Draft new bird and mammal guidance: a consultant's view

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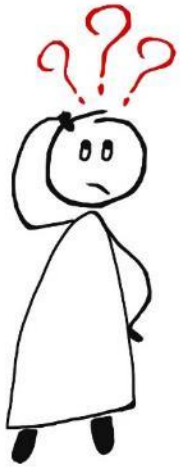
tier3 workshop, 31st August 2022

CEA

CAMBRIDGE ENVIRONMENTAL ASSESSMENTS

What am I going to cover?

- Manousos has provided us with the big picture view from industry
- tier3 will provide us with an overview on the implications for field studies
- I'll provide a consultant's view on some of the rest!
- Topics we noted during the public consultation phase, and some since…



Protection goals:

What are we trying to protect and why?

PGs haven't changed

- Acute risk assessment based on '*no visible mortality*'
  - will vary depending on species in question!
  - Some animals will hide away if feel unwell…does it still count if we can't see them??
- Reproductive risk assessment protection goal ('*no long-term repercussions for abundance and biodiversity*') is too vague – what does this really mean?

Time to revisit what we're really trying to protect?

- Clearly defined protection goals – what we are trying to protect, where, and when
- Build the risk assessment framework around the protection goals
- **Calibrate** the risk assessment framework
  - So far only acute RA has been calibrated, not possible for repro RA
  - New GD may or may not achieve the protection goals!
  - Old scheme may or may not have been adequate!

Toxicity endpoints

Incorporating additional toxicity data

Acute toxicity

- EFSA 2009 allowed geomean LD_{50} for multiple (i.e. >1) acute studies
- EFSA 2021 proposes geomean only possible for >2 species
- Due to confusion over data requirements – only one species required, so should be geomean for >1 spp

Repro toxicity

- Combining repro studies to determine overall NOAEL in EFSA 2009 – not mentioned in EFSA 2021, still possible?

Table 4b. Illustration of how to combine two studies on the same species (example b).

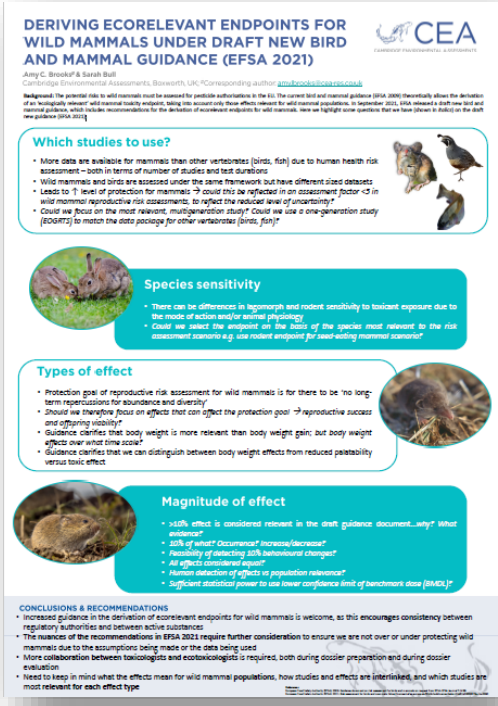
Study 1 Test concentration [mg/kg bw/d]	Effect	Study 2 Test concentration [mg/kg bw/d]	Effect
100	Yes	50	Yes
30	Yes	35	No
3	No	10	No
0	No	0	No
NOAEL	3	NOAEL	35

Metabolites

- EFSA 2021 still proposing using 10x toxicity of parent where no data available
- Has the appropriateness of this 10x factor been assessed since EFSA 2009?

Ecorelevant endpoints for wild mammals

- EFSA 2009 theoretically allows the derivation of an 'ecologically relevant' wild mammal toxicity endpoint, considering only those effects relevant for wild mammal populations
- The draft new B&M guidance provides more detailed recommendations for the derivation of ecorelevant endpoints for wild mammals
- Though an improvement, several questions remain…
- (We presented a poster on this at SETAC Copenhagen)



Wild mammal endpoints, cont.

Which studies to use?

- More data available for mammals than other vertebrates due to HH RA – both number of studies and test durations
- Use same RA framework and PGs for wild mammals and birds but with different datasets
- Leads to increased level of protection for wild mammals – *could this be reflected in an AF<5 for repro RAs to acknowledge the reduced uncertainty?*
- *Could we focus on the most relevant, multigen study? Could we use a 1-gen study (EOGRTS) to match data for other vertebrates (birds/fish)?*

Wild mammal endpoints, cont.

Take into account species sensitivity?

- Can be differences in lagomorph and rodent sensitivity to toxicant exposure due to mode of action and/or animal physiology
- *Could we select the endpoint based on the the species most relevant to the risk assessment scenario e.g. use rodent endpoint for seed-eating mammal scenario?*
- Clearly this would require robust evidence and argumentation, illustrating a genuine difference in sensitivity

Wild mammal endpoints, cont.

