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

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- 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)

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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!***

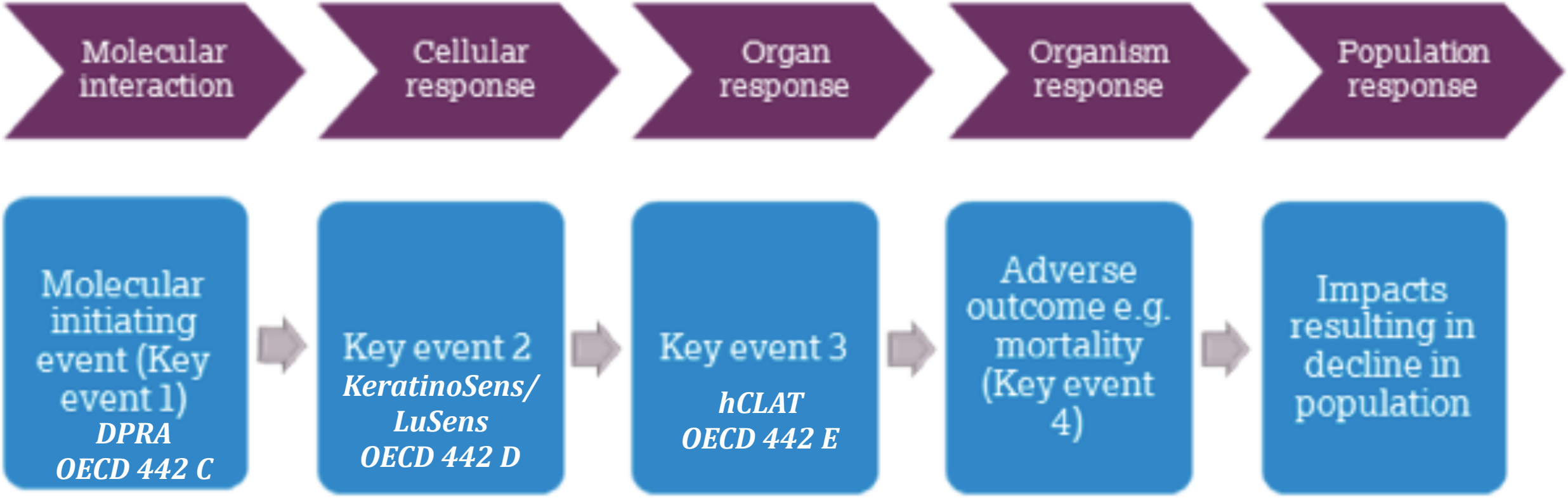
Guideline updating….OECD test guidelines

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?

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Tests effectively Eliminated;

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

<u>New product Development:</u>

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

<u>Regulatory Accepted</u>

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

Should & Can the Animal testing be avoided?

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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
• *Animal testing is still the best way…….there are several researchers who openly / in private conversation, support this view.*	*Avoid animal testing….there are possibly equal number of opinion-leaders who support this view.*

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.