Use of mechanistic information to evaluate the hazard and predict health effects of replacement flame retardants.

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CHE Webinar, June 20

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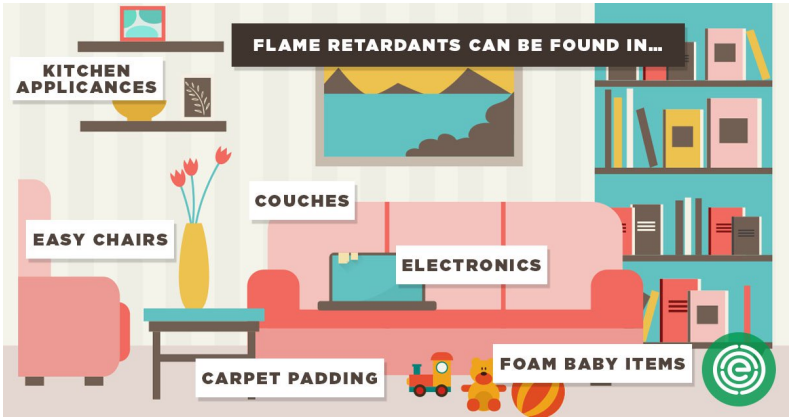
Flame retardants (FRs)

- Added to materials to delay flammability.
- Broadly detected, particularly in dusts and also in human matrices
- People presumably chronically exposed



https://www.ewg.org/enviroblog/2016/08/flame-retardants-why-they-re-our-homes-and-how-avoid-them

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Replacement FRs

Since the years 2000, the long used PBDEs and HBCDD have been restricted, and **100s of diverse chemicals are used as replacement**

- 62 FRs preselected by experts from HBM4EU* - we focus on replacement (non restricted) : 52 FRs
- evaluate their hazard, identify their mechanisms of toxicity.

*hbm4eu scoping document - https://www.hbm4eu.eu/mdocs-posts/scoping-documents-for-2018/

PBDEs: Polybrominated diphenyl ethers; HBCDD: hexabromocyclododecane

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Importance of mechanistic information

62 FRs preselected by experts from HBM4EU* - we focus on replacement (non restricted) : 52 FRs

evaluate their hazard, **identify their mechanisms of toxicity**.

- To predict their impact on health
- To provide a mechanism for health effects
- To identify biomarkers of effects

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Procedure – Collecting toxicological data

Non restricted/replacement only – **52 FRs**

Systematic search for ***in vivo**** **toxicological studies** (open literature and reports from agencies)

results from *in vitro* tests of ToxCast

* Animal studies and human epidemiology studies

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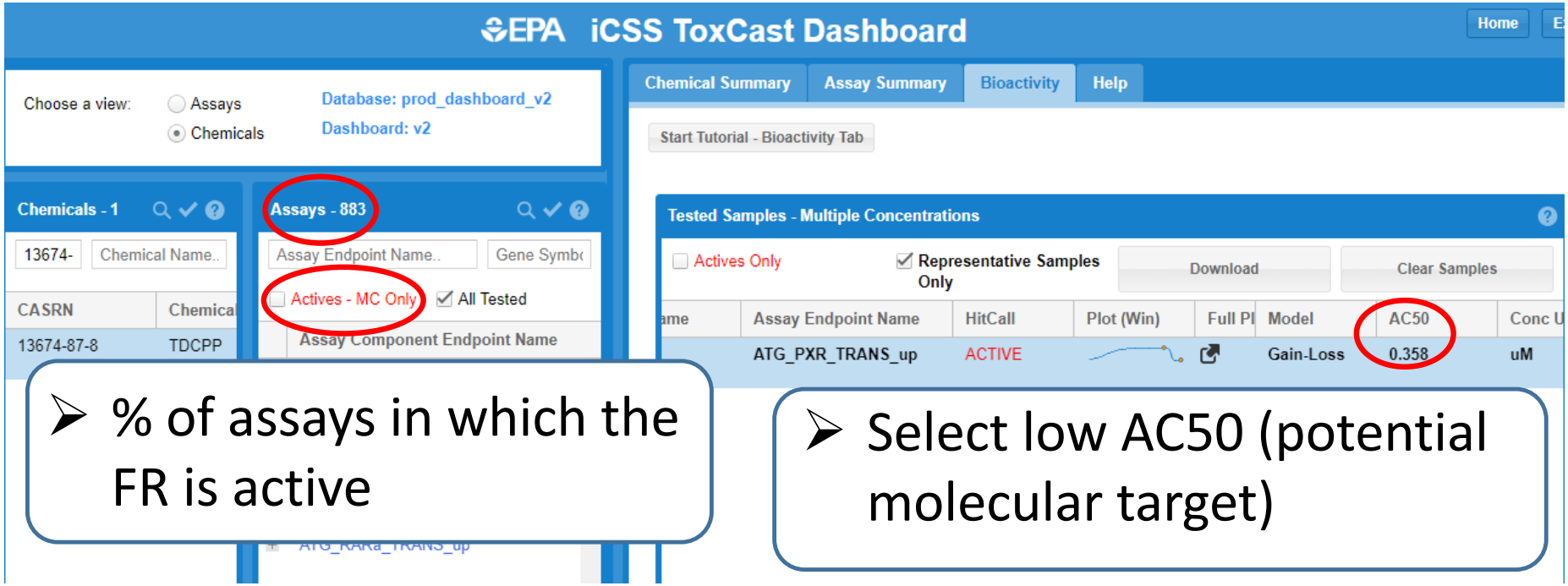
The US-EPA ToxCast programs and dashboard

