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Assessment of formulation containing more than one a.s.

Chloé De Lentdecker

PREV Unit

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Background

- Political and social pressure as regards formulation RA
- Topic discussed at 22nd PSN in October 2017, in July and September 2018 at SANTE/EFSA bilateral TC
- Inconsistent approach taken by applicants and RMSs in the risk assessment of formulated products containing a second a.s.
- According to the legislation a safe use needs to be demonstrated for at least one representative PPP containing the a.s under consideration

-> a combined assessment has to be performed in case the representative formulation contains more than 1 a.s. more consistently

EU legal framework - Human health

- Data requirements for the formulation according to Regulation (EU) 284/2013:
- For **MamTox**, only acute data required:
  - Acute oral toxicity
  - Dermal oral toxicity
  - Inhalation oral toxicity
  - Skin irritation
  - Eye irritation
  - Skin sensitisation
- In the case data on each component of the formulation are available and permit the classification of the formulation, no data might be submitted on the whole PPP.

EU legal framework - Human health

- Only for dermal absorption, studies shall be performed on formulation for representative uses (in use dilution + concentrated form).

In case studies do not correspond with the anticipated exposure situation (for example with regard to the type of co-formulant or the concentration), a justification should be provided.

Default values from the EFSA GD could also be applied.

- Need for supplementary studies on the formulation: case-by-case basis.

However, the type of the study is not mentioned and in practice, rarely requested.

- Data on the formulation not used for the RA (only for classification purpose).

PPP containing more than one a.s.

- Conservative hypothesis: effects used to establish the AOELs for each a.s. in the formulation are considered concentration(dose)-additive by default (expressed as % of respective AOEL).

- For non-dietary exposure, when there is a second a.s. in the formulation, new EFSA calculator permits to consider it.

EU legal framework - Human health

- For **Residues:** no explicitly defined requirement to address a second a.s. in the formulation while legal framework could be open to interpretation.
- Regulation (EU) 283/2013 refers to data requirements for the a.s. however magnitude of residue trials (6.3) should be carried out with the plant production product in accordance with the proposed GAP.
- Dietary exposure estimates (6.9) shall take into account "the possible presence of pesticide residues arising from other sources … (for example use of active substances resulting in common metabolites…)".

EU legal framework - Human health

- Regulation (EU) 284/2013 Section 8 states that «Data and information on residues in or on treated products, food and feed in accordance with Section 6 of Part A of the Annex to Regulation (EU) No 283/2013 shall be submitted, unless the applicant shows that the data and information already submitted for the active substance can be applied. »
- In practice, residue trials in the dossier are often not performed with the notified PPP.
- Reference is made to the GD on residue trials that permits residue data to be translated among most formulation types.

EU legal framework - Human health

- Problem when two a.s. in the formulation release the same metabolite
  - often not considered since residues trials performed with different formulated product of the a.s.
  - may impact consumer RA if metabolite is part of the RD

- According to Regulation (EC) 396/2005:
  - MRL setting should consider human exposure to combinations of active substances and their cumulative and possible aggregate and synergistic effects on human health.

EU legal framework - ERA

- **Fate and behaviour**: Data requirements for the formulation according to Regulation (EU) 284/2013:
  - Rate of degradation in soil: laboratory studies and field studies
  - Mobility in the soil: laboratory studies, lysimeter studies and field leaching studies
  - Estimation of concentrations in soil
  - Readily biodegradation, hydrolysis and aqueous photolysis
  - Aerobic mineralisation in surface water
  - Water/sediment study
  - Irradiated water/sediment study
  - Estimation of concentrations in groundwater: calculation of concentrations in groundwater and additional field tests
  - Estimation of concentrations in surface water and sediment
  - Route and rate of degradation in air and transport via air
  - Estimation of concentrations for other routes of exposure.

EU legal framework - ERA

- For many endpoints, rate and degradation in soil, mobility in soil, aerobic mineralisation in surface water and water/sediment studies, it is requested to perform the test on the formulation only in the case the data performed on the a.s. are considered not representing the fate of the a.s. when it is applied in the formulation.

- In practice, only occasionally, studies with the formulation are available in the dossier.
- But relevant estimated concentrations (predicted environmental concentrations (PEC)) have to be calculated for all active substances and for the formulation when relevant

EU legal framework - ERA

- **Ecotox**: Data requirements for the formulation according to Regulation (EU) 284/2013, not fully consistent e.g.:
  - Birds and Mammals: acute data on formulation for birds triggered,
  - Generally, data are required if the PPP contains two or more active substances for bees, NTAs, soil organisms,
  - Aquatic org: if PPP is 10x more toxic (acutely) for fish and/or invertebrates, chronic study on formulation triggered.

- all endpoints expressed as a.s. also for studies performed on the formulation.

EU legal framework - ERA

- According to Regulation (EU) 284/2013, specific studies with the formulation should be required for some organisms in case the formulation contains more than one a.s.:
  - 10.2.1. If the most sensitive taxonomic groups for the individual active substances are not the same, testing on all three/four aquatic groups, i.e. fish, aquatic invertebrates, algae and, where relevant macrophytes, shall be required.

Toxicity of the formulation

- A comparison between toxicity of the a.s. alone vs toxicity of the a.s. formulated is done.
- In the majority of situations, in case that formulation is not more toxic, the standard assessments presented for the a.s. will be sufficient to conclude on the risk from both a.s. and formulation.
- In the case that the formulation is of higher toxicity:
  - Applicant requested to perform a 'proper' RA addressing the risk from the formulation.
  - In cases where the applicant fails -> conservative approach discussed and agreed at the general experts meeting (Oct 2018) i.e. all toxicity is coming from the a.s. under evaluation, this will then be compared to the exposure assessment for the a.s. which does not consider whether there is exposure to the intact product.

PPP containing more than one a.s.

- By default when data on the formulation alone cannot be used to characterise the risk for representative uses:

-> **Dose addition** risk assessments (acute and chronic endpoints) are needed

-> To facilitate this PEC should be calculated for all active substances

e.g. surface water FOCUS steps when appropriate (e.g. when using Finney equation type approach) can need to be calculated as daily additive concentrations.

Conclusion

- EFSA has to conclude against the approval criteria and this requires safe use(s) for a product to be demonstrated.

-> combined toxicity assessment should be included in the dossier and assessed in the RAR/DAR in a consistent manner from now on.

- An assessment considering the second a.s. should be done using agreed endpoints for the second a.s. from past peer reviewed assessments.

Conclusion – potential consequence

- If no combined assessment considering both a.s. is available in the (D)RAR

-> **data requirement/open point** identified for a proper RA of the formulation in column 4 of the reporting table.

- In the EFSA conclusion:
  - Any particular **concern and/or data gap** could be reported.
  - If a RA for the single a.s. is performed but not for the combination, an **issue that could not be finalised** could be set.
  - In cases higher tier studies are submitted using the formulation (with 2 a.s.), if a high risk is identified, in few cases it could not be possible to determine which substance drives the toxicity -> A **high risk** could be concluded (clearly explained that this is based on data relevant for the two a.s.).

Ideas to be discussed

- MSs' involvement:

Volunteer to work on practical proposal, more structured and scientific instructions:

- WG of the PSN to be created?
- General joint experts' meeting to be organised (all sections)?
- Existing MSs' data collection to be shared?
- Other ideas?

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