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Technical stakeholder event on cumulative risk assessment of pesticides in food

Uncertainty analysis and risk characterisation

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Trusted science for safe food

efsa
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Overview

- Role of uncertainty analysis
- Assessment for German adults
- Extrapolation to other populations
- EFSA conclusions on risk

Role of uncertainty analysis

- Risk managers: "a threshold for regulatory consideration at the 99.9th percentile could be an acceptable target value, *provided that the tier 2 assumptions are sufficiently conservative*"
  - Uncertainty analysis quantifies the degree of conservatism

- Risk managers: "If in the second tier calculation a risk is identified above the threshold for regulatory consideration, then a risk management decision should be considered taking into account all aspects e.g. *all sources of uncertainties and their magnitude or the fact that a result might be driven by outliers*"

Calculated MOETs

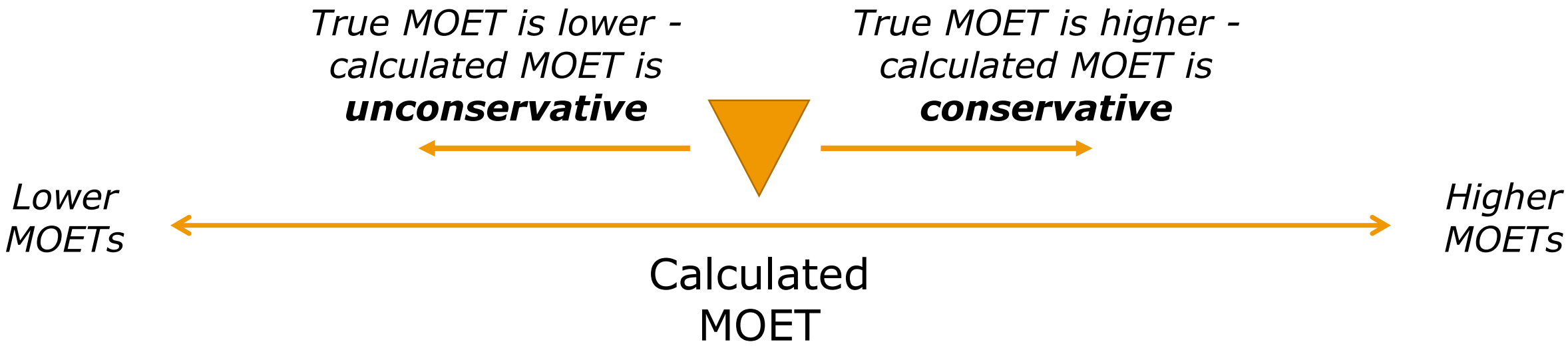
- Calculated MOETs at the 99.9th percentile
- 95% confidence intervals quantify *sampling* uncertainty
- All extend below 100
- Calculation is designed to be conservative
- So: are the MOETs really below 100?

CAG-NAN (brain and/or erythrocyte AChE inhibition):

Country	Population class	99.9th Percentile MOET	95% Confidence interval
Belgium	Adults	102	72 - 162
Czech Republic	Adults	120	87 - 176
Germany	Adults	95	73 - 120
Italy	Adults	96	75 - 149
Bulgaria	Other children	49	36 - 63
France	Other children	59	46 - 74
Netherlands	Other children	52	45 - 62
Denmark	Toddlers	60	50 - 69
Netherlands	Toddlers	40	33 - 50
United Kingdom	Toddlers	61	47 - 76

