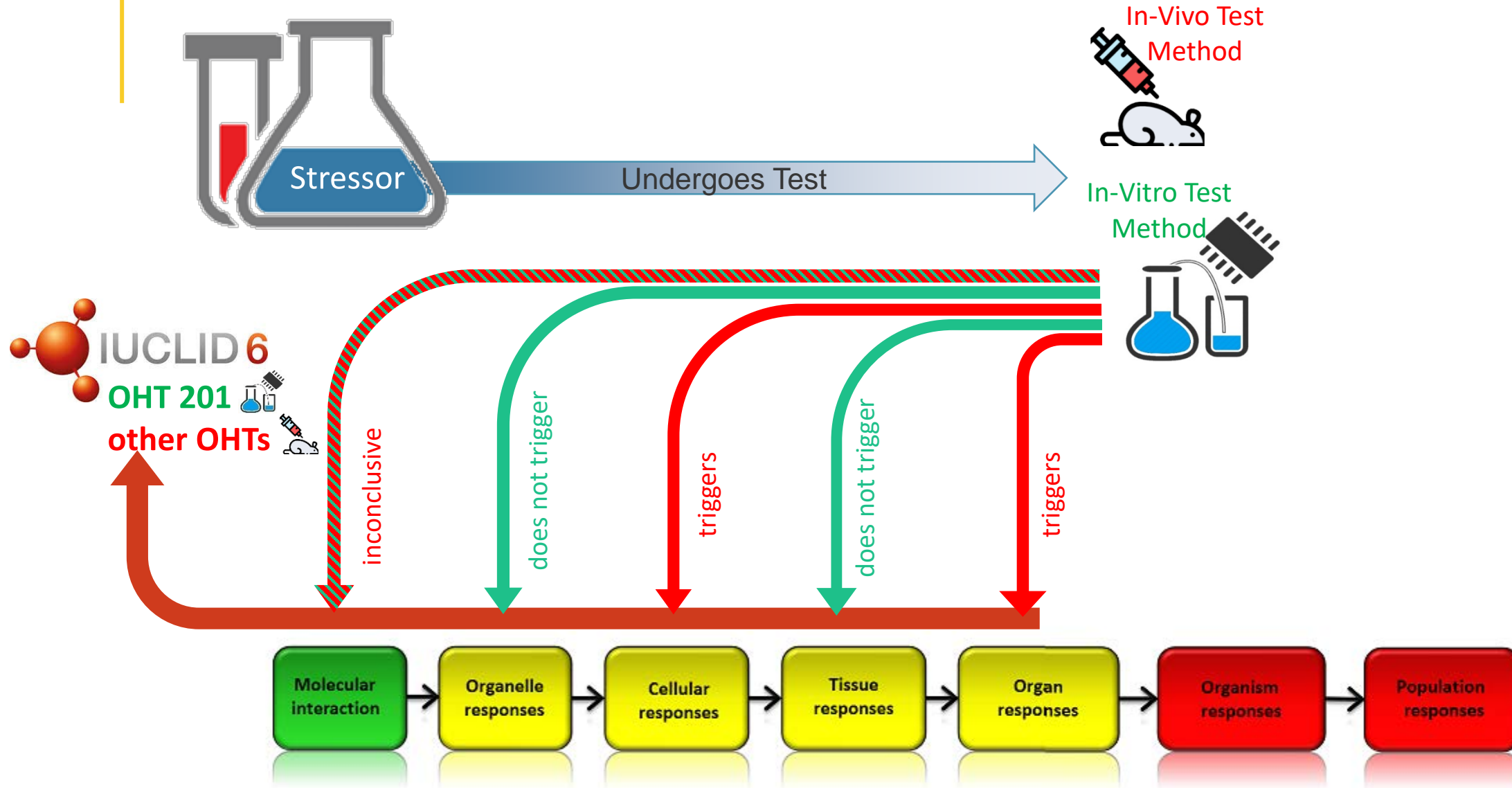
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Stressors - Test Methods - AOPs



