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Probabilistic Dietary Exposure Assessment

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Outline

- Deterministic and probabilistic
  - Variability and uncertainty
  - What are we trying to estimate?
- Needs and challenges in probabilistic assessment
- EFSA PPR Panel Guidance
- Future directions

A personal perspective

Deterministic vs. Probabilistic

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- Deterministic
  - Uses *point estimates* for inputs (consumption, concentration, processing effects, etc.)
  - Generates point estimate of exposure
- Probabilistic
  - Uses *distributions* to take account of variability and uncertainty of inputs
  - Generates a distribution of exposures

Variability and uncertainty

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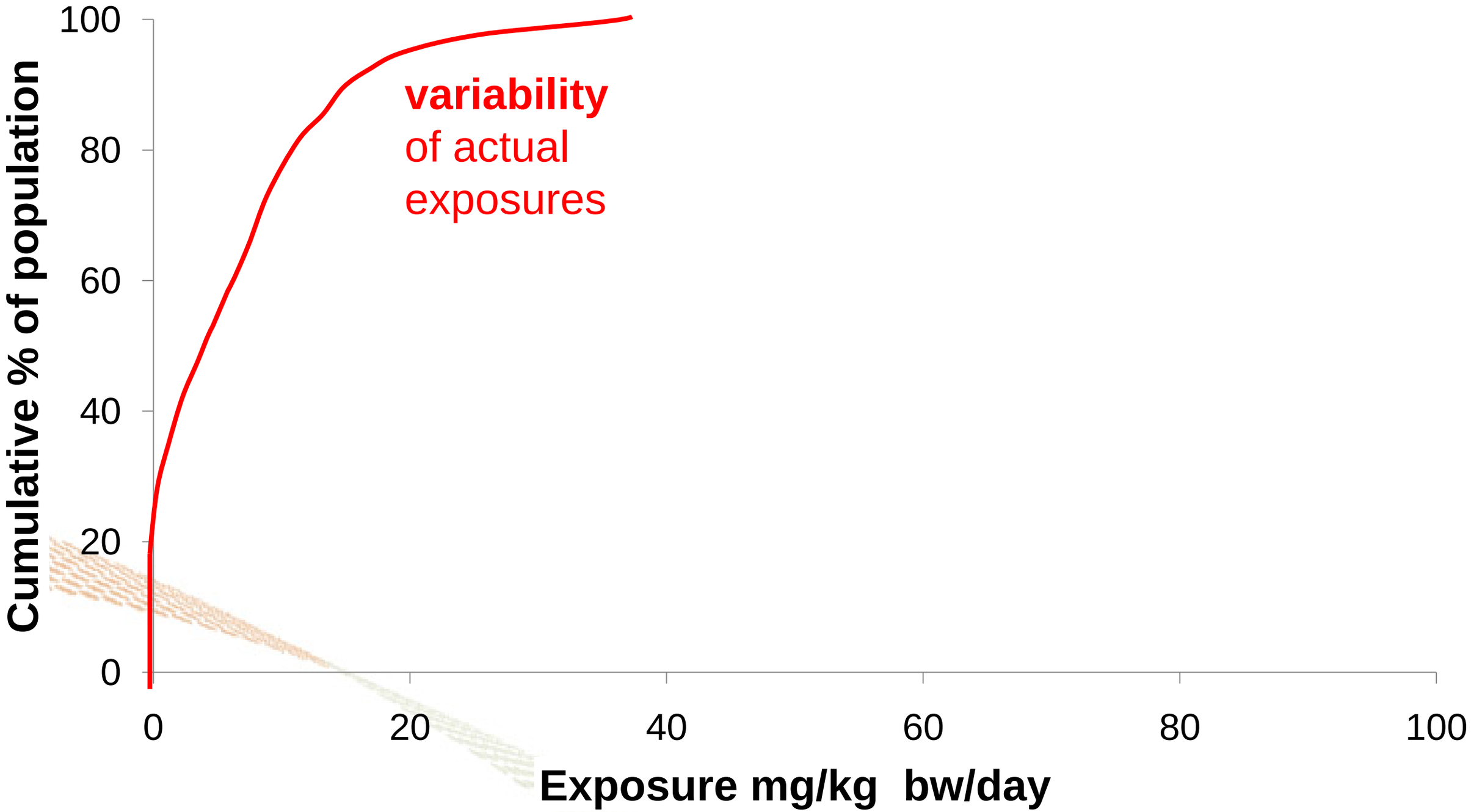

Variability and uncertainty

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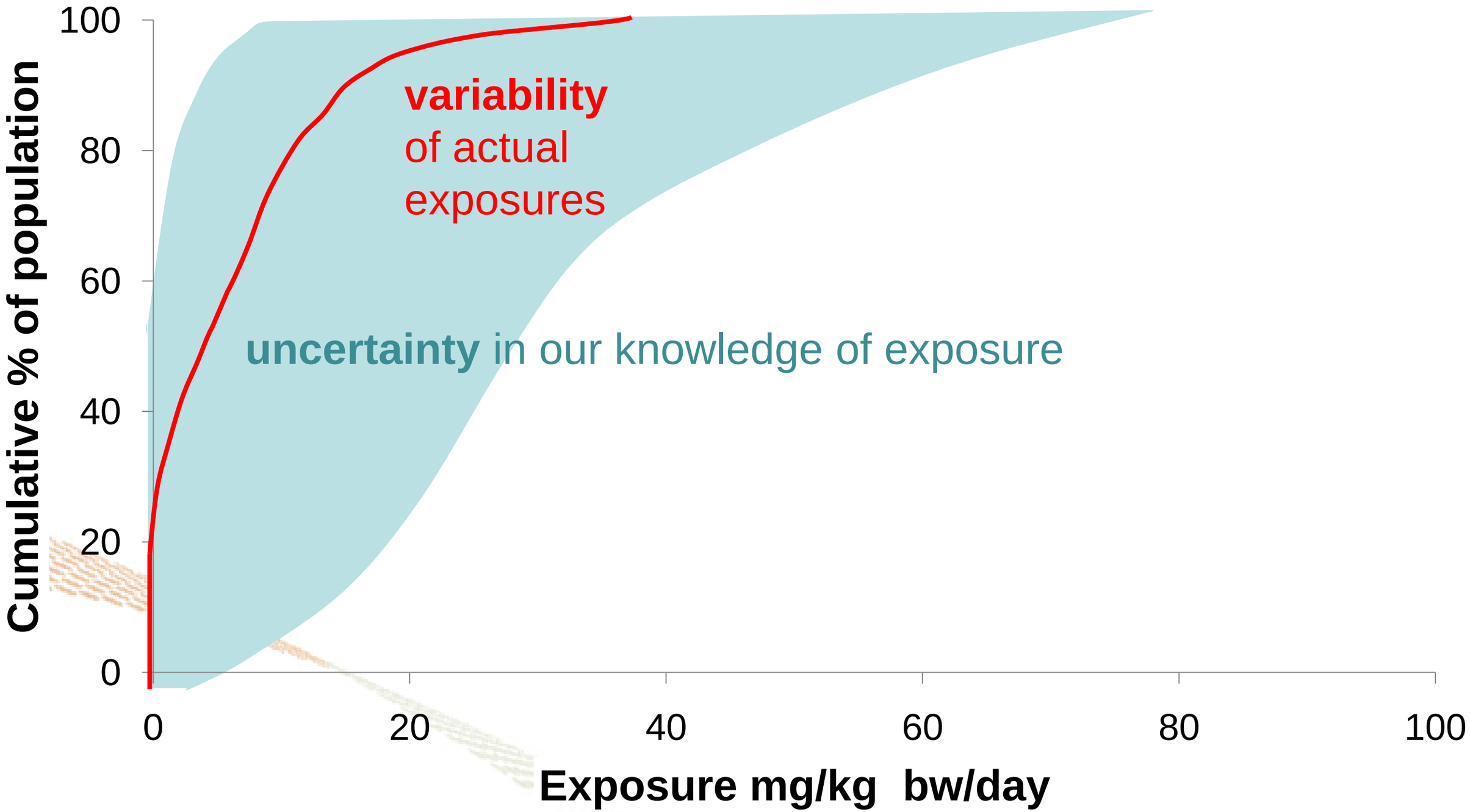