- Part of the shift in toxicity testing toward alternative to animal studies
- ToxCast and Tox21 programs use high throughput methods to test thousands of chemicals over a large spectrum of *in vitro* assays (e.g., in cells).
- Open and easy access to the results through the dashboard for 9076 chemicals in 1192 Assays - https://actor.epa.gov/dashboard/

Data collected from the ToxCast dashboard



- % of assays in which the FR is active
- Select low AC50 (potential molecular target)

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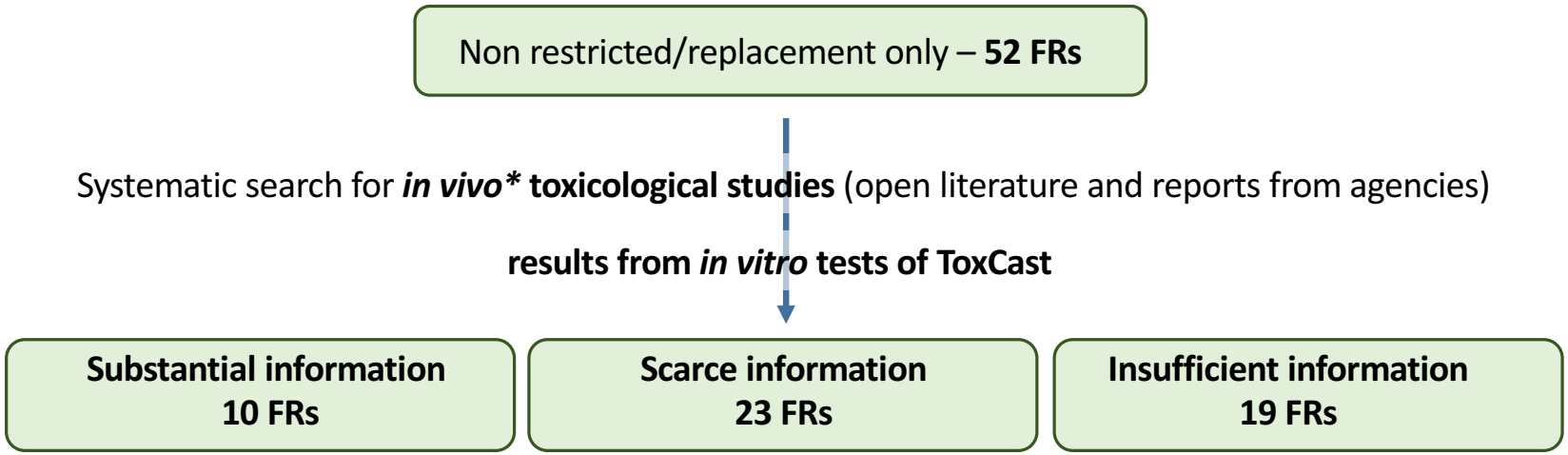
Procedure – toxicological data availability



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* Animal studies and human epidemiology studies

