Naphthalene: Strategy for Risk Assessment

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Gradient

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Key WoE Questions

- Based on observed positives, what hypothesized causal processes are necessary? Sufficient?
- How do they generalize? What other manifestations should they have?
- If hypothesis were wrong, how else would one explain the array of outcomes?

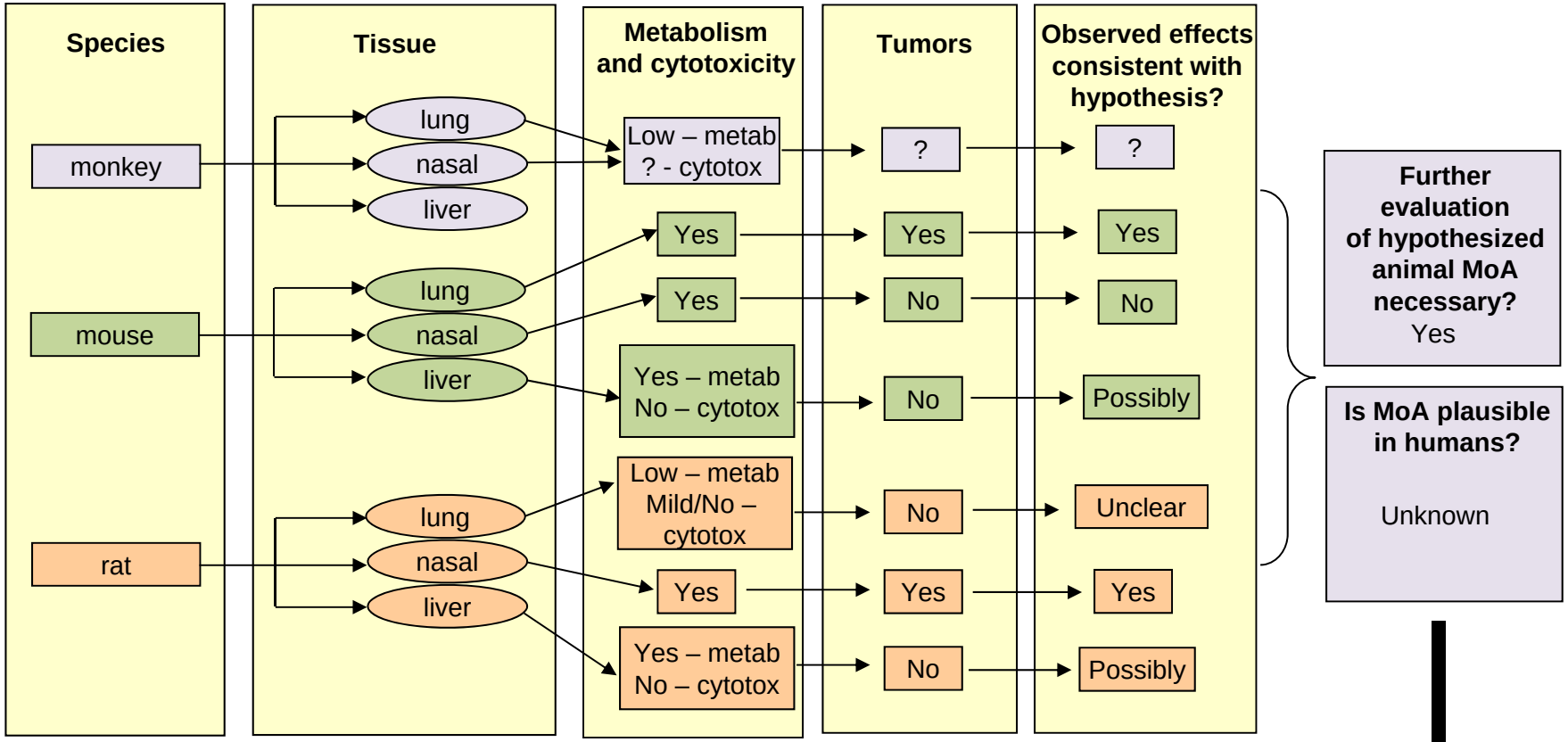
For Observed Outcomes that are Candidates for "Evidence"

- Why we think they happened where they did.
- Why we think they *didn't* happen where they *didn't*.
- Why we think the "did-happen" factors would also apply to the target population.
    - Might apply? Probably apply? Known to apply?
- Are there discrepant observations, and if so, how do we account for them?
- Are our "whys"
    - Observable underlying causes?
    - Reasonable guesses based on wider knowledge, other cases?
    - *Ad hoc* assumptions without evidence, needed to explain otherwise puzzling phenomena?

