



LATEST TRENDS IN SAFETY EVALUATION OF AGROCHEMICALS

THE NEED FOR AUGMENTATION OF REGULATORY PATH

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Contents and flow of thoughts



- *What is bothering the regulators?*
 - *Replace / Reduce Animals!!*
 - *Use alternative methods....in vitro! Use read-across!*
- *History of Guidelines are updates & revisions*
- *Consolidate the guidelines....more data while using the animals*
 - *EOGRTS*
 - *Hormone analysis in OECD 407/408*
- *AoPs, applied in the vitro studies mammalian/fish etc.*
- *Conclusion*



Regulatory Trends in the EU & the US



- *European Union*
 - *REACH, Biocides & Crop care products*
 - *Weight of evidence*
 - *QSAR models*
 - *In vitro methods*
 - *Grouping of substances and read-across*
- *US*
 - *EPA for TSCA & FiFRA (Federal Insecticide, Fungicide, and Rodenticide Act)*



Horizon is constantly moving



- The EU regulators are insisting on use of for all the future registration needs;
 - Read across for Acute oral and dermal toxicity
 - *in vitro* tests for skin irritation/corrosion, eye irritation as well as skin sensitization
 - Inhalation toxicity still remains *in vivo*, but the new guidelines based on Toxic Class criteria use reduced animals.



Options??



Alternative methods....*in silico/in vitro!*

- Grouping & Read-across
- Weight of Evidence/WoE
- QSAR
- Non-animal methods

<https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/weight-of-evidence>



Grouping & Read Across



- Use **relevant** information from analogous substances to predict the properties of the **'target'** substances.
- Eliminate experimental (animal) testing by using the concept.....justifications must establish adequacy and appropriateness of the document.
- Must be Key data based on identifiable with appropriate references to IUCLID(*) substance dataset would be necessary.
- Prediction must be based on **structural similarity / dissimilarity**.
- A read-across approach can be used to defend a conclusion for a property using a **weight-of-evidence** approach. (* International Uniform Chemical Information Database)

<https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>



Read-Across Assessment Framework (RAAF)



Process:

- Check the ***robustness*** of read-across adaptation.
- Hypothesize the justification for using the data from one ***substance structurally related*** substance to the other, for each property.
- Search for experimental data for contradictions against the proposed hypothesis if any.
- Provide credible supporting information.
- Impurities and potentially different substance compositions must but be highlighted



Weight of Evidence (WoE)



Weight of Evidence must be based on;

- *Published literature*
- *Data from **existing studies***
- *Epidemiological data/human experience.*

<https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/weight-of-evidence>



Weight of Evidence (WoE)



Weight of evidence :

- *Includes, as a minimum, two separate study /text book values records for a certain property, **single value from a secondary data source is not sufficient***
- *Domain expert to assess the reliability, relevance, adequacy of the available data to assess combined evidence is adequate to avoid a test*
- *The expert judgement should be transparent and understandable appropriately supported by delineating the process of arriving at conclusion and providing the references.*



QSAR



- Mathematical models (generated based published research data)
- Predict the physicochemical, biological and environmental fate properties of compounds, based on their chemical structure.
- Limitations: Currently (Q)SARs have limitations in accurately predicting complex toxicological properties, not deemed fit for purpose for classification and labelling or risk assessment.

<https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/qsar-models>



QSAR



- Documented format: IULID
- To be used **only when** the test results, are not available
- Consider using additional parameters and link potential interactions between them.
- (Q)SARs may be coupled with other data and used in a weight of evidence approach.
- One study record for each chemical structure for (Q)SAR prediction.



in vitro methods



in vitro methods

- *Test system is **alive, but outside of a living organism***
- *Usually involves isolated cells/immortalized/reconstructed cell lines, rarely tissues or organs*
- *They could be used for supporting part / full replacement of animal tests.*
- *Use of sufficiently well-developed methods in compliance with internationally agreed test development criteria (ECVAM*).*

** European Centre for the Validation of Alternative Methods*

<https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/in-vitro-methods>



in vitro methods



- *2016 onwards, the EU mandates in vitro test methods the default for certain toxicological properties.*
- *No Acute dermal and eye irritation and sensitization tests will be accepted.*
- *Sensitization could be done using LLNA assay but **GPS is a “No-No”!***
- *Regulator **may** accept an **in vitro** assay data, which hasn't been internationally validated, as dossier or support of WoE.*



Consolidate the guidelines....



