Probabilistic Methods for Assessing Dietary Exposure to Pesticides

Andy Hart (Fera, UK)

Technical Meeting with Stakeholders on Cumulative Risk Assessment
EFSA, 11 February 2014

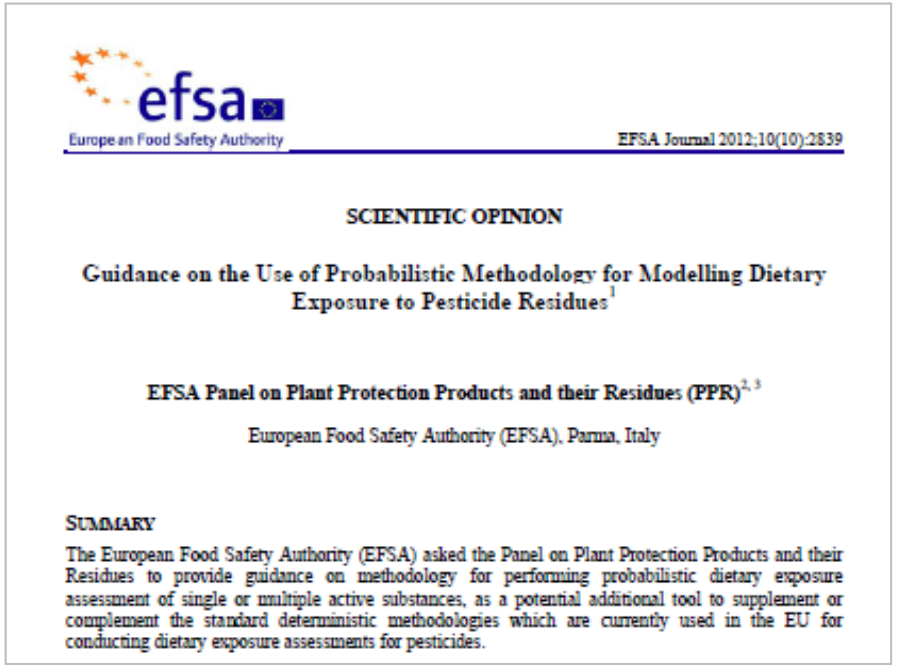
Outline of presentation

- EFSA Guidance on probabilistic assessment
- Deterministic and probabilistic
- Variability and uncertainty
- Needs and challenges in probabilistic assessment
- How these are addressed by the EFSA Guidance
- Communicating results with Risk Managers

EFSA Guidance

Main sections of Guidance:

- Introduction
- Tiered approach
- Problem definition
- Acute exposure
- Chronic exposure
- Cumulative exposure
- Outputs
- Evaluating uncertainties
- Key issues for reporting & peer review
- Interpretation of results & options for risk managers
- Validation
- Software quality requirements
- Conclusions
- Appendix: Case studies



efsa
European Food Safety Authority

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SCIENTIFIC OPINION

Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues[1]

EFSA Panel on Plant Protection Products and their Residues (PPR)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Plant Protection Products and their Residues to provide guidance on methodology for performing probabilistic dietary exposure assessment of single or multiple active substances, as a potential additional tool to supplement or complement the standard deterministic methodologies which are currently used in the EU for conducting dietary exposure assessments for pesticides.