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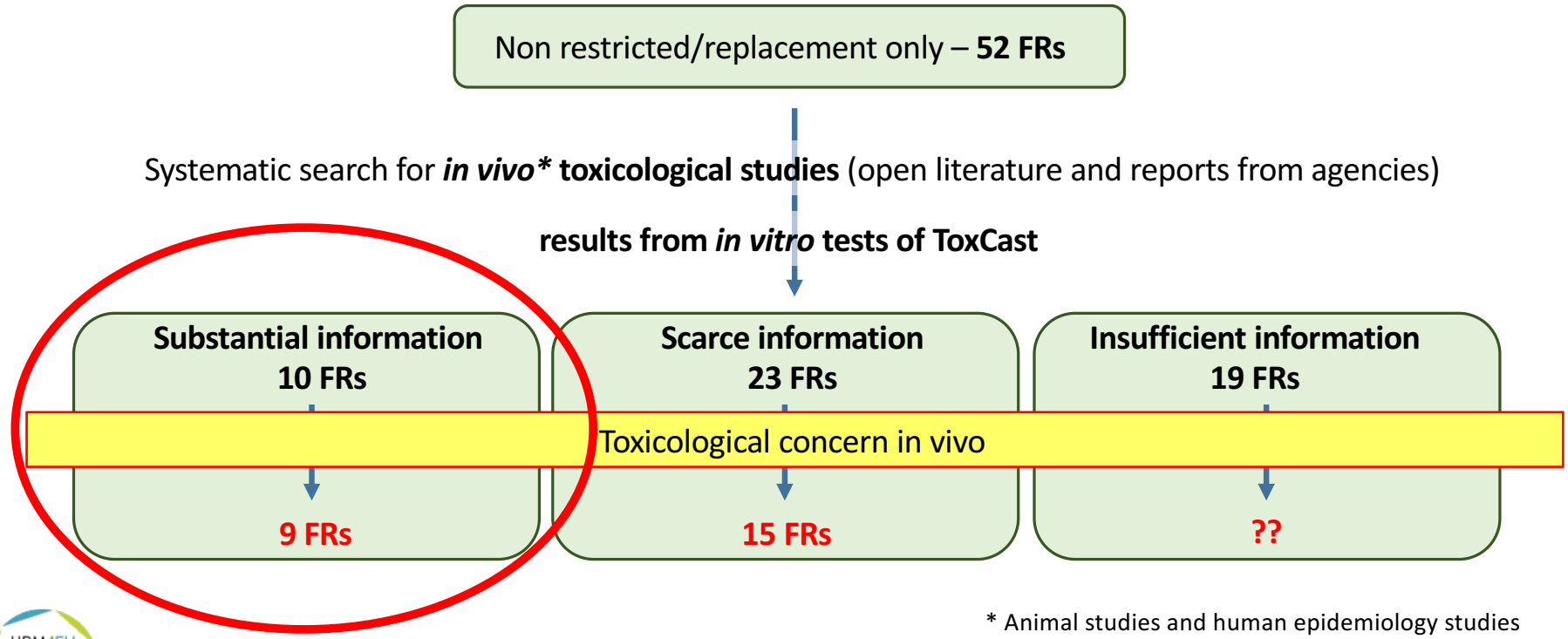
Procedure – evaluation of hazard



* Animal studies and human epidemiology studies

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Focus on 9 FRs – need to identify their mechanisms of toxicity

Substantial information and toxicological concern

9 FRs

- Insufficient to clearly associate health effects to exposure (e.g., lack of human studies)
- **No mechanism of toxicity** clearly identified

→ Use the AOPwiki

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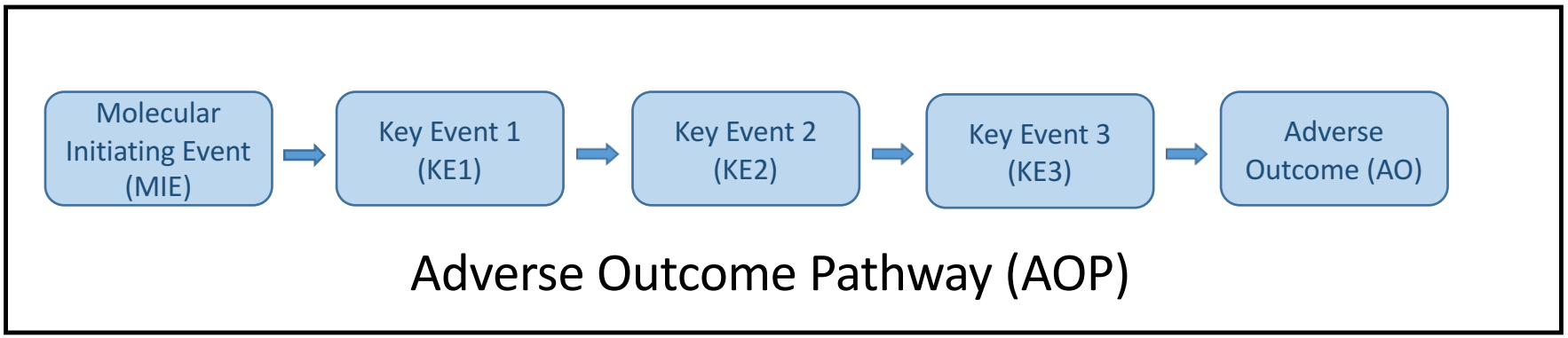
The AOPwiki

- Online knowledge base supported by several international authorities
- Open access to all existing AOPs, MIEs, KEs, AOs
- Each AOPs, MIEs, KEs, AOs has its own page