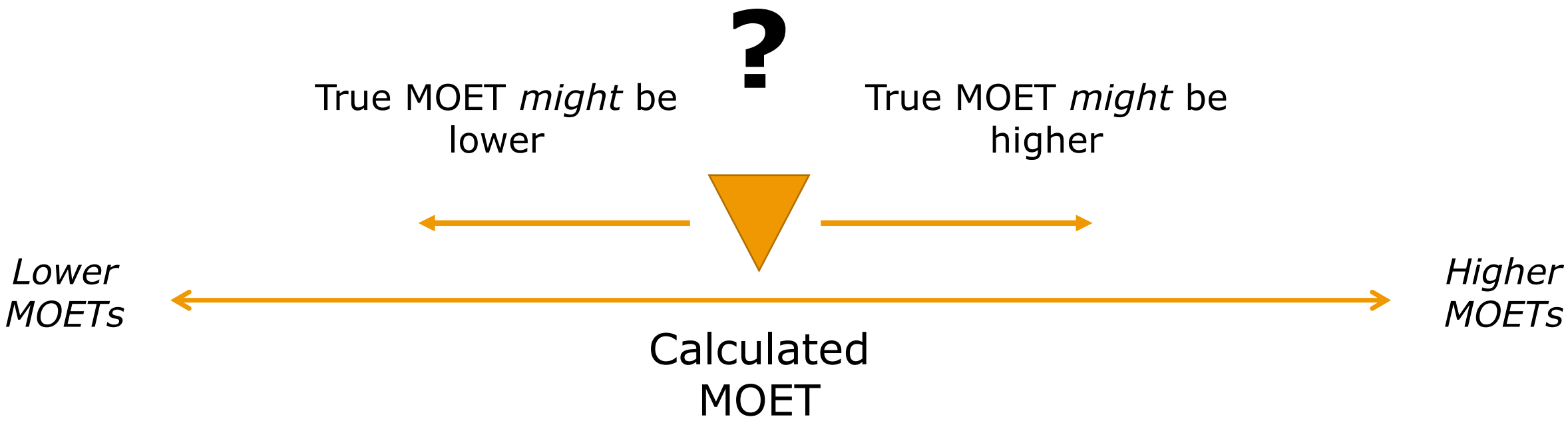
Degree of conservatism

- How different is the *'true' MOET*?