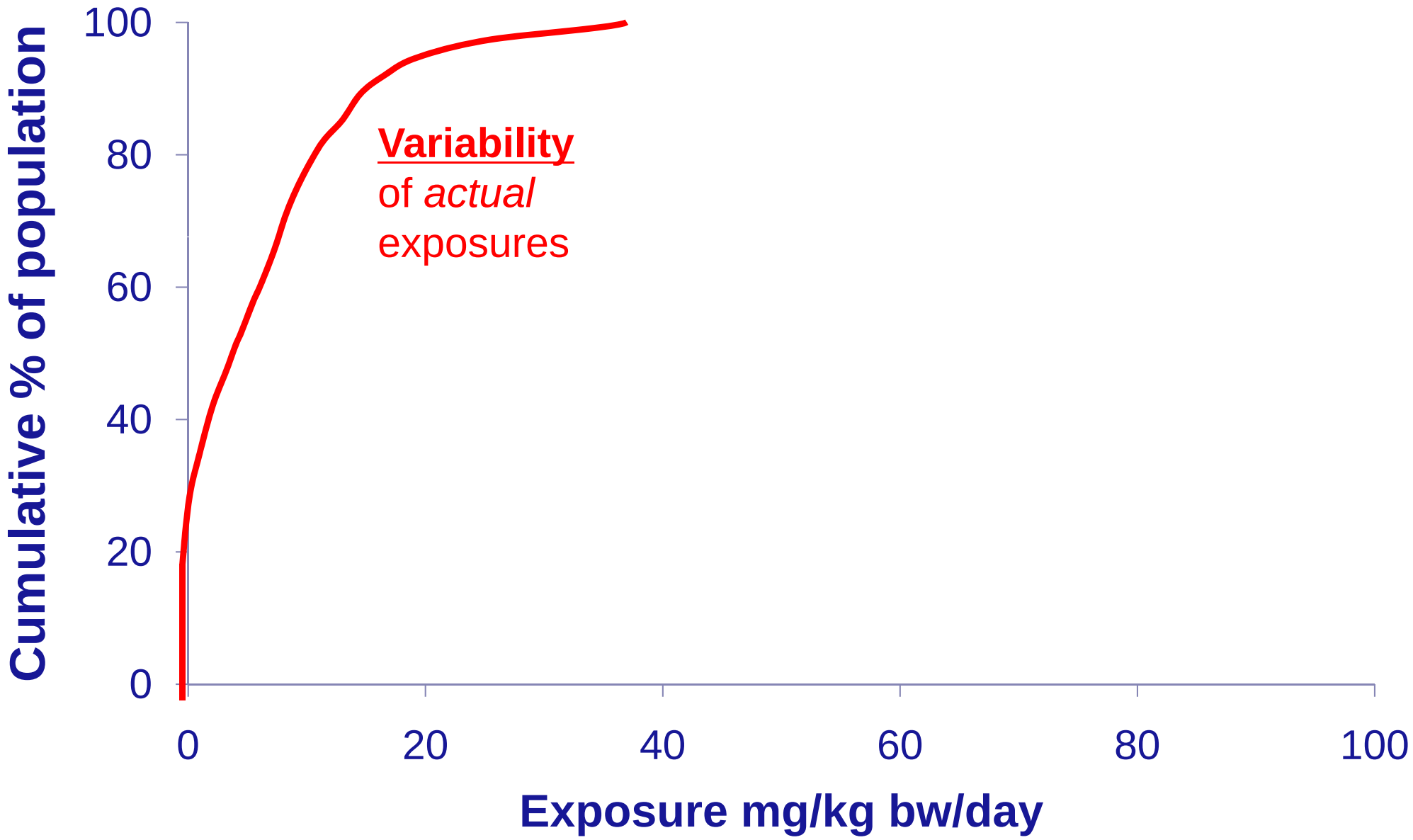
Deterministic vs. Probabilistic

- Real exposures are *variable* and *uncertain*

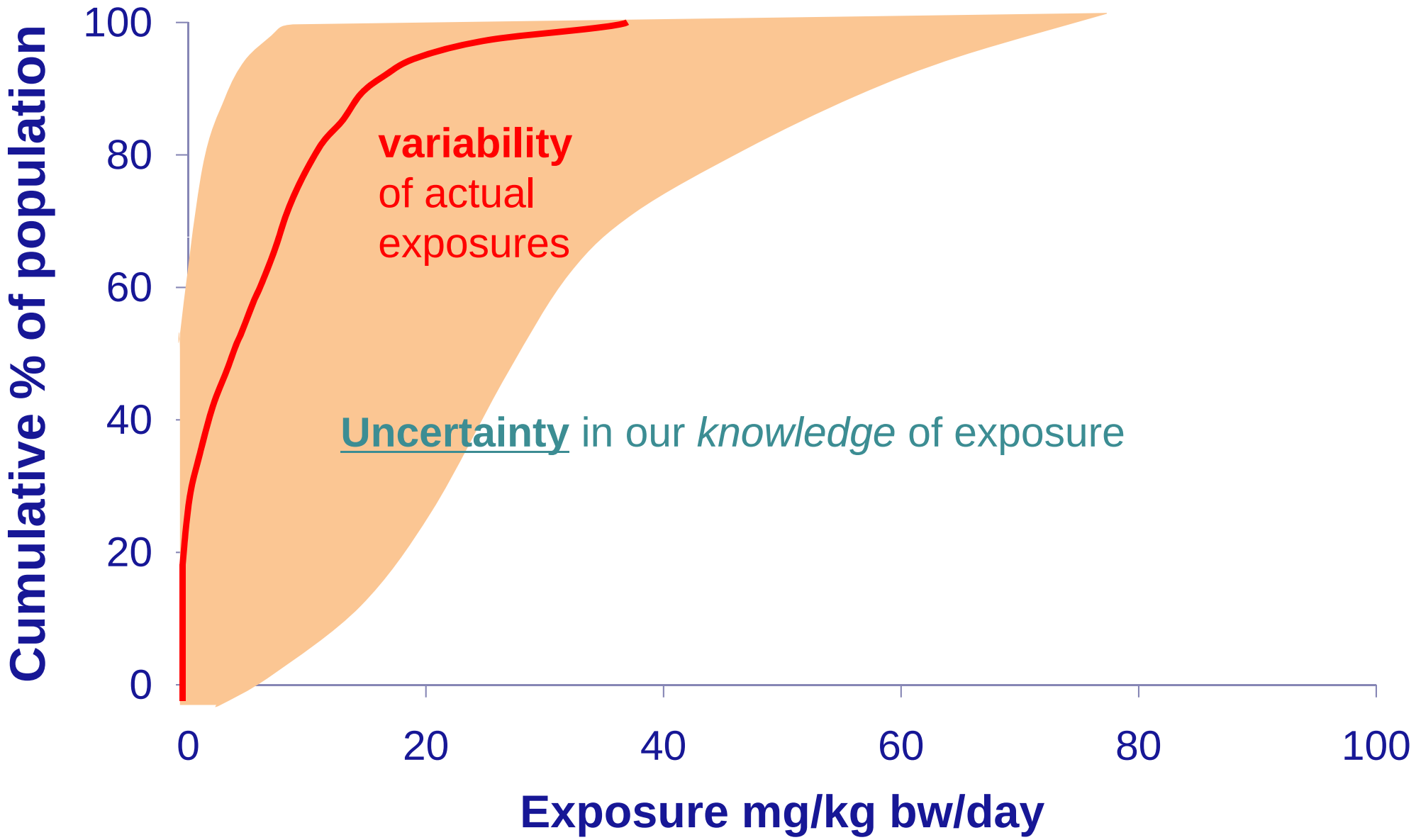
- Deterministic exposure assessment
  - Uses *point estimates* for inputs (consumption, concentration, processing effects, etc.)
  - Generates *point estimate* of exposure (a single value)
  - Intended to be ‘conservative’

- Probabilistic exposure assessment
  - Uses *distributions* to take account of variability and uncertainty of inputs
  - Generates a *distribution* of exposures
  - Intended to represent the real distribution