Experimental evidence for naphthalene carcinogenesis

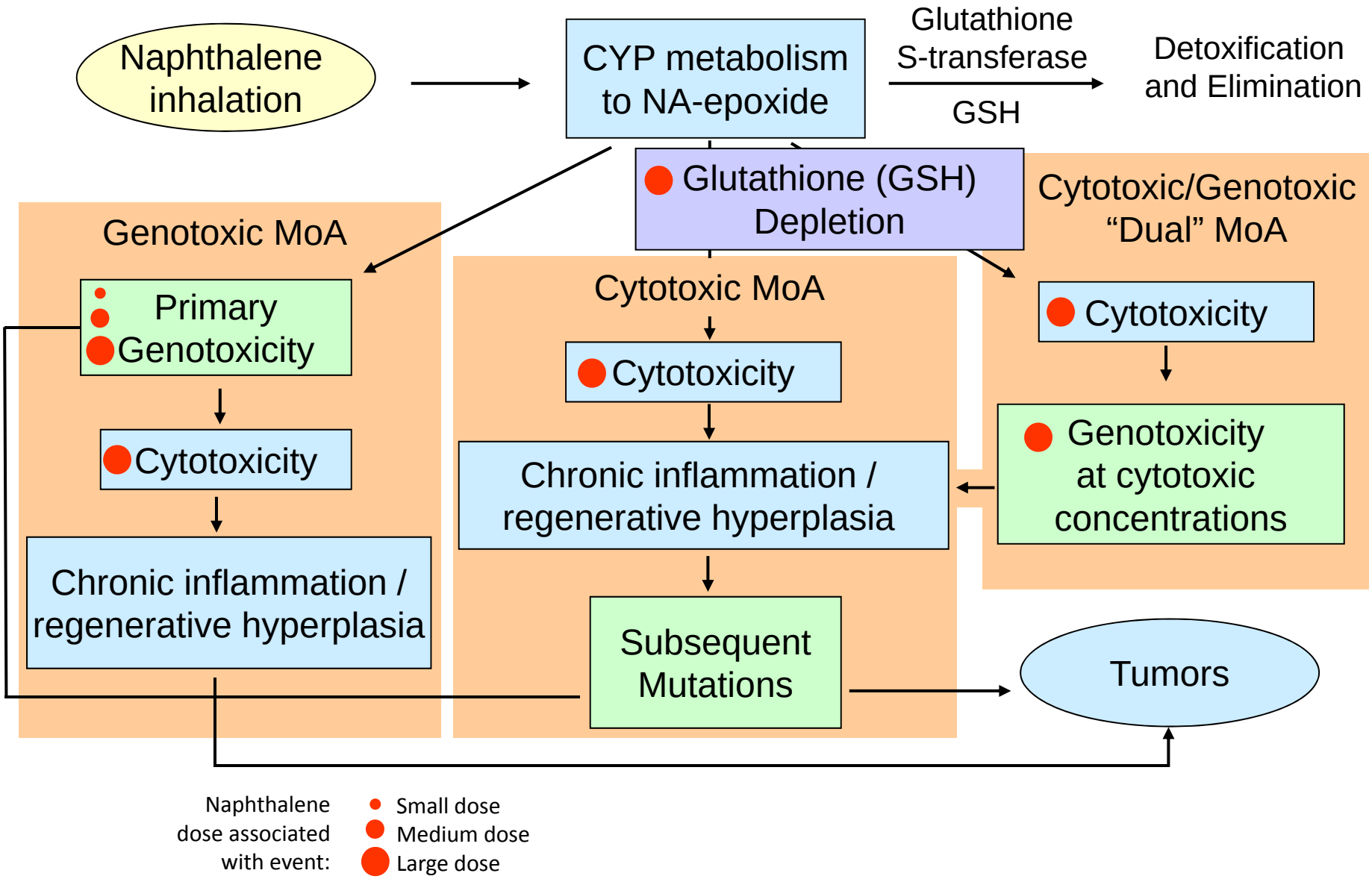
- Inhalation of naphthalene (10-60 ppm) causes olfactory epithelial nasal tumors in rats (but not mice) and benign lung adenomas in mice (but not rats) (NTP, 1992, 2000)
  - › Tumors confined to tissues directly exposed to naphthalene
  - › Tumors associated with widespread cytotoxicity and inflammation
  - › Tissues subject to toxicity are sites of concentrated and localized metabolic activity toward naphthalene
  - › IP injection causes similar pattern of cytotoxicity and metabolic activation, suggesting very specific and local MoA
- No positive human evidence for naphthalene's carcinogenicity – nasal tumors are rare