Adverse Outcome Pathways

Stressors - Test Methods - AOPs



Stressors - Test Methods - AOPs



To be published in late 2020

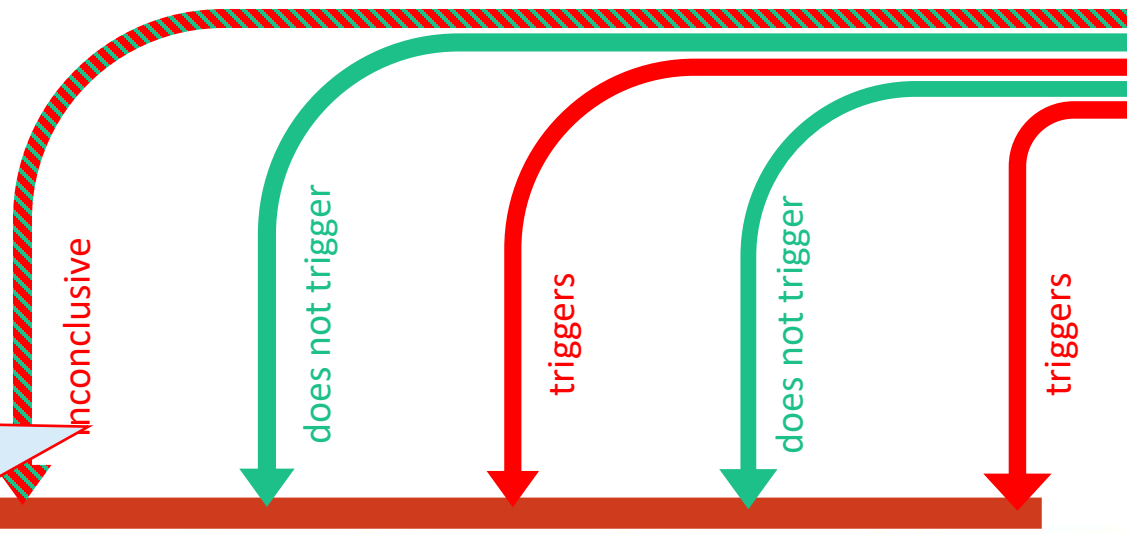
Undergoes Test



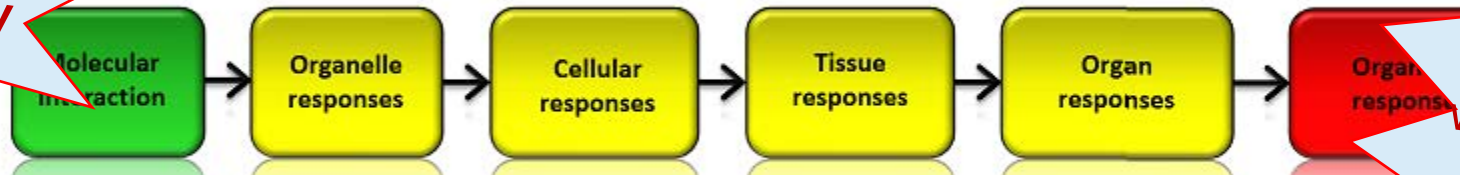
Methods tagged with **ontology** terms

Test Method Dissemination DBs

IUCLID 6
OHT 201
other OHTs