What types of effect are relevant?

- Protection goal of repro RA for wild mammals is for there to be 'no long-term repercussions for abundance and diversity'
- *Should we therefore focus on effects that can directly affect the protection goal i.e. reproductive success and offspring viability?*
- Guidance clarifies that body weight is more relevant than body weight gain; *but body weight effects over what time scale?*
- Guidance clarifies distinction between body weight effects from reduced palatability versus toxic effect

Wild mammal endpoints, cont.

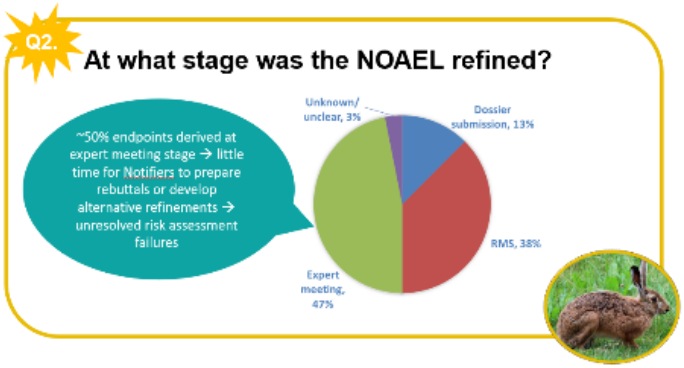
What magnitude of effect is relevant?

- >10% effect is considered relevant in the draft guidance document…*why? What evidence?*
- *Also applies to behavioural effects, but 10% of what? Occurrence? Increase or decrease?*
- *Feasibility of detecting 10% behavioural changes? Use LD_{50}/10 instead (as for birds)?*
- *All types of effects considered equal e.g. pup body weight vs pup survival?*
- *Human detection of effects vs population relevance? Just because we (as humans) can see a difference, does it matter?*
- *Sufficient statistical power to use lower confidence limit of benchmark dose (BMDL)? Change in study design required?*

Wild mammal endpoints, cont.

Can we know earlier what the final endpoint is going to be??

- Clearly the derivation of the toxicity endpoint for wild mammals is key to the risk assessment
- The need for other refinements is determined on this basis
- ~50% endpoints are not finalised until the expert meeting during the EU review (Brooks et al 2020)
- No time for Notifiers to resolve this in terms of rebuttals or generating additional data
- Would be useful to have a conclusion on the endpoint at an earlier stage in the review…



Using historical control data (HCD) in endpoint decisions

- Routinely used in HH RAs but not for ecotox
- Use of HCD theoretically possible under EFSA 2009 but lacking detailed guidance
- Been discussed in several papers since 2009
- Disappointingly, no further guidance is provided in EFSA 2021, stating:

  "It is appreciated that HCD has the potential to make the most use of existing data and hence possibly reduce the likelihood of repeating vertebrate studies, however it is currently not possible to recommend a way forward regarding how to interpret or use HCD. It is recommended that guidance is produced with mammalian toxicology experts. In the meantime, it is recommended to compare data from treated animals with data from concurrent study control."

- Positive that a workshop was organised by AGES in May 2022: 'Preparatory work on how to report, use and interpret historical control data in (eco)toxicity studies' – hopefully, guidance will be developed in time!

What about effects on migratory birds?