Variability and uncertainty

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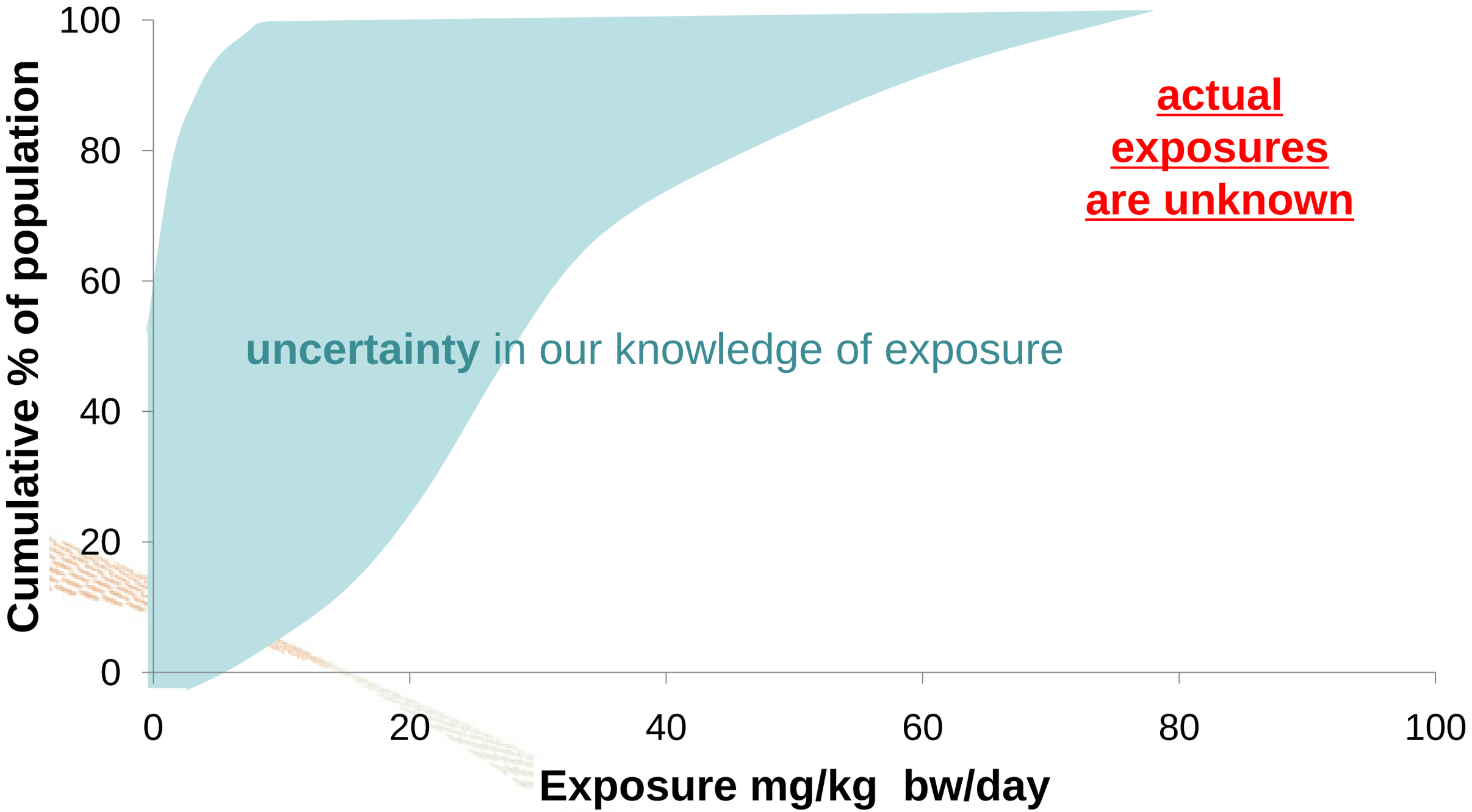

