Rethinking Carcinogenicity Assessment for Agrochemicals

Gina M. Hilton[1], Gregory Akerman[2], James Baldassari[3], Michael Battalora[3], Roland Buesen[4], Amy J. Clippinger[1], Anna Lowit[2], Stephanie Melching-Kollmuss[4], Tzippi Kormos[5], Sabitha Papineni[6], Richard C. Peffer[7], Brandy W. Riffle[8], Natalia Ryan[9], Mitscheli Sanches da Rocha[8], Nicolo Visconti[5], Douglas C. Wolf[9]

[1]PETA International Science Consortium Ltd., [2]United States Environmental Protection Agency, [3]FMC Agricultural Solutions, [4]BASF SE, [5]Bayer CropScience LP, [6]Corteva Agriscience™, [7]Rich Peffer Toxicology Consulting, LLC, [8]BASF Corporation, [9]Syngenta Crop Protection, LLC

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 waivers to determine if sufficient information was available to perform a health protective chronic risk assessment without conducting rodent cancer bioassays.

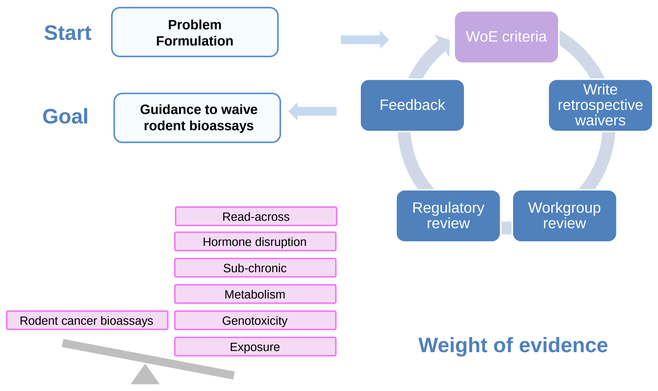
Information used in the WoE include exposure, mode-of-action, physiochemical properties, metabolism, and sub-chronic toxicological data from standard risk assessment endpoints.

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. The results of these analyses will be used to establish the criteria for when the mouse and/or rat cancer bioassay can be waived with sufficient confidence to protect public health.

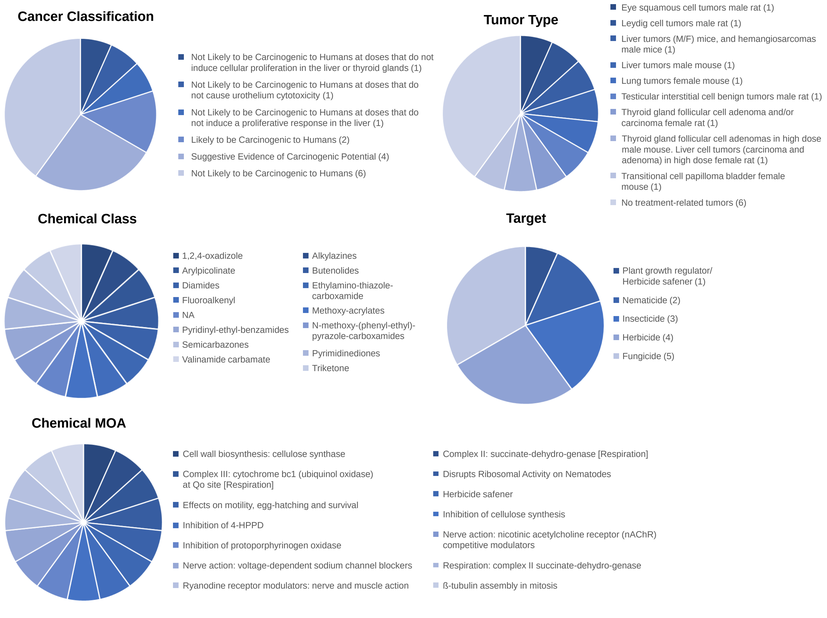
Problem Statement: There are no specific criteria to determine when not to require the Combined Chronic Toxicity/Carcinogenicity studies (OECD 453; 451) for pesticides based on toxicological and exposure data.