Effects tagged with **ontology** terms



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/avt.2017.0017

Adverse Outcome Pathways

AOP Wiki

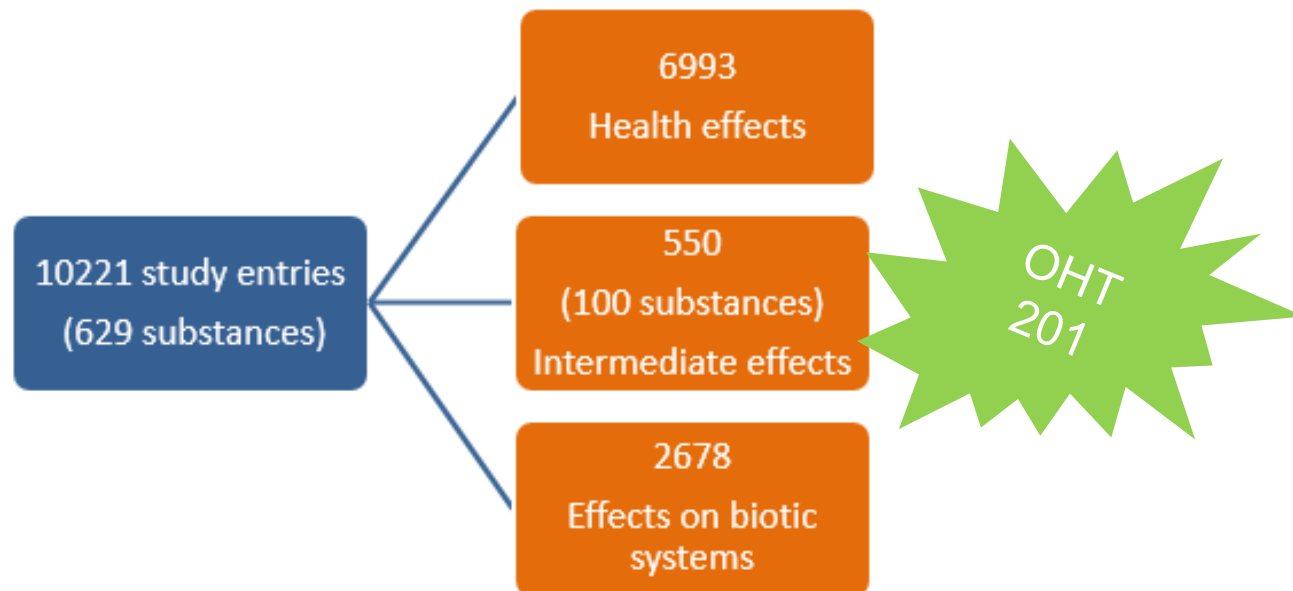


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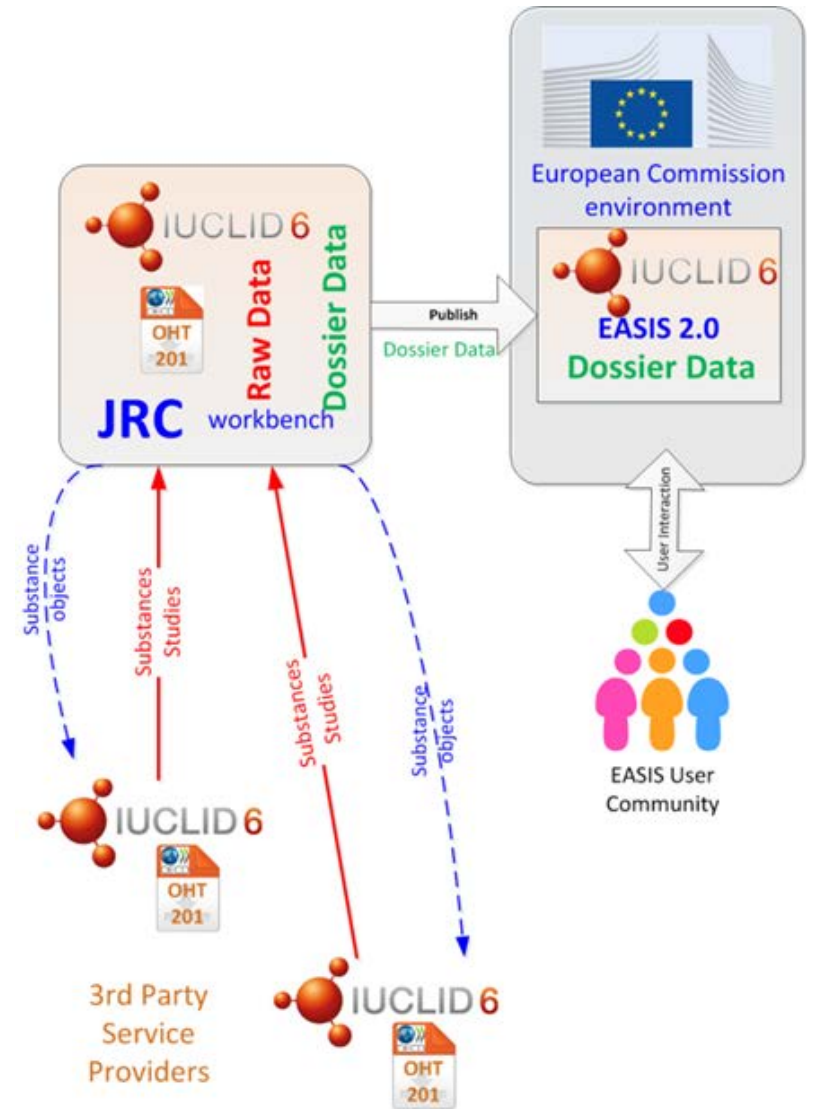
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OHT 201 in EASIS

