

Chances and Challenges in Regulatory Ecotoxicological Mixture Toxicity Assessment for Plant Protection Products

Meet us at booth 55

Judith Neuwoehner, Katharina Benz, Stefanie Grund, Michael Faupel, Felix von Blanckenhagen, Johannes Lückmann

RIFCON GmbH, Goldbeckstr.13, 69493 Hirschberg, Germany, judith.neuwoehner@rifcon.de

Where do we start? The current state of the art....

Regulation (EC) No 1107/2009



- Art. 4: Plant Protection Products (PPPs) ... 'shall have no immediate or delayed harmful effect on human health ... taking into account known and expected cumulative and synergistic effects'
- Art. 29: ... 'interaction between the active substance, safeners, synergists and co-formulants shall be taken into account in the evaluation of PPPs'

Regulation (EC) No 284/2013

... 'any information on potentially unacceptable effects of the PPP on the environment ... shall be included as well as known and expected cumulative and synergistic effects'

established 'one-chemical-at-a-time' risk assessment

attempt to address environmentally relevant mixtures of chemicals

- from PPPs containing more than one active substance
- from sequential or simultaneous use of different PPPs



Implementation of mixture toxicity approaches in

- EFSA Guidance Documents and EFSA Scientific Opinions
- Zonal- and Country-specific Guidance
- EFSA plans a Draft Guidance on Mixture Toxicity for 2018



EFSA Guidance Document on ...

Birds & Mammals ^a



Aquatic Organisms ^b



Bees ^c



SIMILARITIES

- Mixture = PPP with more than one a.s.
- Concentration-addition (CA) - based approach
- First step: Is PPP more toxic than predicted mixture toxicity?
→ Whatever the lower endpoint is should be used in Risk Assessment (RA)

DIFFERENCES

- Mixture toxicity to be addressed in regular RA
- Acute RA: use LD₅₀ (mortality) regardless what species for they were determined
- Reproductive RA: express all a.s. with same mode of action in terms of most toxic a.s. on a molar basis → RA for the group applying the corresponding NOEC for the most toxic a.s.
- NOEC/NOAELs **not** to be used as they represent varying risk/response levels and are dependent on dose spacing

- Mixture toxicity to be addressed in regular RA
- Calculate Model Deviation Ratio (MDR) to account for synergistic/antagonistic effects
- Calculate RQ_{mix} = Sum (PEC/RAC) for higher tier RA
- NOECs can be used as they are seen pragmatically as „low effect concentration“ and not as „no effect concentration“

- Not clearly stated if mixture toxicity has to be addressed in regular RA
- NOECs can be used

EFSA Scientific Opinion on...

Non-target Arthropods ^d



In-soil Organisms ^e



Non-target terrestrial Plants ^f



- CA - based approach is recommended
- for details reference is made to EFSA Opinion on Bees (and NTAs or NTTs) and EFSA GD on Aquatic Organisms

Non-target terrestrial plants:

- Recommended as additional information, mainly for tankmixes of herbicides
- HC₅ or ER_x of the most sensitive species can be taken as a proxy for the ER_x „plants“
- May be used if different off-field deposits (e.g. due to one volatile a.s.) are expected

Zonal- / Country-specific methodologies

NORTHERN ZONE

- if no measured PPP data available for acute and long-term toxicity
- preferably CA, for details reference is made to EFSA GD on B&M and Aquatic Organisms

CENTRAL ZONE



DE^h:

- nothing mandatory, but in UBA text 92/2013 comprehensive review of current state of the art in regulatory mixture toxicity is given



NLⁱ:

- Mandatory for PPP with > 1 a.s. and tankmixes if no measured data are available
- European/zonal approaches overrule NL-approach
- CA-based approach



UK^{j,k}:

- Mandatory for PPP with more than one a.s. if no measured formulation data are available
- For Aquatics: usually only for chronic data necessary as measured acute data with PPP available - approach depends on exposure scenario (entry via drift or drainflow)
- For B&M: acute mixture risk to be assessed with Finney formula (CA), long-term risk according to EFSA (2009)
- Is toxicity of PPP driven by one a.s.?
- For B&M long-term Tier I, a combitox assessment via CA is proposed for future ^l

