DERIVING ECOLOGICALLY RELEVANT ENDPOINTS FOR WILD MAMMAL RISK ASSESSMENTS: 5 years on, what is the state of play?

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Background

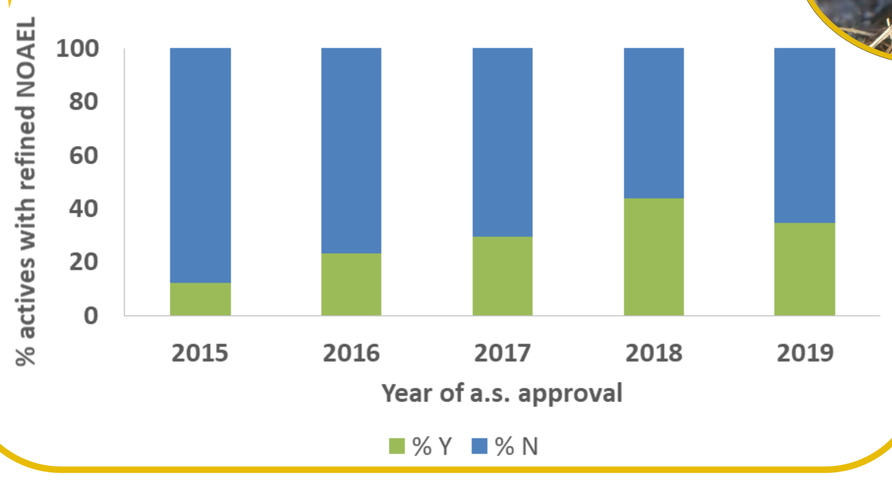
- Default for wild mammal risk assessments is to use the worst-case NOAEL from the toxicology assessment
- Lots of parameters are measured in toxicology studies, which may be relevant for **individual** humans but not for wild mammal **populations**
- The current bird and mammal guidance (EFSA 2009) theoretically allows derivation of 'ecologically relevant' wild mammal toxicity endpoints
- Recommended in EFSA (2015) that wild mammal endpoints should be agreed during EU review of active substances, rather than at Member State (MS) level – **published 5 years ago, so what's happened since?**

The review

- Focused on active substances approved in EU since 2015 (*n* = 117)
- Didn't include any incomplete or rejected actives due to time constraints
- Reviewed EFSA conclusions, dossiers and PRAPeR reports
- **Key Qs:**
  1. **Was the NOAEL refined?**
  2. **At what stage?**
  3. **How?**
  4. **Impact on risk assessment?**

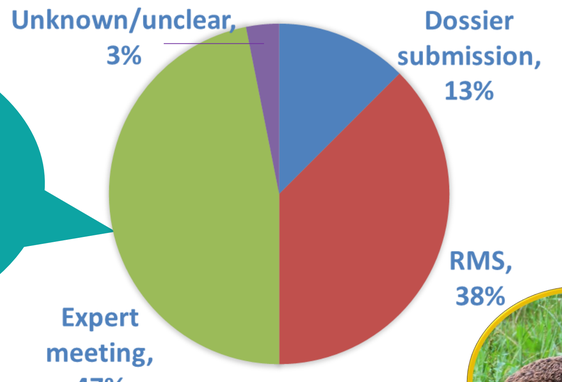
Qs

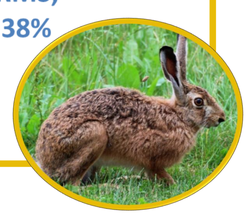
Q1. Was the NOAEL refined?



Q2. At what stage was the NOAEL refined?

~50% endpoints derived at expert meeting stage → little time for Notifiers to prepare rebuttals or develop alternative refinements → unresolved risk assessment failures

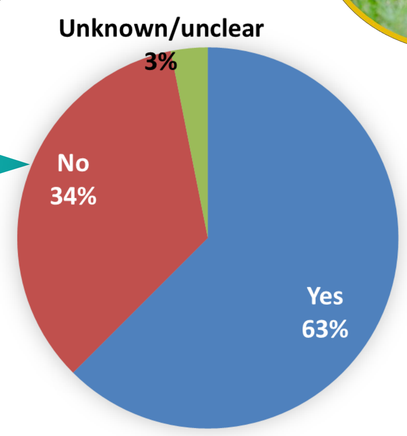




Q3. How was the NOAEL refined?