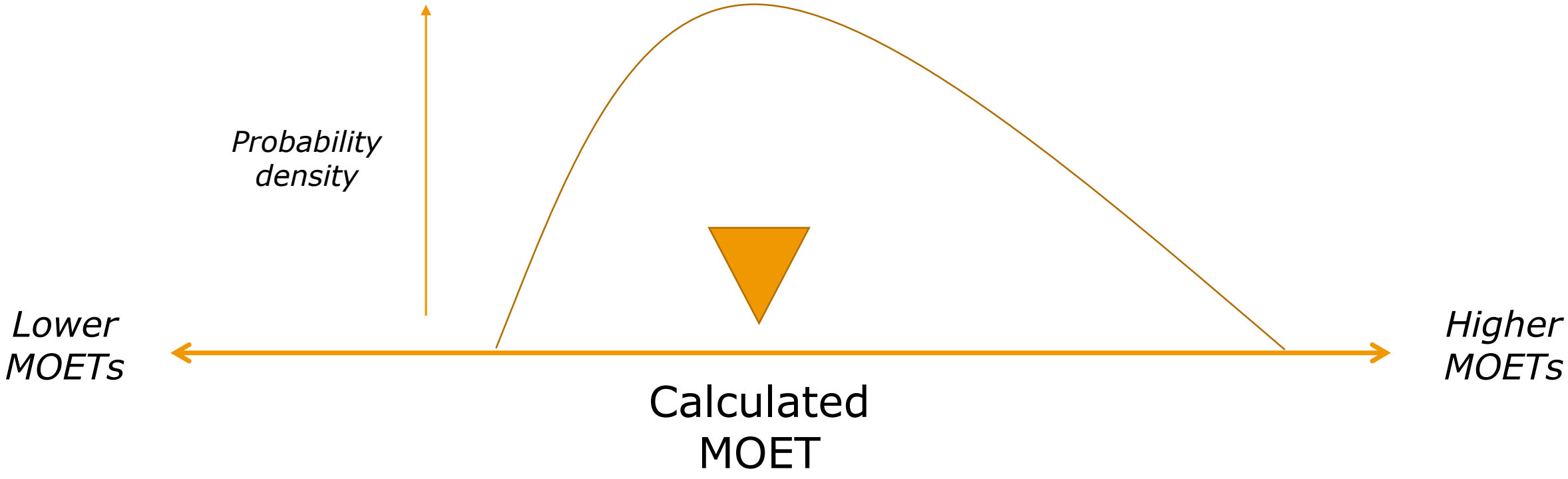
Uncertainty

- The true MOET is *uncertain*



Uncertainty

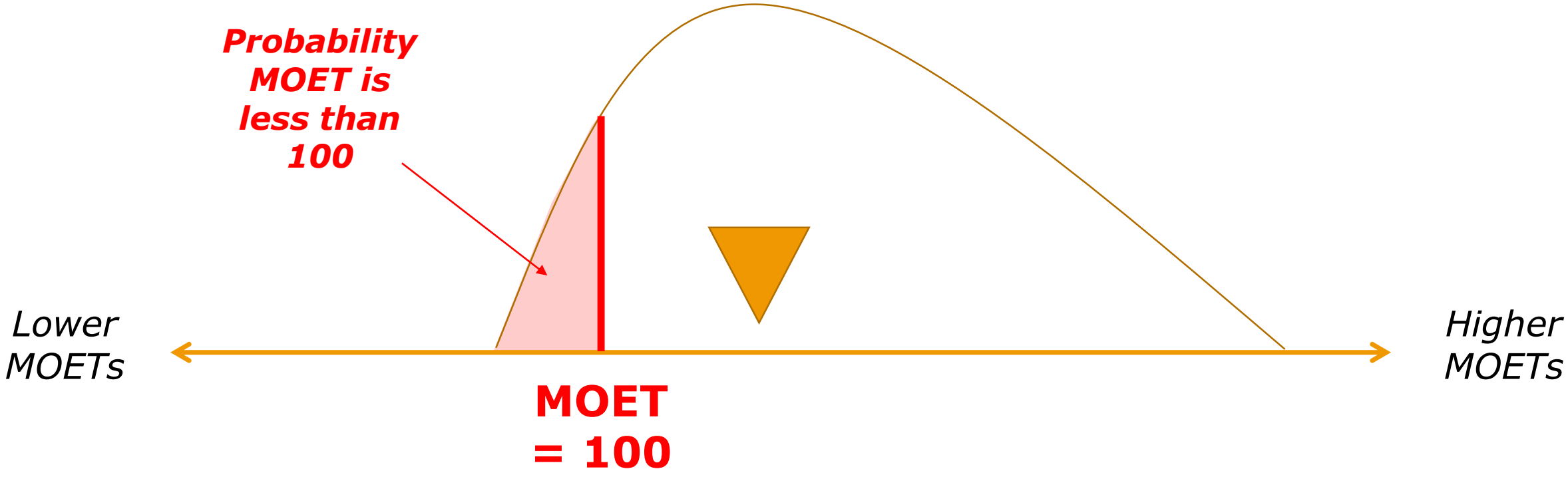
- We quantify uncertainty using *probability*



