

Recommendations for DMA Assessment

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Presenting on behalf of MAA Research Task Force

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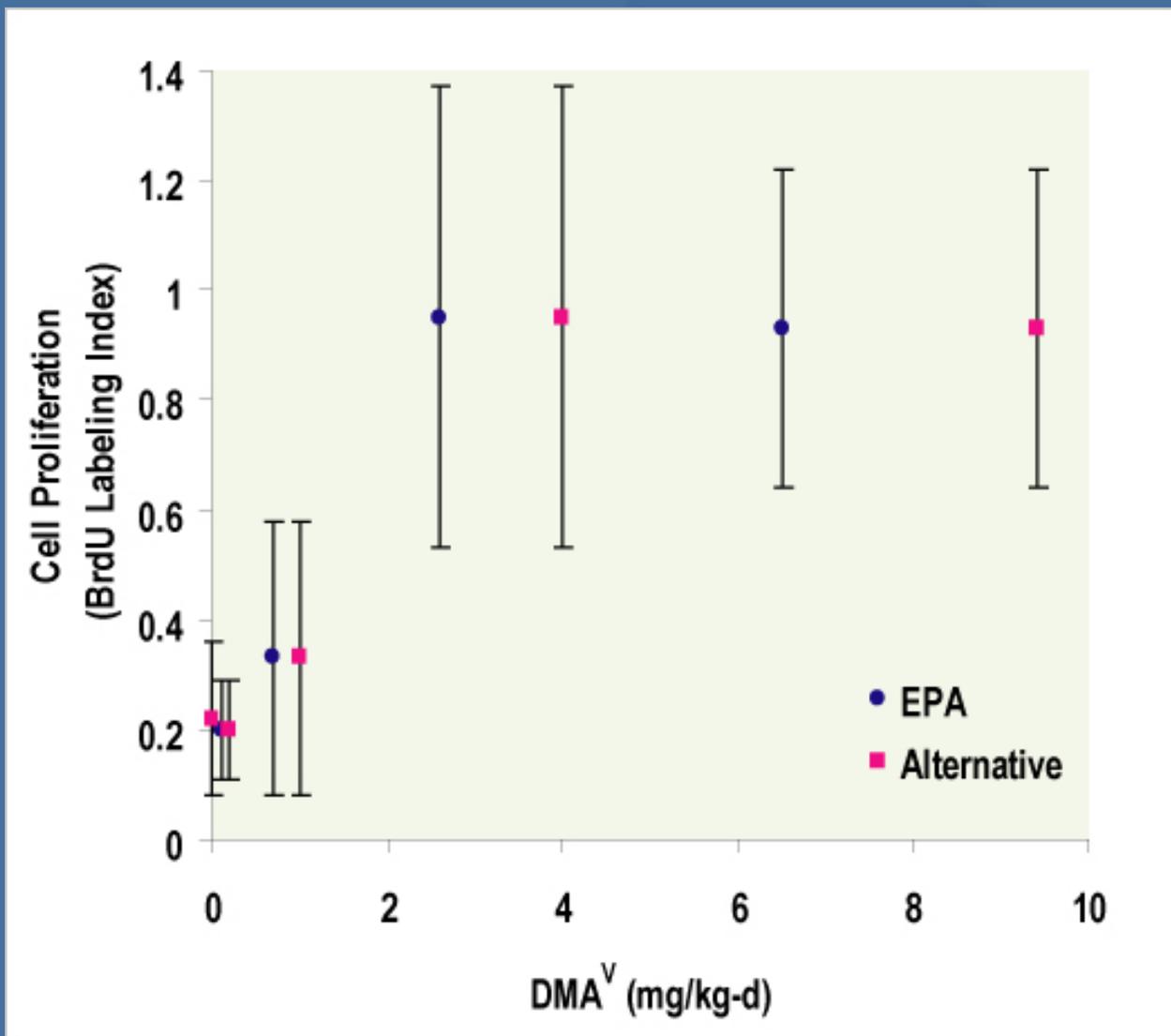
September 12-13, 2005

Recommendations

| Input | Recommended approach | Basis |
|---------------------------------|----------------------|--|
| Dose-Response | Nonlinear | MOA is cytotoxicity followed by regeneration |
| Endpoint | Cell proliferation | Early precursor, rate-limiting step |
| Point of Departure | BMDL ₁₀ | Less statistical uncertainty, but still conservative |
| Interspecies Uncertainty Factor | 1 | Rat more sensitive than human |
| FQPA Safety Factor | 1 | No evidence of increased early life stage susceptibility |