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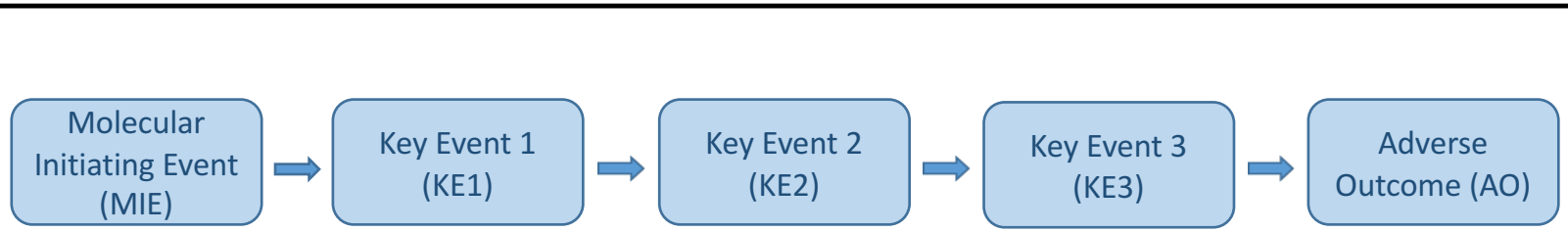
Evidence from Literature (original papers, reports) and ToxCast on **TBBPA, TDCIPP, TPhP, TMPP, TNBP, TBOEP, EHDP, TCIPP and TCEP**

How to merge information from literature and information from the AOPwiki?



Adverse Outcome Pathway (AOP)

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Linking information from literature to existing AOPs

Step 1: **Identify individual biological effects** of the chemical and collect evidences from the literature
„Re-structure“ the complex info from the literature into „individual“ biological effects

Step 2: **Link biological effects to existing Key Events (KE) and AOPs to which they belong** from the AOPwiki
Tricky part - variable/different terminology used in literature vs. Terminology in AOPwiki
> redundancy, > information can get lost

Step 3: **Select AOPs for which we found evidence linking the chemical to at least 3 KEs,** with strong evidence for at least 1 KE, and of good enough quality

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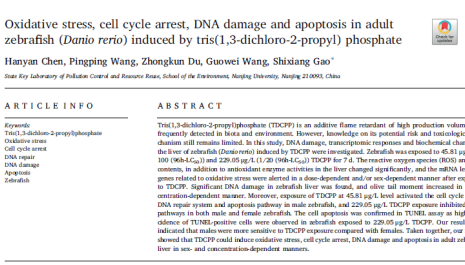
Step 1: Identify individual biological effects

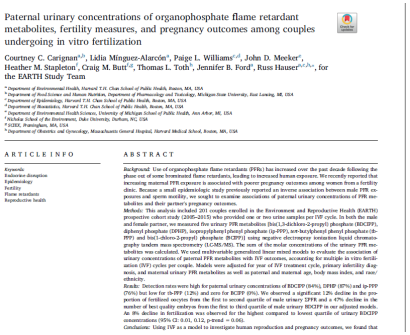


Oxidative stress, cell cycle arrest, DNA damage and apoptosis in adult zebrafish (*Danio rerio*) induced by tris(1,3-dichloro-2-propyl) phosphate

Hanyan Chen, Pingping Wang, Zhongkun Du, Guowei Wang, Shixiang Gao*

ARTICLE INFO

ABSTRACT



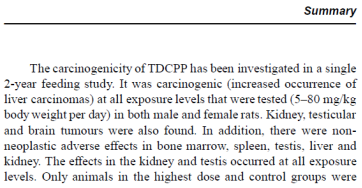
Paternal urinary concentrations of organophosphate flame retardant metabolites, fertility measures, and pregnancy outcomes among couples undergoing in vitro fertilization

Courtney C. Carignan, Lidia Mínguez-Alarcón, Paige L. Williams, John D. Meeker, Heather M. Stapleton, Craig M. Butt, Thomas L. Toth, Jennifer B. Ford, Russ Hauser, for the EARTH Study Team

ARTICLE INFO

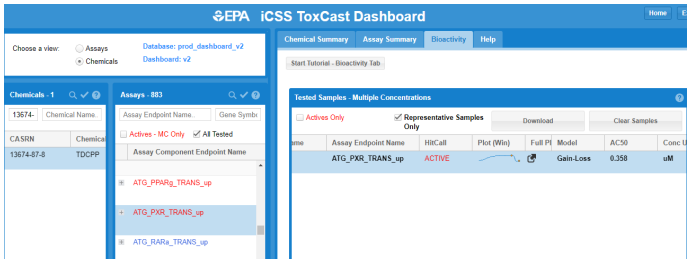
ABSTRACT

Evidence from *in vivo* literature (original papers, reports) and *in vitro* (ToxCast) on TBBPA, TDCIPP, TPhP, TMPP, TNBP, TBOEP, EHDP, TCIPP and TCEP?