Variability and uncertainty



Variability and uncertainty



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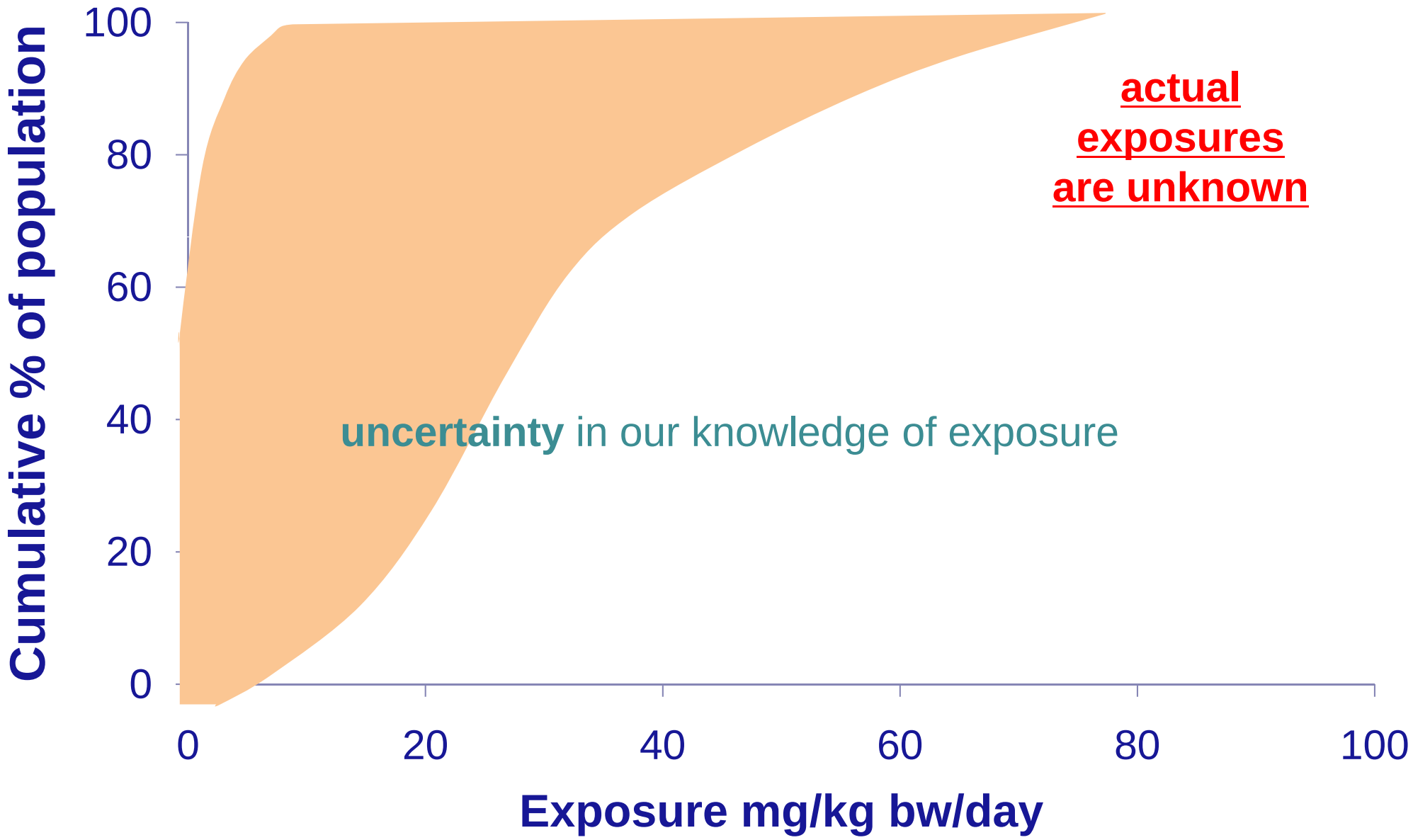

