Better Ways Than the Bioassay: Weight-of-Evidence Approach to Assess Carcinogenicity Potential of Food Use Pesticides

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INTRODUCTION

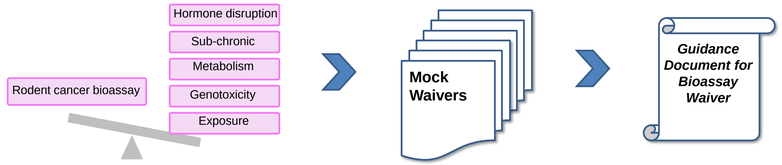
ABSTRACT

Numerous reviews of the rodent cancer bioassay over the past 40 years have raised questions about its relevance and regulatory need to assess risk to human health. As a result, a working group formed the **R**ethinking **C**arcinogenicity **A**ssessment for **A**grochemicals **P**roject (**ReCAAP**) to evaluate the appropriateness of waiving rodent bioassays for the registration of food-use pesticides.

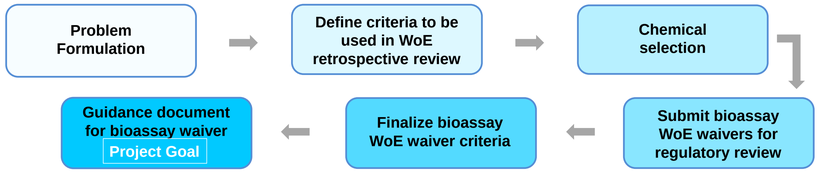
Existing data from pesticides representing different classes of chemistry were reviewed using a weight-of-evidence approach (WOE), and included available information on pesticide mode of action, indication for use, metabolic profile, toxicokinetics, genetic toxicology, histopathology from dose-response studies, tumor formation, hormonal perturbation, immune response, read-across, exposure, use, and other endpoints used in risk assessment.

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.

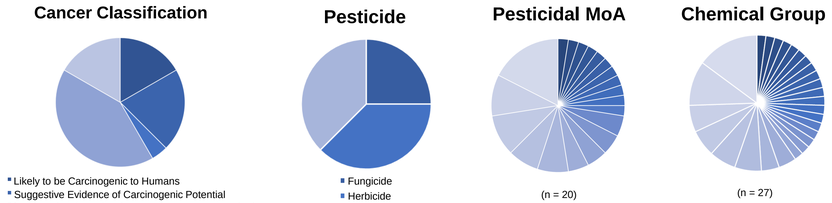
PROJECT OVERVIEW



METHODS



SAMPLE DISTRIBUTION (n = 48 chemicals)



RESULTS

WEIGHT OF EVIDENCE SUMMARIES

Waiver 1

Chemical group: Pyrazole-carboxamide
Pesticidal MoA: Succinate dehydrogenase inhibitor
Exposure: Below level of concern
ADME (oral): Dose-dependent absorption, widely distributed, extensively metabolized, rapidly eliminated
Genotoxicity: Non-genotoxic
Subchronic target organs: Liver and thyroid
Hormone Perturbation: No concern
Immunotox: No concern
Read across: 18 fungicides with same MoA, 9 are well-studied chemicals. Of these, the target organ effects are matching with other SDHIs
Tumor MoA: Rat thyroid follicular cell tumors, would be secondary to UDPGT induction, a MoA that is non-relevant to humans

- **WoE conclusion:** Sufficient data available to extrapolate long-term effects
- **Waive:** Suggested waiver for rat and mouse cancer bioassay

Existing bioassay conclusion: "Not likely to be carcinogenic to humans" at doses that do not induce a proliferative response in the liver

Waiver 2

Chemical group: Valinamide carbamates
Pesticidal MoA: Inhibition of cellulose synthesis
Exposure: Below level of concern
ADME (oral): Rapidly absorbed, widely distributed, extensively metabolized, rapidly eliminated
Genotoxicity: Non-genotoxic
Subchronic target organs: Liver and thyroid
Hormone Perturbation: Limited evidence
Immunotox: 90-d dog: lymphatic edema and atrophy of femoral and sternum bone marrow
Read across: 3 fungicides with same MoA, 2 had similar tumor formation and the same target organ effects, the other had limited data
Tumor MoA: Insufficient information for rat thyroid-pituitary homeostasis, and liver foci test. No significant tumor formation in mice

- **WoE conclusion:** Insufficient data to extrapolate long-term effects
- **Waive:** Suggested waiver for mouse. Data needed to understand tumor formation in rat

Existing bioassay conclusion: "Likely to be carcinogenic to humans" based on female rat thyroid gland follicular cell adenoma / carcinoma combined tumor rates