Summary

The carcinogenicity of TDCPP has been investigated in a single 2-year feeding study. It was carcinogenic (increased occurrence of liver carcinomas) at all exposure levels that were tested (5–80 mg/kg body weight per day) in both male and female rats. Kidney, testicular and brain tumours were also found. In addition, there were non-neoplastic adverse effects in bone marrow, spleen, testis, liver and kidney. The effects in the kidney and testis occurred at all exposure levels. Only animals in the highest dose and control groups were



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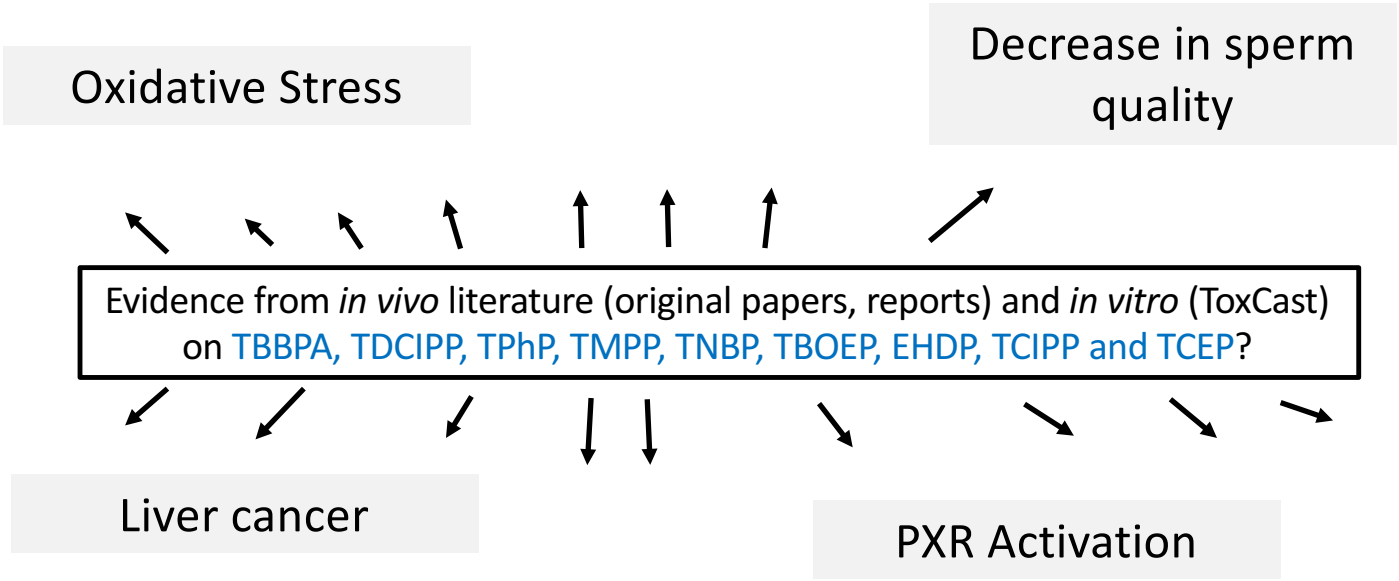
Step 1: Identify individual biological effects



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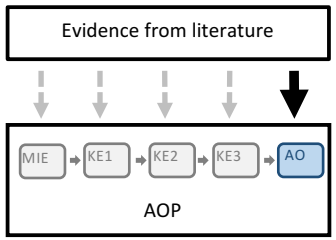
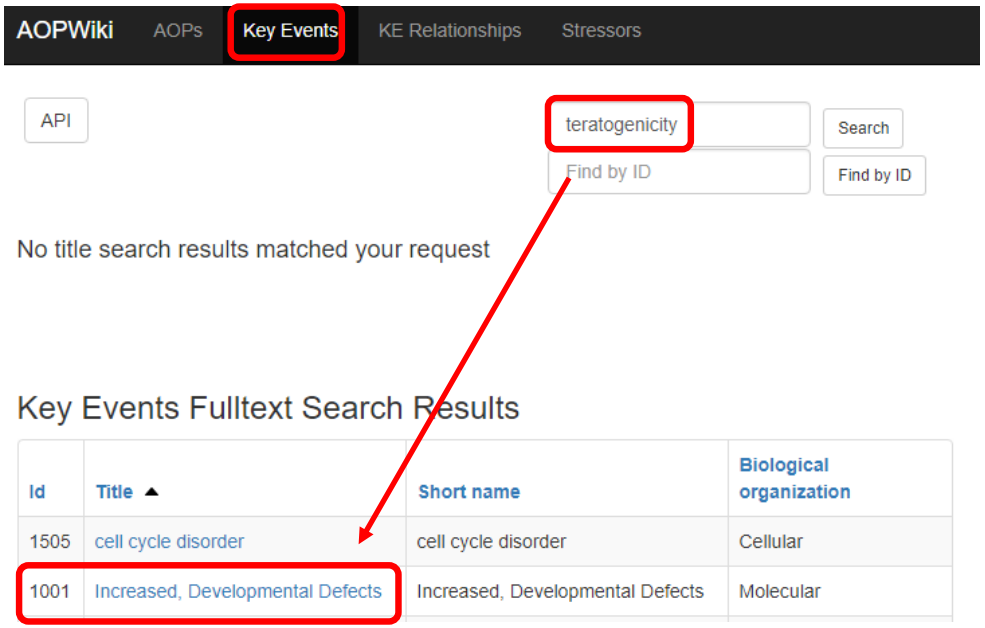
Step 2: Link biological effects to existing Key Events (KE) using AOPwiki