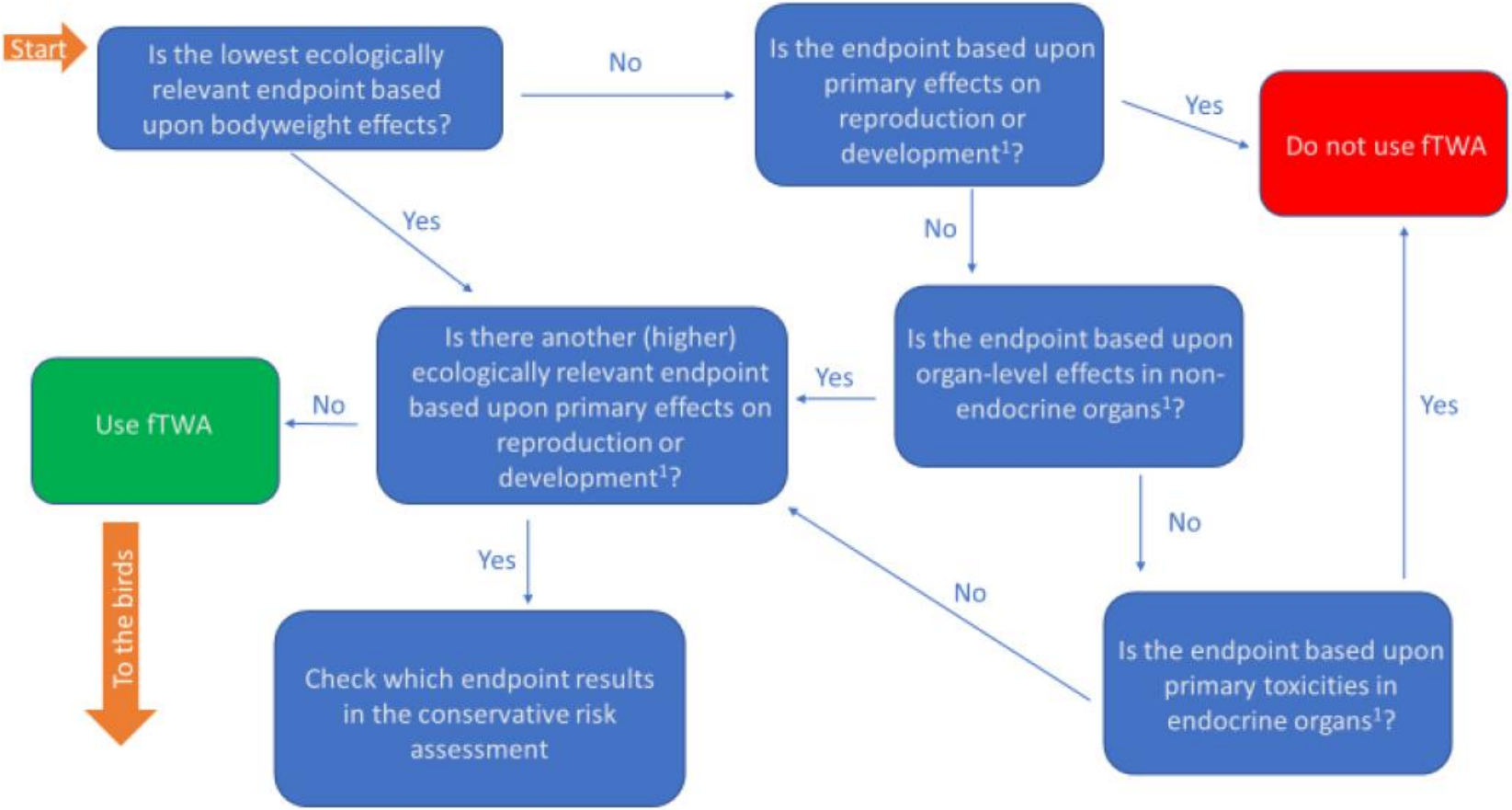
- EFSA 2021 states migratory birds may be particularly sensitive to neurotoxic insecticides
- Effects on cognitive and motor functions, crucial for successful migration
- Substances with a known neurotoxic mode of action require further assessment
  - Compare acute toxicity between passerine and other spp – check if repro AF of 5 is sufficient
  - If no passerine data, refer to mammalian data package for evidence of neurotox effects
  - Unknown whether either of these approaches is robust!
  - May lead to additional testing on passerine spp…
  - What to do if the migratory bird scenario fails?

Time-weighted average factor (f_{twa})

A significant change!

- F_{twa} used to be included by default for spray applications, assuming repro effects were the result of LT not ST exposure (and exposure reduces over time)
- No default f_{twa} under EFSA 2021
- Detailed assessment required for each compound → significant increase in workload for industry, regulators and EFSA – for ecotox and tox experts
- Particularly challenging for birds, less data available, difficult to generate new data due to vertebrate testing
- Evidence that the previous approach was under protective?