- Quantifies the *likelihood* of different degrees of conservatism

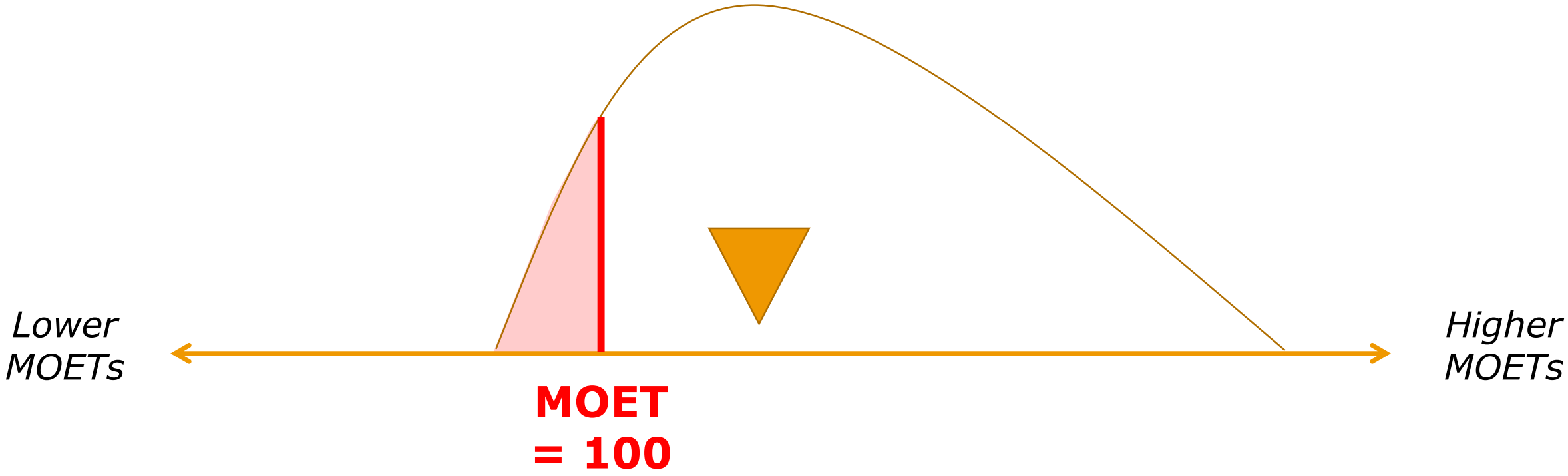
Sufficient conservatism

- "Sufficient conservatism" = *low enough probability* that the true MOET is less than 100



Assessing conservatism

- Identify sources of uncertainty and conservatism
- Quantify the overall uncertainty of the MOET
- Assess probability of MOET < 100



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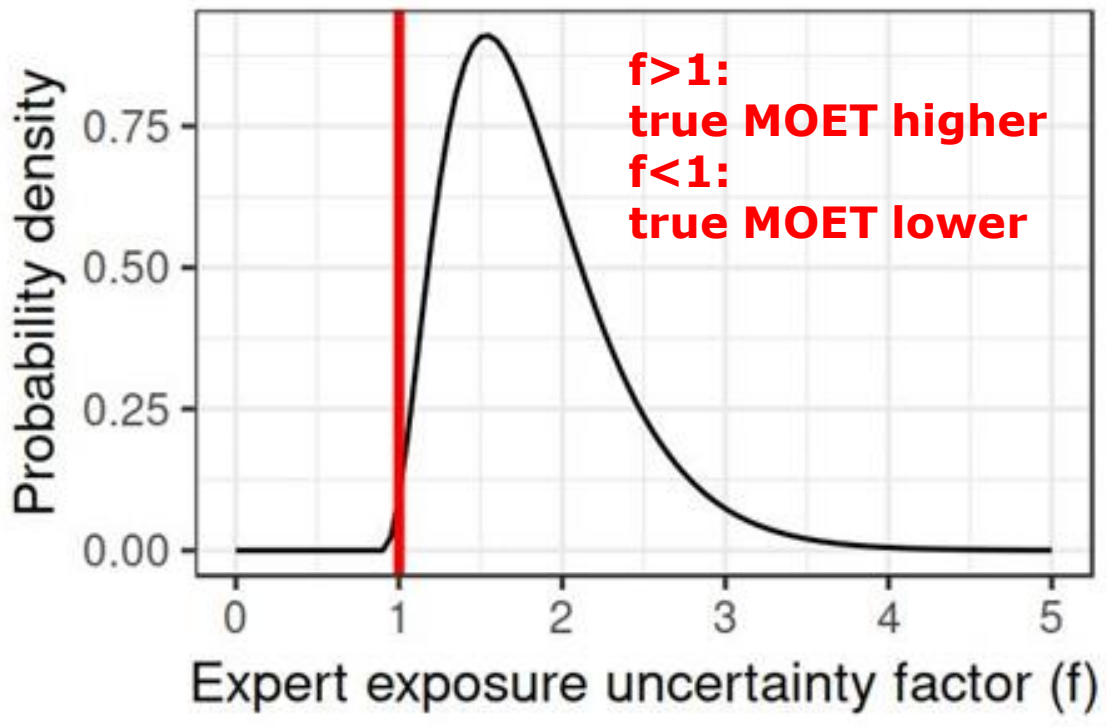
German adults population

- Calculated MOET at 99.9%ile = 95 (95% CI 73 – 120)

- *Main uncertainties affecting exposure for CAG-NAN*:
  - Lack of data on processing (+)
  - Effect of peeling and washing (+)
  - Selective sampling (+)
  - Analytical error (+/-)
  - Conversion to raw primary commodity (-)
  - Commodities not included in modelling (-)

