The Food and Environment Research Agency

2nd International Conference on Risk Assessment

Treatment and expression of uncertainties in risk assessment:

Presentation of the collaborative project

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on behalf of the collaborative project team

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Outline

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- Project objectives
- Requirements for addressing uncertainty
- Existing approaches
- Uncertainty tables
- Next steps

Objective and scope

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- Objective:
  - improve the way uncertainties are treated and expressed in risk assessment

- Scope:
  - concentrated on qualitative and semi-quantitative approaches

Approach

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- Review of existing approaches
- Develop draft framework
- Test framework with case studies:
  - 2 pesticides (environmental & worker risks)
  - PhIP (ILSI-Europe working group)
  - invasive species

Minimum requirements for addressing uncertainty

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- *Systematically* identify sources of uncertainty affecting the assessment
- Evaluate their *combined effect on the outcome*
- Identify and characterise any *deep uncertainties*
- *Communicate* assessment to risk managers

Existing approaches

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- Wide range of quantitative approaches
  - Deterministic, interval, probabilistic, etc.
- Qualitative/semi-quantitative approaches include:
  - Uncertainty tables (e.g. EFSA, REACH, US NRC, Health Canada, Walker et al.)
  - Weight of evidence procedures (e.g. IARC)
  - Evidence maps (Wiedemann et al.)
  - Subjective probabilities (IPCC, Morgan et al., Neutra)
  - Pedigree analysis (van der Sluijs et al., IPCS/WHO)
  - Social/participatory appraisal (Stirling, Wynne etc.)

Tiered approach

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Integrating elements of different approaches

1. List uncertainties. *If any are 'deep',* consider other approaches (e.g. description & social appraisal)

2. Evaluation using adapted **uncertainty tables**

3. *If necessary*, refined evaluation with quantitative methods:
   - target refined approaches on key uncertainties
   - plus uncertainty table for unquantified uncertainties

Two types of assessment question – require different approaches

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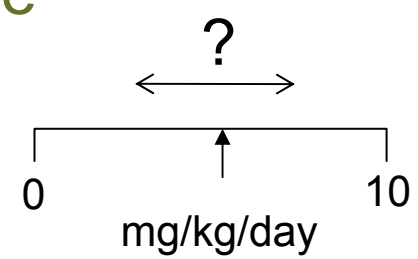
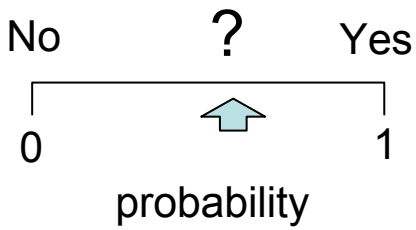
Quantitative questions (e.g. benchmark dose)

- Calculation or measurement; quantitative scale
- Express uncertainty in terms of **how different** the true value could be



Categorical questions (e.g. relevance of effect to humans)

- Weight of evidence; yes/no scale
- Express uncertainty in terms of the **probability** of alternative outcomes



Uncertainty table for **quantitative** questions

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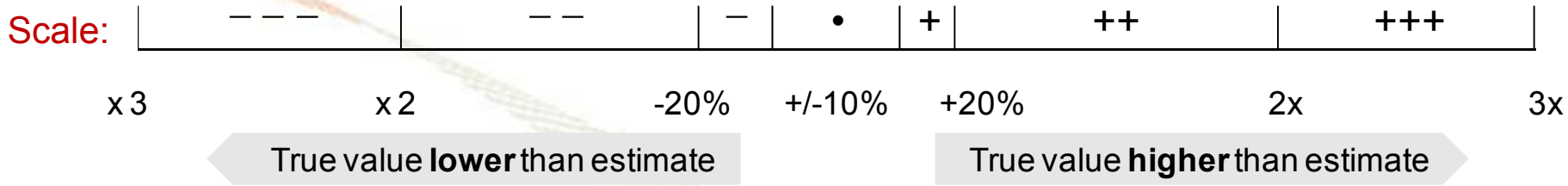
Uncertainties affecting the estimated BMD10/BMDL10 for carcinoma of the ventral prostate for PhIP*	Estimated impact (see scale)
Linear extrapolation of 40wk exposure period. Endpoint in full rat lifetime study is expected to be 2-3 times lower (HESI/MISTEC).	- - -
Dietary exposure may vary +/- 10-20% relative to gavage.	-/+
Small groups (10 control, 15 treated) adequate for this tumour.	•
Histopathological evaluation detailed and well documented.	•
PhIP used had purity of 99.9%.	•
Overall assessment: *'True' BMDL10 likely 2-3 times lower than estimate, mainly due to method used for extrapolating exposure.*	**- - -**