Flow chart for f_{TWA} assessment for mammals



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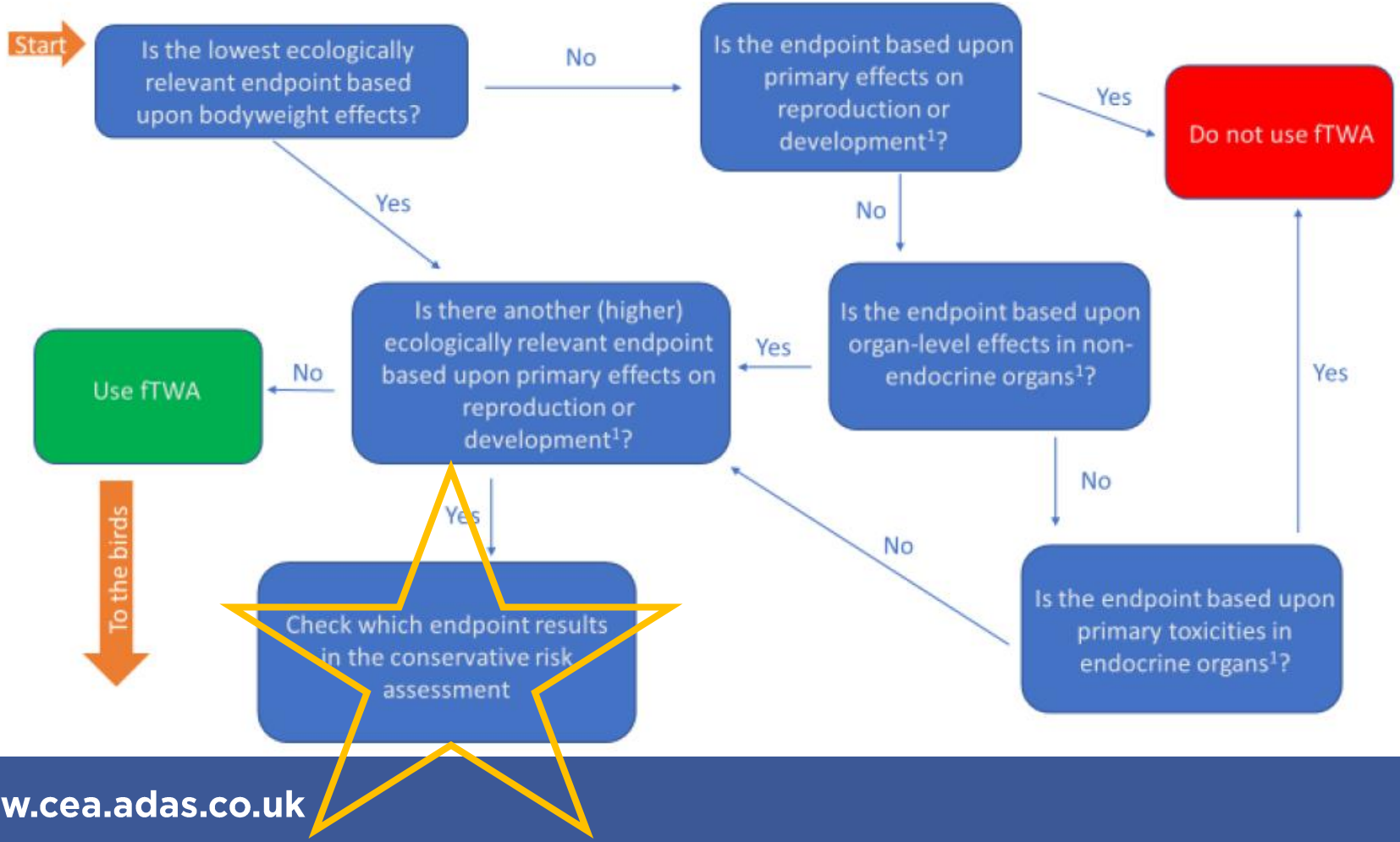
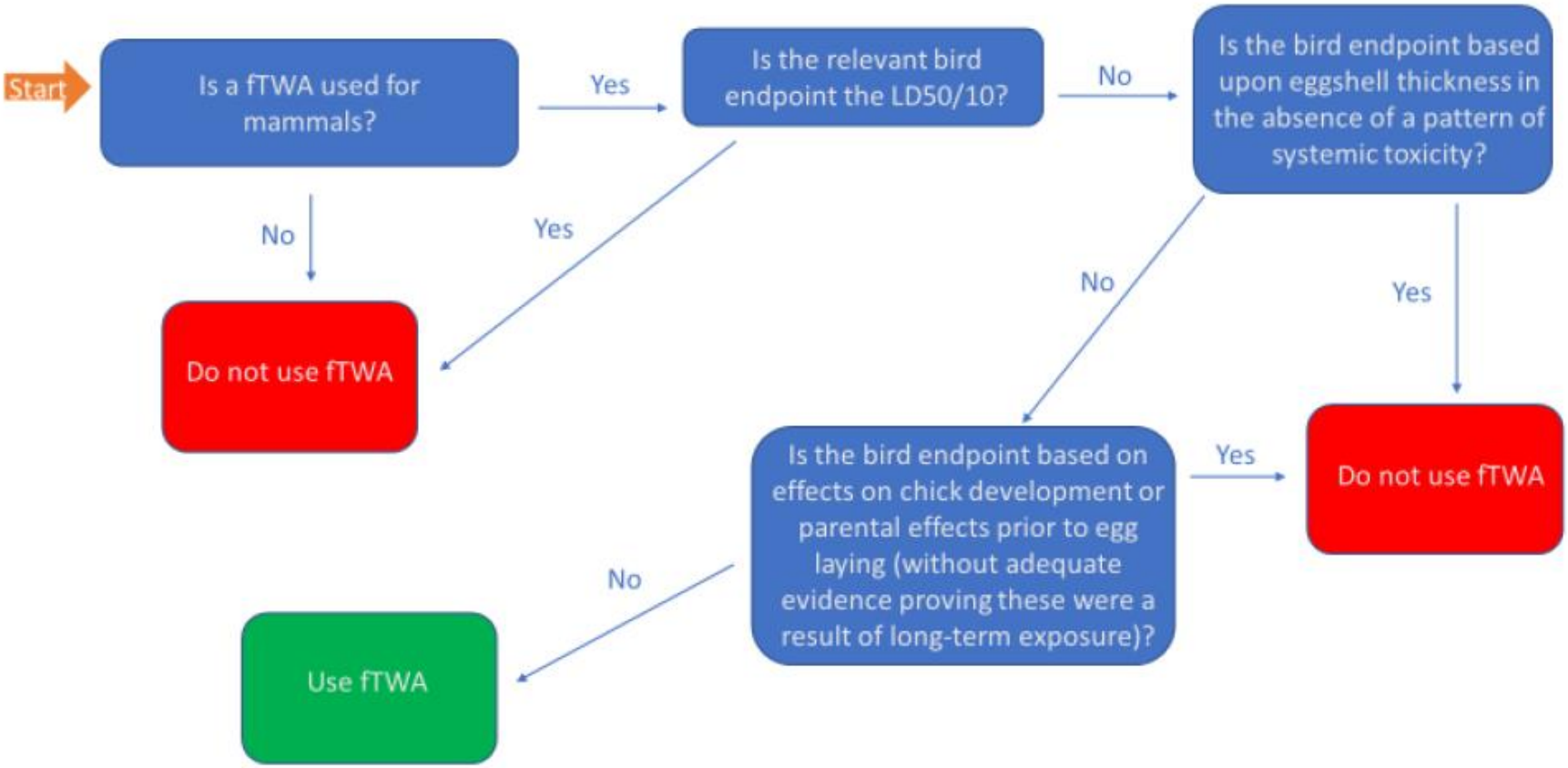
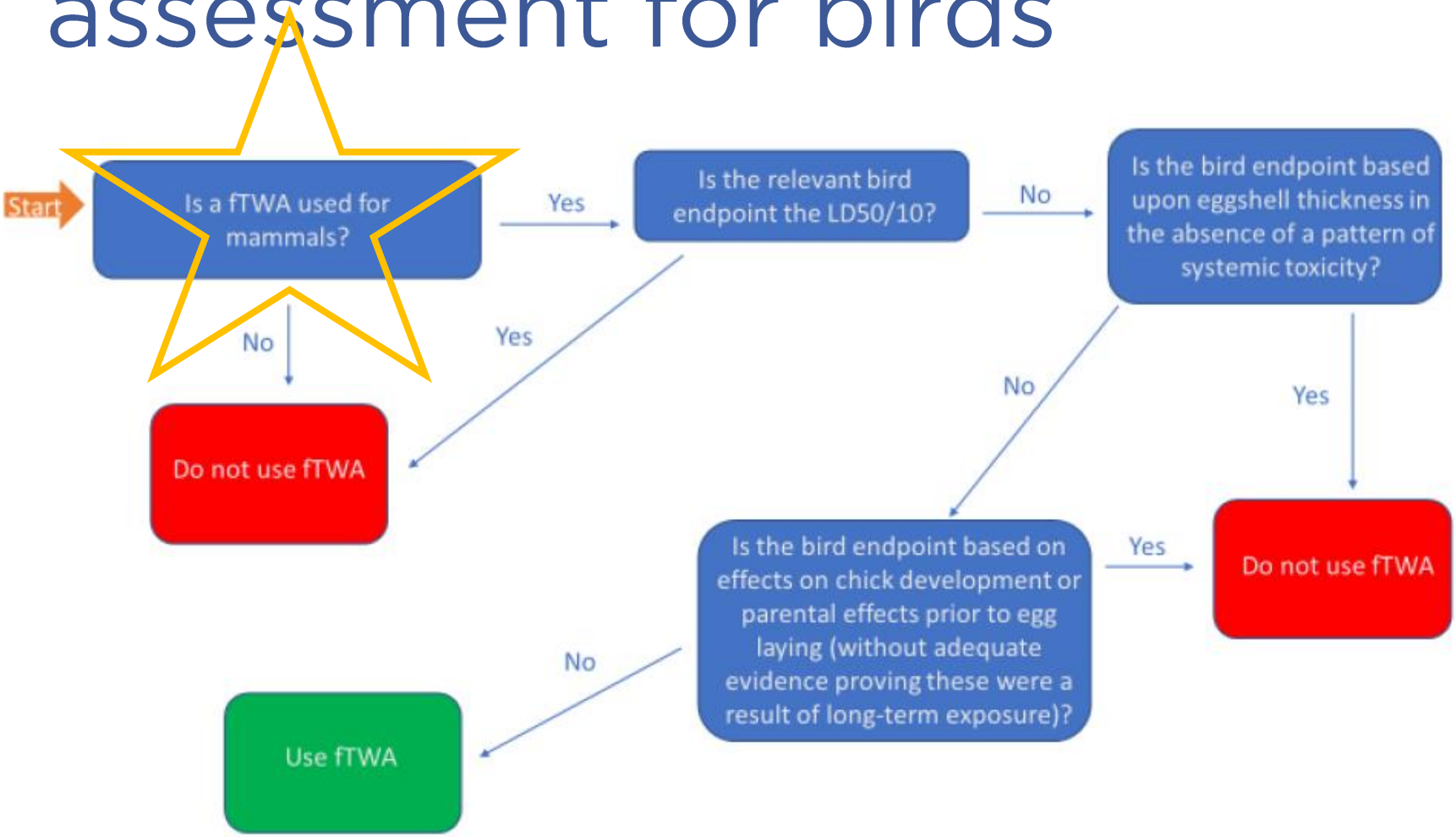


