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Recent Improvements in IRIS

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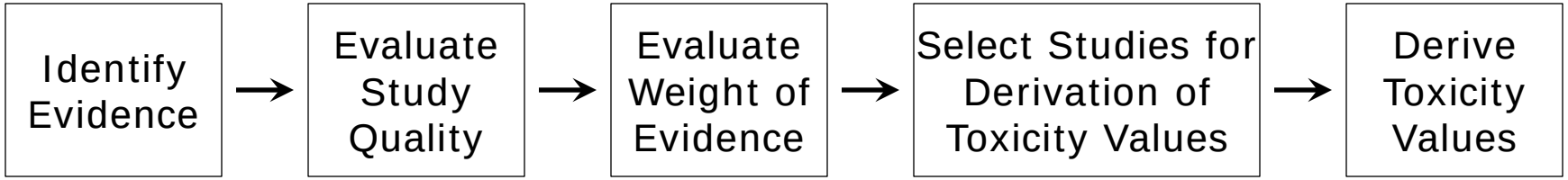
Improving IRIS Assessments through Systematic Review



Source: Adapted from NRC (2011) Figure 2-1

- IRIS assessments are adopting the principles of systematic review
- Greater use of tables and figures for clarity
- Plain-language summary of key conclusions

Example: Identifying and Selecting Pertinent Studies

References identified based on initial keyword search (see Table LS-1): **~20,700 references**

Secondary keyword searching (see Table LS-1): **~14,570 references excluded**

References identified based on secondary keyword search (see Table LS-1): **~6,130 references**

Manual screen of titles/abstracts:
~ 4,940 references excluded
- Not relevant to BaP toxicity in mammals (e.g., toxicity in aquatic species, plants)
- Site-specific risk assessments
- Chemical analytical methods
- Cancer chemotherapy studies

Considered for inclusion in the Toxicological Review: **~1,190 references**; references subsequently evaluated based on Preamble Section 3
Human studies: **~ 200 references**
Animal studies: **~ 200 references**
Other supporting studies: **~ 800 references**
Including:
- Reviews
- Background and physical/ chemical properties
- Animal studies by routes other than oral, inhalation and dermal
- Studies related to mode of action

Manual screen of manuscripts excluded: **~ 365 references**
- Not relevant to BaP toxicity in mammals
- Inadequate basis to infer exposure
- Inadequate reporting of study methods or results
- Animal toxicity studies with mixtures of chemicals
- Abstracts
- Not available in English
- Duplicates

825 references cited in the Toxicological Review
Human studies: **~ 110 references**
- Biomonitoring studies: **~ 70 references**
- Epidemiologic studies of cancer and noncancer disease: **~ 40 references**

Animal studies: **~ 175 references**
- Oral:
  - Subchronic/chronic: **~ 20 references**
  - Reproductive/developmental: **12 references**
- Inhalation (and intratracheal instillation):
  - Subchronic/chronic : **14 references**
  - Reproductive/developmental: **8 references**
- Dermal (cancer): **~ 40 references**
- Other route and short-term studies:
  - Neurotoxicity: **6 references**
  - Immunotoxicity: **~ 45 references**
  - Cancer: **~ 30 references**