* *Draft case study* from ILSI-Europe WG on selection of data for benchmark dose modelling

Uncertainty table for **quantitative** questions

Specify in precise terms the quantity that is being assessed

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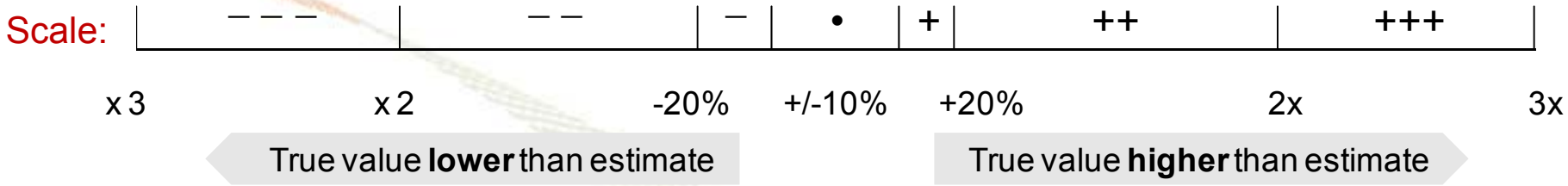

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Uncertainty table for **quantitative** questions

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ILSI Case Study: PhIP = *2-amino-1-methyl-6-phenylimidazol [4,5-b] pyridine*, a genotoxic heterocyclic amine formed in grilling or frying of meat and fish

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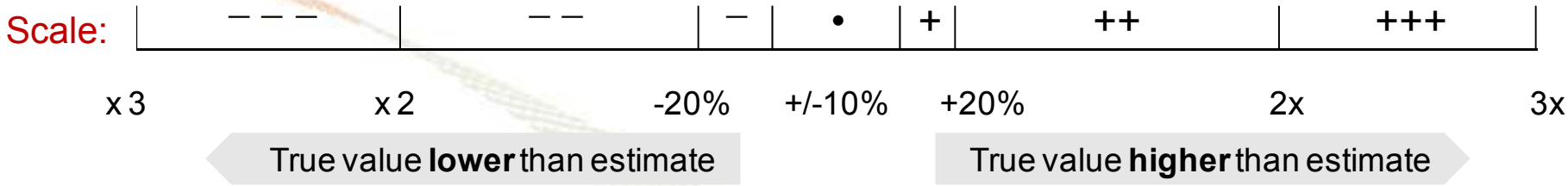

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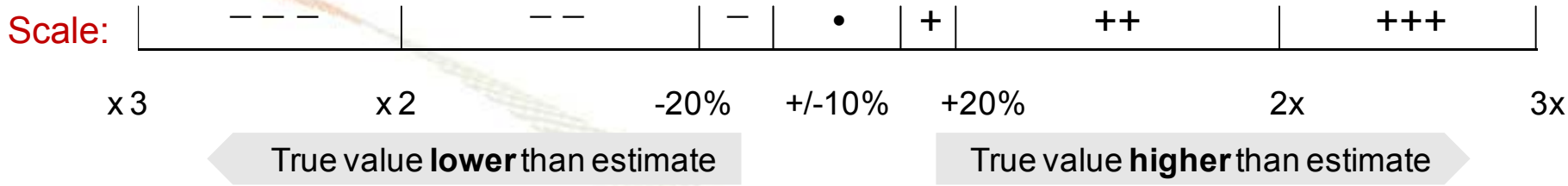
List uncertainties affecting the assessment