actual exposures are unknown

Deterministic assessment

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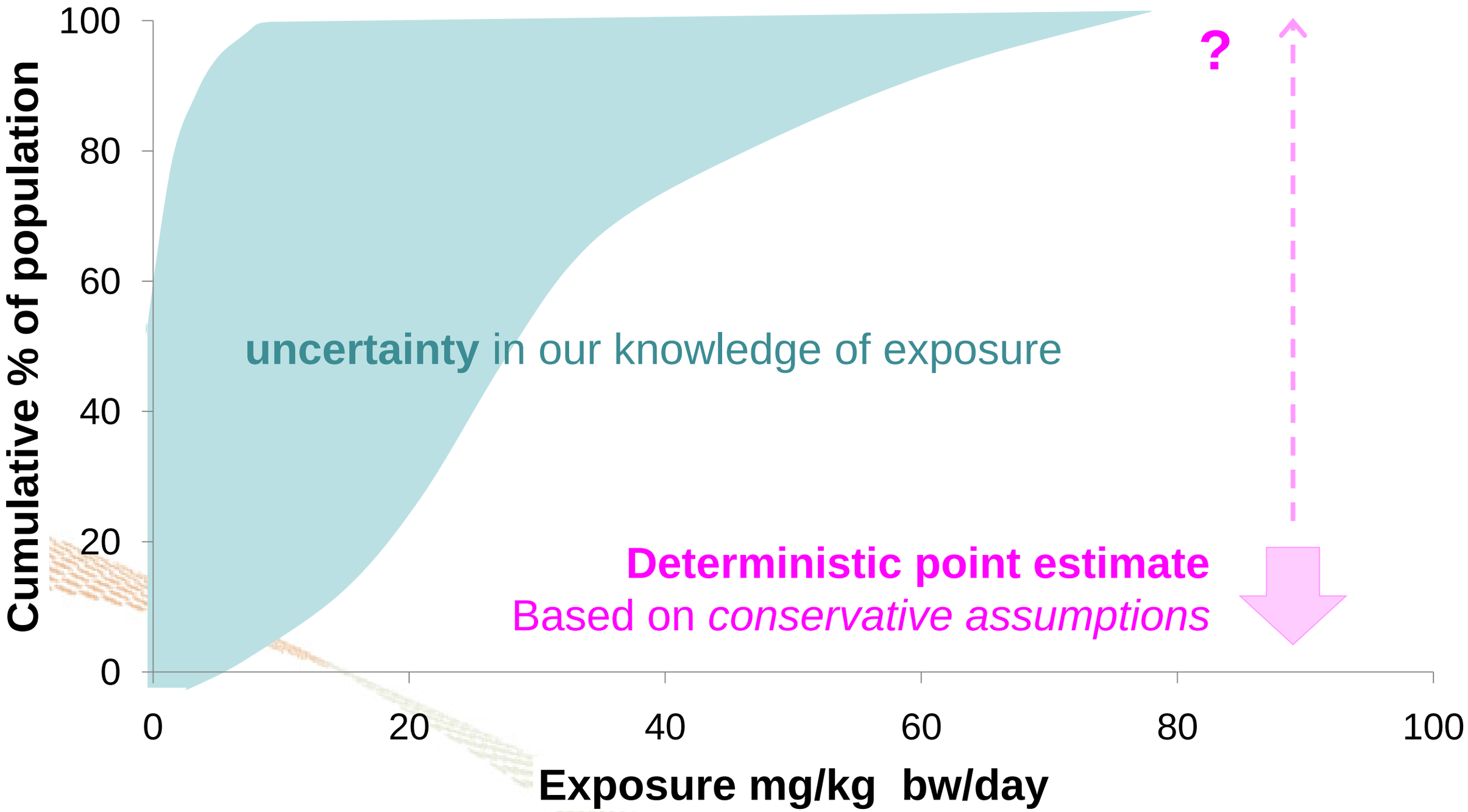

A typical view of probabilistic assessment

- Option for refinement when concern at Tier 1

- More realistic estimates of exposure
- Avoids over-conservative first tier assumptions

- Load my data into available software and press ‘go’

- Compare 95th percentile exposure to reference dose

- Good chance of solving my problem...

Probabilistic assessment

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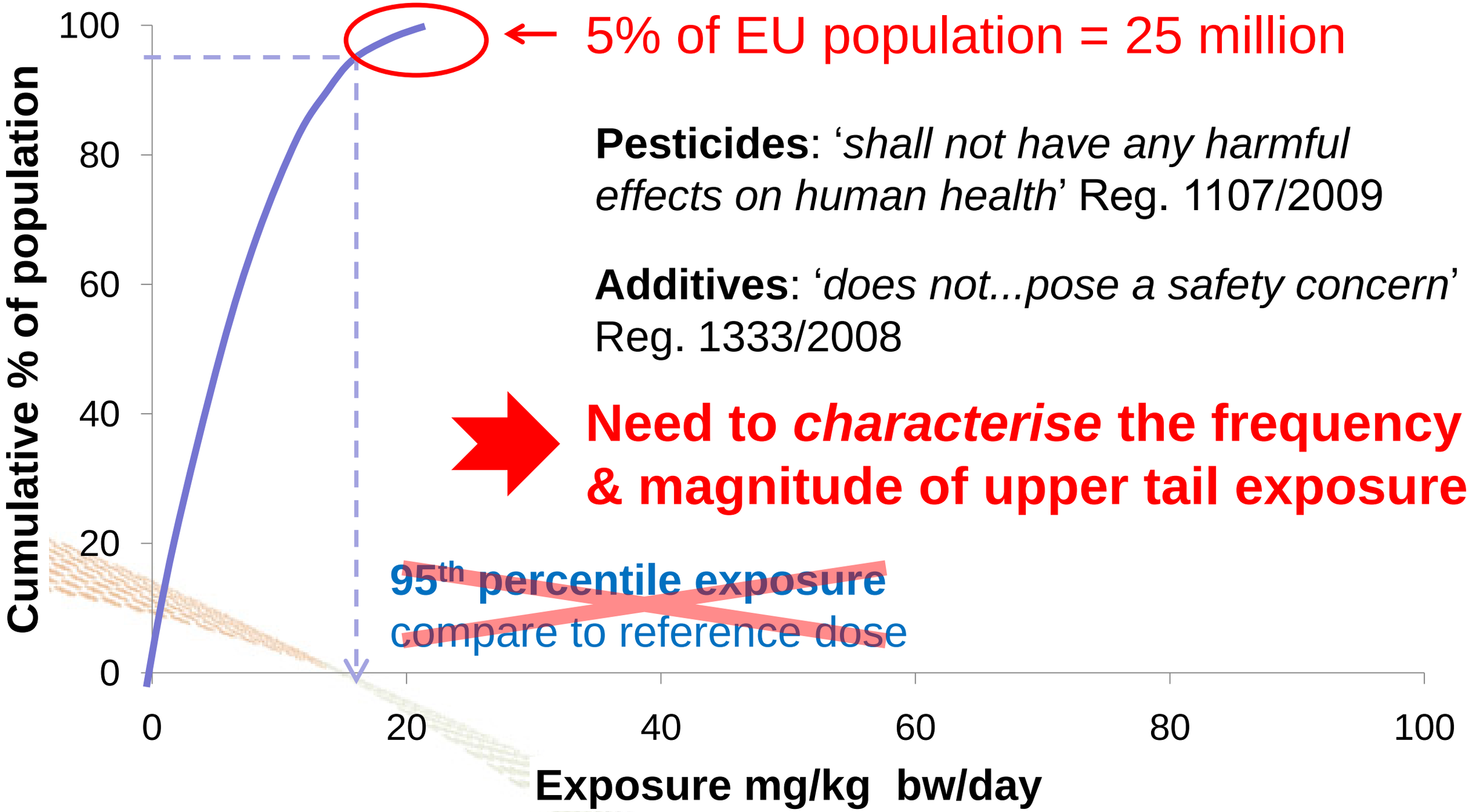


