Mapping a new paradigm for agrochemical carcinogenicity assessment

Gina M. Hilton[1], Raffaella Corvi[2], Mirjam Luijten[3], Jyotigna Mehta[4], Douglas C. Wolf[5]

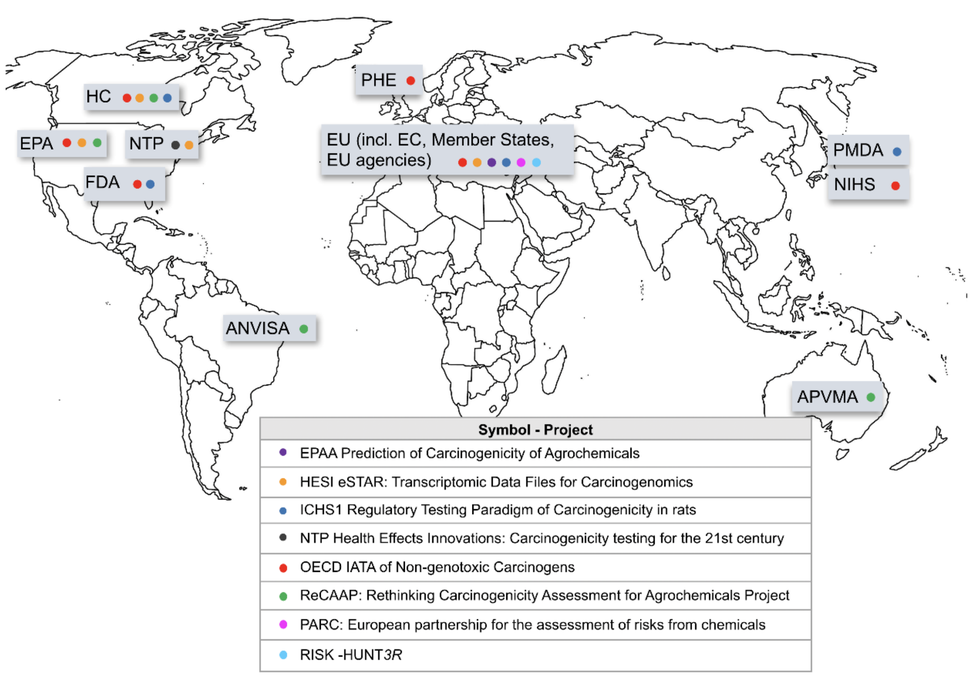
[1]PETA Science Consortium International e.V.; [2]European Commission Joint Research Centre, [3]Center for Health Protection, National Institute for Public Health and the Environment; [4]ADAMA Agricultural Solutions Ltd.; [5]Syngenta Crop Protection, LLC

INTRODUCTION

The rodent cancer bioassay is currently used as a standard approach for assessing carcinogenic potential of agrochemicals. The bioassay is time intensive, uses large numbers of animals, and has limited ability to address human carcinogenicity, which has led to the development of new approaches to facilitate the modernization of carcinogenicity assessment.

Multiple initiatives are actively developing frameworks to structure a new approach to carcinogenicity assessment, including weight of evidence (WoE)-based approaches using *in silico*, *in vitro*, and short-term *in vivo* tests.[1-6]

The mapping exercise presented here aims to scope available approaches, and proposes their integration to provide a harmonized strategy towards a WoE-based carcinogenicity assessment without long-term rodent bioassays.[7]



CONCLUSIONS

- It is possible to determine carcinogenicity potential to protect human health without performing the standard cancer bioassay.
- For a harmonized roadmap to achieve a modern, human relevant carcinogenicity assessment, the following should be considered when building collaboration:
  - Fit-for-purpose new approach methodologies (NAMs) that can be used in the harmonized carcinogenicity assessment.
  - Regulatory needs to establish decision criteria for evaluating a WoE-based carcinogenicity assessment.

OPPORTUNITIES

Identify fit for purpose new approach methodologies that can be used to develop an Integrated Approaches for Testing and Assessment (IATAs).
https://www.oecd.org/chemicalsafety/risk-assessment/iata/

Develop a cluster of IATA case studies that provide examples of weight of evidence based carcinogenicity assessment without rodent cancer bioassays under a variety of legislations.