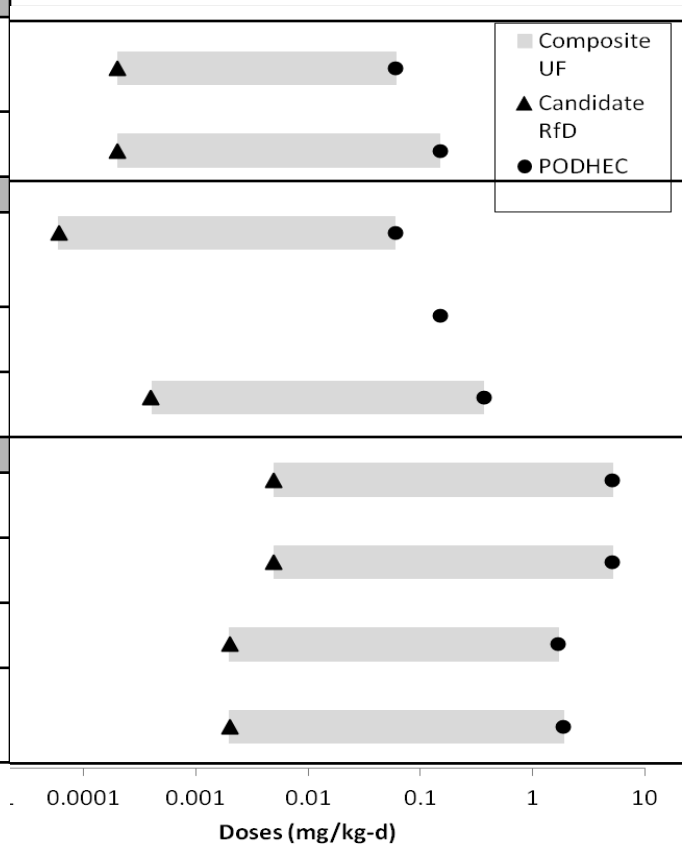
Other supporting studies: **~ 540 references**
- Background & physical & chemical properties: **~ 20 references**
- Mode of action, including genetic toxicology: **~ 380 references**
- Toxicokinetic studies: **~ 125 references**
- Other: **~ 15 references**

Example: Evaluating the Quality of Individual Studies

Diethyl Phthalate – Anogenital Distance Studies (Draft)							
Reference	**Exposure Measure and Range**	**Outcome classification**	**Participant Selection and Comparability**	**Consideration of Likely Confounding**	**Completeness of results**	**Adequate Sample Size**	**Additional Comments - Limitations in Confidence in Results**
Suzuki et al., 2011	Maternal urine (9 – 40 weeks; mean 29 weeks), MEP, 75th percentile = 32 ng/mL	Anogenital distance , measured at birth (1-3 days); blinded to exposure	Japan. Birth cohort; 120 of 344 enrollees excluded because did not delivery at study hospital. Internal comparison group.	Gestational age, birth order, maternal age, maternal smoking and environmental tobacco smoke exposure (stepwise regression); Used SG-corrected urine concentrations	Described as not associated (details not reported)	n = 111 male infants	Relatively low, narrow exposure range. Unclear if approach to dilution adjustment is optimal
Swan 2008; Swan et al., 2005	Maternal urine (3rd trimester), MEP, 75th percentile = 437 ng/mL	Anogenital distance, measured at ages 0 - 36 months; assessors blinded to exposure but no information on agreement between sites / raters	United States (3 sites). Birth cohort; 21 of 172 enrollees excluded because exam not considered reliable (child too active); 2 declined interview); other exclusions based on lack of urine sample. Internal Comparison group	Adjusted for weight percentile and age	Percent change per interquartile increase in metabolite and p-value; also presented as metabolite distribution by 3 categories of anogenital distance	n =106 boys	Is age-size adjustment adequate (considering potential temporal changes in exposure)? No adjustment for urine dilution in model

