CropLife EUROPE

Next Generation Risk Assessment

Proposal on Toxicology Data Requirements for Biological Plant Protection Products, Plant Extracts as an Example

06 March 2024, Christian Strupp

Starting Points

Biopesticides

- Regulated by Reg. 1107/2009 (i.e.: risk assessment and hazard-based classification)
  - Example: plant extracts
- *In Dubio pro Reo*: assumption is that natural origin is not toxic *per se*
- Next Generation Risk Assessment: „what do I need to know“ (and what is „nice to know“, but not compatible with vertebrate protection)
- Endorsing the IBMA Decision Tree and getting concrete on the „how“ when endpoints need to be assessed

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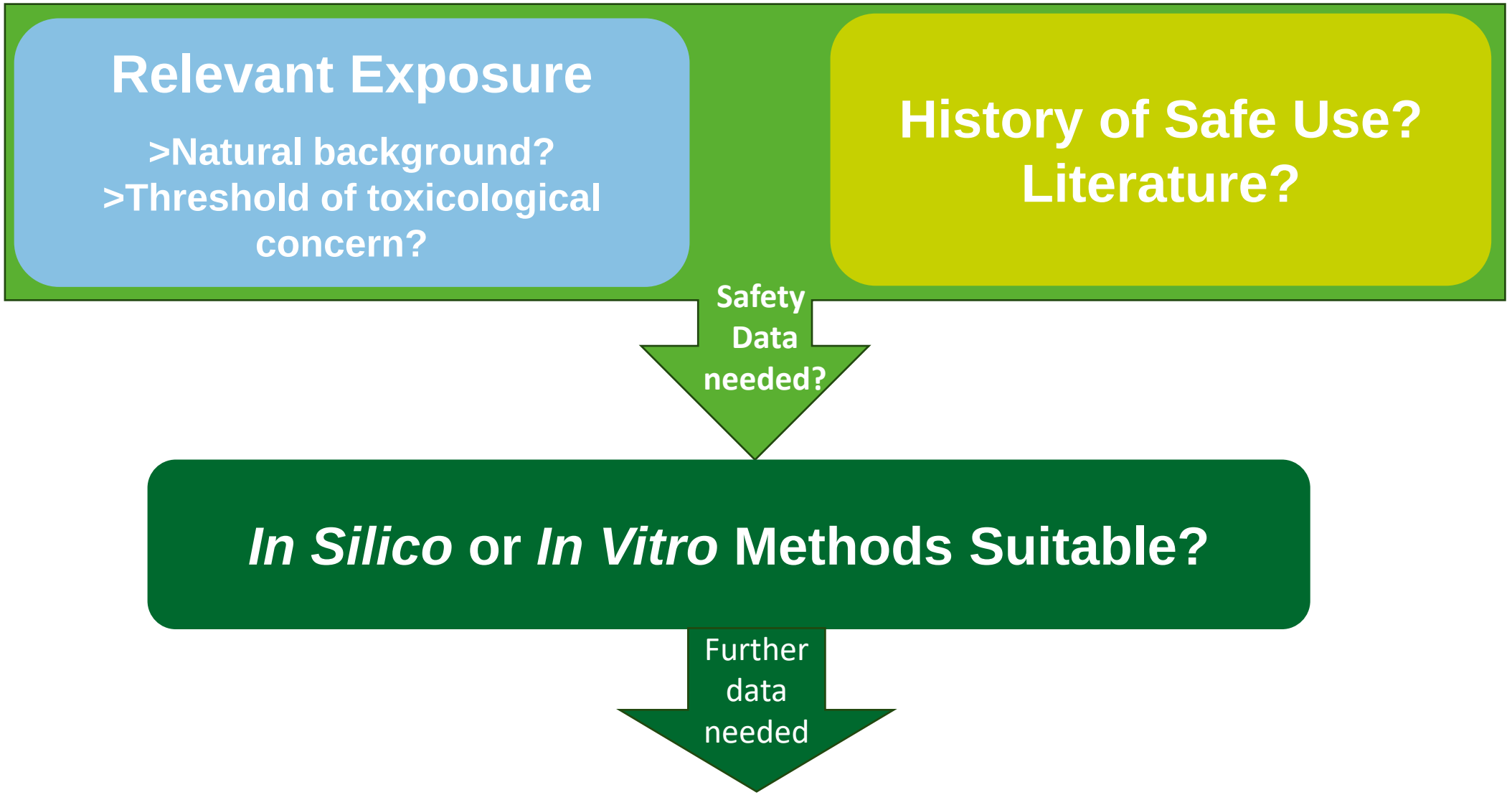
Step 1: Inital Assessment



