European Food Safety Authority

Modelling approaches

Andy Hart, Central Science Laboratory; UK

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What is the current model?

- Exposure model: ETE equations, e.g.

$$ETE = \frac{FIR}{bw} \times C \times PT \times PD \times AV$$

- Toxicity model: lowest LD50 or NOEL

- Risk model: TER + uncertainty factor of 5 or 10

Why consider alternative models?

- To account for avoidance and metabolism
  - Frequently cited as factors reducing acute risk
- To account for non-dietary routes of exposure
  - Dermal: evidence from lab and field studies
  - Drinking water: evidence from incident reports
- An empirical model may give better predictions
  - Equations based on field data may predict mortality more accurately than the ETE-TER approach

Avoidance and metabolism (1)

- PPR Opinion on methamidophos
  - AV in current ETE equation is inappropriate
  - Avoidance usually cessation of feeding driven by dose, not a partial reduction driven by concentration

- PPR Opinion on pirimicarb
  - Proposed an alternative exposure-toxicity model
  - Improved representation of avoidance
  - Takes account of metabolism/elimination

$$Acute\ Dose = AVT \times e^{-k \times AVD} + \frac{(FPM \times C)}{(bw \times k)} \times (1 - e^{-k \times AVD})$$

Avoidance and metabolism (2)

- Working group:
  - Reviewed PPR pirimicarb model
  - Considered industry model under development
    - More explicit modelling of ADME processes

- Conclusions:
  - These approaches require more research before they could be recommended for routine use (e.g. 1st tier)
    - Premature to settle on a single model
    - Uncertainty about applicability to different substances
    - Uncertainty about extrapolation between species

Avoidance and metabolism (3)

- **Draft recommendations:**
  - Modelling of avoidance and metabolism can be one option for refined assessment
    - EFSA or industry approach may be considered
    - Model, assumptions and input data will require detailed explanation and justification in every case
  - Specialised dietary studies could also be considered
    - Assess effect of avoidance and metabolism directly for relevant species, and/or provide inputs for modelling
    - Study design and choice of species require detailed explanation and justification in every case

Dermal exposure (1)

Evidence that dermal exposure can be important:

- Laboratory studies
  - Driver et al. 1991 – dermal contributed more than dietary for quail exposed to methyl parathion
  - CSL 2006/7 – dermal contributions measured for pigeons exposed to 3 different OPs
- Analysis of field data
  - Mineau 2002 – occurrence of avian mortality predicted by toxic potential ($HD5s/m^2$) and dermal toxicity index

Dermal exposure (2)

Options for modelling dermal exposure:

- Theoretical model
  - ETE-style equations available in literature
  - But – deposition of substance on animal depends on behaviour and is very difficult to model
- Empirical model
  - Updated Mineau model correctly predicts occurrence of mortality in high proportion of avian field studies
  - But – need to resolve questions and uncertainties before recommending for regulatory use

Analysis of avian field studies (1)

- Large number of studies collated by Pierre Mineau
  - All OPs and carbamates
  - Arable, orchard and forestry uses
  - Aerial, airblast and ground sprays
  - Most involved searching for dead birds
  - Some with residue analysis
  - Some with bird censuses
  - Some measured cholinesterase inhibition