Naphthalene effects across species and tissue



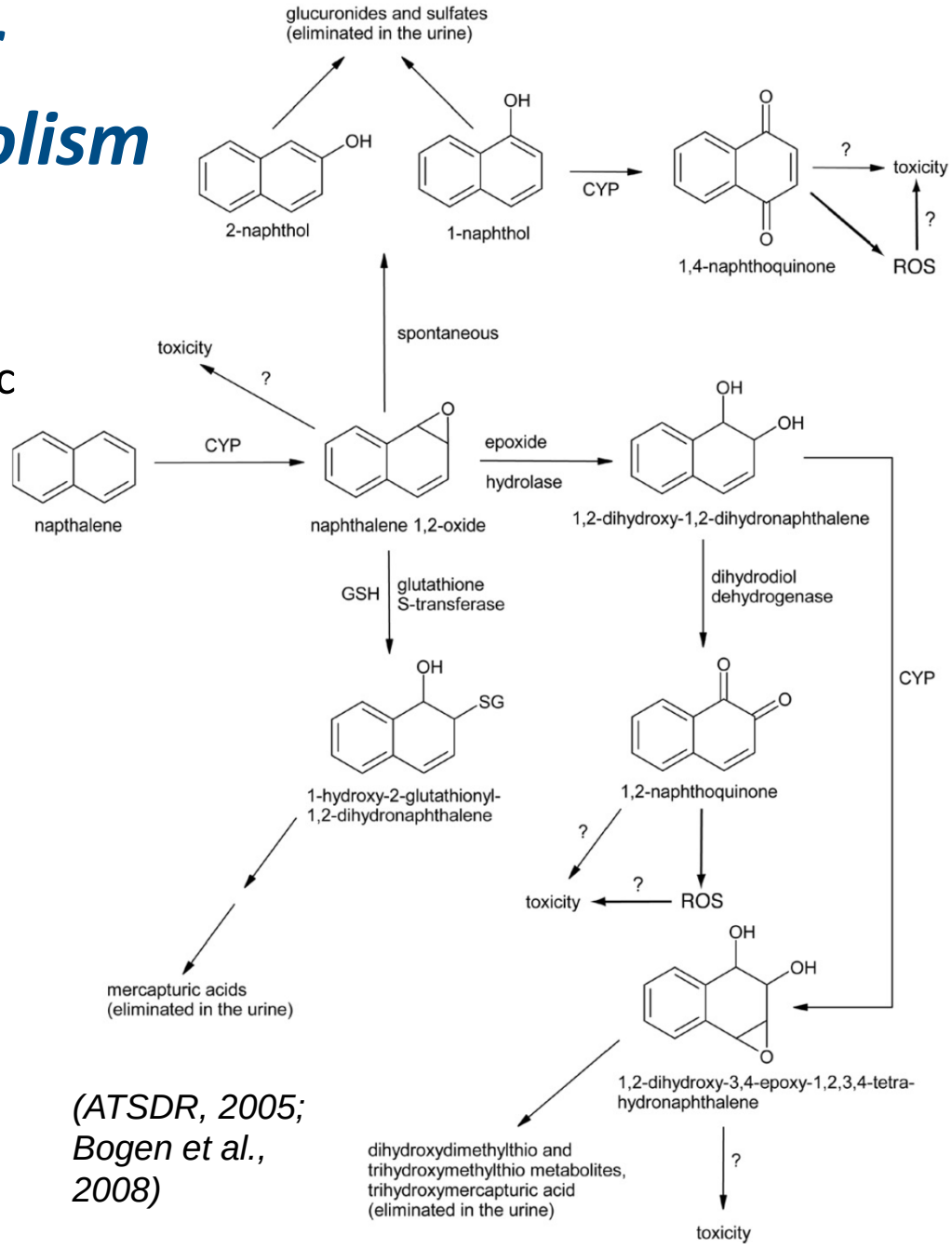
- Given the inconsistency across animal tissues and species, why should we assume human lung tissue will respond like the mouse lung or the rat nose?
- How might we account for the observed outcomes? What are possible reasons for lack of tumors in the mouse nose? And how might our understanding of this change our proposed animal MoA?
- Need to understand MoA in animals before extrapolation to humans is possible.