Waiver 3

Chemical group: Sulfonamide (similar)
Pesticidal MoA: Herbicide safener - induces metabolizing enzymes to increase rate of herbicide metabolism
Exposure: Below level of concern
ADME (oral): Rapidly absorbed and rapidly excreted mostly in urine, primarily unchanged
Genotoxicity: Non-genotoxic
Subchronic target organs: Urinary tract
Hormone Perturbation: No concern
Immunotox: No concern
Read across: No additional concerns for chronic effects or tumor formation
Tumor MoA: Tumors associated with proliferation and formation of urinary tract crystals/calculi (typically high-dose)

- **WoE conclusion:** Sufficient data available to extrapolate long-term effects
- **Waive:** Suggested waiver for rat and mouse cancer bioassay

Existing bioassay conclusion: "Not likely to be carcinogenic to humans" at doses that do not cause urothelium cytotoxicity

Waiver 4

Chemical group: Benzamide
Pesticidal MoA: Inhibition of cell division
Exposure: Below level of concern
ADME (oral): Rapidly absorbed (88%) and metabolized extensively. No TK data available
Genotoxicity: No concern
Subchronic target organs: Liver, thyroid and testes
Hormone Perturbation: Liver mediated clearance of thyroid and steroid hormones - not relevant to humans
Immunotox: No concern
Read across: Not conducted, as no similar chemicals identified
Tumor MoA: CAR & PPARalpha induced liver tumors; liver UGT mediated thyroid tumors; enhanced liver induced testosterone clearance as MoA for leydig cell tumors

- **WoE conclusion:** Sufficient data available to extrapolate long-term effects
- **Waive:** Suggested waiver for rat and mouse cancer bioassay

Existing bioassay conclusion: "Not likely to be carcinogenic to humans" at doses that do not result in induction of hepatic cell proliferation or metabolic enzymes leading to disruption of thyroid or gonadal endocrine axes.

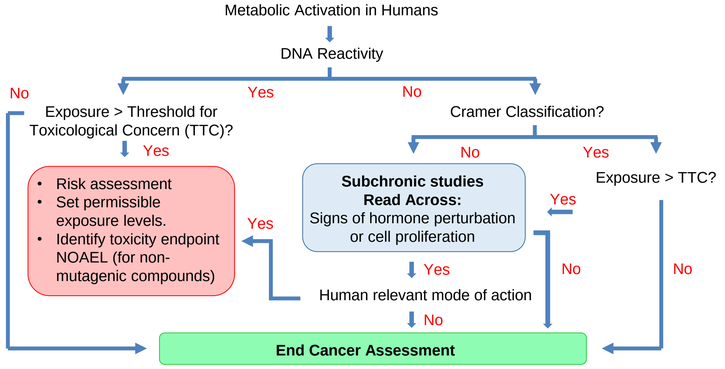
Waiver 5

Chemical group: Semicarbazone
Pesticidal MoA: Sodium-channel inhibitor
Exposure: Below level of concern
ADME (oral): Low oral absorption; limited metabolization, accumulation in fat (steady-state is reached after 3 weeks)
Genotoxicity: No concern
Subchronic target organs: Body weight (gain), liver, spleen, red blood cells, thymus/lymph nodes
Hormone Perturbation: No evidence from limited in vitro and robust in vivo studies
Immunotox: Not immunotoxic determined in rat in vivo studies
Read across: Not conducted, as no similar chemicals identified
Tumor MoA: No tumors

- **WoE conclusion:** Sufficient data available to extrapolate long-term effects
- **Waive:** Suggested waiver for rat and mouse cancer bioassay

Existing bioassay conclusion: "Not likely to be carcinogenic to humans." Negative in long-term and carcinogenicity studies in rats and mice.

POTENTIAL WOE DECISION TREE



CONCLUSIONS

- The rodent cancer bioassay is being conducted for pesticides where it is not always needed to adequately address carcinogenicity to humans.
- This project uses a weight-of-evidence approach to demonstrate when rodent bioassays can be waived while still generating the same conclusions and protection of human safety for food-use pesticides.
- Mock waivers include existing information on human exposure, toxicity, metabolism, mode of action, and other critical components relevant to the protection of human health.
- The waivers can be used by the EPA to help inform a guidance document for waiving the rodent cancer bioassay for food-use pesticides.

Decision tree adopted and modified from:
Samuel M. Cohen, et al., Current Opinion in Toxicology, 3: 6-11, 2017
Samuel M. Cohen, et al., Regulatory Toxicology and Pharmacology, 103: 100 – 105, 2019

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