Efforts aimed at achieving maximal data by adding additional endpoints in the existing animal testing guidelines

- *OECD 443-EOGRTS- The Extended One Generation Reproduction Toxicity Test*
 - *Developmental Tox guideline with **immuno** and **neurotox** cohorts*
- *OECD 407/408*
 - ***Hormone analysis** (T3, T4, TSH & Testosterone estimation mandatory)*
 - ***On horizon: Plasma concentration for establishing limit of exposure!***



Guideline updating....OECD test guidelines



Year	No of Guidelines revised	% revised	Revision per year
2018	15	20.8%	20.8%
2017	4	5.6%	5.6%
2016	14	19.4%	19.4%
2015	8	11.1%	11.1%
2008-2014	11	15.3%	2.2%
1998-2007	8	11.1%	1.1%
1981-1997	12	16.7%	1.0%
	72		



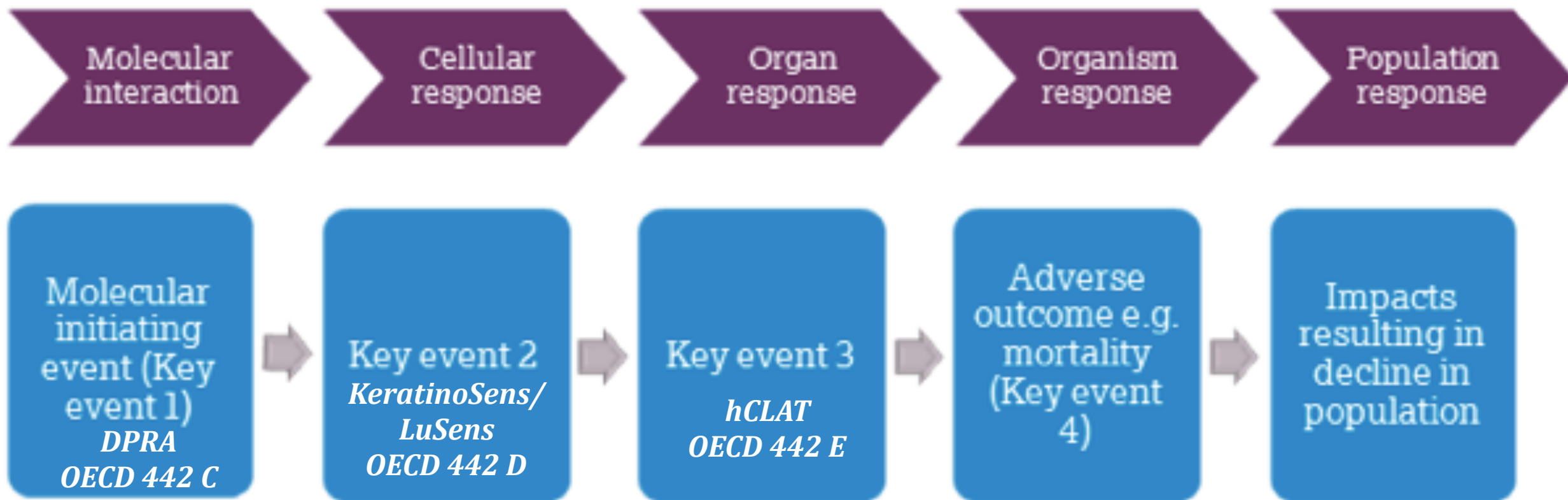
The Guideline Horizon @ OECD is constantly changing!



- **77** changes in the past **10** years
- **30** of the **72** OECD test guidelines, have been released focused on *in vitro* methods aimed at animal study replacement!
- **15** of the **30** have been released during 2016 till date!
- EU regulators: **completely stopped** acceptance of Guinea Pig Maximization test for Skin sensitization w.e.f. October 11, 2016!!
- Rest of the changes aimed at bring in options to **reduce animals/reduce pain/discomfort**/achieve more from the existing guidelines with additional biomarkers chipped in!



AOPs are on horizon...



Kinetic DPRA on its way....

NC3Rs Pathways-based approaches resource: Issue 6: August 2018



Should & Can the Animal testing be avoided?



Tests effectively Eliminated;

- *Rodent Acute Oral /Dermal toxicity, Skin and eye irritation, skin sensitization ,*

New product Development:

- *LD50/LC50/metabolism based tests using specific cell system using human primary/immortalized/iPSC derived differentiated cells*
- *Zebra fish embryo*

Regulatory Accepted

- *Skin & Eye Irritation / corrosion tests*
- *Skin sensitization using battery of tests driven by AoPs*



Should & Can the Animal testing be avoided?



Animal testing be best avoided,

- **NC3Rs:** *wherever, the test **unequivocally** establishes that the expected safety assessment needs should be met with by the alternative tests!*
- **Antithesis:**
 - *Animal testing is still the best way to find new treatments for patients Garattini S, Grignaschi G, Eur J Intern Med (2016), <http://dx.doi.org/10.1016/j.ejim.2016.11.013>*



Rational thinking is the need of the hour!!!



For Animal testing	Against Animal testing
<ul style="list-style-type: none"><i>Animal testing is still the best way.....there are several researchers who openly / in private conversation, support this view.</i>	<p><i>Avoid animal testing....there are possibly equal number of opinion-leaders who support this view.</i></p>

Our take @ JRF:

- Equilibrium is the law of the universe!*
- It ensures steady state and stability!*
- Wide pendulum swings are anti-stability!*



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Thank you so much Audience.