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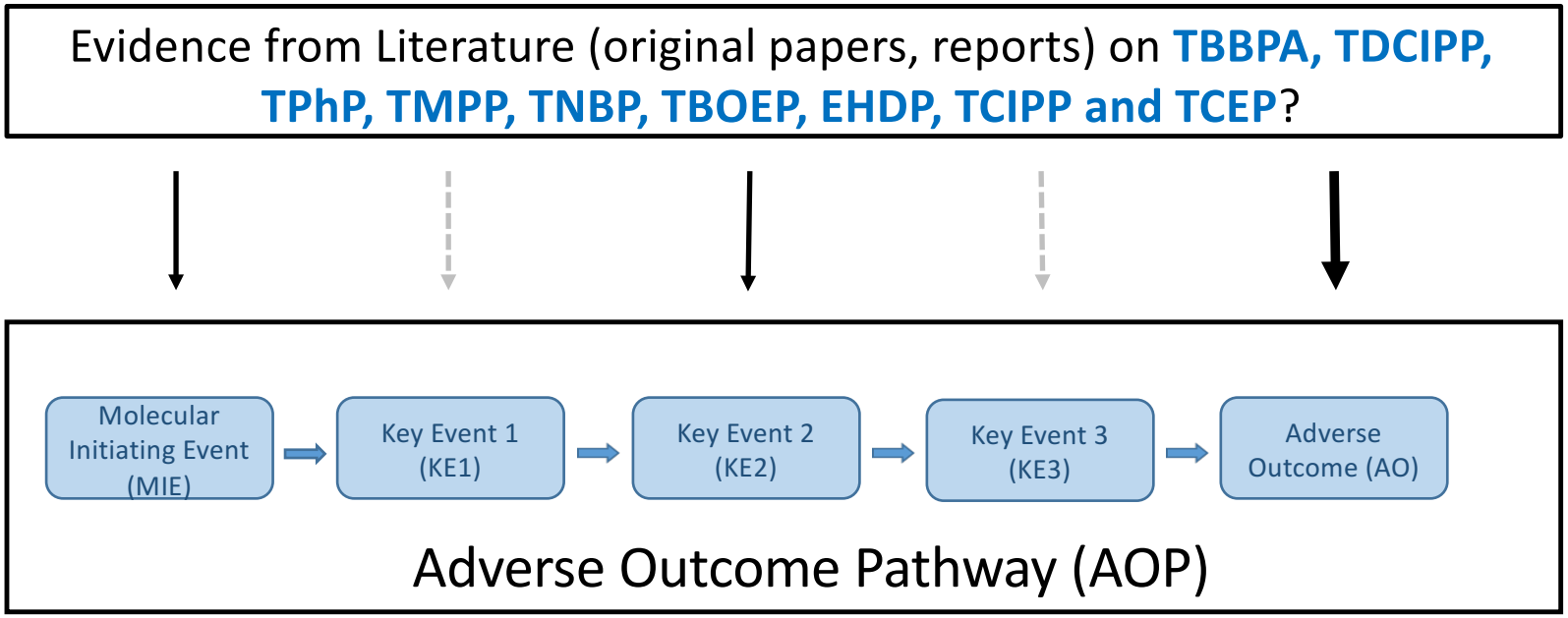
Step 3: Select “plausible AOPs” (chemical linked to 3 or more KEs)