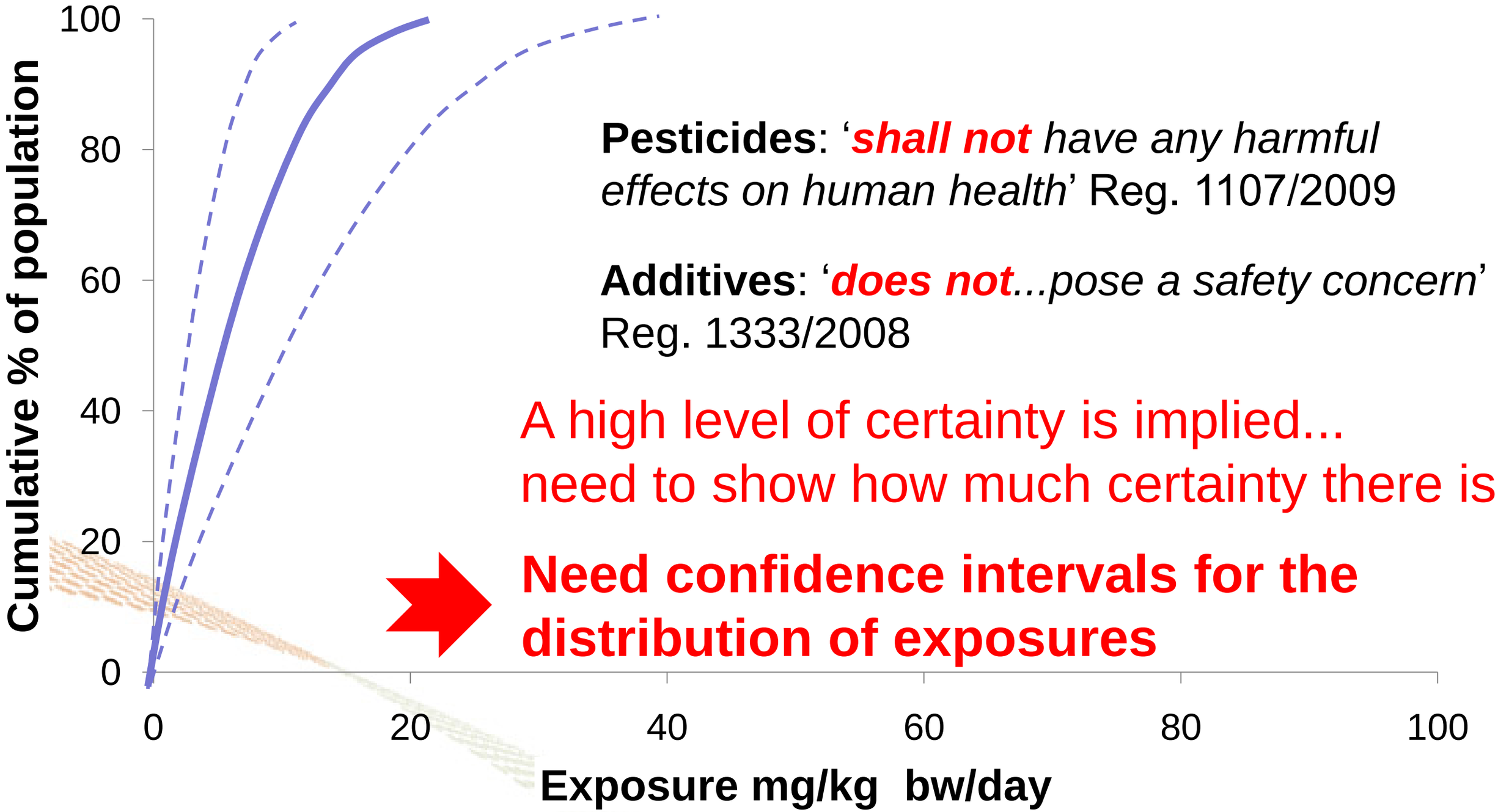
← 5% of EU population = 25 million

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

Additives: '*does not...pose a safety concern*' Reg. 1333/2008

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

Additives: '***does not****...pose a safety concern*' Reg. 1333/2008

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

Need confidence intervals for the distribution of exposures

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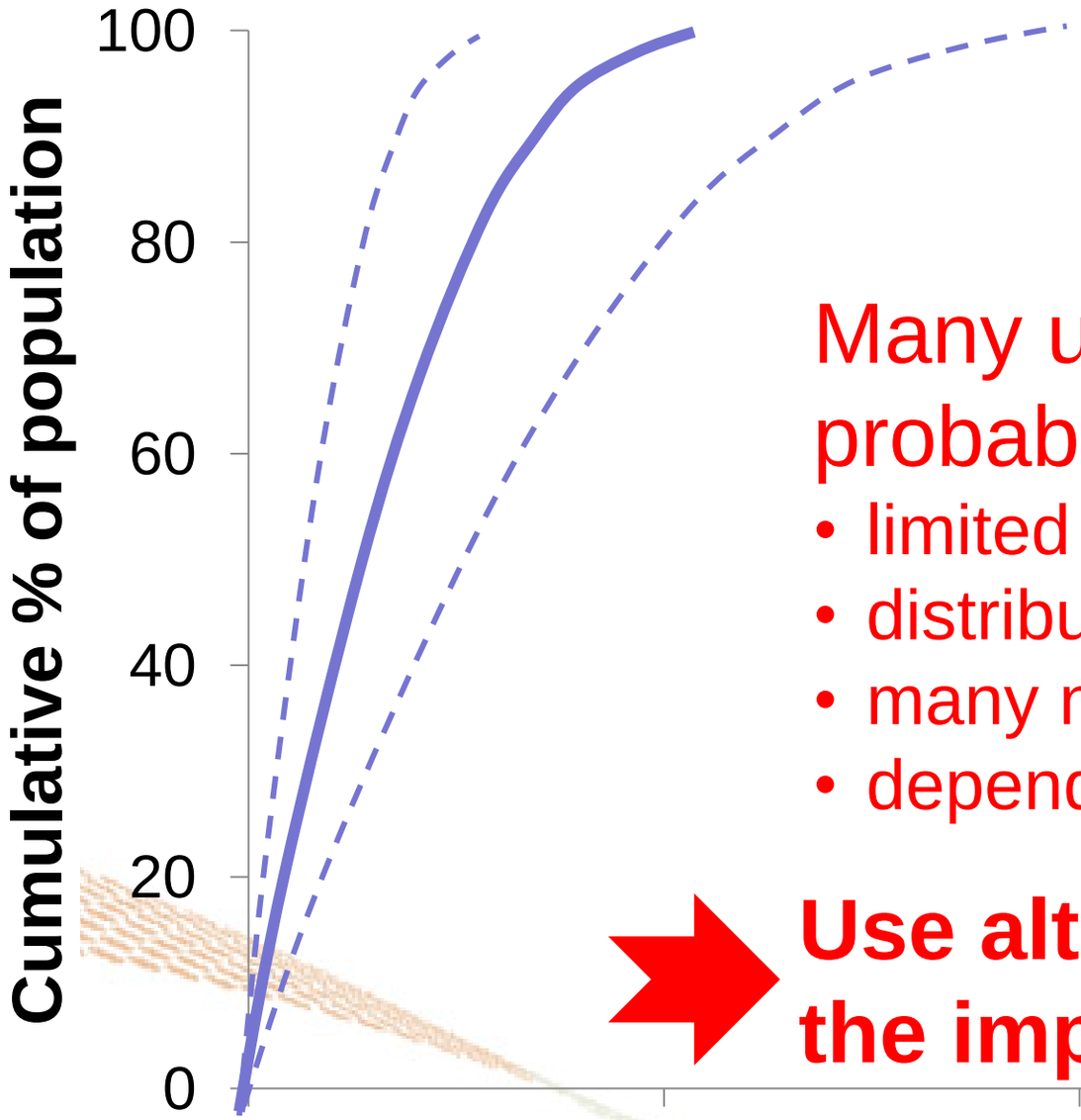