Flow chart for f_{TWA} assessment for birds



Flow chart for f_{TWA} assessment for birds



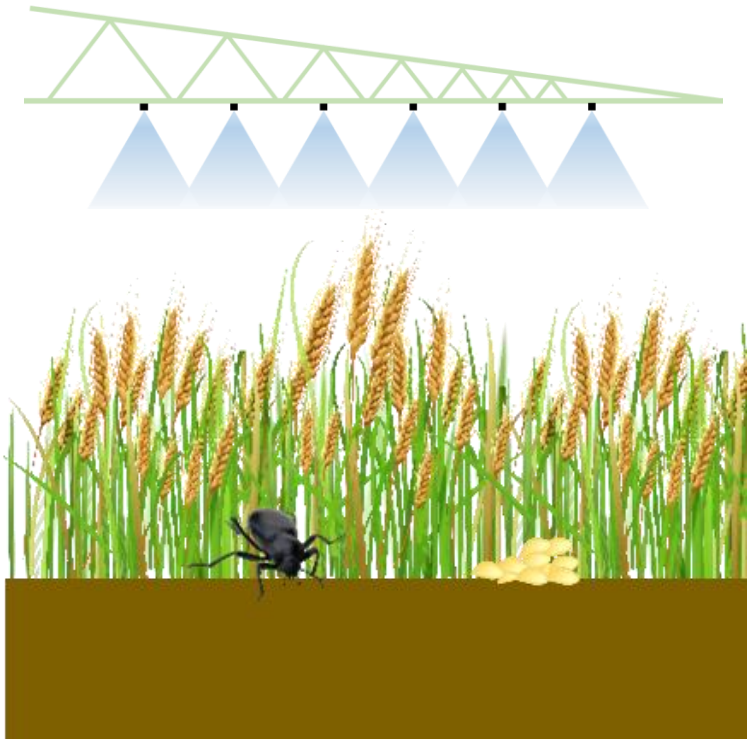
Implications for residue decline studies

- Residue decline (DT_{50}) refinement was very important for some compounds to demonstrate low risks – residues on crop, weeds, arthropods, etc
- If criteria for f_{twa} cannot be fulfilled, DT_{50} refinement cannot be used…
- Conclusion on f_{twa} assessment won't be known until after EU review – at which point, data and DT_{50} already generated
- Significant additional refinements will be required to demonstrate low risks if can't be used – may not be possible in all cases
- Ironically, Appendix O (performing and interpreting residue trials) is now much improved!

Residue data (RUD)

Good news!

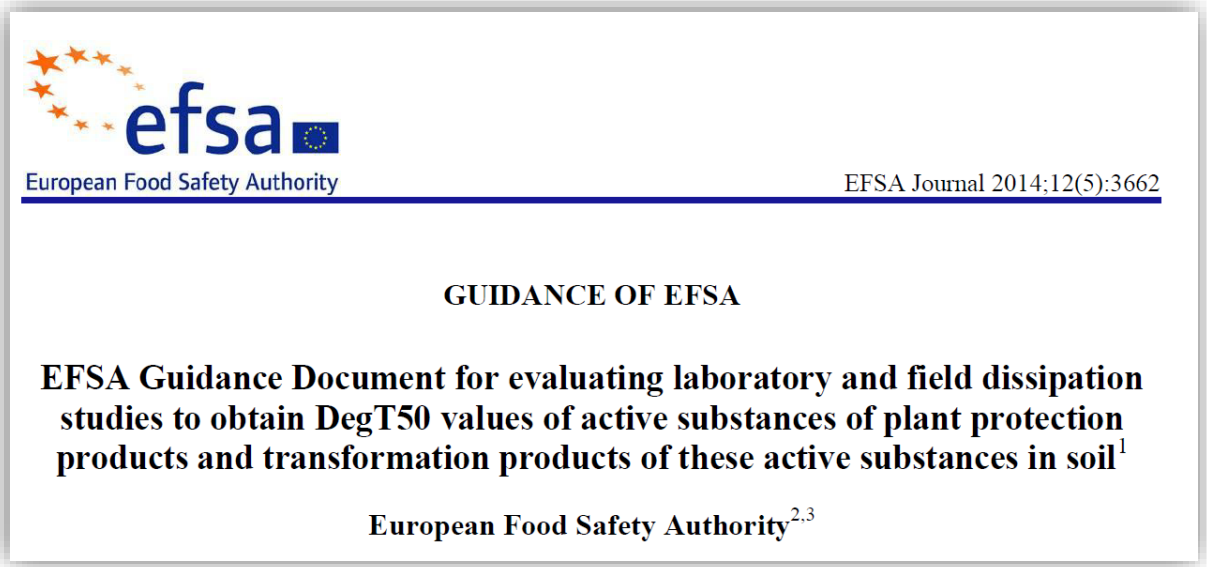
- Positive news that additional available residue data have been incorporated into the RUD database
- Also positive that RUDs can be refined beyond using the defaults in the guidance
  - either merging with existing dataset (i.e. just adding further trials)
  - Replacing existing dataset (i.e. better dataset than exists in GD)