METHODS

PROJECT OVERVIEW



SAMPLE DISTRIBUTION (n = 15 chemicals)



WEIGHT OF EVIDENCE

I. Purpose of Analysis
II. Summary of Use Profile, Exposure, and Hazard Considerations
  a. Use and Exposure Profile
  b. Toxicity Profile
III. Detailed Study Waiver Request
  a. Physical-Chemical Properties
  b. Use Pattern and Exposure Scenarios
  c. Toxicity
    i. Acute Toxicity
    ii. Subchronic Toxicity
    iii. Evidence of Hormone Perturbation
    iv. Evidence of Immune Suppression
    v. Genetic Toxicity
    vi. ADME
    vii. Special Studies and Endpoints
  d. Literature Review
  e. Evidence of Chronic Toxicity from Related Chemicals
  f. Proposed Points of Departure, and Prospective Risk Assessment

Read-across information to be considered at each step of the WoE

Next steps in WoE:

- Blinded chemical weight of evidence (WoE) assessment using drafted framework
- Identify new approach methodologies (NAMs) that can be used to support the WoE assessment
- Develop a suggested read-across approach to be used in the WoE assessment
- Finalize information to be included in the WoE framework
- Publish workgroup reporting framework and waiver case studies

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.
- This project used a weight-of-evidence approach to demonstrate when rodent carcinogenicity tests can be waived while still generating the same conclusions and protection of human safety for food-use pesticides.
- Retrospective waivers include existing information on human exposure, toxicity, metabolism, mode of action, and other critical components relevant to the protection of human health.
- US EPA, Health Canada PMRA, and Australia APVMA are actively reviewing and providing feedback on retrospective waivers to inform what information is needed in a weight-of-evidence-based assessment to support a health protective risk assessment