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Acute Toxicity

Note: this is for the „technical material“ – end-use product may need a classification enabling package

Traditional Requirements	Proposed	Reason
Acute Oral in Rodent	-	Has no effects on registrability; repeated dose data can be used to judge if „very toxic, toxic, harmful…“
Acute Dermal in Rodents		
Acute Inhalation in Rodents		
Skin Irritation	Only calculation method (information on known ingredients)	Has no effects on registrability – recommend safety goggles
Eye Irritation		
Skin Sensitization	1. Accept classification 2. Calculation method or *in vitro* **3. LLNA**	Only property that is reported from the field. LLNA enables quantitative risk assessment.
Phototoxicity	***In Vitro* if triggered** (same trigger as conventional PPPs)	Possible for plant-derived products, validated *in vitro* method

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Repeated Dose Toxicity

Traditional Requirements	Proposed	Reason
Subchronic Rodent	**Repeated Dose study** (for example, „smart“ repeated dose with omics, or traditional OECD 408 or combined with repro OECD 421/422) **Flexibility needed to allow to generate the best data for the substance in question**	Identification of toxicological potential: • By activated pathways (omics) • Target organ and adversity (standard study) – enabling risk assessment
Subchronic Non-Rodent	-	Not justified for BioPPPs (HESI and NC3Rs projects, EFSA assessment)

Note: if step 1 results in a case of safe use with no triggers, no studies may be needed

Note: no RfDs if NOAEL >1000 mg/kg bw/d.

Note: As long as regulated under Reg. 1107/2009, reference doses should be derived with a safety factor of 100 (legal minimum). This is not science, but arbitrary.
No additional uncertainty factor are recommended for BioPPPs („*in dubio pro reo*“), and it is proposed to introduce the possibility to reduce <100 if toxicokinetic or – dynamic data allow.

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Modes of Action of Potential Concern: Carcinogenicity

Traditional Requirements	Proposed	Reason
Bacterial Gene mutation	1. QSAR (if applicable) **2. Ames**	„Need to know“ - potential mode of action. Follow up *In Vivo,* if positive.
Mammalian cell gene mutation	-	
Mammalian cell clastogenicity/aneugenicity	1. QSAR (if applicable) **2. Micronucleus *in vitro***	„Need to know“ – potential potent mode of action. Follow up *In Vivo,* if positive.
„At least one *in vivo* study“	-	Only if triggered – may be added to repeated dose work
Carcinogenicity in rats Carcinogenicity in mice	1. Is there chonic exposure? >TTC? 2. Triggers (ToxCast, literature, pesticidal mode of action relevant for humans)? 3. Only consider data generation when (a) indications of genotoxicity, or (b) true proliferative lesions at human relevant exposures or doses driving the NOAEL	Predictive power poor; mechanistic approach superior

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Modes of Action: Reproductive Toxicity

Traditional Requirements	Proposed	Reason
Rat Developmental toxicity	1. Exposure during pregnancy? >TTC? Pesticidal mode of action relevant for humans? Literature? **2. Rat developmental toxicity**	No reliable *in vitro* model yet
Rabbit developmental toxicity	-	
Rat multigeneration	Only if repeated dose work indicates effects on reproductive organs at human relevant exposures or driving the NOAEL	Only if truly „need to know“

Others

Traditional Requirements	Proposed	Reason
Endocrine/Neurotoxicity	1. Assess available data (key: repeated dose or smart omics study, rat developmental toxicity) 2. Further data generation only if effects on endocrine or nervous system driving the NOAEL	No adversity – no „need to know“

In Conclusion

Check what is known: history of use? relevant exposure?

„*In Dubio Pro Reo*“ for BioPPPs - No to low exposure = no to low risk

Start with key work to assess toxicological potency

Follow up „where the data leads you“ – „need to know“

→ needed: committal dialogue between regulators and data generators ahead and during data generation (interactive registration process) – divergence of view can only be addressed when data still can be generated (regulatory process)

→ Priority to address highly potent modes of action that may affect the reference doses for risk assessment (genotoxicity, developmental toxicity)

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Thank You

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