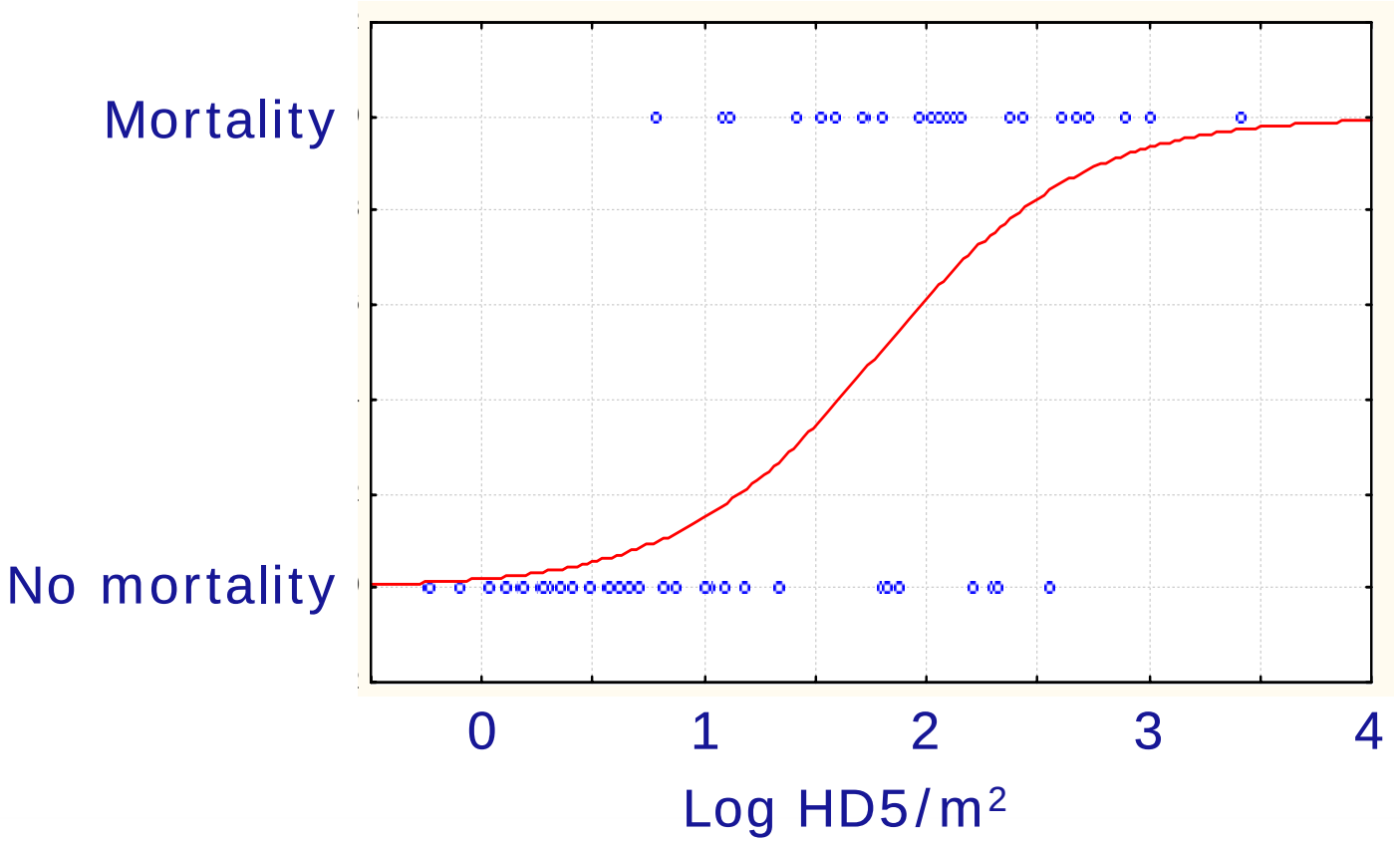
Analysis of avian field studies (2)

- Mineau classified studies according to impact:
  1. No impact or slight, sublethal effects
  2. Compound-related mortality

- Looked for factors that can predict compound-related mortality
  - Original results published by Mineau (2002)
  - Updated analysis in preparation

Analysis of avian field studies (3)

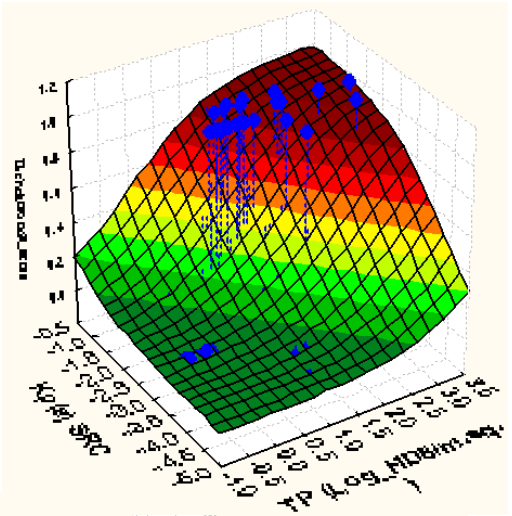
- Risk of mortality is positively correlated with the number of lethal doses applied per square metre

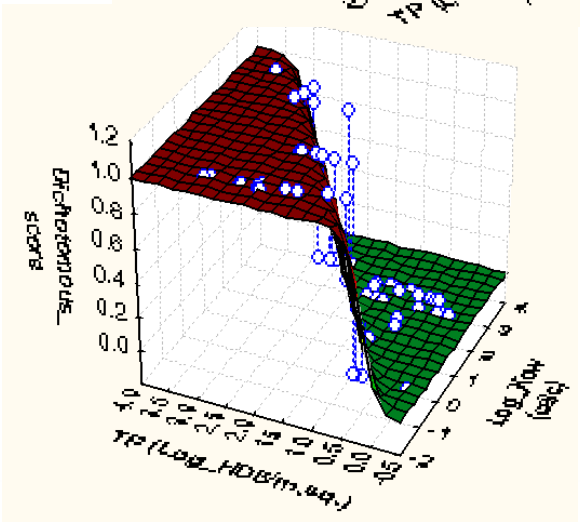


Analysis of avian field studies (4)