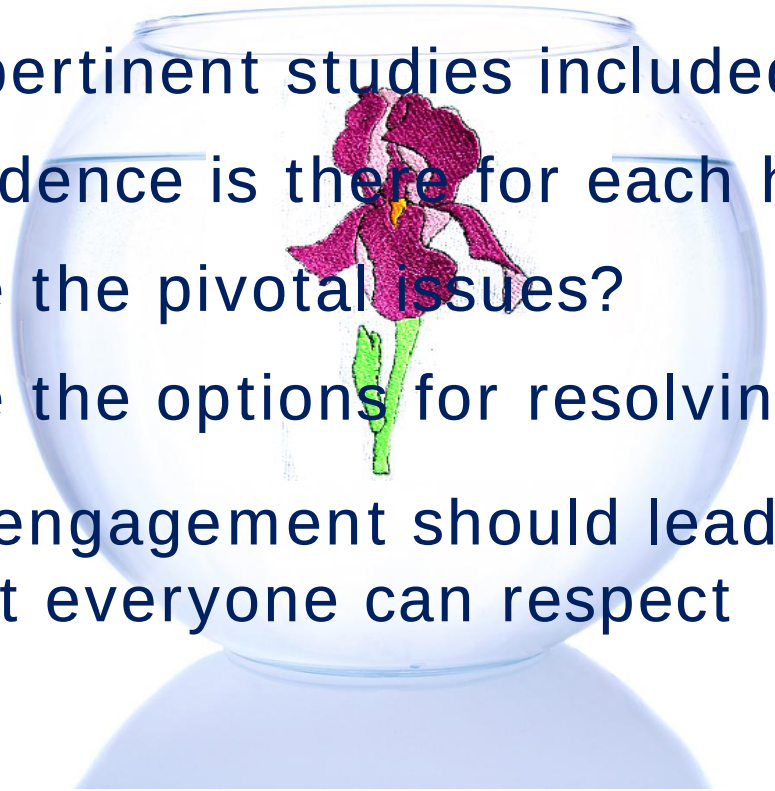
Example: Deriving Toxicity Values

Endpoint and Reference	POD_{HED}[a]	POD type	UF_A	UF_H	UF_L	UF_S	UF_D	Composite UF	Candidate value (mg/kg-d)
DEVELOPMENTAL									
Neurodevelopmental impairments in rats Chen et al., 2012	0.01	$BMDL_{1SD}$	10	10	1	1	3	300	2×10^{-4}
Cardiovascular effects Jules et al., 2012	0.15	LOAEL	3	10	10	1	3	1000	2×10^{-4}
REPRODUCTIVE									
Decreased ovary weight and ovarian follicles in rats Xu et al., 2010	0.37	$BMDL_{1SD}$	3	10	1	10	3	1000	4×10^{-4}
Decreased sperm count in mice Mohamed et al., 2010	0.15	LOAEL	3	10	10	10	3	10000	Not calculated due to UF > 3000
Cervical epithelial hyperplasia Gao et al. (2011)	0.06	$BMDL_{10}$	3	10	1	10	3	1000	6×10^{-5}
IMMUNOLOGICAL									
Decreased thymus weights Kroese et al., 2001	1.9	$BMDL_{1SD}$	3	10	1	10	3	1000	2×10^{-3}
Decreased serum IgM in rats De Jong et al., 1999	1.7	NOAEL	3	10	1	10	3	1000	2×10^{-3}
Decreased serum IgA in rats De Jong et al., 1999	5.2	NOAEL	3	10	1	10	3	1000	5×10^{-3}
Decreased number of B cells in rats De Jong et al., 1999	5.2	NOAEL	3	10	1	10	3	1000	5×10^{-3}



Improving IRIS Assessments through Early Public Engagement

- Public engagement will occur early during draft development
  - Are the pertinent studies included?
  - What evidence is there for each health effect?
  - What are the pivotal issues?
  - What are the options for resolving the issues?
- Early public engagement should lead to an outcome that everyone can respect



Ensuring High-Quality Assessments through Improved Peer Review

- Peer review panels will be larger
- In pivotal areas, there will be multiple experts to provide different perspectives
- EPA will post the names of potential reviewers and ask for comment on their expertise and conflicting interests

Summary

Improved product	IRIS assessments are becoming more clear, more concise, more systematic
Improved process	IRIS is committed to early public engagement during draft development
Improved peer review	More transparent peer review should ensure impartiality and high scientific quality
Improved throughput	We invite your suggestions for how to complete more assessments in less time

Thank you for participating today!