Assessment of Plant Protection Products and Biocides: Recent Developments and Future Perspectives of Using Non-Animal Methods

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Minimising animal testing: the legal requirements and the future of regulatory science

In 2023, the European Commission committed to phasing out animal tests for all regulated chemicals, including plant protection products (PPPs) and biocides.[1]

Here, we review:

- The availability of validated non-animal tests that are accepted by EU regulators
- Approaches to assess PPPs and biocides that are ready to be implemented or that will be ready in the near future
- Endpoints that require further resources

Many validated non-animal approaches are already available for regulatory use for the assessment of PPP and biocidal active ingredients and formulations. Further resources and investment will aid the phasing out of animal tests for all regulated chemicals.

"MEMBER STATES SHALL ENSURE THAT, WHEREVER POSSIBLE, A SCIENTIFICALLY SATISFACTORY METHOD OR TESTING STRATEGY, NOT ENTAILING THE USE OF LIVE ANIMALS, SHALL BE USED INSTEAD OF A PROCEDURE."

Article 4, Principle of replacement, reduction and refinement. Directive 2010/63/EU of 22 September 2010 on the protection of animals used for scientific purposes.

"TESTING ON VERTEBRATES FOR THE PURPOSES OF THIS REGULATION SHALL BE UNDERTAKEN ONLY WHERE NO OTHER METHODS ARE AVAILABLE."

Article 62, Sharing of tests and studies involving vertebrate animals. Regulation (EC) No 1107/2009 of The European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market.

RESEARCH REGULATION

"IN ORDER TO AVOID ANIMAL TESTING, TESTING ON VERTEBRATES FOR THE PURPOSES OF THIS REGULATION SHALL BE UNDERTAKEN ONLY AS A LAST RESORT."

Article 62, Data sharing Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products.

Non-animal methods accepted by regulators

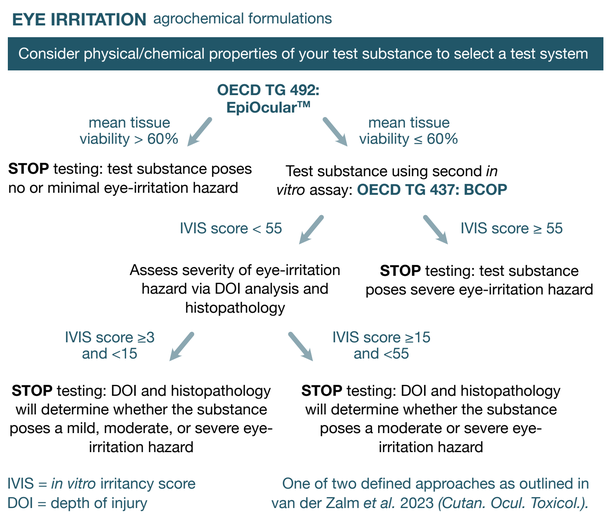
The *in vivo* eye and skin irritation tests using rabbits (OECD TG 405 and TG 404) have significant limitations, including variability and lack of human relevance.[2-5]

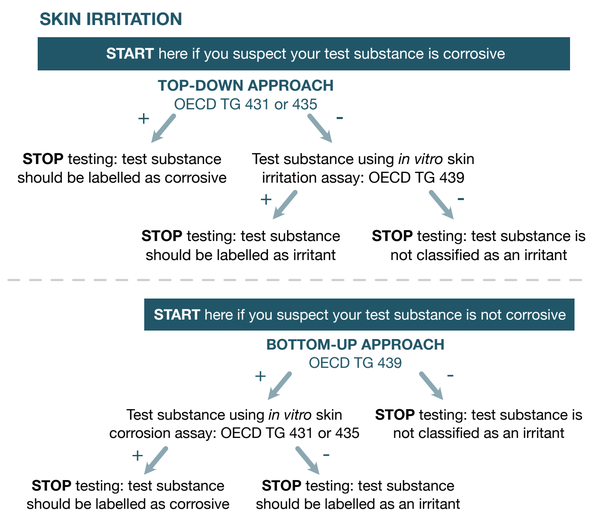
Data obtained exclusively from *in vitro* methods can be used to discriminate eye and skin irritation potential.[6,7]

Discrimination among the GHS categories for eye damage and irritation using:

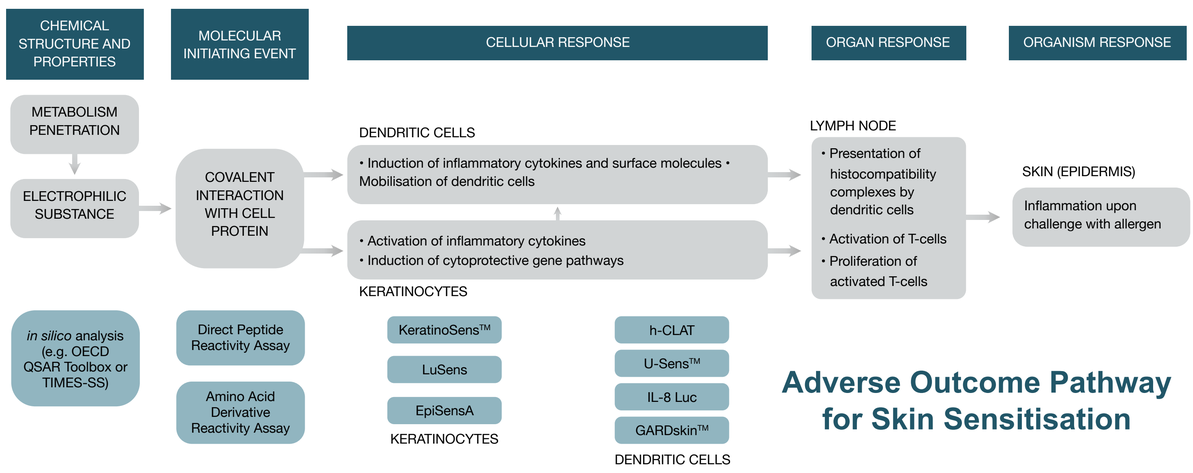
- OECD TG 467: Defined Approaches for Serious Eye Damage and Eye Irritation[8]
- OECD TG 492B: Reconstructed Human Cornea-Like Epithelium (RCHE) Test Method for Eye Hazard Identification[9]

Discrimination among the hazard categories for eye and skin irritation can be done using a combination of methods (see approaches on the right).[10-12]





Recently validated methods ready for implementation



Adverse Outcome Pathway for Skin Sensitisation

OECD guideline 497: Defined Approaches on Skin Sensitisation:[13]

- *In silico*, *in chemico*, and *in vitro* methods that produce results as, if not more, predictive of human outcomes as the *in vivo* local lymph node assay[14,15]
- Integrative testing strategy which can discriminate among three GHS categories for chemicals[13]
- Accepted under Biocidal Products Regulation (BPR)

Similar validated assays will be included in this defined approach:

- EpiSensA[16]
- GARDskin™ [17]

Both are applicable to difficult-to-test substances (as demonstrated by method developers).[18,19]

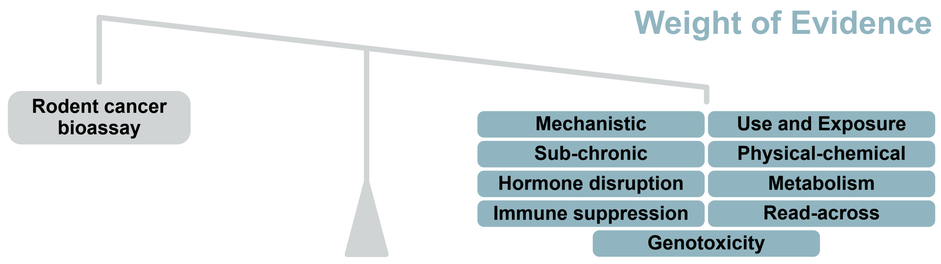
Endpoints requiring further resources

Carcinogenicity

- The currently required rodent cancer bioassay lacks reproducibility and translatability[20-22]
- Efforts are underway to modernise carcinogenicity assessment with cell transformation assays and *in silico* methods informed by adverse outcome pathways[23,24]
- **Re**thinking **C**arcinogenicity **A**ssessment for **A**grochemical **P**roject (**ReCAAP**): framework to support a weight of evidence assessment without rodent bioassays to fulfill regulatory requirements

ReCAAP Case Studies:

- Retrospective studies of registered active ingredients with risk assessment data[25]
- Prospective studies of new active substances without submitted data[26]
- OECD IATA Case Study on Carcinogenicity (publicly available in September 2024)



Endocrine disruption

- Tiered approach includes *in vitro* methods[27]
- Currently, *in vivo* follow-up of positive *in vitro* results
- Lack of confidence in *in vivo* results[28-31]
- Resources required to further develop robust *in vitro* methods[32]

Retrospective analyses

Acute dermal toxicity

After review of 300 chemicals, the US Environmental Protection Agency (EPA) concluded that dermal acute toxicity studies affected the labelling of fewer than 1% of pesticides, if any.[33]

- US EPA waives the requirement for pesticides active ingredients and formulations
- Canada's Pest Management Regulatory Agency removed the routine requirement[34]

Oral 90-day study in dogs

Rarely informs risk assessment when the 90-day study in rodents has also been conducted.

Since 1998, fewer than 5% of US EPA pesticide risk assessments have been informed by the 90-day dog study.[35]

EFSA's ongoing retrospective analysis preliminarily supports waiving of the dog study unless scientifically justified.[36]

References

Find the literature and policies cited in this poster at:

Learn more about the Science Consortium's work at: