Rethinking Carcinogenicity Assessment for Agrochemicals

Gina M. Hilton[1], Gregory Akerman[2], James Baldassari[3], Michael Battalora[3], Amy J. Clippinger[1], Rhian Cope[4], Amber Goetz[5], A. Wallace Hayes[6], Anna Lowit[2], Sabitha Papineni[7], Richard C. Peffer[8], Brandy Williamson Riffle[9], Mitscheli Sanches da Rocha[9], Natalia Ryan[5], Edward Scollon[10], Nicolo Visconti[11], Douglas C. Wolf[5], Zhongyu Yan[12]

[1]PETA Science Consortium International e.V. – Stuttgart, Germany; [2]United States Environmental Protection Agency – Washington, D.C. US; [3]FMC Corporation – Newark, US; [4]Australian Pesticides and Veterinary Medicines Authority – Armidale New South Wales, Australia; [5]Syngenta Crop Protection, LLC – Research Triangle Park, US; [6]University of South Florida – Tampa, US; [7]Labcorp Early Development Laboratories Inc. – Greenfield, US; [8]Rich Peffer Toxicology Consulting, LLC – Greensboro, US; [9]BASF Corporation – Research Triangle Park, US; [10]Valent U.S.A. LLC – San Ramon, US; [11]Bayer CropScience LP – St. Louis, US; [12]Corteva Agriscience™ – Indianapolis, US

Problem Statement: There are no specific criteria to determine when not to require the Combined Chronic Toxicity/Carcinogenicity studies (OECD 453; 451) for pesticides based on toxicological and exposure data.

INTRODUCTION

For the past 40 years, questions have been raised about the relevance and regulatory utility of rodent cancer bioassays in human health risk assessment. As a result, a working group of experts from different sectors have formed the **R**ethinking **C**arcinogenicity **A**ssessment for **A**grochemicals **P**roject (**ReCAAP**) to determine the appropriateness of and criteria for waiving rodent cancer bioassays for the registration of food-use pesticides.

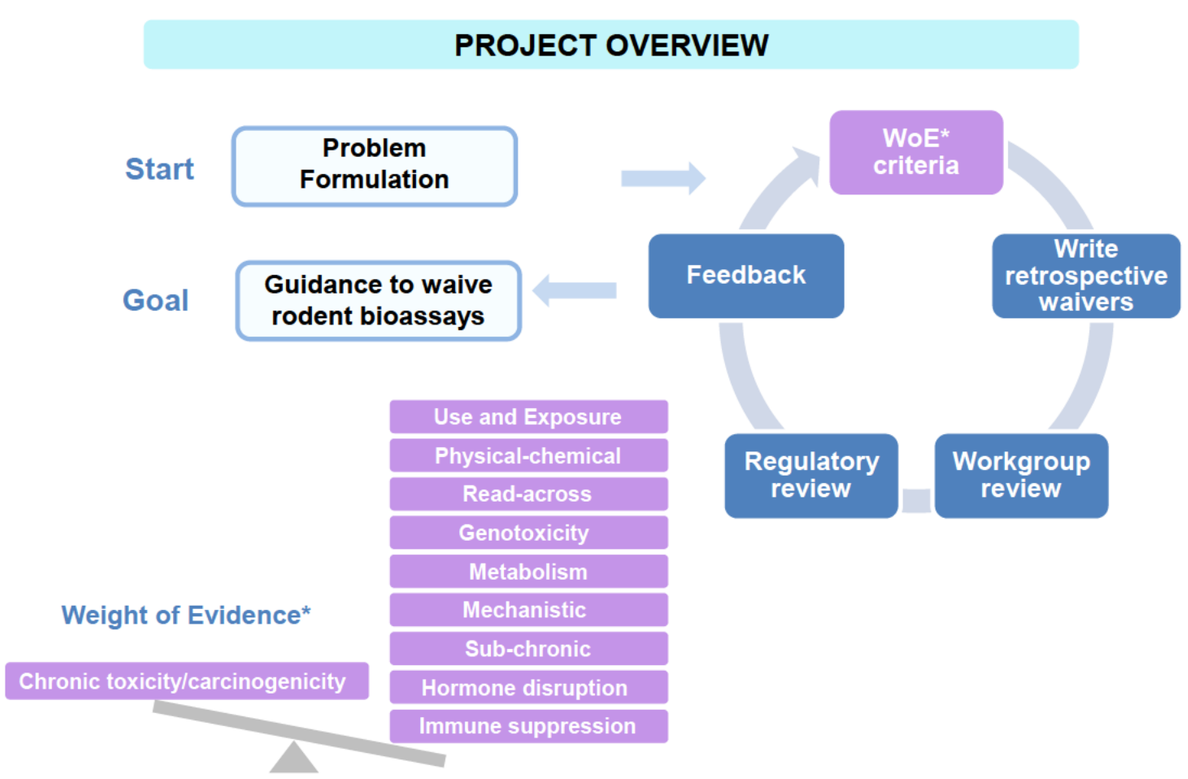
A weight of evidence (WoE) reporting framework, which outlines a suggested assessment of publicly available information, was used to draft carcinogenicity study waiver rationales to determine if sufficient information was available to perform a health protective chronic risk assessment without conducting rodent cancer bioassays.