In addition to effect of toxicity:

- Indirect-acting substances: high K_{ow} increases risk
  - OPs requiring activation
  - **72% predicted correctly**
- Direct-acting substances: high K_{ow} decreases risk
  - Carbamates, OPs not requiring activation
  - **98% predicted correctly**





Analysis of avian field studies (5)

- Taking account of K_{ow} significantly improves prediction of mortality
  - Better than the existing ETE-TER approach
  - Ideally make use of this in risk assessment
  - Reduce frequency of false positives and negatives

- BUT
  - Mechanism of K_{ow} effect is uncertain
  - Direction of effect different for direct and indirect-acting anticholinesterases: reason not yet clear
  - Uncertainty about application to other chemistries
  - Some questions about quality and classification of field studies

Analysis of avian field studies (6)

Work group actions underway:

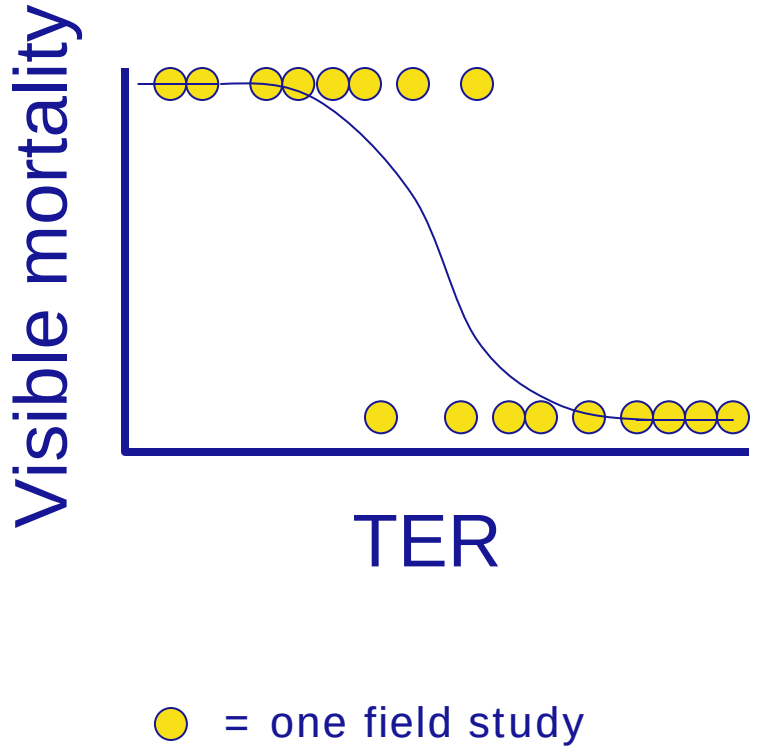
- Re-evaluate summaries of all field studies
- New classifications, taking account of uncertainty
  - Separate classifications by Mineau, CSL and industry
- Seek extra industry studies with different chemistries
- Seek expert advice on mechanisms involved
- Seek advice on relation to population effects

Possible outcomes

1. No use of field study model – if unreliable
2. Use field study model to replace ETE-TER
   - for all substances, or
   - for selected substances (e.g. anticholinesterases)
3. Use field study model as a check for when to consider dermal exposure
4. Use field studies to calibrate ETE-TER approach

Calibration of ETE-TER approach

- Apply proposed assessment procedure to each substance
- Compare TERs with impacts in field
  - where data exist!
- Estimate frequency of impacts at TER = 10



Note: calibration accounts indirectly for other factors influencing risk e.g. dermal exposure, avoidance, metabolism

Calibration of ETE-TER approach

FIR/bw, PD	RUD, PT	Calibration factor (CF)	% visible mortality at TER=10	% substances fail at tier 1
Mean*	90th %ile*	?	?	?