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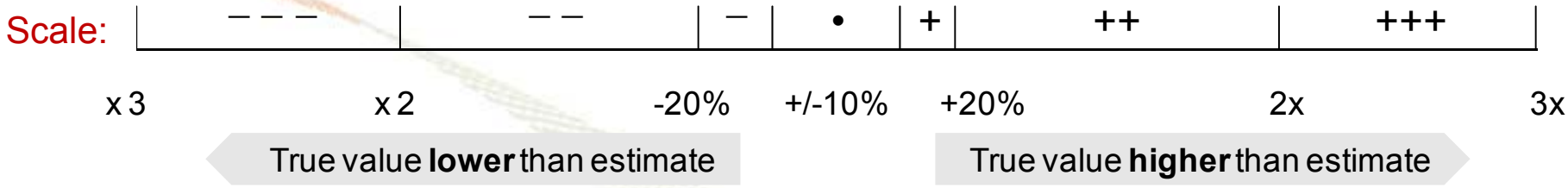
Small groups (10 control, 15 treated) adequate for this tumour.	•
Histopathological evaluation detailed and well documented.	•
PhIP used had purity of 99.9%.	•
MDL10 likely 2-3 times lower than ed for extrapolating exposure.	**- - -**

Define a scale for estimating impact of uncertainties



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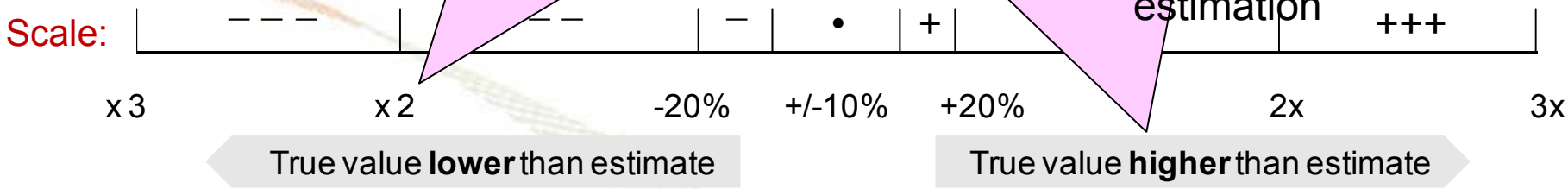
Define scale quantitatively and/or qualitatively

If preferred, define scale in terms of over- and under-estimation



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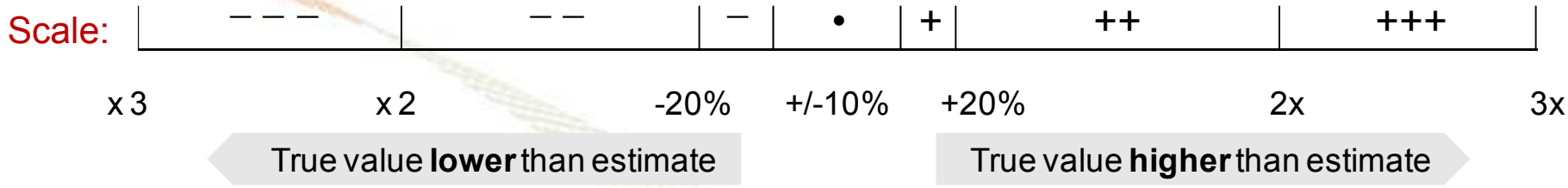
Small groups (10 control, 15 treated) a	•
Histopathological evaluation detailed a	•
PhIP used had purity of 99.9%.	•
Overall assessment: *'True' BMDL n estimate, mainly due to method used for extrapolating exposure.*	**- - -**

Estimate the impact of each uncertainty on how different the 'true' value might be ('?'=cannot evaluate)



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Estimate the *combined* impact of all the uncertainties (*judgment not calculation*)

Scale: – – – | – – | – | • | + | ++ | +++

x 3 | x 2 | -20% | +/-10% | +20% | 2x | 3x

True value **lower** than estimate

True value **higher** than estimate

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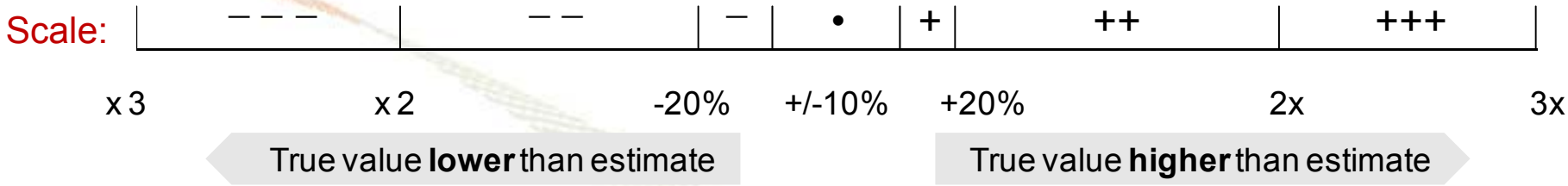
Add a narrative description of overall uncertainty for use in assessment summary