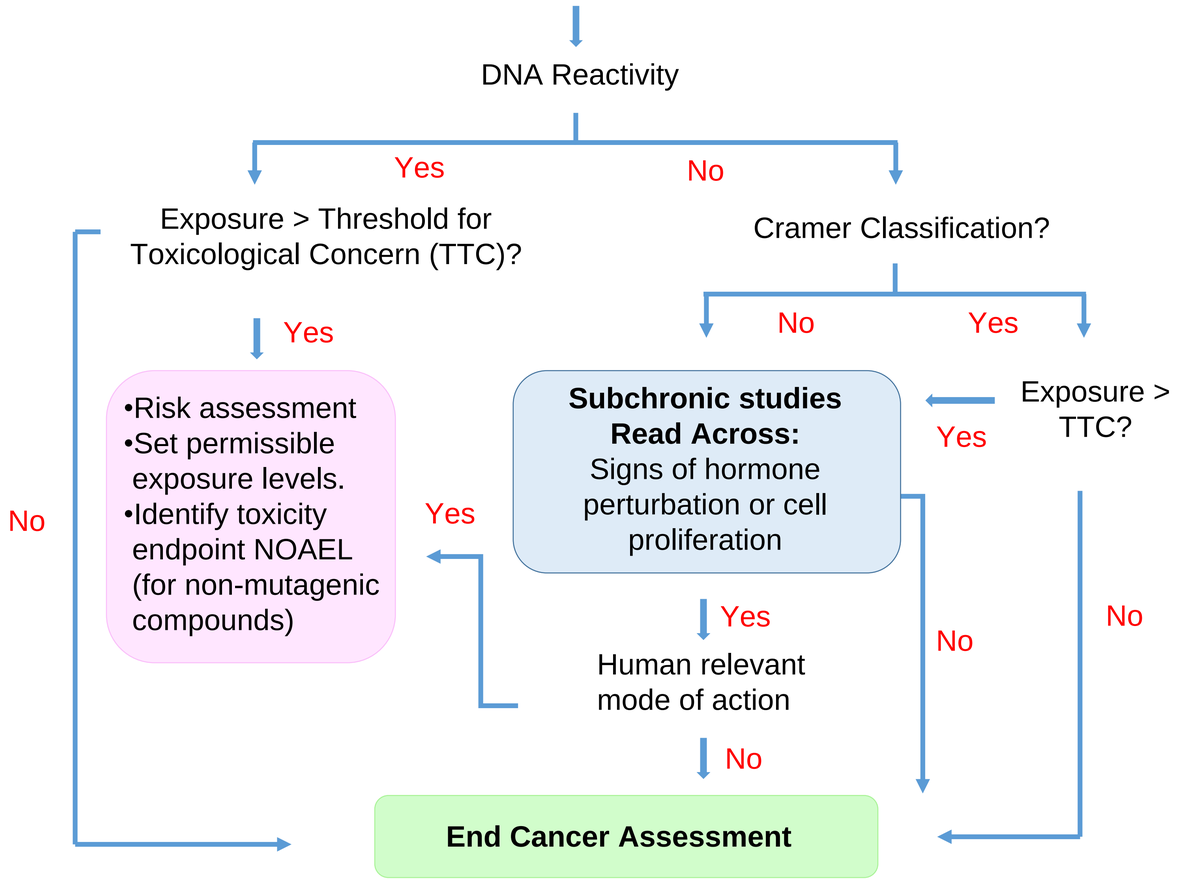
Identify relevant initiatives and research projects, to design a harmonized roadmap that will permit achieving a modern, human relevant carcinogenicity assessment.[7]

Cited Literature

[1]Cohen, S., *et al.*, 2019. Regulatory Toxicology and Pharmacology: https://doi.org/10.1016/j.yrtph.2019.01.017
[2]Harrison and Doe, 2021. Toxicology Research: https://doi.org/10.1093/toxres/tfab064
[3]Heusinkveld, H. *et al*., 2020. Critical Reviews in Toxicology: https://doi.org/10.1080/10408444.2020.1841732
[4]Hilton, G. *et al*., 2022. Regulatory Toxicology and Pharmacology: https://doi.org/10.1016/j.yrtph.2022.105160
[5]Jacobs, M. *et al*., 2020. Archives of Toxicology: https://doi.org/10.1007/s00204-020-02784-5
[6]Luijten, M. *et al*., 2020. Regulatory Toxicology and Pharmacology: https://doi.org/10.1016/j.yrtph.2020.104789
[7]Hilton, G. et al., 2022. Regulatory Toxicology and Pharmacology: https://doi.org/10.1016/j.yrtph.2022.105301

MAPPING & ALIGNMENT

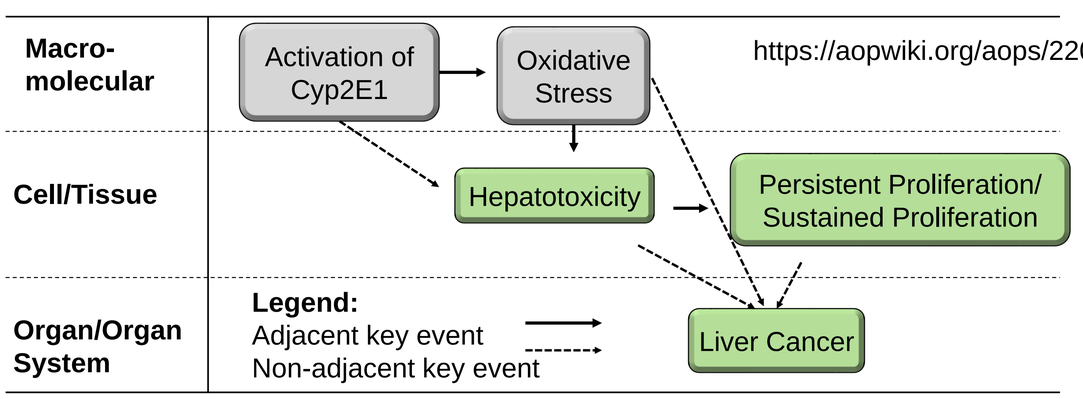
Adapted Cohen *et al.* decision tree for carcinogenicity assessment[1]



Illustrative ReCAAP reporting framework[4]

I. Purpose of Analysis
II. Study Waiver Request
a. Nomenclature
b. Physical-Chemical Properties
c. Use Pattern and Exposure Scenarios
d. ADME and Toxicokinetics
e. Toxicity
  i. Acute Toxicity
  ii. Subchronic Toxicity
  iii. Genetic Toxicity
  iv. Evidence of Hormone Perturbation
  v. Evidence of Immune Suppression
  vi. Mechanistic Studies to Support a Proposed Mode of Action
f. Evidence of Chronic Toxicity from Related Chemicals
g. Proposed Risk Estimates

Examination of AOPs for mechanistic WoE[3,6]



Email contact: GinaH@thepsci.eu

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