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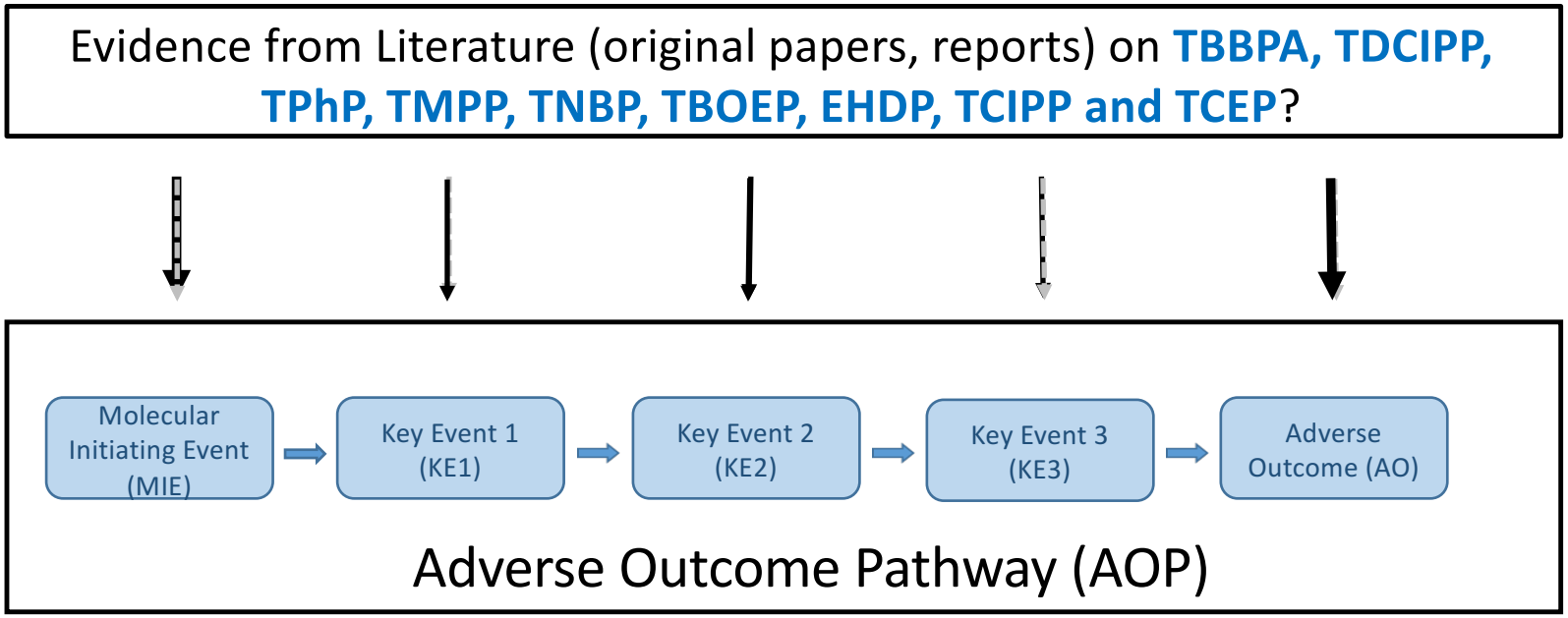

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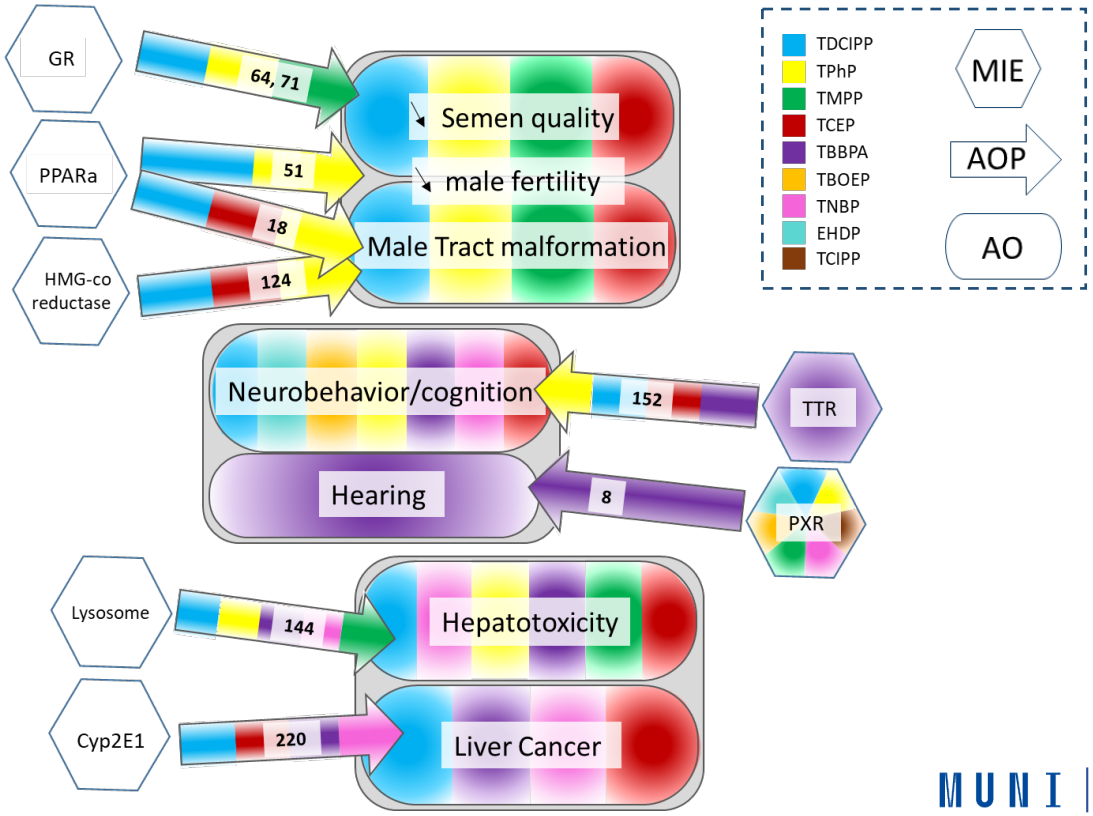
Most relevant AOs and corresponding plausible AOPs for Cat I FRs

