IS THE EXTRAPOLATION OF MAMMALIAN MDRs TO BIRDS SCIENTIFICALLY JUSTIFIED?

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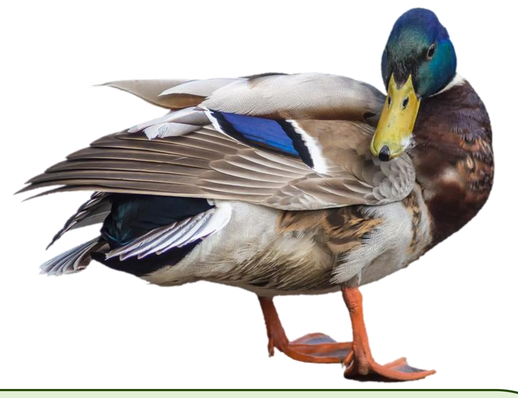
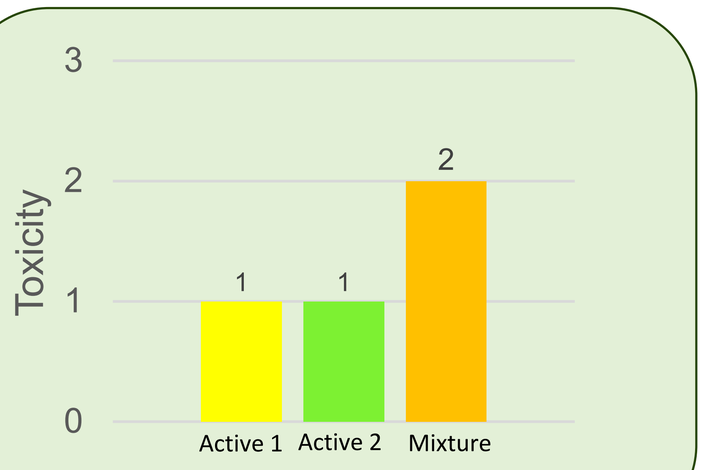


Mixture Toxicity

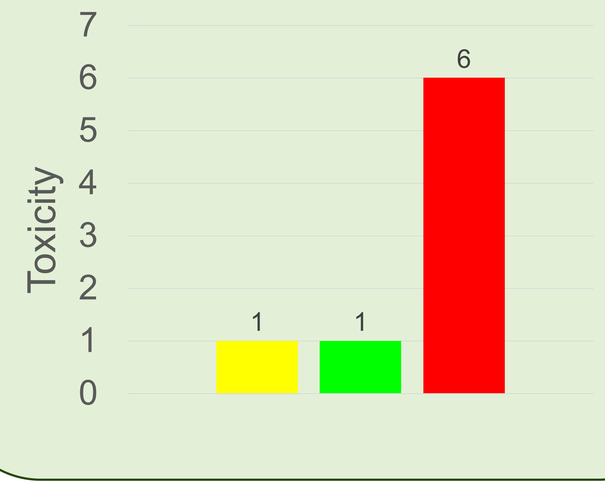


Dose Addition (DA): Mixture toxicity predicted based on additivity of toxicity of single actives[1]

1 + 1 = 2

Deviation from theory of dose addition toxicity can be quantified as **Model Deviation Ratio (MDR)**!

1 + 1 = 6



Effects in mixtures deviate from dose addition of toxicity of single active substance
→Over-Additivity of effects
→*EFSA GD 'Possible synergistic interaction assumed'*

Background

- EFSA (2023)[2] → mixture toxicity assessment using DA for plant protection products (PPPs)
- Where formulation data available, MDRs used to assess departures from additivity.
- MDR > 3 → potential synergistic effects requiring additional safety factor → potential impact on mixture RA.
- Bird formulation studies rarely available, leading to proposed extrapolation from mammals