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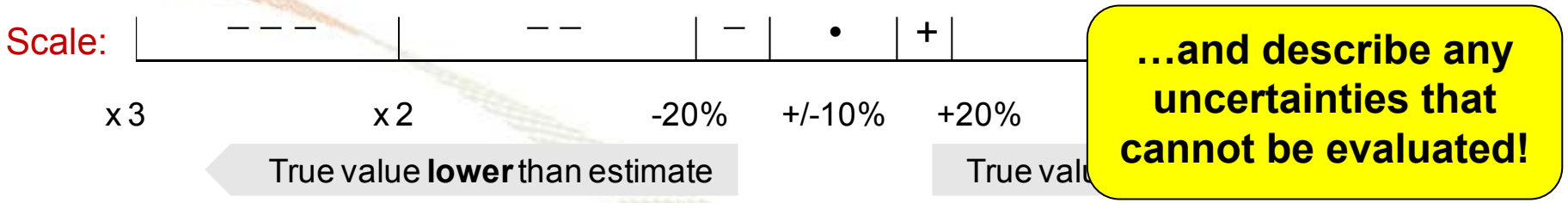

…and describe any uncertainties that cannot be evaluated!

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Two types of assessment question – require different approaches

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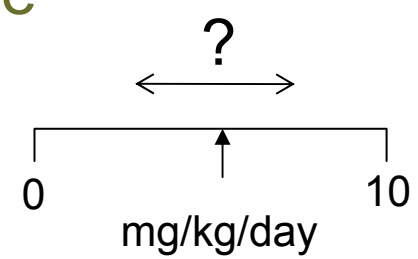

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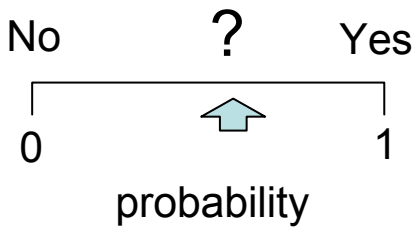

Uncertainty table for **categorical** questions

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Are prostate tumours a relevant endpoint in humans for PhIP*?	Influence on conclusion
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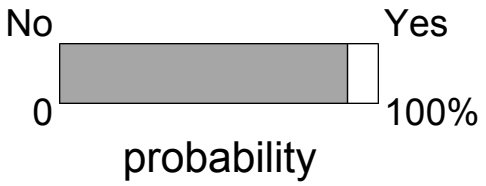
Line of evidence 2: human studies *Strength:* Consumption of very well-done meat associated with increased risk. *Strength:* RR=1.01-1.48 for highest quintile of PhIP exposure *Uncertainty:* No data on adducts in prostate (but adducts found in mammary tissue).	↑↑
Overall assessment: prostate tumours very likely to be relevant in humans for PhIP– probability about 90%	

Key:
Up arrows – tending to 'yes'
Down arrows – tending to 'no'

↑↑↑ could be sufficient alone
↑↑ contributes importantly
↑ minor contribution
● no influence
? unable to evaluate

(and similarly for ↓, ↓↓, ↓↓↓)



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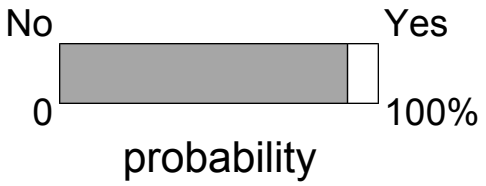

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Overall assessment: prostate tumours very likely to be relevant in humans for PhIP– probability about 90%	

List & summarise lines of evidence relevant to the question

ws – tending to 'yes'
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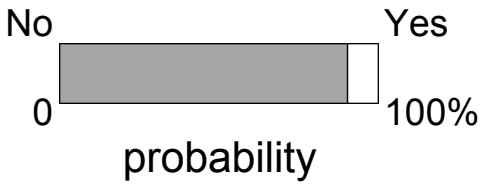

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List strengths & uncertainties affecting each line of evidence

Key:

…ws – tending to 'yes'
…rrows – tending to 'no'

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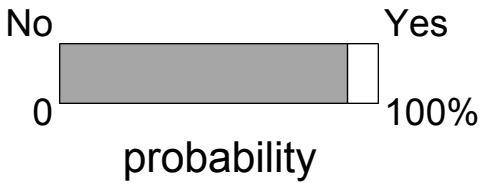

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Line of evidence 2: human *Strength:* Consumption of very v associated with increased risk. *Strength:* RR=1.01-1.48 for high exposure *Uncertainty:* No data on adducts in prostate (but adducts found in mammary tissue).	
Overall assessment: prostate tumours very likely to be relevant in humans for PhIP– probability about 90%	

Evaluate **influence** of each line of evidence, taking account of strengths & uncertainties

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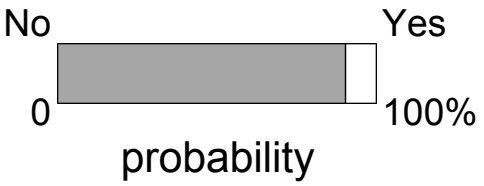

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Considering all lines of evidence, evaluate the probability that the answer to the question is positive, and express numerically and/or verbally

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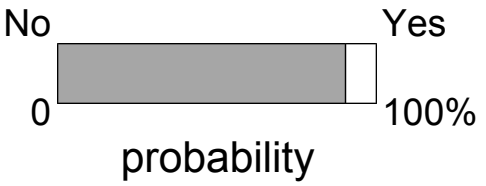

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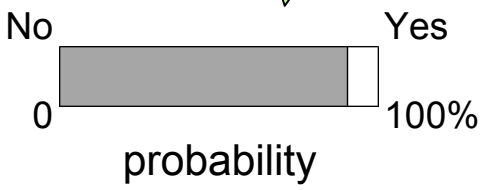
?
(a)

Drawing a probability line may help



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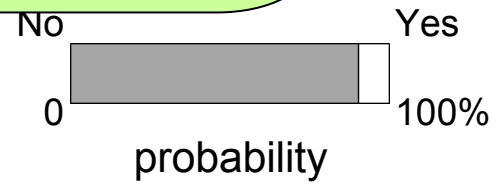
Overall assessment: prostate tumours very likely to be relevant in humans for PhIP– probability about 90%	

Key:
Up arrows – tending to 'yes'
Down arrows – tending to 'no'

↑↑↑ could be sufficient alone
↑↑ contributes importantly
↑ minor contribution
● no influence
luate

↓↓, ↓↓↓)

Present the outcome in narrative form suitable for use in assessment summary



* *Draft case study* from ILSI-Europe WG on selection of data for benchmark dose modelling

Uncertainty table for **categorical** questions

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Are prostate tumours a relevant endpoint in humans for PhIP*?	Influence on conclusion
Line of evidence 1: animal studies *Strength:* Treatment-related dose response for very rare tumour in male rats. *Strength:* DNA adducts in rat prostate gland. *Strength:* Pathogenesis same as in humans. *Uncertainty:* Specific F344 strain, in 1 lab. *Uncertainty:* Relevance to humans is uncertain.	↑↑
Line of evidence 2: human studies *Strength:* Consumption of very well-done meat associated with increased risk. *Strength:* RR=1.01-1.48 for highest quintile of PhIP exposure *Uncertainty:* No data on adducts in prostate (but adducts found in mammary tissue).	↑↑
Overall assessment: prostate tumours very likely to be relevant in humans for PhIP– probability about 90%	

Key:
Up arrows – tending to 'yes'
Down arrows – tending to 'no'

↑↑↑ could be sufficient alone
↑↑ contributes importantly
↑ minor contribution
● no influence
? unable to evaluate

(and similarly for ↓, ↓↓, ↓↓↓)

…and describe any uncertainties that cannot be evaluated

* *Draft case study* from ILSI-Europe WG on selection of data for benchmark dose modelling