Figure 2: Illustration of major results from literature/ToxCast/AOP search for Category I FRs

Major AOs are indicated (in ovals) with corresponding plausible AOPs (arrows with their number from the AOP-wiki) and MIE (in hexagons). A color code indicates for which Cat I FR the AOP is a plausible mechanism, or the AO or MIE has been reported. No colors at MIE indicate that the effects of FRs have not been reported so far or AC50 from ToxCast was above 1µM. Several other AOs, AOPs and MIEs not illustrated in this figure have been investigated and are listed in Supplementary Table S3. (Disclaimer: because of dynamic nature of AOP-Wiki, the information on AOPs presented in the paper reflects state of the art as of June 2018, when the information from AOP-Wiki was collected).

https://rdcu.be/boCGI



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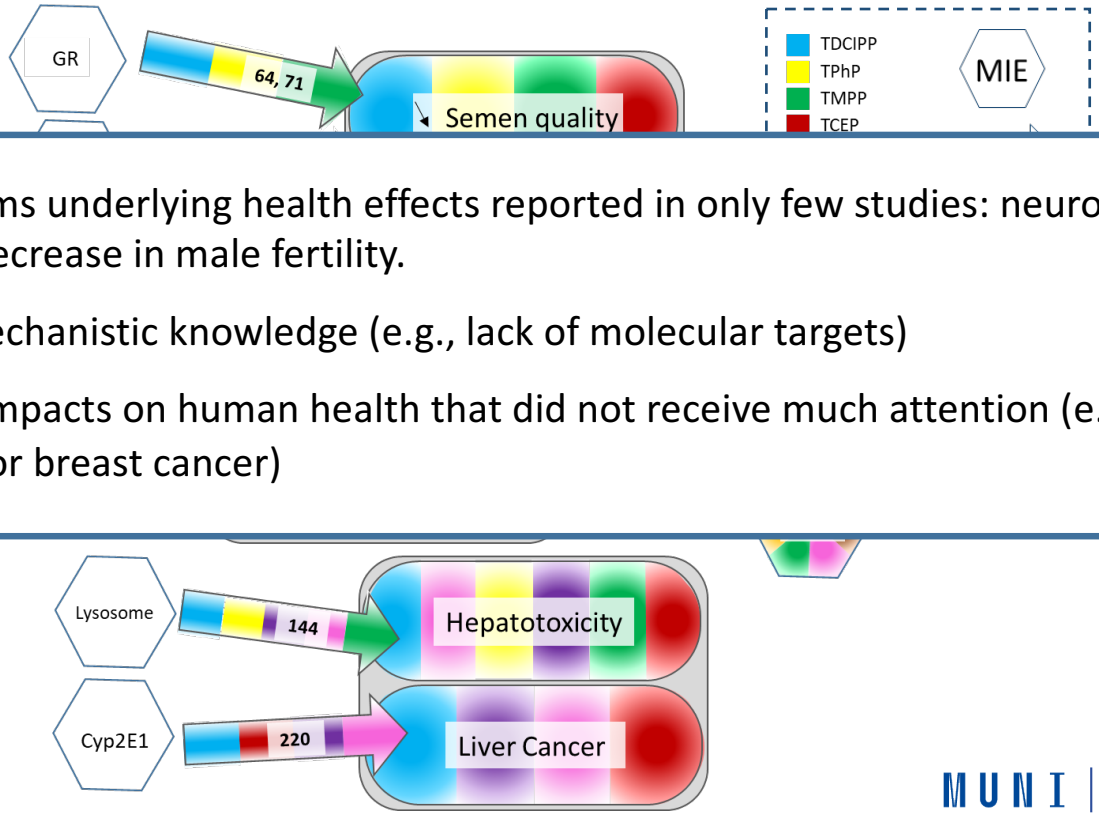

Figure 2: Illustration of major results from literature/ToxCast/AOP search for Category I FRs

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when the information from AOP-Wiki was collected).

- Identify mechanisms underlying health effects reported in only few studies: neurotoxicity, hepatotoxicity and decrease in male fertility.
- Identify gaps in mechanistic knowledge (e.g., lack of molecular targets)
- Predict potential impacts on human health that did not receive much attention (e.g., metabolic disorders or breast cancer)

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Conclusions

For replacement chemicals with rather little toxicological data available:

- Information from ToxCast can be a useful to predict toxicological concern (e.g. PBP).

However, no/low activity in ToxCast assays does not necessary imply low toxicological concern in vivo.

- AOP wiki is useful to make optimum use of the data available to identify mechanisms, predict potential impacts on human health and identify gaps in mechanistic knowledge

However it still has limitations, e.g. incomplete representativity of the biological processes

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Thanks to HBM4EU project team for initial structure of compound categorization.

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Thank you for your attention!