Hypothesized Modes of Action (MoA)



Proposed Scheme for Naphthalene Metabolism

- Primary metabolite (NA-epoxide) not directly genotoxic or mutagenic.
- Downstream metabolite (1,2-NAquinone) is genotoxic/mutagenic, but not likely to form until GSH depleted at cytotoxic concentrations.
- Suggests primary genotoxic mode of action not likely.



(ATSDR, 2005; Bogen et al., 2008)

Hypothesis

- High-dose cytotoxicity is hypothesized to be necessary for tumor formation in rat nose and mouse lung – and presumably, in any human target tissue.

- Mice have nasal toxicity without tumors, showing that cytotoxicity, even if necessary, is not sufficient. Some rat/mouse difference must make naphthalene sufficient to cause tumors in rat nose but not in mouse nose.

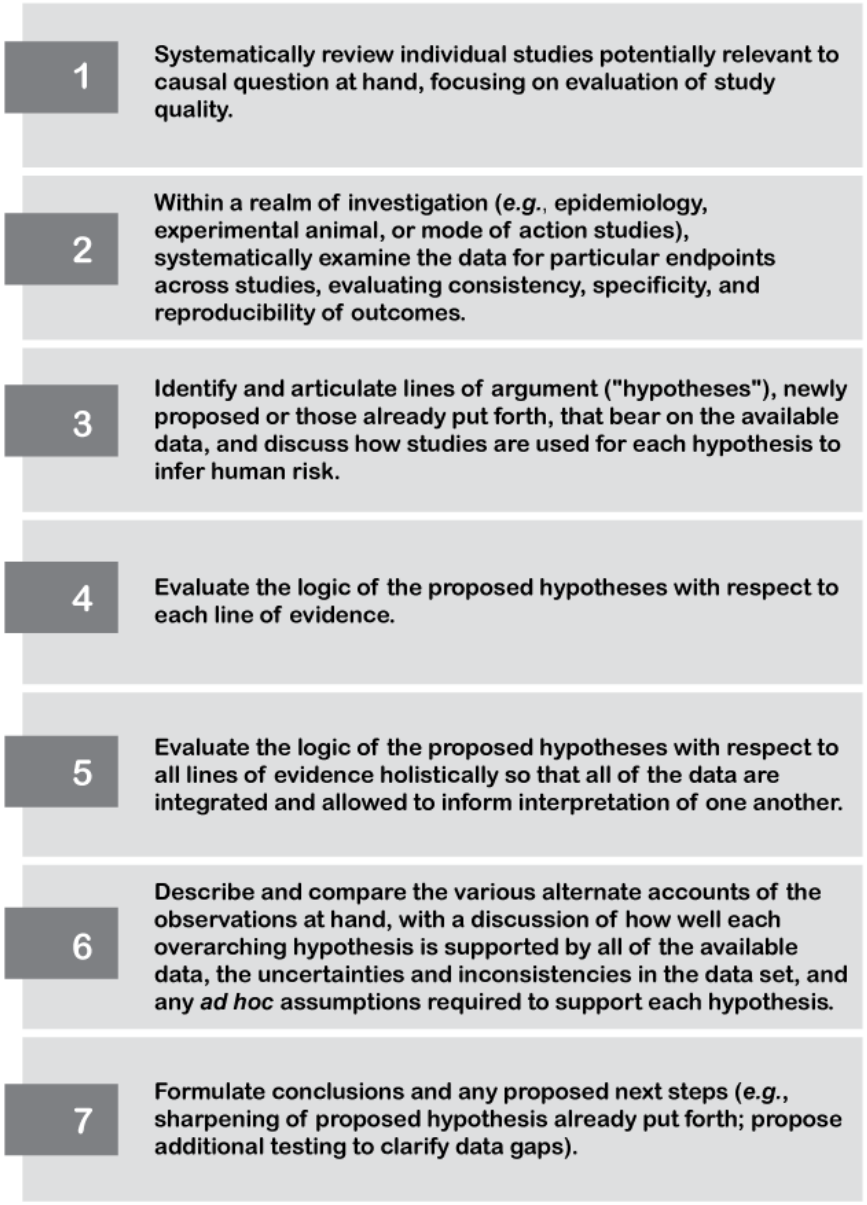
- A candidate difference is that, in rat but not mouse nose, high doses produce genotoxic metabolites after GSH depletion.