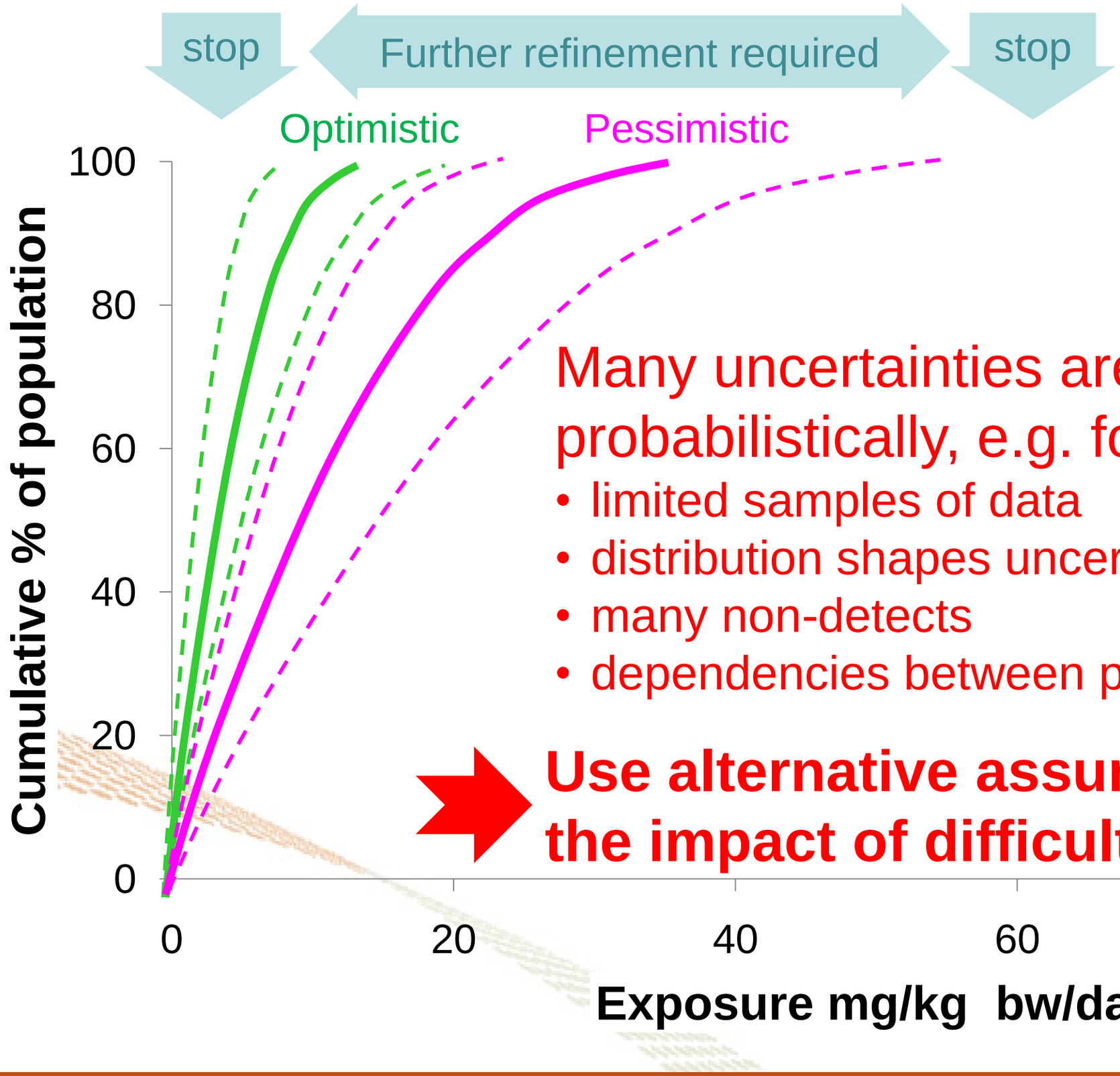
Many uncertainties are difficult to quantify probabilistically, e.g. for pesticides:

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

Use alternative assumptions to explore the impact of difficult uncertainties

Compare to Reference Dose:

stop | Further refinement required | stop



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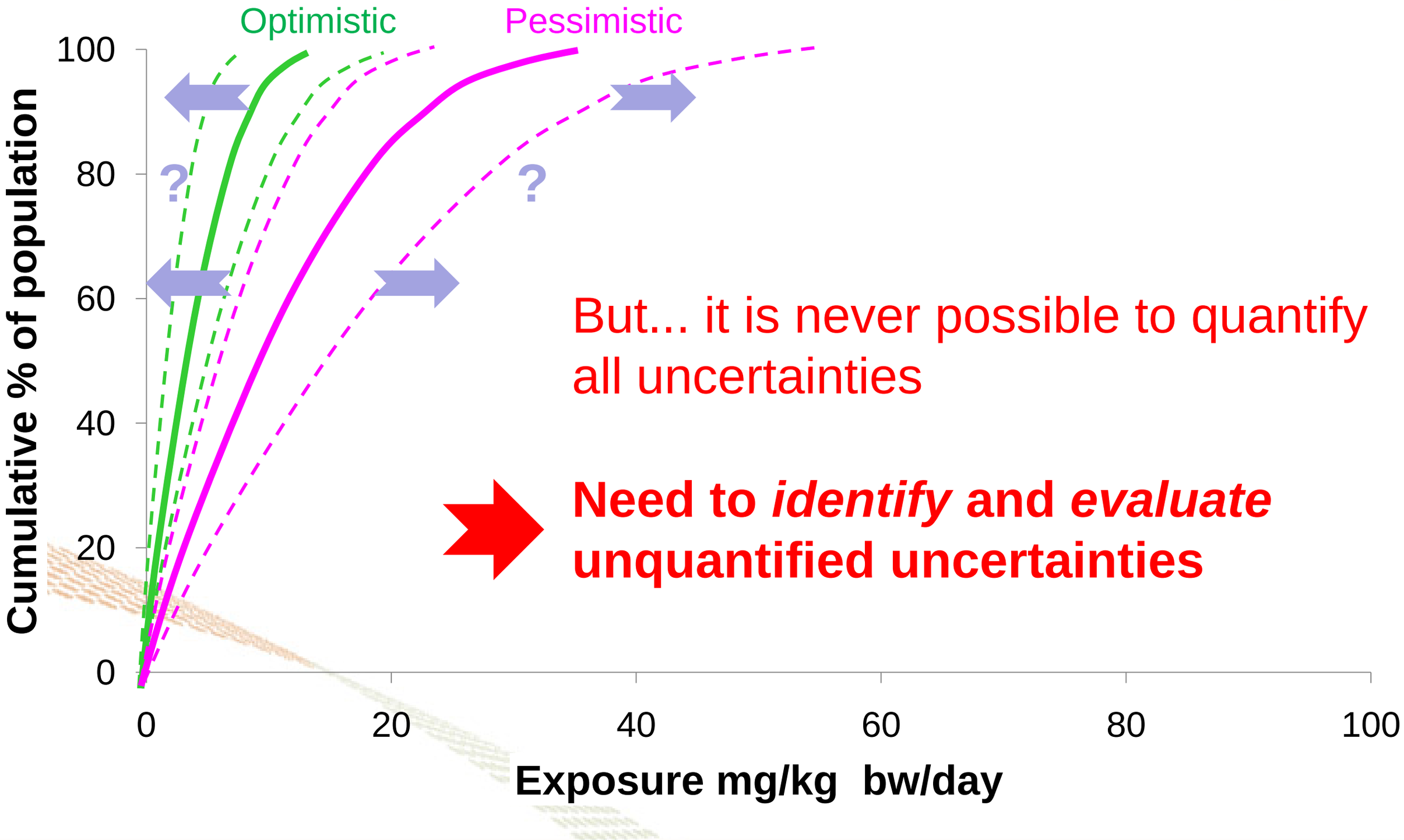