% actives attempting an 'eco-relevance' argument?

Other arguments for ↑/↓ endpoint:
- Reinterpretation of effects observed/recalculation of exposure dose during toxicology expert review
- Benchmark dose modelling
- Merging of datasets
- Artefact of dose-spacing
- Inclusion/exclusion of studies from wider data package



What approaches used to determine the final NOAEL?

- NOAEL considered an **artefact of dose-spacing**
- **Benchmark dose modelling** (LL BMD_5 accepted for reduced pup body weight)
- **Reinterpretation of effects** observed in critical study
- **Reinterpretation of exposure dose** in critical study
- **Inclusion** of additional studies considered relevant for wild mammal populations
- **Exclusion** of studies considered non-relevant for wild mammal populations

Which tox studies used to define the final NOAEL?

Rat multi-generation study (*n*=23)
Rabbit developmental study (*n*=5)
Rat developmental study (*n*=2)
Rat neurotoxicity study (*n*=1)
2 year rat chronic toxicity and oncogenicity study (*n*=1)

What type/size of effects defined the final NOAEL?

Conclusions for other active substances specifically stated that these types of effects are not relevant for wild mammal populations!

- Offspring viability: < and >10% ↓
- Litter size: < and >10% ↓
- Abortions: ↑ occurrence
- Body weight (parental and offspring): < and >10% ↓
- **Body weight gain:** < and >10% ↓
- Copulatory behaviour: absence in F0 but not F1 males
- Sexual development: 1.5-2 days' delay
- **Delayed ossification:** 25% litter incidence
- **Skeletal variations:** ↑ occurrence
- Reduced auditory startle reflex: 24-40% ↓
- **Kidney effects:** deterioration observed

Q4. What impact did the NOAEL refinement have on the risk assessment?

~50% risk assessments that passed **now fail** due to NOAEL conclusion

~13% risk assessments that failed **now pass** due to NOAEL conclusion

~39% risk assessment outcomes **unchanged** by the NOAEL conclusion

CONCLUSIONS & RECOMMENDATIONS

- **More collaboration between toxicologists and ecotoxicologists** may help avoid changes in NOAEL at late stage of EU review process e.g. co-authorship of derivation of eco-relevant NOAEL for wild mammals between tox/ecotox experts; have a **combined tox/ecotox PRAPER meeting**, clearly discussing effects observed and their eco-relevance
- Regulators to more **clearly communicate** the evaluation process when defining the wild mammal NOAEL, describing any concerns raised and the associated reasons for these concerns; ideally regulators would follow a formalised framework for their evaluation e.g. Lewis et al.
- More guidance needed for regulatory ecotoxicologists regarding **what types of effects and what magnitudes of difference to the control** are eco-relevant and **more understanding of the toxicology data package** – this is highlighted by all stakeholders in public consultation comments on EFSA (2009)
- It appears that less evidence/argumentation is required to decrease a NOAEL (by regulators/EFSA) compared to potentially increasing it
- The final NOAEL conclusion is sometimes influenced by the impact on the risk assessment conclusion – if it passes, sometimes a more conservative endpoint is accepted; this can be problematic for **future national authorisations** with different GAPs
- **Reporting** of discussion regarding deriving eco-relevant endpoint within dossiers is inconsistent – can be in the MCA, MCP or Vol 1 sections of the dossier – this should be agreed at EU level (MCA wild mammal section seems most relevant); should include the reasons why the NOAEL was selected rather than referring to PRAPeR report etc.
- Multigeneration rat studies predominantly used to define the NOAEL – **BMD modelling** may have been a useful refinement for some of these actives now that the approach is supported by EFSA, though further work is required to define acceptable levels of response for each type of effect e.g. is a 10% change in bodyweight acceptable?