Combining multiple studies to derive toxicity values: **Path forward as envisioned by the NRC**

IRIS Workshop on the NRC Recommendations

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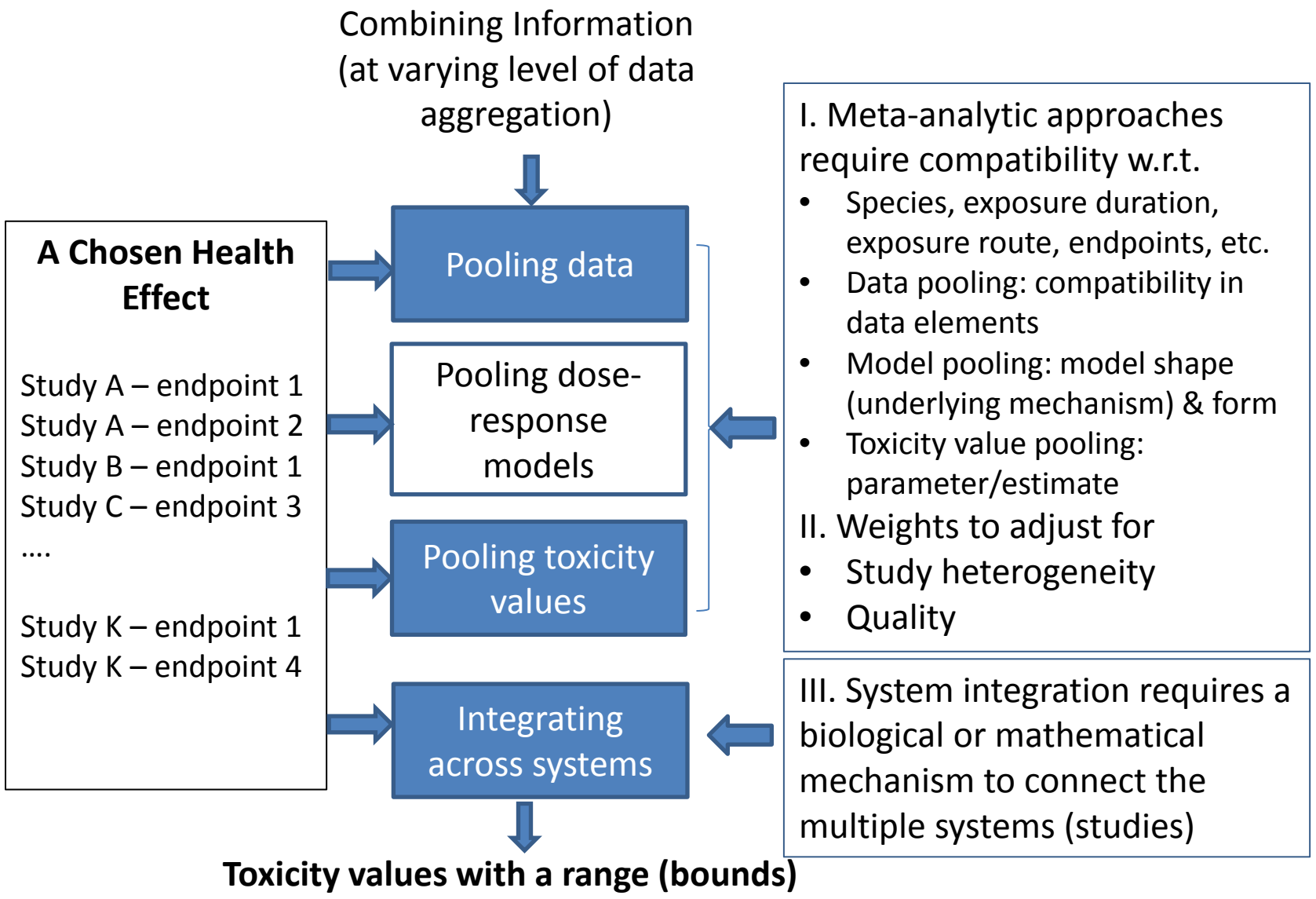
NRC Formaldehyde Committee (2011) Recommendation

Integrate information across multiple studies to derive toxicity values (reference values & unit risks)