But... it is never possible to quantify all uncertainties

Need to *identify* and *evaluate* unquantified uncertainties

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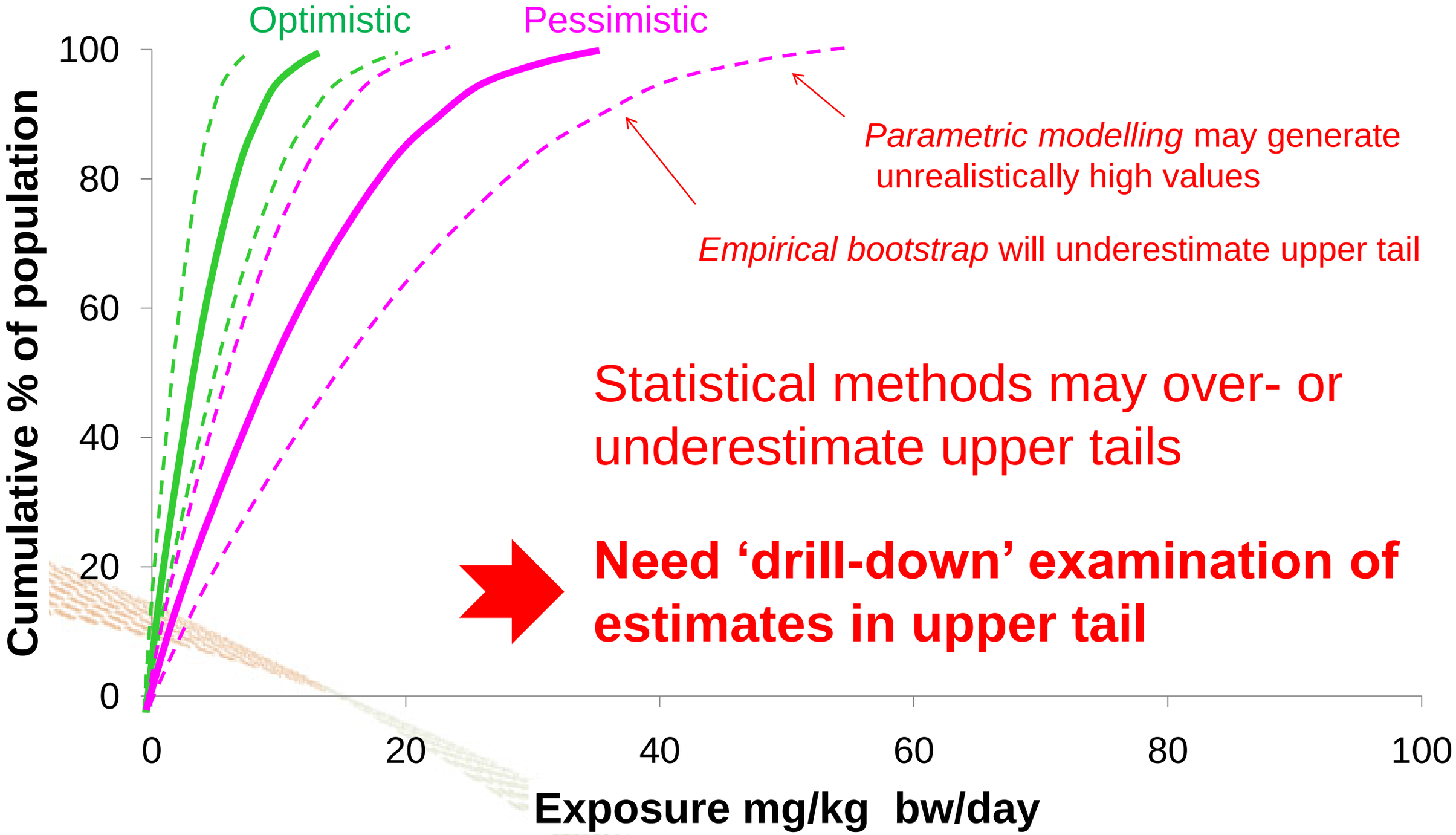

Parametric modelling may generate unrealistically high values

Empirical bootstrap will underestimate upper tail

Statistical methods may over- or underestimate upper tails

Need 'drill-down' examination of estimates in upper tail

Needs identified so far...

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- 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

New PPR Panel Guidance

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- Published 5 October 2012
- How does it address the needs identified above?

New PPR Panel Guidance

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

- *Start* with **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*

New PPR Panel Guidance

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- 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

New PPR Panel Guidance

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- 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