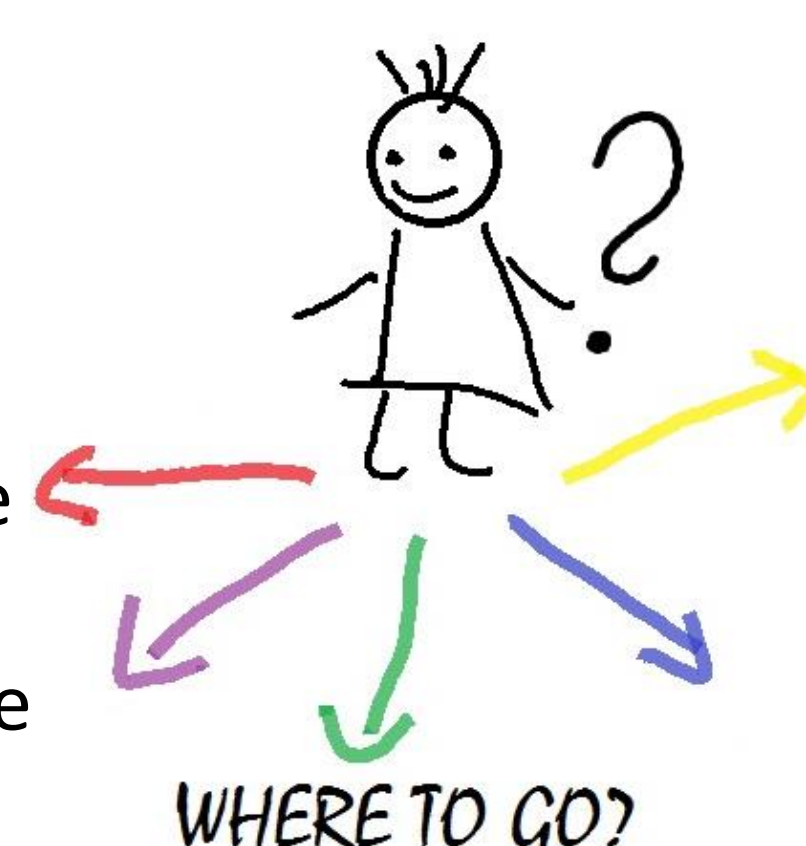
SOUTHERN ZONE



FR^m: calculate mixture toxicity by the Finney formula (CA)

Challenges

- Every section / country recommends CA-based approach, but always slightly adapted → Harmonization? Need for consistent terminology!
- Often not strictly the same toxicological endpoints are used
- Accept NOECs/NOELs as model input parameters as pragmatic approach?
- Can higher tier studies with mono-formulations/one a.s. be used in a refinement?
- How to consider exposure? Complex (PPP with one stable and one unstable a.s., use of time-weighted-average, different exposure/entry routes, multiple applications...)
- Assess mixture toxicity only if exposure is relevant? (e.g. if a.s.1 and a.s.2 biodegrade rapidly, then mixture toxicity assessment not necessary?)
- How to address sequential / simultaneous use of PPPs?



Chances

- every section / country recommends CA – based approach
- Pragmatic assumptions were made (endpoints for same biological effect in the same species under identical test conditions as input data not always necessary, use of NOECs partly allowed)
- Implementation of mixture toxicity assessments so far possible without the need for additional testing

^a Guidance Document on Risk Assessment for Birds & Mammals on request from EFSA. EFSA Journal 2009; 7(12):1438

^b Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013; 11(7):3290

^c EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees) (published on July 04, 2013, updated on 04 July 2014). EFSA Journal 11(7): 3295.

^d Scientific Opinion addressing the state of the science on risk assessment of plant protection products for non-target arthropods. EFSA Journal 2015; 13(2):3996

^e Scientific Opinion addressing the state of the science on risk assessment of plant protection products for in-soil organisms. EFSA Journal 2017; 15(2): 4690

^f Scientific Opinion addressing the state of the science on risk assessment of plant protection products for non-target terrestrial plants. EFSA Journal 2014; 12(7):3800

^g Guidance Document on Work-Sharing in the Northern Zone in the Authorization of Plant Protection Products. Version 5.0 from April 2016

^h Bundesamt für Verbraucherschutz und Landwirtschaft (2011) Organisation und Durchführung von Beratungsgesprächen und Pre-Meetings in

Zusammenarbeit mit dem Bundesinstitut für Risikobewertung, dem Julius Kühn-Institut und dem Umweltbundesamt

ⁱ Ctgb (2016) Evaluation Manual for the Authorisation of Plant Protection Products and Biocides according to Regulation (EC) No 1107/2009, National Part, Plant protection products, Chapter 7 Ecotoxicology, Appendix A: Combination Toxicity, Version 2.1 of October 2016.

^j UK CRD. Ecotoxicology Guidance. Formulation studies and combined risk assessment in ecotoxicology: Guidance on the need for studies and their use in risk assessment. Downloaded from <http://www.hse.gov.uk/pesticides/resources/E/CRD-Formulation-Guidance-ecotox.pdf> (December 2016)

^k UK CRD (2012) Ecotoxicological risk assessment for plant protection products with multiple active substances. Downloaded from http://www.hse.gov.uk/pesticides/resources/E/ECOTOX_multiple_active_substances.docx (February 2017)

^l Krämer, W. Effects towards harmonization: Achievements and current developments in the central zone. 16th International Fresenius ECOTOX Conference. Aquatic and Terrestrial Ecotoxicology and Risk Management. 6-7 December 2016, Mainz, Germany

^m Commission d'Etude de la Toxicité des produits antiparasitaires à usage agricole et des produits assimilés des matières fertilisantes et des supports de culture (2004) Environmental risk assessment for plant protection products. Revision 6-5