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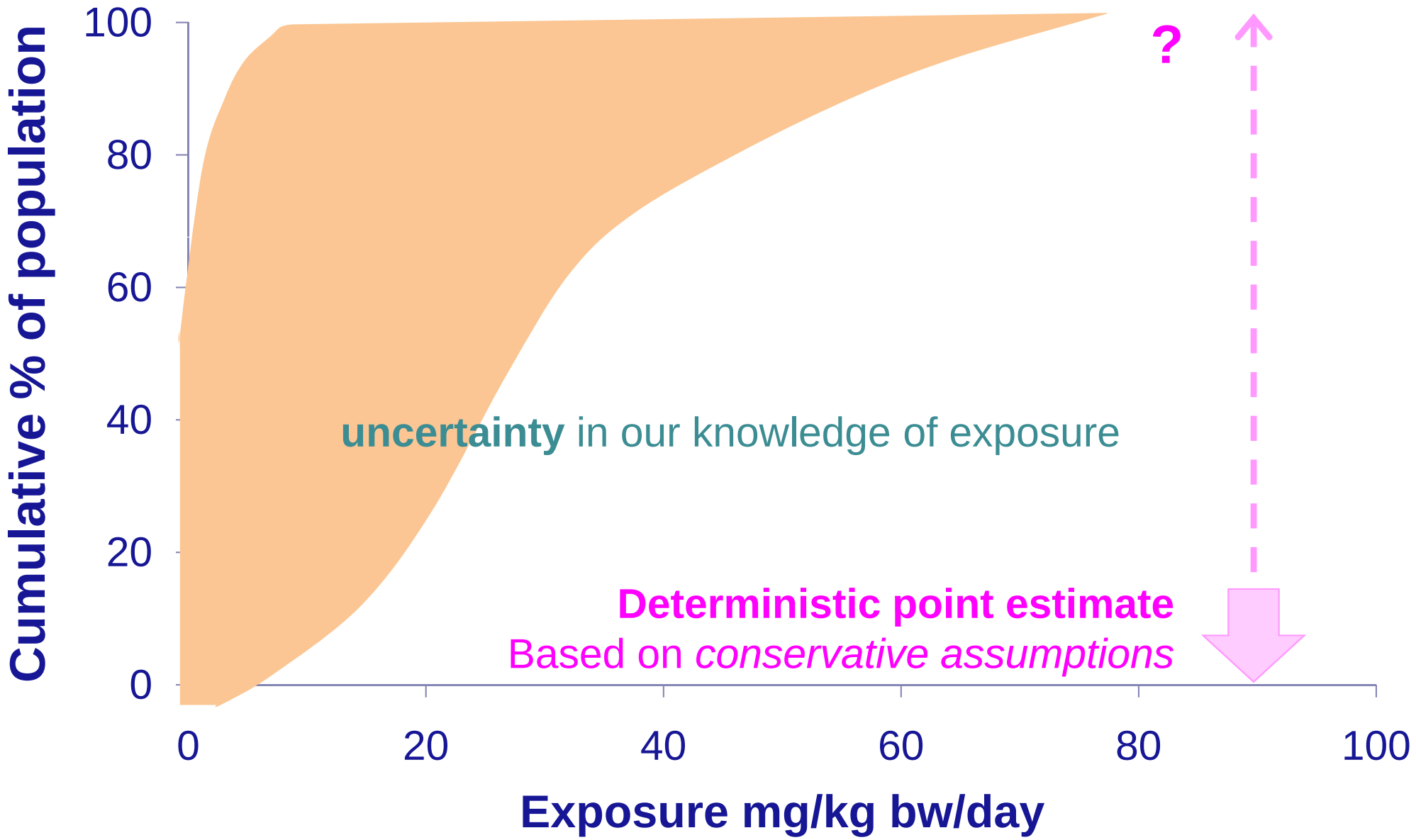
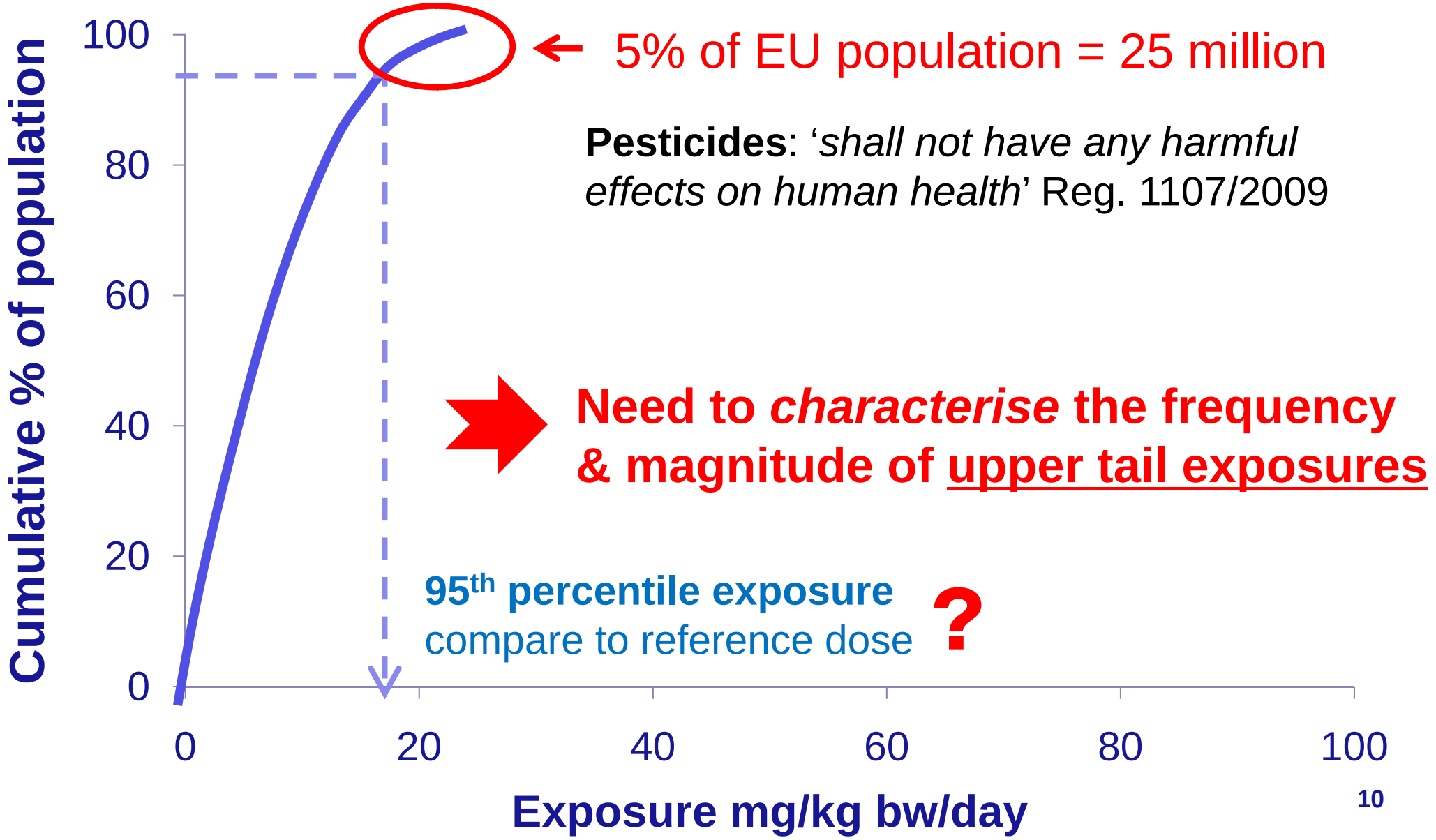
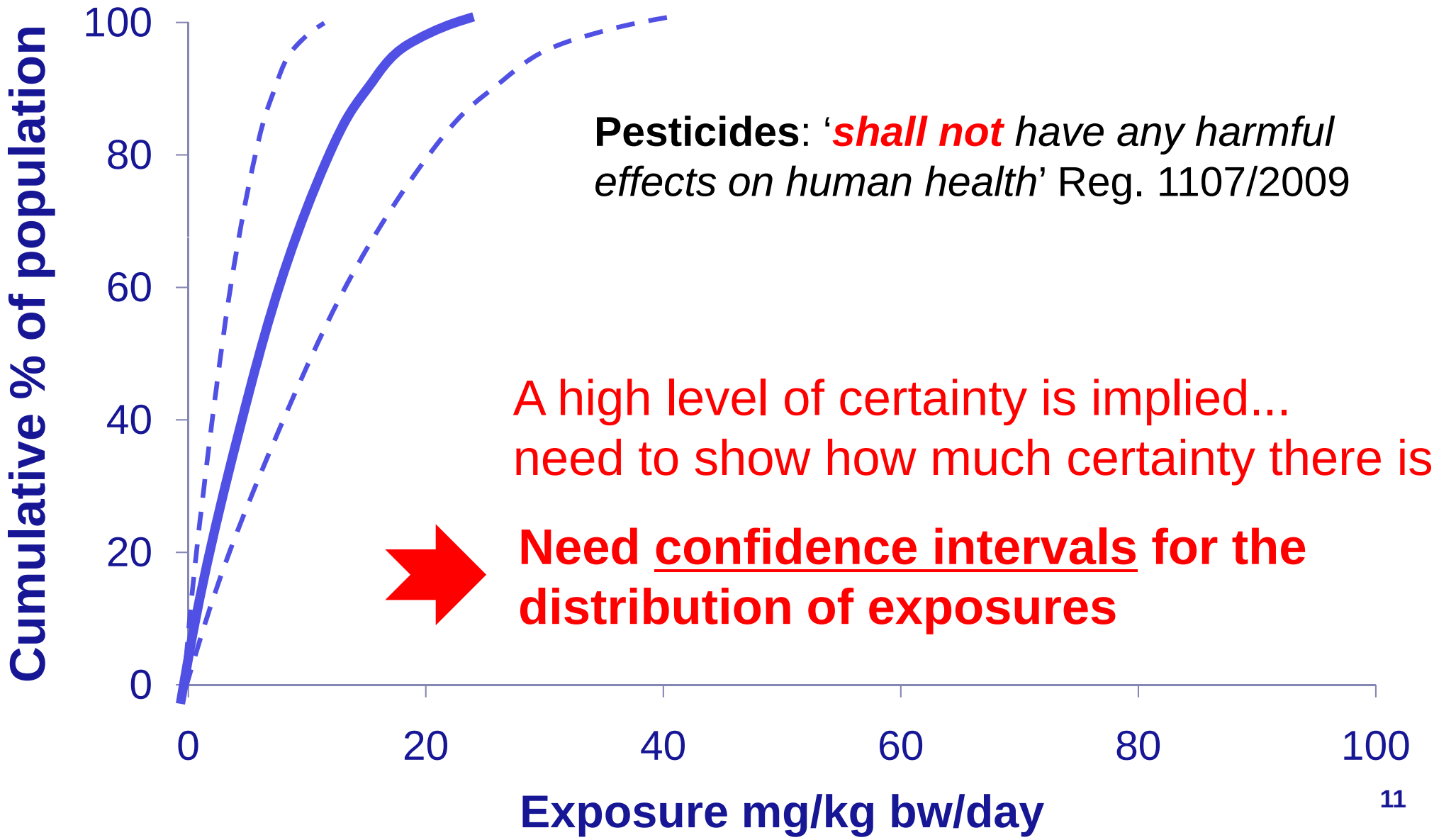