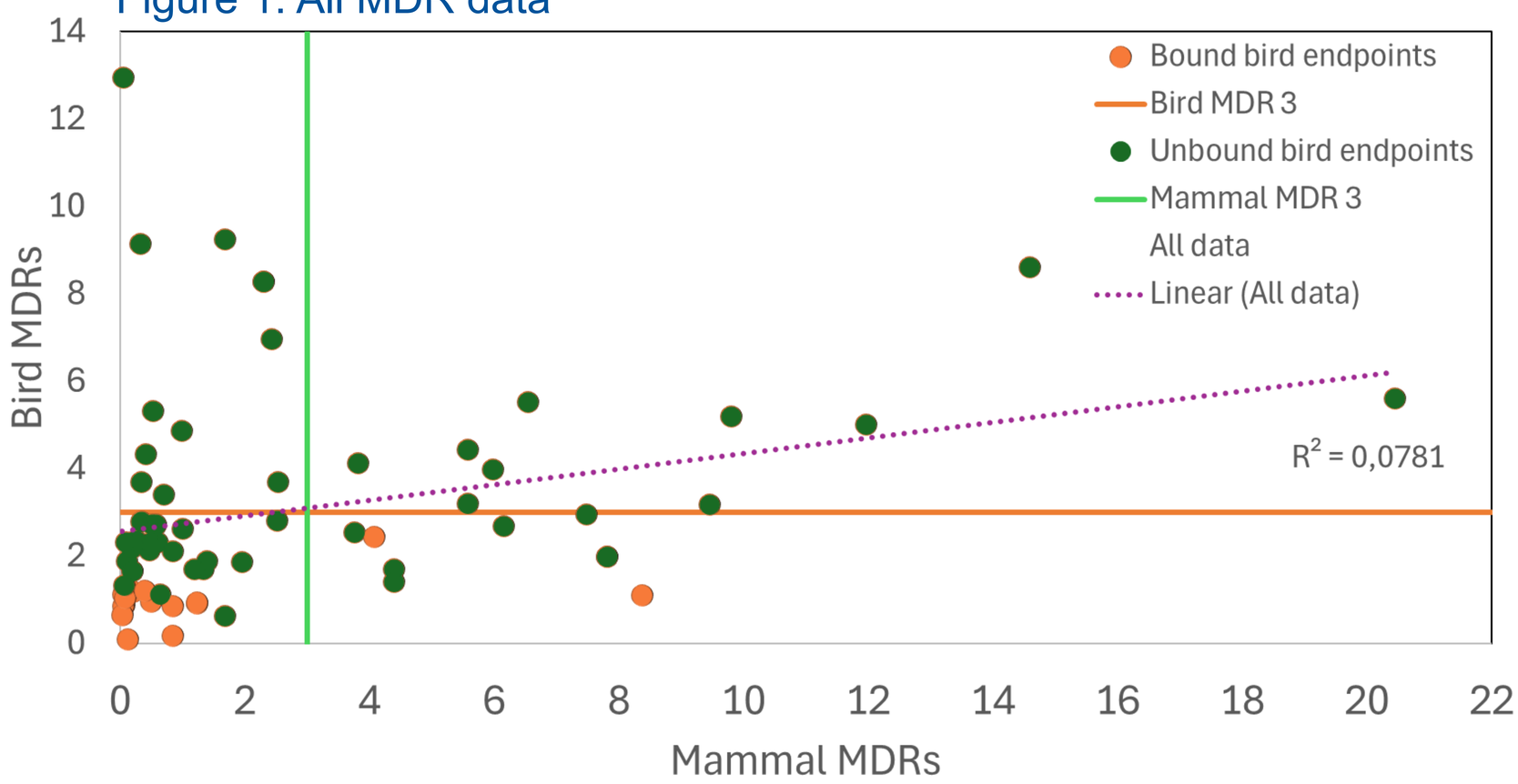
Objectives

- Evaluate whether extrapolating mammalian MDRs to birds is scientifically justified
- Identify drivers of differences in mixture toxicity between birds and mammals

Methods

- Analysis of acute toxicity data - derive MDRs for 84 PPPs (Figure 1)
- Evaluation of study design, physiology, and toxic units (TUs)
- Comparison of bird and mammal datasets by formulation type, pesticide class, and mode of action (MOA)

Figure 1. All MDR data



Results

- No correlation between MDRs for birds and mammals (Figure 1)
- All bird MDRs > 3 driven by unbound limit test endpoints (LD_{50} > 2000 mg/kg/bw/d)
- Definite dose–response endpoints consistently produced MDRs < 3
- Most mammalian MDRs > 3 originated from studies based on OECD TG 423[3] with 300 < LD_{50} < 2000 mg/kg bw/d driven by higher toxicity of single actives
- No consistent trends by formulation type, pesticide, MOA

Summary and Conclusion

– Differences between mammals and birds are driven by unbound endpoints
– Reliable extrapolation from mammals to birds is not supported by the obtained data
– Current OECD TG are not appropriate to derive a robust MDR value
– Differences in animal physiology and/or bioavailability of the active ingredient might result in taxon-specific toxicity profiles
→ **High Model Deviation Ratios (MDRs) do not represent scientifically justified potential synergistic effects**

→**Regulatory takeaway:** Routine extrapolation of mammalian MDRs to birds may overestimate the risk of mixture toxicity and might lead final misinterpretation mixture toxicity.

References:
1 Canadian Centre for Occupational Health and Safety CCOHS (2019). Chemicals and Materials. Synergism and related terms. Fact sheet last revised: 2019-01-23. Fact sheet confirmed current: 2024-11-07. www.ccohs.ca/oshanswers/chemicals/synergism.pdf.
2 EFSA (2023). Risk assessment for birds and mammals. EFSA Journal, 21(2):7790.
3 OECD (2002). Test No. 423: Acute Oral Toxicity – Acute Toxic Class Method. OECD Guidelines for the Testing of Chemicals.

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