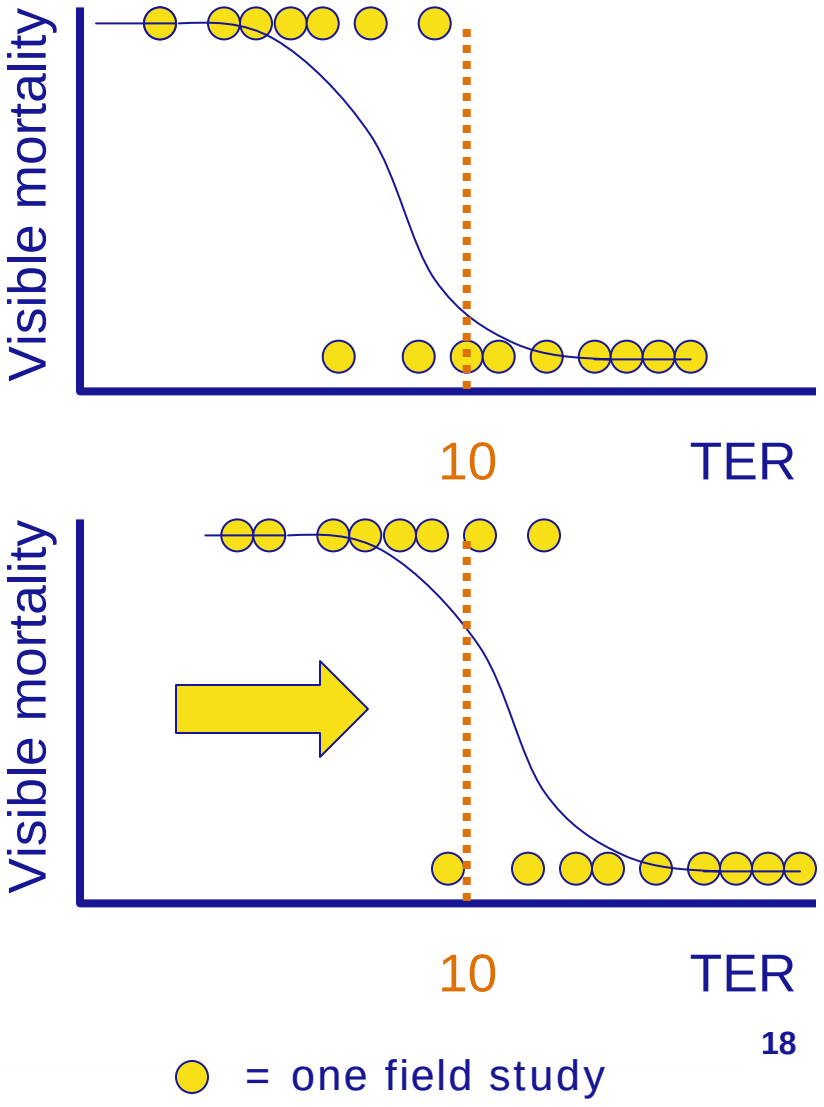
- Initial result may not give desired level of conservatism at TER = 10
- Introduce a **CALIBRATION FACTOR** to adjust level of conservatism

* Choice of value not yet decided, e.g. mean, 90%ile, 95%ile

Calibration of ETE-TER approach

- Apply proposed assessment procedure to each substance
- Compare TERs with impacts in field
- Estimate frequency of impacts at TER = 10

- Change calibration factor, recalculate TERs, estimate new frequency of impacts at TER=10
  - E.g. reduce CF, increase TERs
  - increase impacts at TER=10
  - reduce fail rate at tier 1/2



Calibration of ETE-TER approach

FIR/bw, PD	RUD, PT	Calibration factor (CF)	% visible mortality at TER=10	% substances fail at tier 1
Mean	90th %ile	1	20*	50*
Mean	90th %ile	0.8	30*	35*
Mean	90th %ile	0.6	40*	10*

Choose CF to achieve desired level of conservatism

* Example for illustration – numbers are fictional

Calibration of ETE-TER approach

- Choice of calibration factor & level of conservatism will be left to the relevant authorities
- EFSA can advise on science, e.g. implications for populations

Calibration of ETE-TER approach

- Calibration only possible with appropriate field data
- Best dataset is for acute risks to birds
- Limited dataset on short-term population declines in small mammals
  - Calibration will be more uncertain
- Almost no data on reproductive effects on birds
  - Quantitative calibration not possible – Working Group will summarise available evidence qualitatively

Other routes of exposure

- Exposure via drinking water
  - Will provide ETE-style equations
- Exposure to solid formulations (incl. granules)
  - Some field studies available – analyse if time permits
  - Otherwise, refer reader to existing publications including SCP Opinion on fosthiazate

Summary

- Make best possible use of field study data
  - Partially or wholly replace ETE-TER in tier 1?
  - And/or calibrate ETE-TER approach
  - Accounts for combined effect of all factors influencing risk

- Tier 1 method for exposure via drinking water
- Approaches for solid formulations
- Refer reader to approaches for addressing avoidance and metabolism in refined assessments

- Some issues require longer term research

Questions for discussion

- We are considering to use an empirical model for RA for certain compounds. Your views on this idea would be welcome.
- We are proposing to calibrate the ETE equation using data from field trials. Is this a reasonable approach? Will this provide sufficient info for regulatory impact assessment?
- What could be the role of a body burden model in RA?