A common view of probabilistic assessment

- Option for refinement when deterministic estimate raises concern
- More realistic estimates of exposure
- Avoids over-conservative first tier assumptions
- Load my data into available software & press ‘go’
- Compare 95th percentile exposure to reference dose

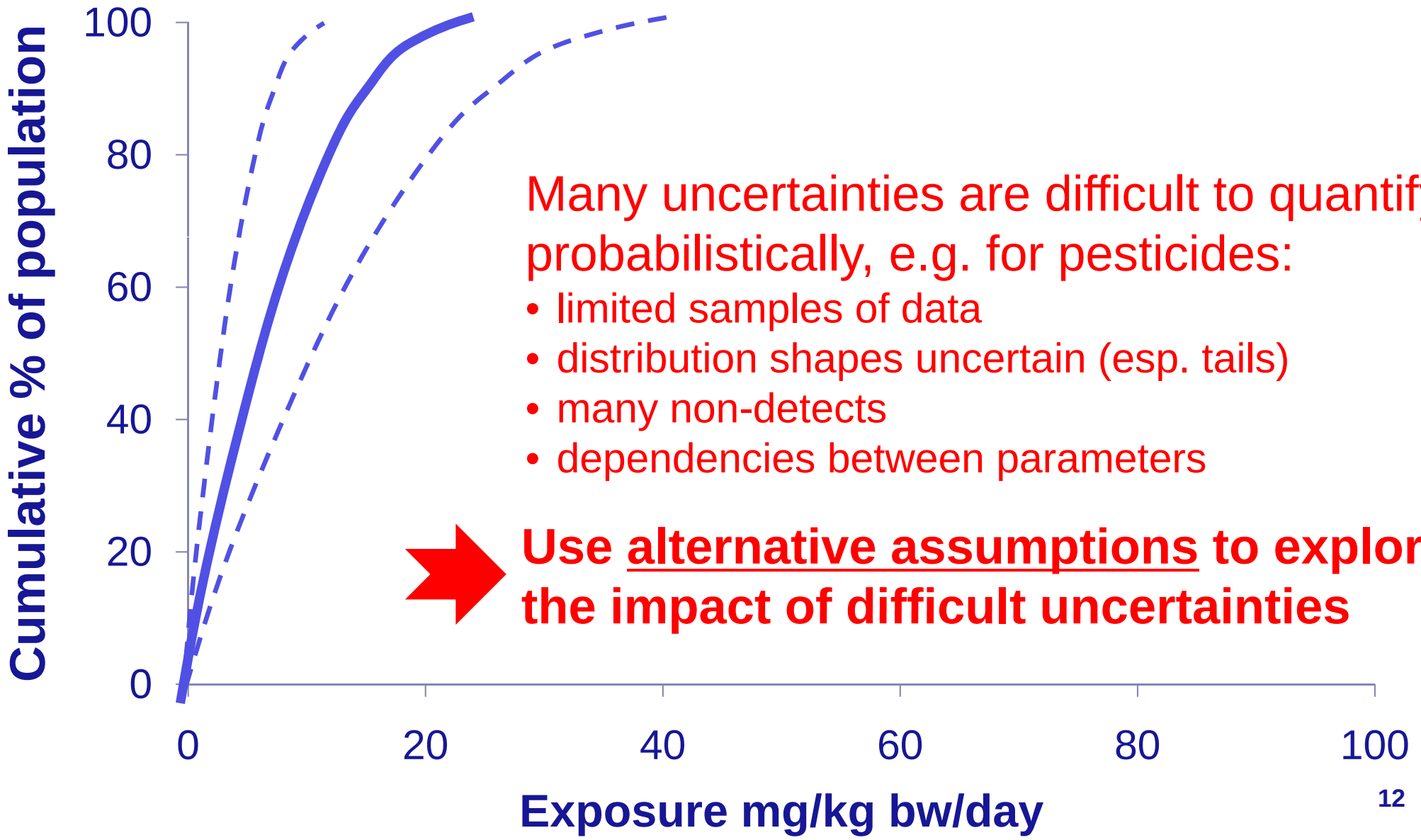

100
80
60
40
20
0
Cumulative % of population
0
20
40
60
80
100
Exposure mg/kg bw/day
5% of EU population = 25 million
Pesticides: 'shall not have any harmful effects on human health' Reg. 1107/2009
Need to characterise the frequency & magnitude of upper tail exposures
95th percentile exposure
compare to reference dose
?