Combining evaluations for multiple questions

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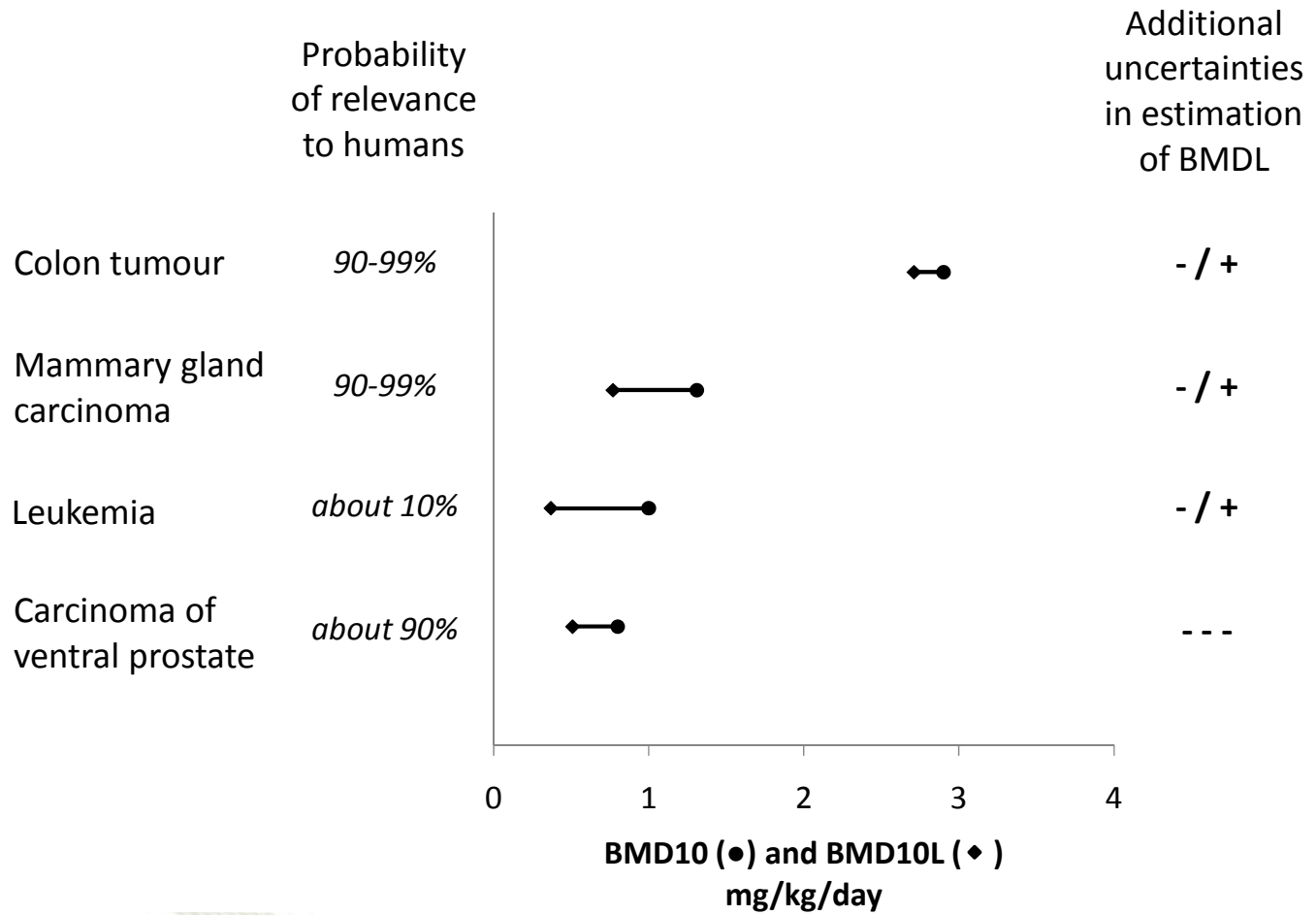
Present results in ways that help draw overall conclusions



e.g. benchmark dose estimation for PhIP*

* *Draft case study* from ILSI-Europe WG on selection of data for benchmark dose modelling

Communication with risk managers

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Draft template for managers' summary:

1. Overarching summary of uncertainties, including quantitative bounds or probabilities where applicable
2. Overall judgment of confidence
3. Where uncertainty is great, identify major sources
4. Clearly acknowledge the presence of any uncertainties which were unquantifiable
5. Supporting information

Derive summary directly from uncertainty tables.

Next steps

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- Workshop session tomorrow:
  - Discussion and feedback
  - Suggestions for further work
- After conference:
  - Refinement of approach
  - Additional case studies