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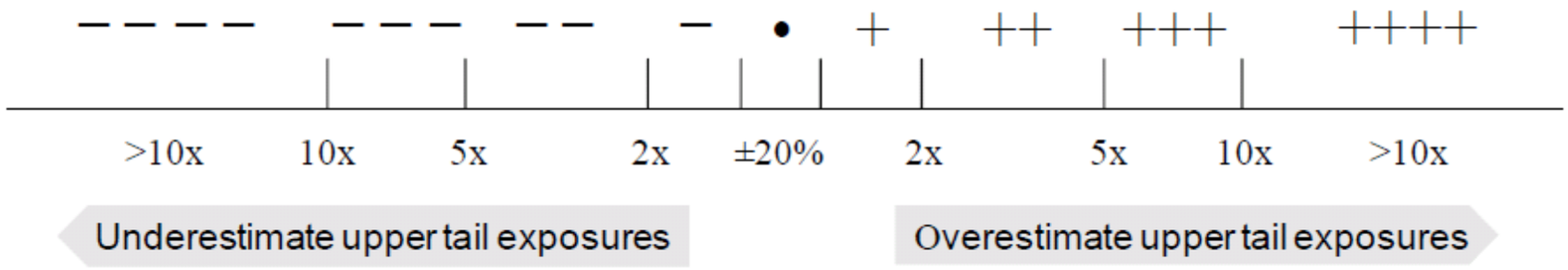
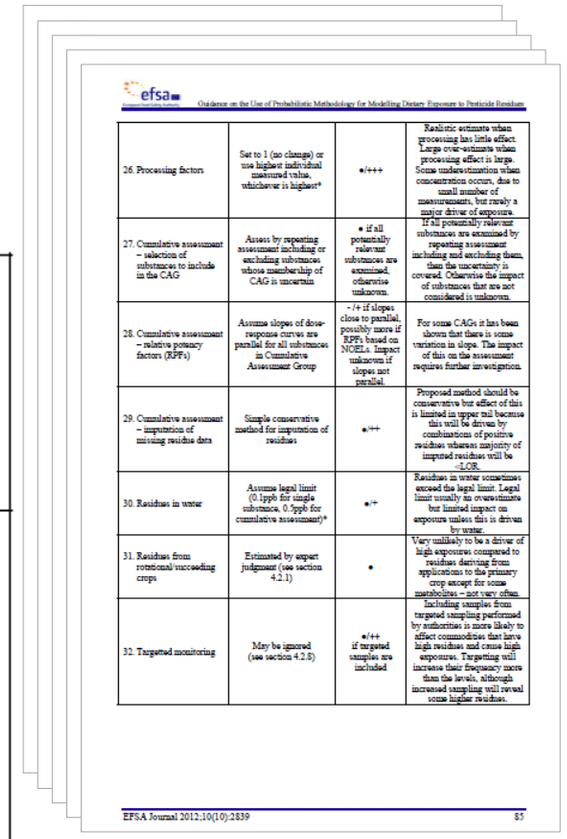
- Evaluate the impact of unquantified uncertainties



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


efsa — Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues

26. Processing factors	Set to 1 (no change) or use highest individual measured value, whichever is highest*	•/+++	Realistic estimate when processing has little effect. Large over-estimate when processing effect is large. Some underestimation when concentrations occurs, due to small number of measurements, but rarely a major driver of exposure.
27. Cumulative assessment – selection of substances to include in the CAG	Assess by repeating assessment including or excluding substances whose membership of CAG is uncertain	• if all potentially relevant substances are examined, otherwise unknown.	If all potentially relevant substances are examined by repeating assessment including and excluding them, then the uncertainty is covered. Otherwise the impact of substances that are not considered is unknown.
28. Cumulative assessment – relative potency factors (RPFs)	Assume slopes of dose-response curves are parallel for all substances in Cumulative Assessment Group	- /+ if slopes close to parallel, possibly more if RPFs based on NOELs. Impact unknown if slopes not parallel	For some CAGs it has been shown that there is some variation in slope. The impact of this on the assessment requires further investigation.
29. Cumulative assessment – imputation of missing residue data	Simple conservative method for imputation of residues	•/++	Proposed method should be conservative but effect of this is limited in upper tail because this will be driven by combinations of positive residues whereas majority of imputed residues will be <LOR.
30. Residues in water	Assume legal limit (0.1ppb for single substance, 0.5ppb for cumulative assessment)*	•/+	Residues in water sometimes exceed the legal limit. Legal limit usually an overestimate but limited impact on exposure unless this is driven by water.
31. Residues from rotational/succeeding crops	Estimated by expert judgment (see section 4.2.1)	•	Very unlikely to be a driver of high exposures compared to residues deriving from applications to the primary crop except for some metabolites – not very often.
32. Targeted monitoring	May be ignored (see section 4.2.8)	•/++ if targeted samples are included	Including samples from targeted sampling performed by authorities is more likely to affect commodities that have high residues and cause high exposures. Targeting will increase their frequency more than the levels, although increased sampling will reveal some higher residues.

EFSA Journal 2012;10(10):2839 85

An additional need...

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- Effective communication with risk managers

- Characterisation of upper tail exposures:
  - Person-days per million exceeding effect level
  - Confidence intervals for quantified uncertainties
  - Potential impact of unquantified uncertainties
- Question for *toxicologists*:
  - Characterise severity of effects at this level
- Question for *risk managers*:
  - Is all this consistent with ‘not any harmful effects’ ?

Another key need:
Calibrate deterministic assessment

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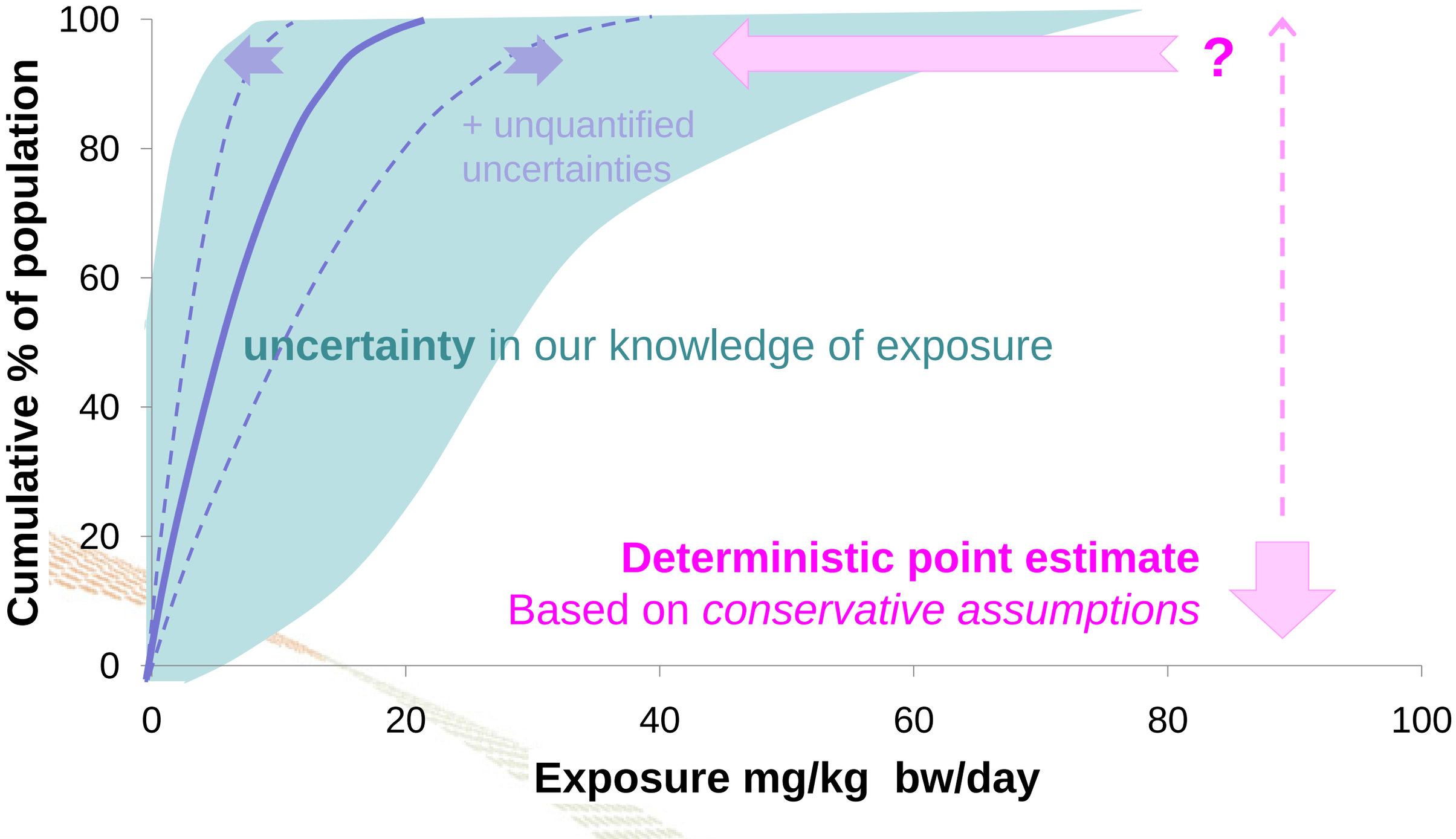