Pesticides: '***shall not*** *have any harmful effects on human health*' Reg. 1107/2009

A high level of certainty is implied...
need to show how much certainty there is

Need <u>confidence intervals</u> for the distribution of exposures



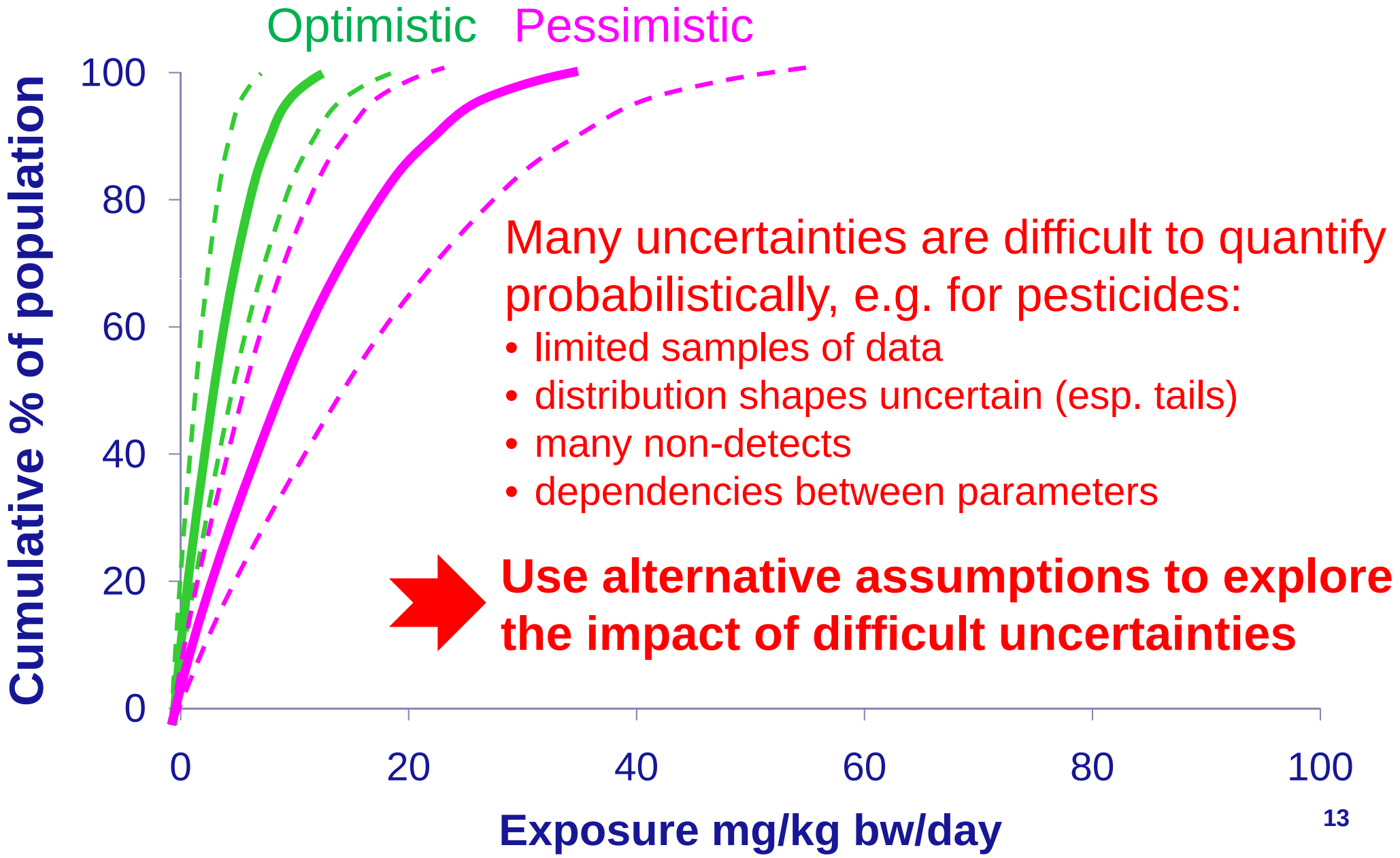
Many uncertainties are difficult to quantify probabilistically, e.g. for pesticides:

- limited samples of data
- distribution shapes uncertain (esp. tails)
- many non-detects
- dependencies between parameters

Use <u>alternative assumptions</u> to explore the impact of difficult uncertainties

Compare to Reference Dose:

stop | Further refinement required | stop



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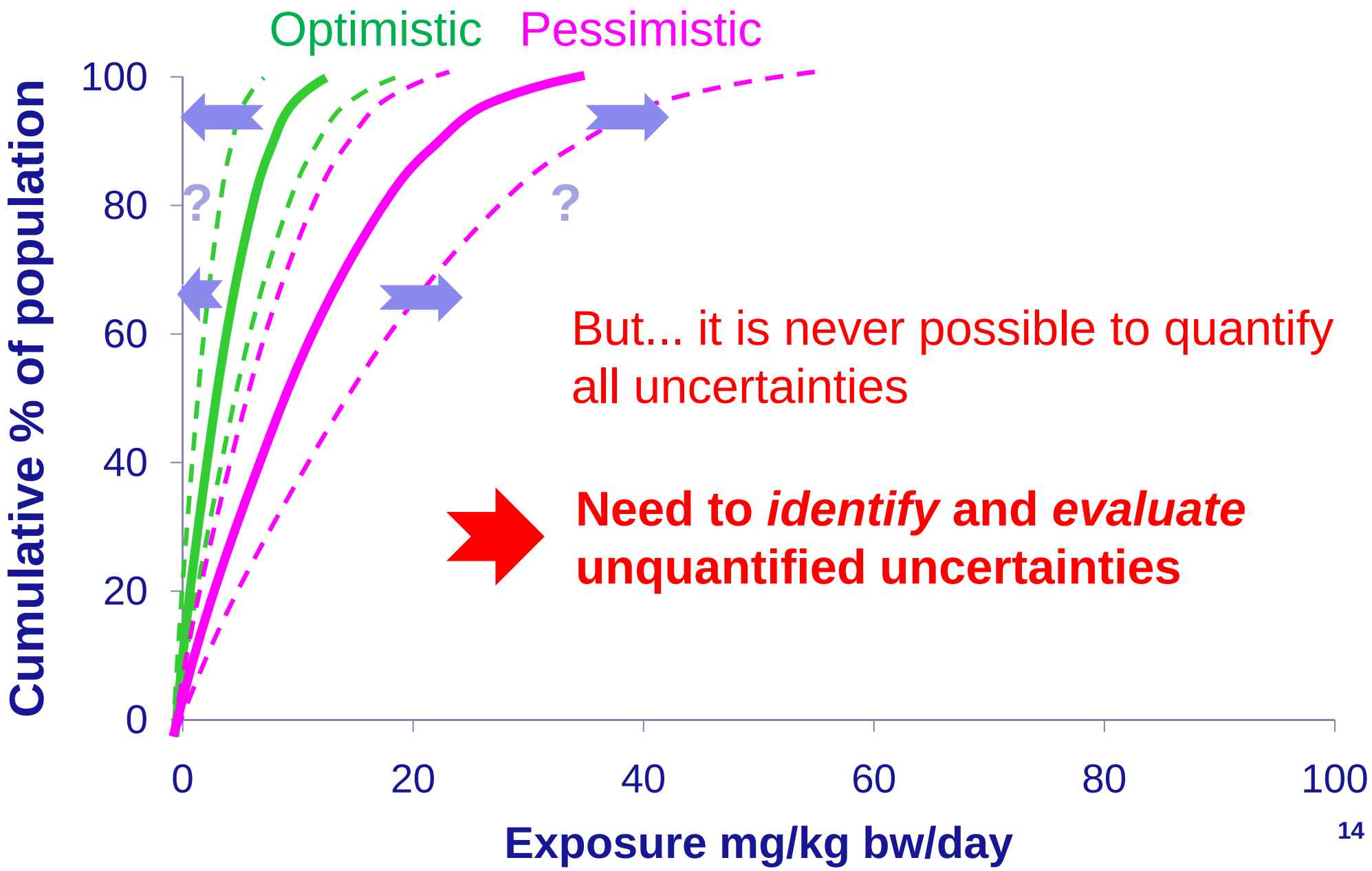
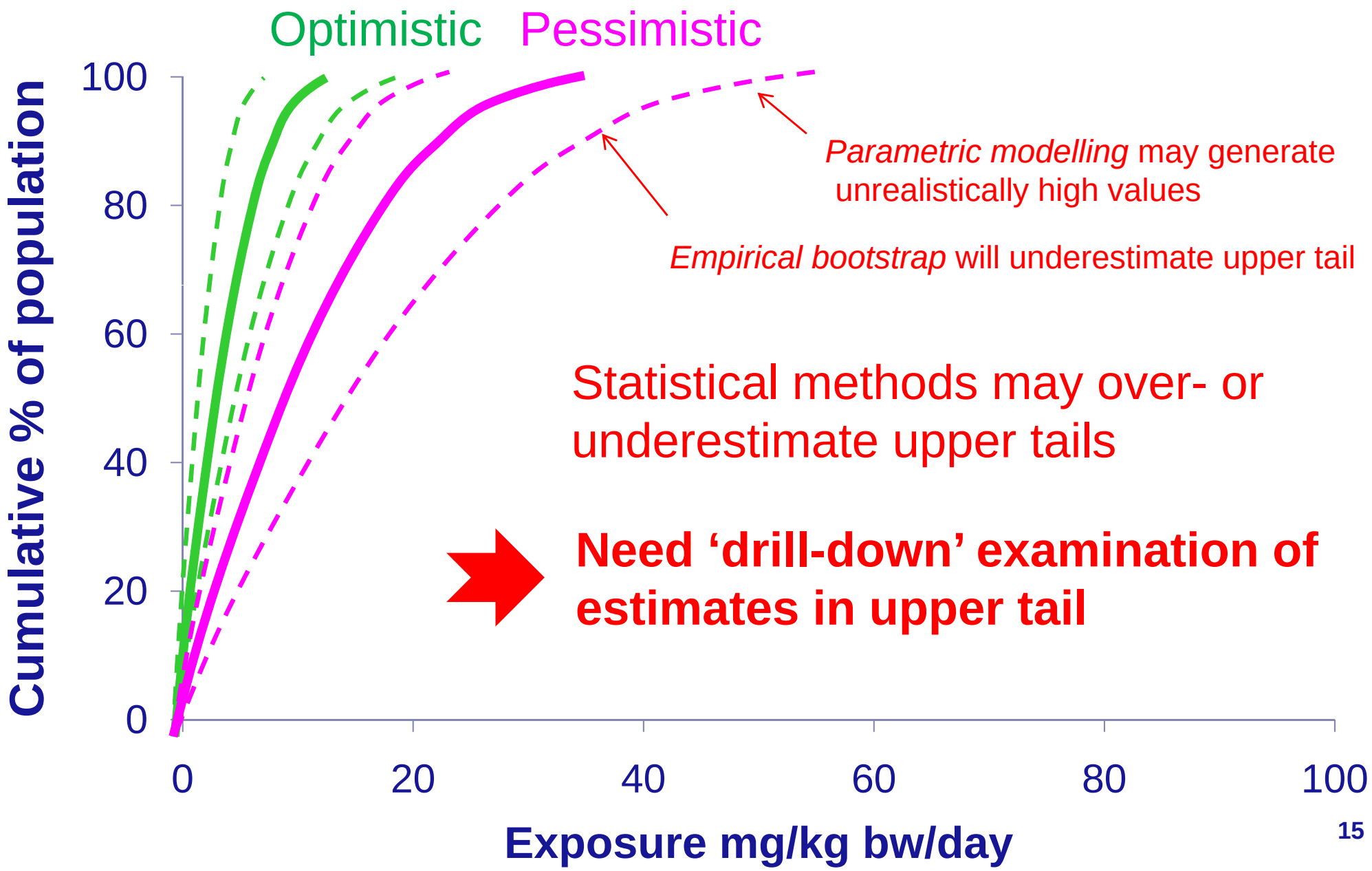


But... it is never possible to quantify all uncertainties

Need to *identify* and *evaluate* unquantified uncertainties


Optimistic
Pessimistic
100
80
60
40
20
0
Cumulative % of population
0
20
40
60
80
100
Exposure mg/kg bw/day
Parametric modelling may generate unrealistically high values
Empirical bootstrap will underestimate upper tail
Statistical methods may over- or underestimate upper tails
Need 'drill-down' examination of estimates in upper tail

Key needs in probabilistic assessment

- Focus on characterising upper tail exposures, not on an arbitrary percentile of the distribution
- Give confidence intervals for quantified uncertainties
- Use alternative assumptions to assess uncertainties that are difficult to quantify probabilistically
- Evaluate the impact of unquantified uncertainties
- ‘Drill-down’ to check for over- and underestimation in upper tail

PPR Panel Guidance

- How does it address the needs identified above?