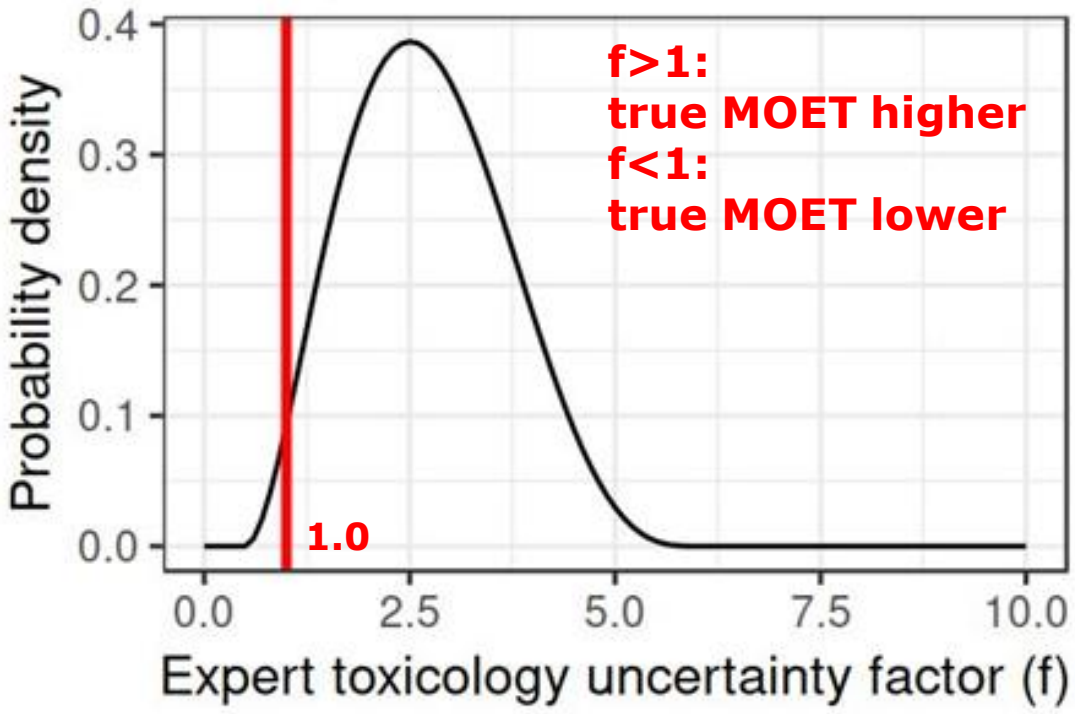


+ Tend to make the true MOET higher
- Tend to make the true MOET lower

German adults population

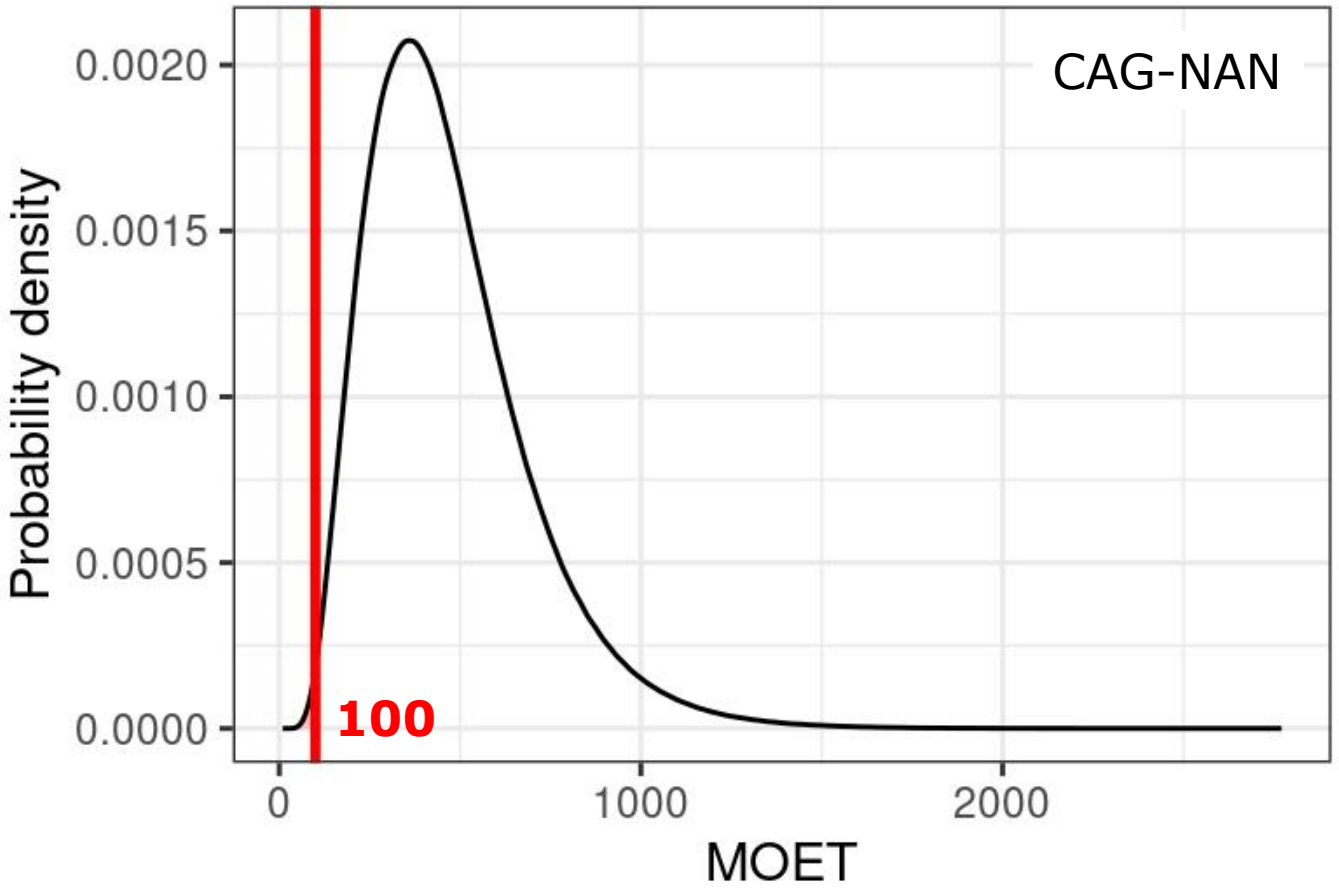
- Calculated MOET at 99.9%ile = 95 (95% CI 73 – 120)

- *Main uncertainties affecting toxicology for CAG-NAN*:
  - NOAELs underestimate BMDL20 (+)
  - Effect of gavage dosing (+)
  - Use of repeated dose studies (+)
  - Carryover between days (-)
  - First-pass metabolism at low doses (+)
  - Non-approved substances (limited -)



German adults population

- Calculated MOET at 99.9%ile = 95 (95% CI 73 – 120)
- Combined impact of exposure and toxicology uncertainties on the MOET at 99.9%ile exposure for *German adults*
- 0.28% probability that true MOET is less than 100
  - *Quantifies* degree of conservatism



