Assessing Human Carcinogenicity Risk Without the Rodent Cancer Bioassay

Abstract #2752

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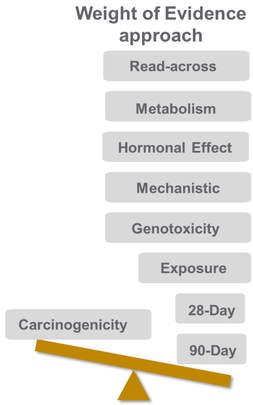
Introduction

- Rodent cancer bioassays are required by regulatory authorities for the carcinogenicity assessment of agrochemicals, pharmaceuticals, industrial chemicals, food additives, and environmental pollutants.
- Over the past 50 years, a lot has been learned about cancer biology; the approach to testing carcinogenic potential in humans has not kept up.
- The cancer bioassay is being conducted for pesticides where it is not always needed to adequately address carcinogenicity to humans.

Objectives



- Develop a framework to determine when the rat and/or mouse cancer bioassays can be waived via a weight of evidence-based approach for food-use agrochemicals.
- Ensure sufficient information to support registration decisions that are protective of public health and the environment while avoiding the generation of data that does not influence the scientific certainty of a regulatory decision.
- Develop an approach to inform the chronic risk assessment without the requirement of a chronic or carcinogenicity study point of departure (POD).

Draft Carcinogenicity Waiver Reporting Framework

- The WoE assessment include use pattern, exposure scenario, mode-of-action (MoA), physiochemical properties, metabolism and toxicokinetics, and sub-chronic toxicological data from standard risk assessment endpoints.
- Evidence of Chronic Toxicity from Related Chemicals.
- Proposed Points of Departure and Prospective Risk Assessments.

Results

Case Studies

SDHI fungicide; nematicide, blocks cellular respiration

ACCase insecticide; disrupts fatty acid biosynthesis

Isoxazoline insecticide; GABA-gated chloride channel allosteric modulator

Read Across Chemicals

- Larger chemical base for read across
- 23 chemicals in the FRAC Group
- 13 chemicals registered by the US EPA
- 13 chemicals considered in read across.

- Moderate chemical base for read across
- 25 chemicals in the IRAC Group
- 20 chemicals registered by the US EPA
- based on structural similarity [Tanimoto] 3 chemicals considered in read across.

- Small chemical base for read across
- 2 chemicals in the IRAC Group
- 0 chemicals registered by the US EPA
- Incorporated veterinary medicines
- 6 chemicals considered in read across.

R&D Findings

Key targets of toxicity were the liver and thyroid.
MoA evidence supported mechanistic understanding.
Passed MOE based risk assessment.

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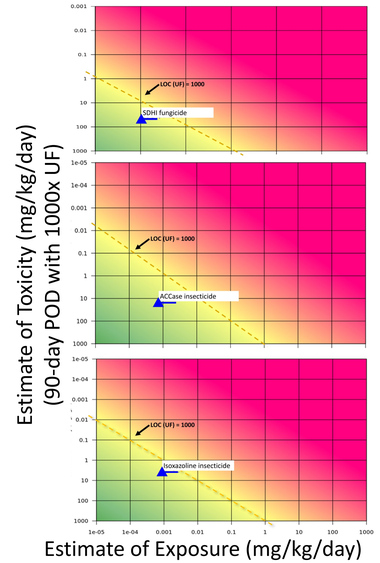
Key targets of toxicity included several tissues and organs; peroxisome proliferation in female mice.
Evidence supported changes in liver were secondary consequence to altered lipid metabolism.
Passed MOE based risk assessment.

Risk Plots



The yellow dotted line represents the MOE between the anticipated chronic NOAEL assuming a 1000X UF and Syngenta's modeled exposure values (in mg/kg/day). The blue pyramid marker and horizontal blue line ▲— represents the range of exposures for all U.S. population subgroups for total food and drinking water exposures resulting from all proposed used in the U.S. for each compound above.

Conclusions

- A weight of evidence (WoE) framework outlining the assessment of available information enabled the construction of waivers as case-studies to determine the sufficiency of available data and application of criteria for waiving rodent cancer bioassays for the registration of food-use agrochemicals.
- Read across, exposure-based margins of exposure and alternative modes of action further support this use of a WoE approach.
- The use of a structured framework to determine if sufficient information is available to perform a health protective chronic risk assessment without conducting rodent cancer bioassays showed that the cancer bioassay may not be needed to address carcinogenicity risk and protect human health.

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