Calibrating the deterministic Tier 1

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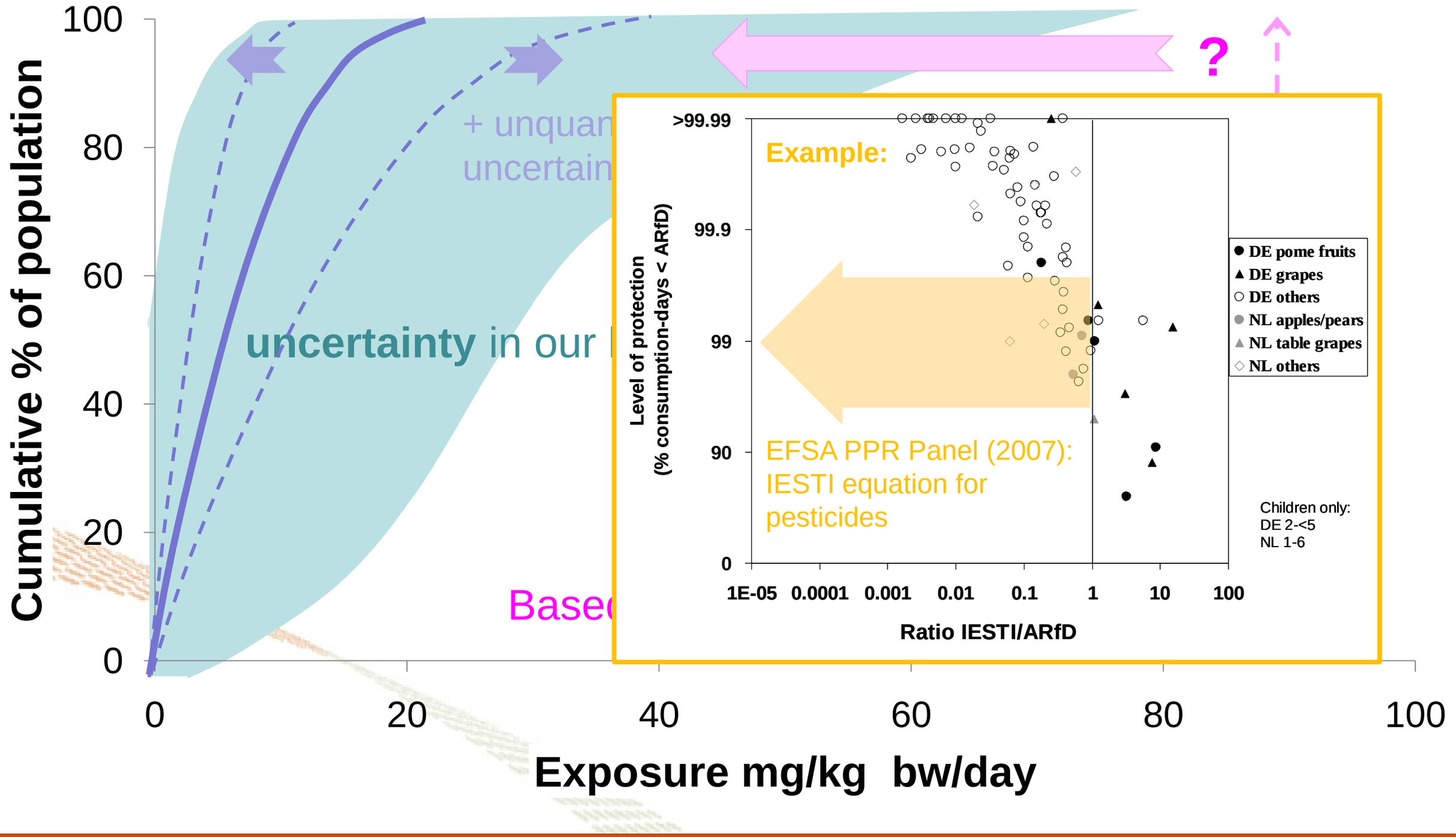

Some future directions

- Probabilistic calibration of deterministic approaches
- Simulation studies on treatment of unit-to-unit variability of pesticide residues for PPR Guidance
- Methods & software for cumulative and aggregate exposure assessment (FP7 project ACROPOLIS)
- Improved statistical methodology:
  - Usual intakes and life time exposure
  - Modelling upper tail exposures

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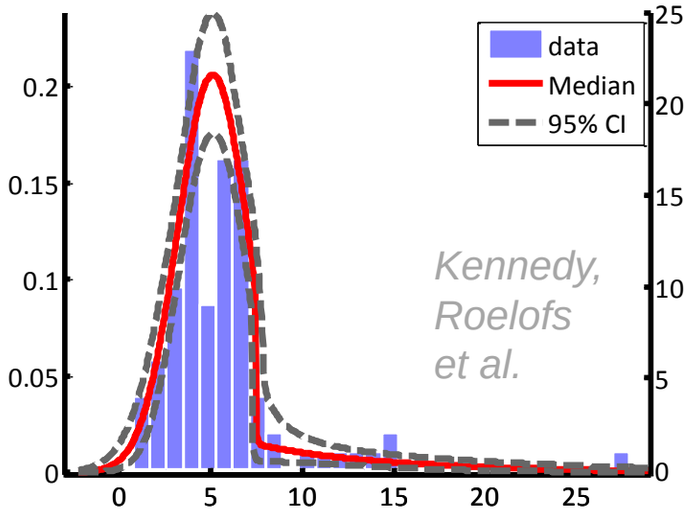
EU project ACROPOLIS

- Improved cumulative exposure assessment and cumulative hazard assessment;
- To integrate cumulative and aggregate risk models in a web-based tool, including accessible data for all stakeholders;
- Improving the understanding of cumulative risk assessment methodology of different stakeholders.
- For more information: http://acropolis-eu.com/



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- and underestimation in upper tail
- Communicate effectively with risk managers
- Calibrate first tier deterministic approaches