PPR Panel Guidance

- Use alternative assumptions to assess uncertainties that are difficult to quantify probabilistically

- Start with a ***Basic Assessment*** using **Optimistic and Pessimistic assumptions** for:
  - Residue distribution (bootstrap vs. lognormal)
  - Sampling uncertainty (bootstrap vs. parametric)
  - Unit-to-unit variability (none vs. conservative est.)
  - Non-detects (zero vs. Limit of Reporting)
  - Processing effects (zero vs. deterministic estimate)
  - % crop treated (approx. estimate vs. 100%)
  - Residues in water (zero, legal limit)
  - etc...
- If important, quantify further in ***Refined Assessment***

PPR Panel Guidance

- Focus on characterising upper tail, not an arbitrary percentile
- Give confidence intervals for quantified uncertainties

Exposure levels expressed as % of reference dose and/or Margin of Exposure

Exposure levels		Number of person-days per million exceeding exposure level	
% of ARfD	MoE*	Optimistic model run	Pessimistic model run
1	10000	2000 (500 – 7000)	5000 (1000 – 17,000)
10	1000	500 (200 – 1200)	1500 (300 – 4000)
50	200	50 (10 – 500)	400 (100 – 1300)
100**	100	10 (<10 – 50)	60 (20 – 300)
200	50	<10 (<10 – 10)	10 (<10 – 40)
500	20	<10 (<10 - <10)	<10 (<10 – <10)

Frequency of exceedance per million

Optimistic & Pessimistic assumptions

Estimated frequencies & confidence intervals

'<' = below resolution of model

PPR Panel Guidance

- Evaluate the impact of unquantified uncertainties
- 'Drill-down' to check for over- and underestimation in upper tail

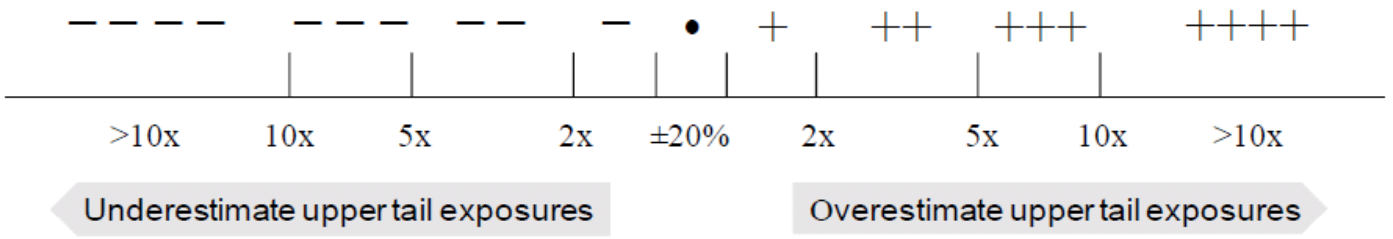
Exposure levels		Number of person-days per million exceeding exposure level		Additional considerations & uncertainties[65]
% of ARfD	MoE*	Optimistic model run	Pessimistic model run	
1	10000	2000 (500 – 7000)	5000 (1000 – 17,000)	*Indicate overall direction and magnitude of additional uncertainties, e.g., by inserting summary text from bottom row of uncertainty table (see Section 8).*
10	1000	500 (200 – 1200)	1500 (300 – 4000)	
50	200	50 (10 – 500)	400 (100 – 1300)	
100**	100	10 (<10 – 50)	60 (20 – 300)	
200	50	<10 (<10 – 10)	10 (<10 – 40)	*Identify or omit results that are based on clearly unrealistic extremes of input distributions.*
500	20	<10 (<10 - <10)	<10 (<10 – <10)	*Use '<' to indicate results that are below the sensitivity of the model.*

Evaluation of unquantified uncertainties

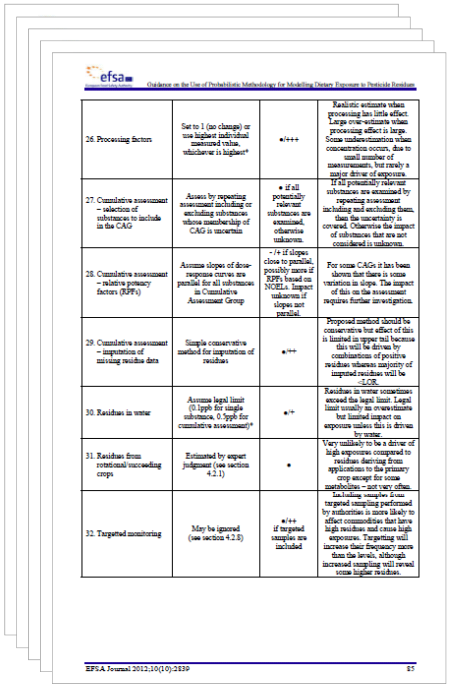
Findings from drill-down check of tail results

PPR Panel Guidance

- Evaluate the impact of unquantified uncertainties



Assessment component	Approach in pessimistic model run	Subjective evaluation of impact on the upper tail exposures	Brief explanation of evaluation
1. Modelling food consumption	Empirical + bootstrap; examine which commodities contribute to upper tail exposures §¶	• (common foods and large survey) - - / • (small survey and/or rare foods)	Model is limited to intakes observed in survey. With large surveys this will cause no underestimation for common foods. Tendency to underestimation if there is limited data for the foods driving exposure
2. Use of old food consumption survey data	Not considered	• (*sometimes* - /+)	Little effect unless consumption has recently changed for a food with high residues



Cumulative exposure

- Everything so far applies equally to both single substance *and* cumulative assessments

- In addition, for cumulative assessments:
  - Use Relative Potency Factors to combine exposure contributions of different substances in CAG
  - For acute exposure, take account of correlations between concentrations of different substances in same food type
    - Use statistical models to fill gaps in residue database

Section 6 of Guidance

An additional challenge...

- Communication and interpretation of results

- Exposure assessment characterises the upper tail:
  - Person(-day)s per million exceeding effect level
  - Confidence intervals for quantified uncertainties
  - Potential impact of unquantified uncertainties
- Question for *toxicologists*:
  - What is the likelihood & severity of effects for these upper tail exposures?
- Question for *risk managers*:
  - Are results consistent with ‘not any harmful effects’ ?

Summary

- Focus on characterising upper tail exposures, not on an arbitrary percentile of the distribution
- Give confidence intervals for quantified uncertainties
- Use alternative assumptions to assess uncertainties that are difficult to quantify probabilistically
- Evaluate the impact of unquantified uncertainties
- ‘Drill-down’ to check for over- & underestimation in tail
- Communicate and interpret results