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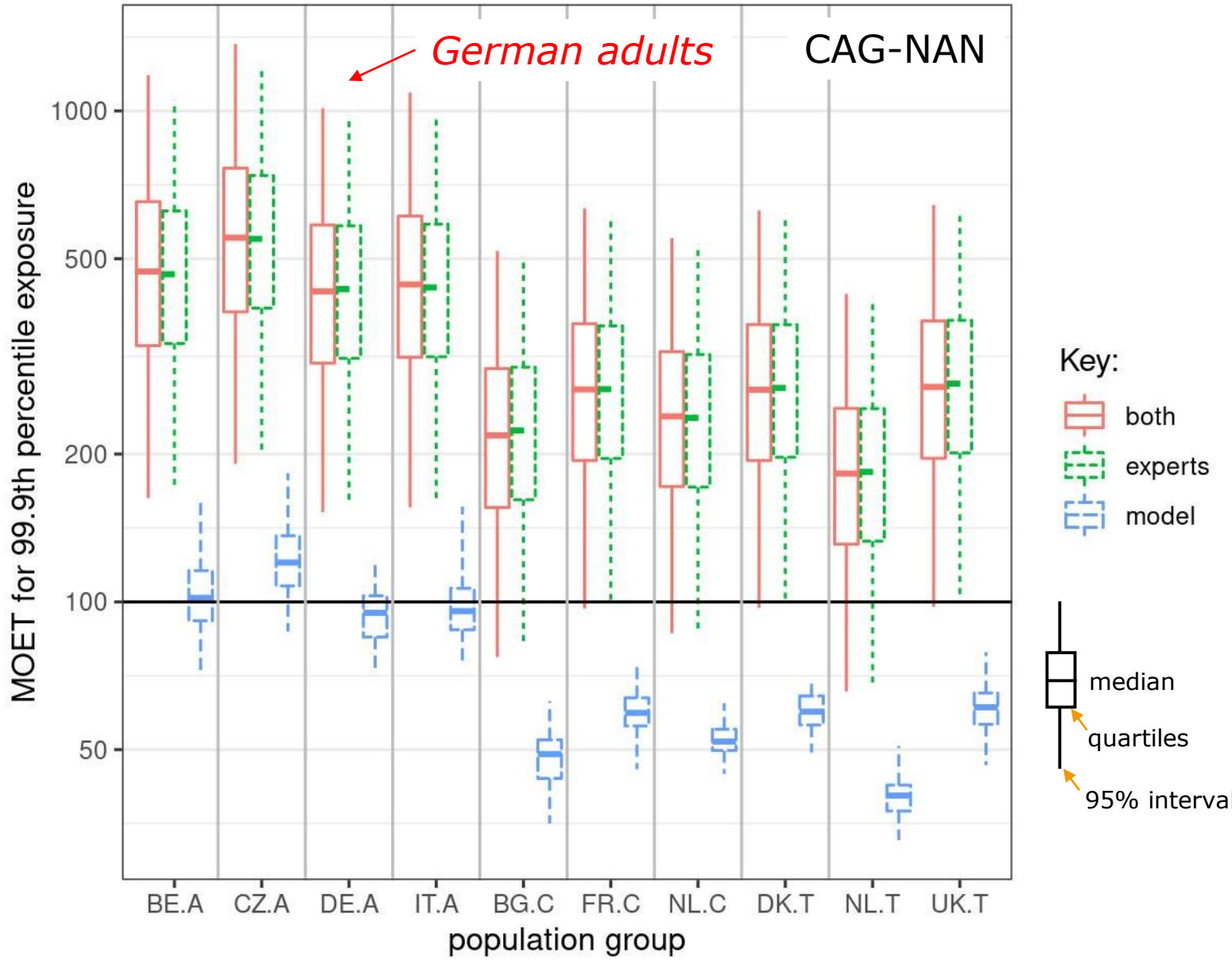
Extrapolation to other populations

Key findings:

- Additional uncertainties (green) much wider than those quantified by model (blue)
- Large impact of conservative assumptions



Overall uncertainty & risk characterisation

Final expert judgement for **CAG-NAN**, taking account of:

- dependencies between toxicological and exposure uncertainties
- differences between populations

Population	Probability from earlier steps	Final probability MOET<100	Certainty that the threshold for regulatory consideration is not reached
Belgian adults	0.20%	< 1%	> 99% certainty (almost certain)
Czech Rep. adults	0.07%	< 1%	> 99% certainty (almost certain)
German adults	0.28%	< 1%	> 99% certainty (almost certain)
Italian adults	0.25%	< 1%	> 99% certainty (almost certain)
Bulgarian children	6.8%	1 - 10%	90 - 99% certainty (very likely to extremely likely)
French children	2.8%	< 5%	> 95% certainty (extremely likely to almost certain)
Dutch children	4.6%	1 - 10%	90 - 99% certainty (very likely to extremely likely)
Danish toddlers	2.8%	< 5%	> 95% certainty (extremely likely to almost certain)
Dutch toddlers	12%	5 - 20%	80 - 95% certainty (likely to very likely)
United Kingdom toddlers	2.7%	< 5%	> 95% certainty (extremely likely to almost certain)