Information used in the WoE included exposure, mode-of-action, physiochemical properties, metabolism, and sub-chronic toxicological data from standard risk assessment endpoints.

These data were analyzed to determine if there would have been sufficient information to perform a health protective chronic risk assessment without performing rodent cancer bioassays.

METHODS

PROJECT OVERVIEW



FRAMEWORK

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
   - h. Conclusion

Disclaimer: The views expressed in this poster are those of the author(s) and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency, Australian Pesticides and Veterinary Medicines Authority, Brazilian Health Regulatory Agency, and Health Canada Pest Management Regulatory Agency.

CASE STUDY

Weight of Evidence	Chemical
Intended Use / Chemical Class / MOA	Herbicide safener; arylsulfonyl-benzamides; induce herbicide metabolizing enzymes
Physical-Chemical Properties	Molecular weight = 374.41 Vapor pressure = 6 x 10-9 Pa at 20ºC Log Kow = -0.80
Use Pattern & Exposure Scenarios	Uses: corn, sorghum, turf, and ornamentals Exposure: human dietary
Acute Toxicity (EPA Category)	Oral (III); Dermal (III); Inhalation (III); Eye (IV); Dermal Irritation (IV); Skin Sensitization (Negative)
Subchronic Toxicity NOAEL (mg/kg/day)	28 day (dog): 92/314 (M/F) 90 day (mouse, rat, dog): 1110/398 (M/F), 58/70 (M/F), 221 (M/F) Primary results: lymphocytolysis in the thymus, kidney, and urinary tract. The urinary tract was the common target
Evidence of Hormone Perturbation	Offspring: pup body weight decrease Maternal: organ weight changes in spleen and urinary tract Reproductive: reduced rearing index Effects are unlikely to be due to a hormone-disruption mechanism
Evidence of Immune Suppression	No evidence of treatment-related immunotoxicity
Genetic Toxicity	Non-genotoxic
ADME	Rapidly absorbed and then rapidly excreted, primarily unchanged, and predominantly in the urine
Read-Across	One sulfonamide antimicrobial, sulfanilamide chemical class used for read-across based on structural similarity. Chemical showed similar toxicity via urinary calculi formation
Special Studies	No indication of induction of AhR, CAR, PXR, or PPARα nuclear receptors. PBPK model to determine the dietary chronic exposure level in humans that could lead to urinary concentrations. Negligible concern for tumor formation.
Proposed Risk Estimate	• 58 mg/kg/day = NOAEL from 90-day rat study • 1000X UF = total uncertainty factor (10X inter-species, 10X intra-species, 10X subchronic to chronic) • cPAD = 0.058 mg/kg/day • % cPAD = 0.4% (calculated with most sensitive exposure estimate) • 0.4% is below EPA level of concern
Conclusions	Both the rat and the mouse carcinogenicity studies should be waived. A health-protective chronic risk assessment endpoint can be derived based on the subchronic point of departure. PBPK modeling confirms that human risk is negligible at and below this dietary concentration.

CONCLUSIONS & NEXT STEPS

Conclusions

- Currently, there are no specific criteria to determine when not to require the Combined Chronic Toxicity/Carcinogenicity studies (OECD 453; 451) for pesticides based on toxicological and exposure data.
- The workgroup used an iterative approach, incorporating regulatory feedback to identify critical information to be considered in a WoE determination of the need for rodent cancer bioassays.
- Case study waiver rationales included existing information on human exposure, toxicity, metabolism, mode of action, and other critical components relevant to the protection of human health were developed to refine the proposed framework.

Next steps

- A publication of the ReCAAP framework is currently in preparation.
- Facilitate use of the ReCAAP framework to support waiver rationales for WoE assessment of chronic toxicity/carcinogenicity.
- Identify new approach methodologies (NAMs) that can be used in the WoE assessment.

Acknowledgments
The United States Environmental Protection Agency (EPA), Health Canada Pest Management Regulatory Agency (PMRA), Australian Pesticides and Veterinary Medicines Authority (APVMA), and the Brazilian Health Regulatory Agency (ANVISA) collaborated to provide critical feedback to identify information needs to be considered in waiver rationales to support a health protective risk assessment.