EASIS = **E**ndocrine **A**ctive **S**ubstances
Information **S**ystem



To be published in the coming weeks!



Substances


 Datasets **Dossiers**

▶ Advanced search

629 results found

 Sort by **Name (A-Z)**

tau-Fluvalinate				21/06/2019 17:30	
Subject name	tau-Fluvalinate	Submission type	OECD harmonised templates	Dossier UUID	ca650fdd-53a6-472d-ade3-ac873f2159b4
tris(2-chloroethyl) phosphate (TCEP)				13/12/2019 15:30	
Subject name	tris(2-chloroethyl) phosphate (TCEP) / 204-118-5 / tris(2-chloroethyl) phosphate / 115-96-8	Submission type	OECD harmonised templates	Dossier UUID	ca3e95c3-b02e-496f-ba19-05659101a1a2



tris(2-chloroethyl) phosphate (TCEP)

ca3e95c3-b02e-496f-ba19-05659101a1a2


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UUID: ca3e95c3-b02e-496f-ba19-05659101a1a2

OECD harmonised templates

tris(2-chloroethyl) phosphate (TCEP)

General information 1

A Physico-chemical properties

B Degradation and accumulation

C Effects on biotic systems 4

D Health Effects 2

E Analytical methods

F Pesticide residue chemistry

G Efficacy

H Emissions from treated articles

I Intermediate effects 12

Dossier Submission Type

Dossier name (given by user)

tris(2-chloroethyl) phosphate (TCEP)

Version

oecd 4.0

Submission Type

OECD harmonised templates

Dossier Subject

Dossier Subject

tris(2-chloroethyl) phosphate (TCEP) | tris(2-chloroethyl) phosphate | tris(2-chloroethyl) phosphate | 115-96-8

Dossier creation date/time

2019-12-13T16:30:12

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

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BPI; Study title (a): Investigation of cytotoxic, genotoxic,

UUID: eee9c20b-8b1b-4920-a417-eba41d575187

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Administrative data
Endpoint

 intermediate effects, other
TCEP binding to nuclear receptors

Type of information

calculation (if not (Q)SAR)

Cross-reference

#...	Reason / purpose	Related information	Remarks	Action
1	reference to same study	experimental study Danio rerio (previous name: Brachydanio rerio) static embryo-rearing water (60 mg/L instant ocean salts ... 120 h		

Data source

tris(2-chloroethyl) phosphate (TCEP)

ca3e95c3-b02e-496f-ba19-05659101a1a2


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

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Administrative data

Endpoint

short-term toxicity to fish

Evaluation of the endocrine disrupting effects of TCEP on zebrafish

Type of information

experimental study

Data source

Reference

publication | The combination of in silico and in vivo approach... | Yang Wu Guanyong Su Song Tang Wei Liu Zhiyuan ... | 2017

Data access

data published

Materials and methods

Principles of method if other than guideline

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Materials and methods

Principles of method if other than guideline

AB wild-type embryos were exposed from 3 to 120hpf. Twenty-four embryos were randomly selected and placed in three beakers (25 mL). Each beaker contained 10 mL TCEP solution, and the vehicle control group and test groups were performed in triplicate. Exposures were conducted in an incubator maintained in a stable environment during the experiment (photoperiod: 14/10 h light/dark; static; temperature: 27 ± 1 °C). The experiment was terminated at 120 hpf. To avoid evaporation of the test solution, beakers were covered with a breathable membrane.