Deposition factors

Also good news!

- Positive news that the deposition factors have been updated using info from EFSA 2014
- Presented in Annex B for individual scenarios



efsa
European Food Safety Authority

EFSA Journal 2014;12(5):3662

GUIDANCE OF EFSA

EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil[1]

European Food Safety Authority[2,3]

Seed treatments

Can now only have PT or PD, not both

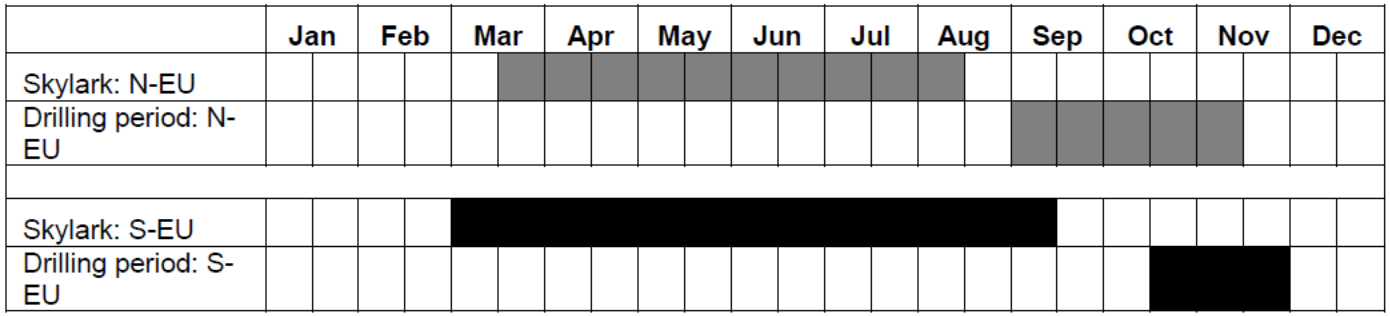
- EFSA 2021 states that it is not appropriate to refine both PD and PT for seed treatment scenarios
- Other food items aside from treated seeds are available in drilled fields e.g. weed seeds, arthropods
- If the underlying studies for PT and PD have been correctly designed, it should still be possible to achieve PT and PD values within-field
- Hopefully this text will be edited allowing refinement of PT and PD if the underlying studies have been suitably designed to avoid double counting

How many seeds need to consume to cause effects?

- EFSA 2021 proposes calculating no. seeds required to achieve the regulatory acceptable dose
- No guidance for what is and isn't acceptable
- More useful to determine the foraging area required to achieve this dose, and how that compares to the foraging area required to achieve their daily food intake?
- Guidance would be required regarding what is and isn't acceptable for such a foraging area assessment

Reproductive RAs for autumn applications

- Some seed treatments drilled in autumn
- Outside of bird breeding periods
- EFSA 2021 still requires a repro RA to be performed for this
- Could a refinement option be included for assessing the overlap between drilling periods and breeding times for focal species?



Residue decline, but over what period?

- EFSA 2021 allows a DT_{50} to be included in Tier 2 treated-seed risk assessments (pending successful f_{TWA} assessment)
- Still unclear what the relevant exposure period is for calculation of the f_{TWA} for treated seed scenario
- For seedlings, a 21-d period is clearly mentioned, but no such statement is made for the exposure to seeds scenario
- Clarity is required as MSs currently use different exposure periods in their evaluations
- Depending on the chosen values, the impact on the risk assessment can be significant

Secondary poisoning

New ‘benthic’ scenario to be assessed

- EFSA 2021 proposes a new food chain exposure scenario, the ‘benthic invertebrate-eating bird/mammal’
- Ok for birds, but which mammal species feed exclusively on very small sediment-associated aquatic worms? E.g. Pyrenean desman?
- More appropriate to assume a mixed diet of other macro-invertebrates?
- EFSA 2021 proposes using data from *Lumbriculus variegatus* bioaccumulation study – appropriate?
- Initial review indicates 13-26% compounds will trigger this assessment (Weyman *et al* 2022)