- Sub-cytotoxic exposures in humans is hypothesized to be insufficient to cause tumors owing to lack of necessary cytotoxicity and lack of low-dose genotoxicity sufficient to affect tumor risk.

Seven Steps of the HBWoE Approach

Applied to Naphthalene –

Rhomberg, LR; Bailey, LA; Goodman, JE. 2010. "Hypothesis-based weight of evidence: A tool for evaluating and communicating uncertainties and inconsistencies in the large body of evidence in proposing a carcinogenic mode of action - Naphthalene as an example." Crit. Rev. Toxicol. 40 :671-696.



- Systematic review, evaluate study quality
- Consistency, specificity within Epi, within Tox
- Articulate logic for why data constitute “evidence”
- Evaluate hypotheses: w.r.t Epi; w.r.t Tox
- Evaluate evidence for epi/tox commonality in causes
- Formulate competing “accounts” – sets of explanations of outcomes
- Conclusions, identify studies that can sharpen

New and Upcoming Naphthalene Research

- Animal studies
  - 90-day rat low-exposure (1 ppm) inhalation study shows minimal to no effect (Dodd et al., 2011)
- Epidemiology reviews
  - Lewis (2011), Magee et al. (2010)
- Metabolism/Toxicokinetic studies
  - CYP2F2 knockout mouse (Li et al., 2011) – CYP2F2 key for lung but not nasal metabolism
  - Mouse nasal uptake (Morris et al., 2012) – Naphthalene readily taken up in mouse olfactory
  - PBPK model (Campbell and Clewell work in progress)
  - Naphthalene metabolism mass-balance study in rat, mouse and monkey nose (Buckpitt et al., work in progress)

New and Upcoming Naphthalene Research (cont.)

- Mode of Action studies
  - Protein adduct studies (Pham et al. in press)
  - DNA adduct studies in rat nose and mouse lung (Bucholz et al. work in progress)
  - Mutagenesis study (Meng et al., 2011) – no increase in p53 mutant fraction in rat nasal respiratory and olfactory epithelia (up to 30 ppm naphthalene)
  - Naphthalene cytotoxicity and metabolites in human lung and nasal cells in vitro (Recio/Kedderis in press)
  - Genomics (Clewell work in progress)
  - Proposed MoA – aryl amidase pathway (Piccirillo et al. 2012)

Approaches to QRA:
Inhalation Cancer Toxicity Value

- Refined “Bad Actor” identification?
- Key MoA Component DR
  - › tumor data (BMDL);
  - › gene expression data (BMDL);
  - › cytotoxiticy (BMDL);
  - › respiratory hyperplasia data (BMDL)
- Application to Possible Different Target in Humans?