Test material

Specific details on test material used for the study

Tris(2-chloroethyl) phosphate (TCEP) was purchased from AccuStandard.

Sampling and analysis

Analytical monitoring

yes

Details on sampling

TOP

tris(2-chloroethyl) phosphate (TCEP)

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To avoid evaporation of the test solution, beakers used for the exposure were covered with a breathable membrane.

Details on analytical methods

Concentrations of TCEP in exposure solutions were confirmed by LC-MS/MS. No statistically significant difference (t-test, $p > 0.01$) was observed between measured and nominal concentrations of TCEP, suggesting minimal error from solvent configuration or adsorption of the container wall.

Test solutions

Vehicle

yes
Dimethyl sulfoxide (DMSO)

Details on test solutions

A stock solution of TCEP was prepared in dimethyl sulfoxide (DMSO), stored at -20 °C and diluted with embryo-rearing water (60 mg/L instant ocean salts in aerated distilled water) to final concentrations immediately before use. The final concentration of solvent (DMSO) in test solutions was less than 0.1%.

Test organisms

Test organisms (species)



tris(2-chloroethyl) phosphate (TCEP)

ca3e95c3-b02e-496f-ba19-05659101a1a2



I Intermediate effects 12

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Basic info (previous name: brachydanio rerio)

Details on test organisms

AB wild-type zebrafish embryos were used for the toxicity test.

Study design

Test type

static

Water media type

other: embryo-rearing water (60 mg/L instant ocean salts in aerated distilled water)

Limit test

no

Total exposure duration

120 h

Test conditions

Test temperature

Temperature: 27 ± 1 °C

Nominal and measured concentrations

Unit	Value
mg/L	0.05
µg/L	5
µg/L	50
µg/L	500
µg/L	5000

↑
TOP

tris(2-chloroethyl) phosphate (TCEP)

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Intermediate effects 12

201 Intermediate effects 12

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Details on test conditions

Photoperiod: 14/10 h light/dark cycle

Reference substance (positive control)

not specified

Results and discussion

Effect concentrations

#..	Key r...	Dur...	Dose des...	Effect ...	Nominal / m...	Conc. ba...	Basis for...	Remarks o...	Action
1	120 h	LC50	>= 3748.46 <= 3748.46 µg/L		nominal	test mat.	mortality	other: The LC50 value at 72 hpf was 3748.46 µg/L and remained constant from 72 to 120 hpf, consistent with morphology effects across time.	
2	120 h	other: Effective	>= 2.85 <= 28.5		nominal	test	mortality	other: Exposure of zebrafish embryos/larvae to TCEP from 3 to 120	

↑ TOP

tris(2-chloroethyl) phosphate (TCEP)

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⋮ ?

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4	120 h	other: Effective concentration	$\geq 2.85 \leq 285$ 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.
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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

tris(2-chloroethyl) phosphate (TCEP)

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View Dossiers

Results and discussion

Observations

1 **Level of biological organisation observed**

molecular

Concentration range tested

>= 100 <= 300 ng/L

Type of dose metric

effective concentration

with or without hCG

Effect concentration

>= 100 <= 300 ng/L

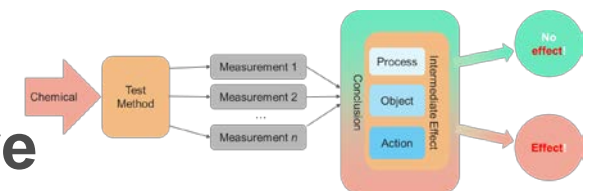
Remarks on result

other: Significant decrease at 100 and 300 ug/mL when compared to controls (no hCG) Significant decrease at 300 ug/mL when compared to hCG controls (hCG + TCEP mix).



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...

III. Establish Scientific Confidence in NAMs and Demonstrate Application to Regulatory Decisions	12
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OECD Harmonised
Template 201 is
explicitly
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

***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.*

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 purposes¹⁸ 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.

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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