Overall uncertainty & risk characterisation

- Corresponding probabilities for other CAGs

Population	Probability MOET <100 at 99.9%ile exposure		
	CAG-NAM: Motor Division	CAG-TCF Hypothyroidism	CAG-TCP Parafollicular cell hypertrophy, hyperplasia and neoplasia
Belgian adults	< 1%	< 1%	< 1%
Czech Rep. adults	< 1%	< 1%	< 1%
German adults	< 1%	< 1%	< 1%
Italian adults	< 1%	< 1%	< 1%
Bulgarian children	< 5%	5-10%	< 1%
French children	< 5%	< 5%	< 1%
Dutch children	< 1%	1-5%	< 1%
Danish toddlers	< 5%	5-15%	< 1%
Dutch toddlers	< 5%	10-15%	< 1%
United Kingdom toddlers	< 5%	5-10%	< 1%

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EFSA Conclusions

Overall, taking account of the available data and the uncertainties involved, it is concluded that:

- cumulative exposure to pesticides that have **acute effects on the nervous system** *does not exceed the threshold for regulatory consideration established by risk managers*
- cumulative exposure to pesticides that have **chronic effects on the thyroid** *does not exceed the threshold for regulatory consideration established by risk managers*

Thank you

Thank you for your attention

Questions and comments welcome!

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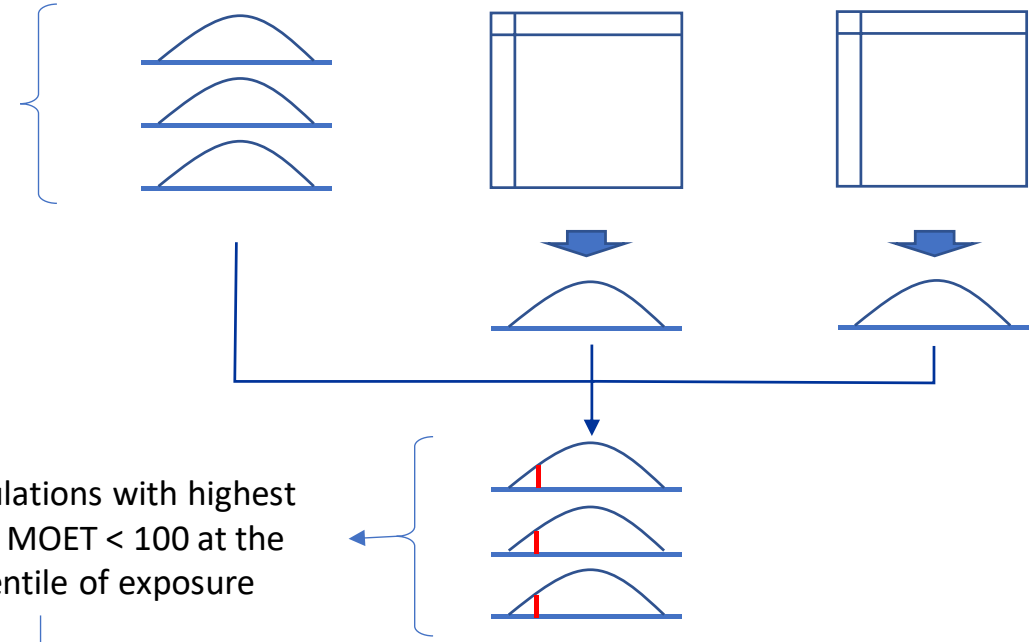
Flow chart of method from draft Reports

Uncertainty distributions for MOET at the 99.9th percentile of exposure, produced by probabilistic modelling

Model output for each population

Individual uncertainties - toxicology

Individual uncertainties - exposure



EKE Q1: evaluation of each individual uncertainty FOR GERMAN ADULTS using +/- scale

EKE Q2: overall toxicology & exposure uncertainties FOR GERMAN ADULTS

Prioritise populations with highest probability of MOET < 100 at the 99.9th percentile of exposure

Combine distributions by 1D Monte Carlo simulations assuming independence – one for each population

Final assessment of P(MOET<100) for populations of most concern using approximate probabilities

EKE Q3: overall uncertainty taking account of dependencies and population-specific issues

Implications of results for EFSA PRIMo populations

Considered in conclusion section of report