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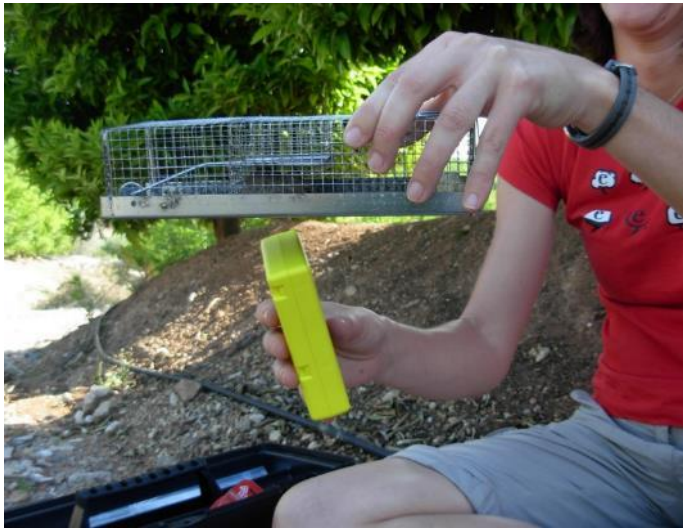
Calculator tool

Where is it?

- Lack of calculator tool when EFSA 2021 released
- Meant that the full impact of the changes in the GD couldn't be easily determined
- Understand it will be available later this year for testing by some stakeholders
- No 2nd round of commenting on the guidance document, only the calculator tool…?
- Concerns about accessibility of online platform e.g. if system goes down – will there be some sort of back up available?



From Tier3 website ☺

Higher-tier studies (briefly!)

Statistical power?

- EFSA 2021 states that Tier 3 effect studies should have sufficient statistical power
- Not been routinely assessed in the past
- For some studies the statistical power will be difficult to predict in advance
- Could historical control data be used to predict whether a study design will have sufficient power to detect effects?

Food availability?

- EFSA 2021 recommends that food availability in the test site and surrounding area should be assessed
- Unclear what data are required, how this will be judged or what would be deemed acceptable
- Usually, test sites are selected due to high abundance of birds and/or mammals, which would indicate that food is available
- Unclear what the additional benefit is of also measuring food availabilities

- Thanks to tier3 for inviting me to present today
- Thanks to:
  - Helena Crosland (CEA)
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  - Gabe Weyman (Gabe Weyman Consulting Ltd)
  - Alan Lawrence (Alan Lawrence Ltd)
  - Kevin Brown (Brown Environmental Ltd)
  - Nina Hallmark and Markus Ebeling (Bayer AG CropScience)

  for valuable discussions during the public consultation phase

Any questions?

Contact the author: amy.brooks@cea-res.co.uk

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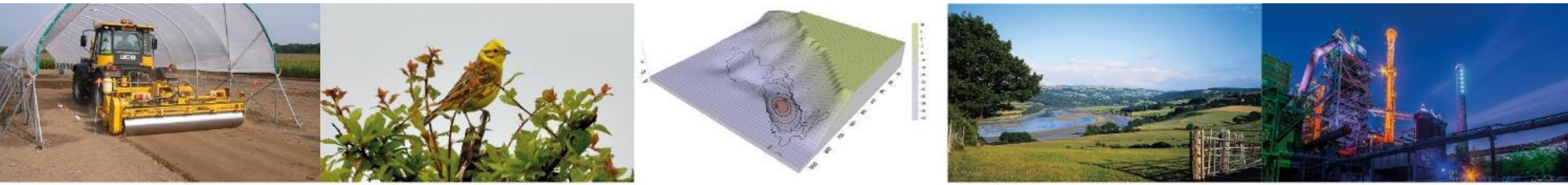

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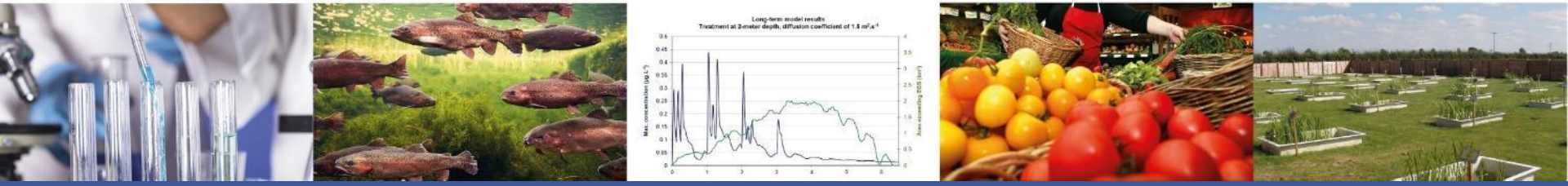
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