

Understanding Context of Use: Case Studies Mammalian Median Lethal Dose (LD₅₀) in Ecological Assessment at U.S. Environmental Protection Agency

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Background: Ecological Risk Assessment

- EPA's Office of Pesticide Programs (OPP) registers conventional pesticides
- The Environmental Fate and Effects Division (EFED) conducts the needed ecological risk assessments
- Registrants submit required data, as specified in the Code of Federal Regulations (40 CFR 158), to assess risk to non-target animals and plants
- Rat *in vivo* acute oral toxicity LD₅₀ data are used as a surrogate to assess risk to all mammalian wildlife
- The data are used for risk estimation (comparison of hazard and exposure) and precautionary and compulsory label statements to minimize the potential harm to non-target organisms

Mammalian Risk Assessment (1)

- OPP uses the T-REX model to assess Acute risk as a function of acute oral toxicity and dietary dose (both mg/kg-bw)
- “Kenaga Nomogram,” based on empirical residue studies of foraging items, converts application rate (lb/acre) to mg/kg-bw dose
- Foraging items are categorized as short grass, tall grass, broadleaf plants, fruits/pods, arthropods, seeds

Mammalian Risk Assessment (2)

- Risk is estimated for 3 size classes of mammals (15g, 35g, 1000g)
- T-REX adjusts dose for body weight and ingestion rate
- Risk quotient (RQ) is dietary dose/LD₅₀
- Acute non-listed mammal level of concern (LOC) is RQ = 0.5
- At 1 lb/acre, exposure doses range from 0.51 mg/kg-bw (1000-g mammal eating seeds) to 229 mg/kg-bw (15-g mammal eating short grass)

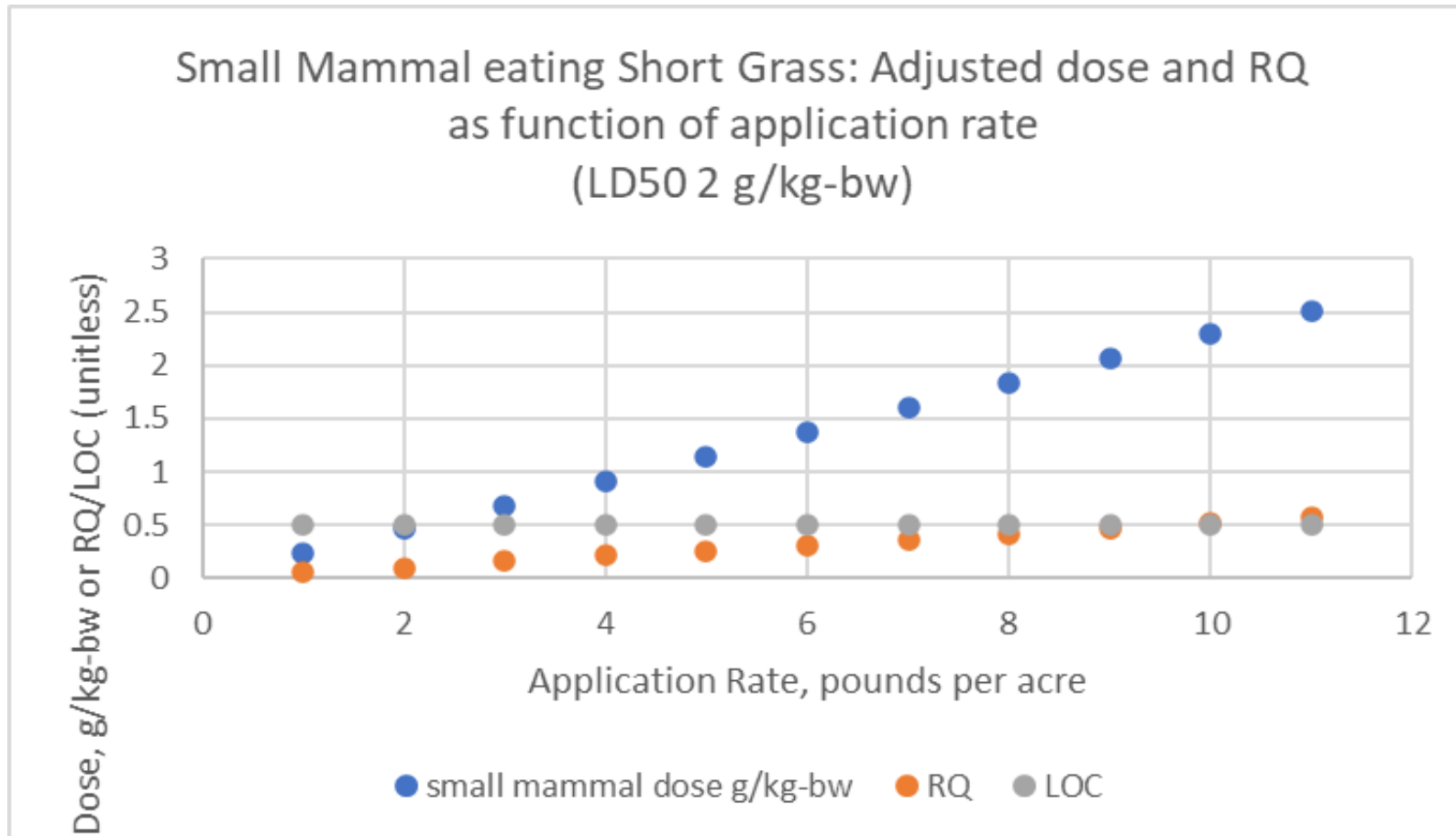
CATMoS (Collaborative Acute Toxicity Modeling Suite)

- Product of a 2018 ICCVAM workshop (32 international groups)
- *In silico* method that predicts rat acute oral LD₅₀ based on chemical structure
- Predictions include upper and lower CL determined from a variability analysis quantifying the uncertainty accompanying the experimental LD₅₀ values.
- We compared CATMoS results to OPP empirical data from *in-vivo* studies for 178 active ingredients
- Generally, CATMoS predictions of >2000 mg/kg-bw were reliable

Use of >2000 mg/kg-bw Prediction in Mammal Assessment

- 2000 mg/kg-bw is a common limit dose for pesticides expected to be non-toxic
- A threshold application rate (lb/acre) could be determined, assuming $LD_{50} = 2000$, below which all size classes and diets have RQs below Level of Concern, 0.5
- For the highest body-weight adjusted dose (small mammal eating short grass) this single application rate is about 10 lb/acre

Analysis of 2000 mg/kg-bw LD₅₀ versus Highest-Dose Scenario



Conclusions

- CATMoS predictions of LD₅₀ are reliable above 2000 mg/kg-bw
- For highest dose T-REX scenario (small mammal eating short grass), use of a >2000 mg/kg-bw CATMoS estimate would result in “low risk” for application rates below about 10 pounds per acre
- The results support potentially relying on CATMoS predictions *in lieu* of *in vivo* testing in some cases depending on considerations such as the LD₅₀ prediction and the proposed application rate