Weight of Evidence	Chemical A	Chemical B	Chemical C
Intended Use / Chemical Class / MOA	Herbicide; pyrimidinedione; inhibit the plant enzyme protoporphyrinogen oxidase (PPO)	Fungicide; strobilurin; inhibit mitochondrial respiration at complex III	Herbicide safener; arylsulfonyl-benzamides; induce herbicide metabolizing enzymes
Physical-Chemical Properties	Molecular weight = 500.9 g/mol Vapor pressure = 4.5 x 10-15 Pa at 20ºC Log Kow = 2.6	Molecular weight = 365.32 Vapor pressure = 5.5 x 10-3 mPa at 20ºC Log Kow = 3.6	Molecular weight = 374.41 Vapor pressure = 6 x 10-9 Pa at 20ºC Log Kow = -0.80
Use Pattern & Exposure Scenarios	Uses: barley, wheat, grasses, olive trees and pomegranate trees, legumes, stone fruits, tree nuts, cereal grains, grapes, cotton, and sun flower Exposure: human dietary and drinking water	Uses: cereal grains, legumes, foliage, soybeans, canola, bulb onion, green onion, leafy vegetables; peas and beans, fruiting vegetables, tree nuts, sunflower, cottonseed, alfalfa, peanut, grass, fodder, and hay Exposure: human dietary and drinking water	Uses: corn, sorghum, turf, and ornamentals Exposure: human dietary
Acute Toxicity (EPA Category)	Oral (III); Dermal (III); Inhalation (IV); Eye (III); Dermal Irritation (IV); Skin Sensitization (Negative)	Oral (IV); Dermal (IV); Inhalation (II); Eye (III); Dermal Irritation (IV); Skin Sensitization (Negative)	Oral (III); Dermal (III); Inhalation (III); Eye (IV); Dermal Irritation (IV); Skin Sensitization (Negative)
Subchronic Toxicity NOAEL (mg/kg/day)	28 day (mouse, rat, dog): 12.8/63.4 (M/F); 13.4/43.6 (M/F); 30 (M/F) 90 day (mouse, rat, dog): 12.4/51.8 (M/F); 10.5/12.6 (M/F); 10 (M/F) Primary results: porphyria and anemia, plus secondary effects in the spleen, bone marrow and liver	90 day (mouse, rat, dog): 33.2/43.8 (M/F); 41.7/48.1 (M/F); 8.9/8.5 (M/F) Primary results: decreases in body weight and food consumption, and increased liver weights	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 effects: increased stillborn pups, decreased viability and lactation indices, decreased pre-weaning body weight, and change in hematological parameters Maternal effects: decreased food intake, body weight and changes in hematological parameters Effects are unlikely to be due to a hormone-disruption mechanism	Offspring: skeletal variations (highest dose); decreased body weight and body weight gains Maternal: decreased body weight and body weight gains Effects are unlikely to be due to a hormone-disruption mechanism	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	No evidence of treatment-related immunotoxicity	No evidence of treatment-related immunotoxicity
Genetic Toxicity	Non-genotoxic	Non-genotoxic	Non-genotoxic
ADME	Rapidly absorbed after oral dosing and is extensively metabolized, with no obvious alerts for bioaccumulation or toxic metabolites. Sex-dependent difference in excretion at the low-dose level resulted in males having up to 3X higher internal exposures than females	Rapidly absorbed after oral dosing and is extensively metabolized, with no obvious alerts for bioaccumulation or toxic metabolites	Rapidly absorbed and then rapidly excreted, primarily unchanged, and predominantly in the urine
Read-Across	6 PPO inhibiting herbicides used for read-across. Similar subchronic, developmental, reproduction, immunotoxicity, and genotoxicity results across all read-across chemicals.	8 strobilurin fungicides used for read-across. Similar subchronic, developmental, reproduction, immunotoxicity, and genotoxicity results across all read-across chemicals.	1 sulfonamide antimicrobial, sulfanilamide chemical class) used for read-across based on structural similarity. Chemical showed similar toxicity via urinary calculi formation
Special Studies	Mechanistic total porphyrin analysis in rat: statistically significant effects on porphyrin metabolism could be detected at exposure concentrations below those associated with adverse hematological effects.	No mechanistic 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 Chronic Population Adjusted Dose (cPAD) for Dietary Risk Assessment Based on Subchronic Point of Departure (POD)	• 10.5 mg/kg/day = NOAEL from 90-day rat study • 1000X UF = total uncertainty factor (10X inter-species, 10X intra-species, 10X extrapolation from subchronic to chronic) • cPAD = 0.0105 mg/kg/day • % cPAD = 87% (calculated with most sensitive exposure estimate) • 87% is below EPA level of concern	• 8.5 mg/kg/day = NOAEL from 90-day dog study • 100X UF = total uncertainty factor (10X inter-species, 10X intra-species) Note: additional 10X extrapolation from subchronic to chronic not applied for dog due to literature support that chronic studies do not generate significant differences in NOAEL between 3 month and 1yr studies. • cPAD = 0.085 mg/kg/day • % cPAD = 19% (calculated with most sensitive exposure estimate) • 19% is below EPA level of concern	• 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
Summary of Chronic Toxicity/Carcinogenicity from Read-Across Chemicals	• 4 read-across chemicals classified as 'Not likely to be carcinogenic to humans' • 2 chemicals classified as 'Likely to be carcinogenic to humans'. One chemical based on liver adenomas and carcinomas in mice and rats, and the other based liver adenomas and carcinomas in male mice and pancreatic adenomas in male rats.	• 7 read-across chemicals classified as 'Not likely to be carcinogenic to humans' • 1 read-across chemical classified as 'Likely to be carcinogenic to humans' based on combined hepatocellular and biliary carcinomas in female rats at a high dose (no liver effects noted in 90-day study)	• 1 read-across chemical – not classified by rodent cancer bioassays • The calculi-based mode of action is characterized by the toxic, proliferative, and tumorigenic effects only occur in the presence of calculi (under high dose conditions) • Read-across showed similar toxicity via urinary calculi formation. No additional concern for chronic or carcinogenic toxicity
Proposed Waiver Assessment	Both the rat and the mouse carcinogenicity studies should be waived. Subchronic toxicology data is in line with non-tumorigenic read-across chemicals, indicating porphyria and anemia. Read-across chemicals that do produce tumors have more severe subchronic effects, that support a plausible MOA. A conservative, health-protective chronic risk assessment endpoint can be derived based on the subchronic point of departure.	Both the rat and the mouse carcinogenicity studies should be waived. For most read-across chemicals, chronic effects were predicted by subchronic study histopathological findings. The subchronic NOAEL for this chemical was based on body weight changes, so there was no indication that tumors would develop in a chronic study. A conservative, health-protective chronic risk assessment endpoint can be derived based on the subchronic point of departure.	Both the rat and the mouse carcinogenicity studies should be waived. Subchronic and ADME studies, combined with read-across information, provide strong support for a defined, threshold-based mode of action for tumor formation. A conservative, 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.