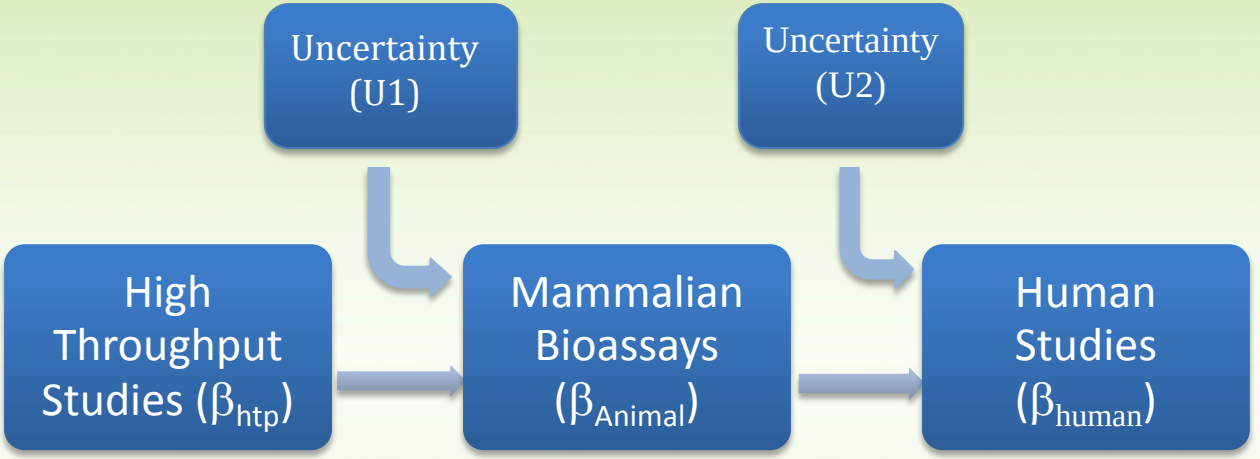
- A single study is unlikely to trumpet all others
- Multiple studies and multiple endpoints afford more robust and sufficient dose-response information
- As a result , toxicity values are more reliability, and support evaluation of uncertainty and variability

NRC IRIS Committee (2014)

- EPA made substantial efforts to change and improve the IRIS process following the “road map” suggested by the NRC Formaldehyde Committee (2011)
- The NRC IRIS committee was charged to reviewed the progress made to IRIS process and to provide additional recommendations
- The report contains discussions and illustrations of relevant technical approaches to integrating multiple studies in deriving toxicity values


Combining Information (at varying level of data aggregation)
A Chosen Health Effect
Study A – endpoint 1
Study A – endpoint 2
Study B – endpoint 1
Study C – endpoint 3
….
Study K – endpoint 1
Study K – endpoint 4
Pooling data
Pooling dose-response models
Pooling toxicity values
Integrating across systems
I. Meta-analytic approaches require compatibility w.r.t.
• Species, exposure duration, exposure route, endpoints, etc.
• Data pooling: compatibility in data elements
• Model pooling: model shape (underlying mechanism) & form
• Toxicity value pooling: parameter/estimate
II. Weights to adjust for
• Study heterogeneity
• Quality
III. System integration requires a biological or mathematical mechanism to connect the multiple systems (studies)
Toxicity values with a range (bounds)

System Integration: A Simple Bayes Model Frame to Integrating Multiple Studies (Fig 7-3)



$$\beta_{animal} / \beta_{htp} = U_1$$

$$\beta_{human} / \beta_{animal} = U_2$$

β can be any appropriate dose-response parameter such as BMD

Table 7-3: An Example

Data systems	Param. BMD_{10}	BMDL (95%)	Uncertain. Ratio U	Human-equiv. RfD	Prior (log) for human
High-throughput data only	0.1	0.07	U_1=1000	0.000007	Log BMD_{10}+logU_1+logU_2 ~ N(-2.30,3.71^2)
Animal assays only	0.85	0.15	U_2=10	0.015	
Bayes Integration HTP + animal	0.85	0.048		0.048	log BMD_{aniaml}+logU_2 ~ N(-1.65, 1.46^2)
Human studies only	0.05	0.019		0.019	
Byes Integration HTP + animal + Human	0.066	0.026		0.026	

Bayes Priors and Posteriors in the Example

Data systems	Statistics	Prior distribution (for human)	Posterior distribution (for human)
High-throughput data only	BMD=0.1; BMDL=0.07; U=1000	log BMD_{htp}+logU_1+logU_2 ~ N(-2.30,3.71^2)	-
HTP+animal	Log(BMD)=-0.161; SD=0.9	log BMD_{aniaml}+logU_2 ~ N(-1.65, 1.46^2)	log BMD_{animal} is the posterior based on the prior log BMD_{htp}+logU_1
HTP + animal + Human studies	Log(BMD)=-3.0; SD=0.5		log BMD_{human} ~ N(-2.72, 0.224)

The NRC Envisions

- Existing methods in principle can be adapted to integrate multiple studies systematically
- New methods are needed in the toobox
- Applications require case-by-case adaptation
- Experience-based guidance needed for appropriate methods
- A critical role EPA plays in this effort