Cell Proliferation

Endpoint Selection



Benchmark Dose (BMD) Analysis

- BMD Approach

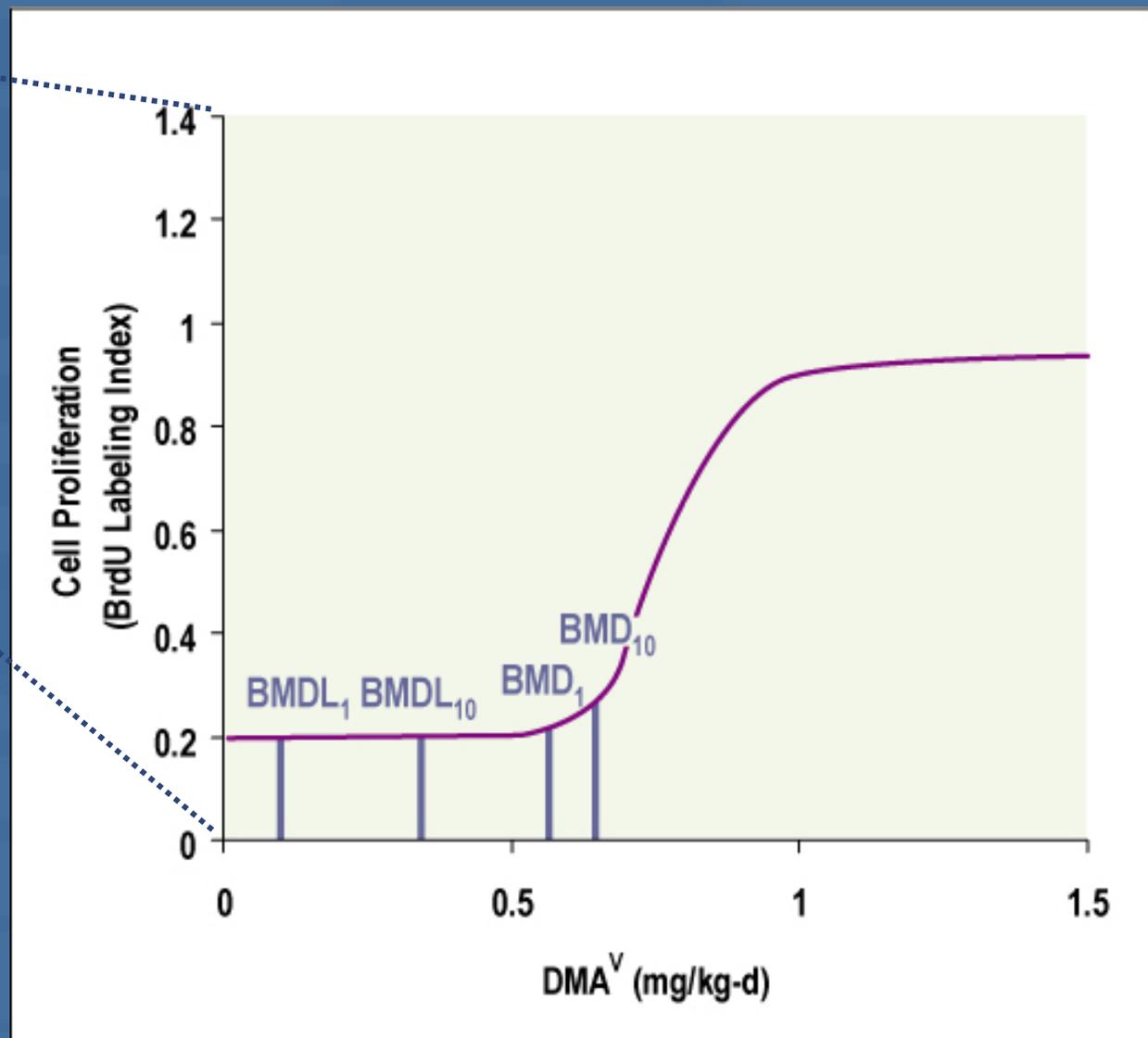
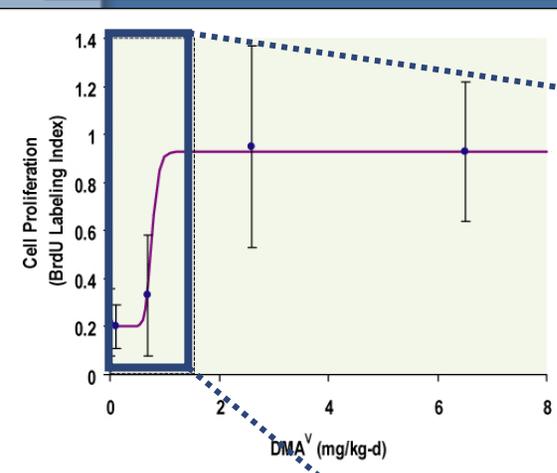
- ◆ Conservative, scientifically sound estimate of point of departure

- Hill Model

- ◆ Determines a change in response based on a certain percent of the maximum value
- ◆ Appropriate for cell proliferation data
- ◆ Allows for non-linearity (approximate step function)
- ◆ Zero slope not allowed (i.e., not a threshold model)

Hill Model

BMD Analysis



BMDL₁₀ vs. BMDL₁

BMD Analysis

- BMD₁₀ (0.65 mg/kg/d) and BMD₁ (0.54 mg/kg/d) are similar
 - ◆ Suggests steep dose-response curve
 - ◆ Increases confidence that low dose causing cell proliferation appropriately identified
- Increase in cell proliferation at BMD₁₀ modest and within variability in controls
 - ◆ approximately 35%
- Less uncertainty associated with BMD₁₀ than BMD₁ because BMD₁₀ smaller 95% CI

Interspecies-Toxicokinetics & Toxicodynamics

Uncertainty Factors

- Rats uniquely susceptible to DMA-induced cell proliferation and eventual tumor formation
 - ◆ Rats generate far more TMAO (indicating highly reactive DMA^{III} intermediate formed) than other species, including humans
- Toxicokinetic uncertainty factor less than 1 appropriate
- In vitro studies show comparable cytotoxicity of DMA^{III} in rats & humans, supporting a toxicodynamics factor of 1

- No evidence of increased susceptibility in early life stages
 - ◆ No developmental or reproductive toxicity at doses that are less than maternally toxic doses
 - ◆ No age-dependent differences in susceptibility to chemically-induced bladder cancer
 - Urinary anatomy and physiology developed by birth
 - Bladder cancer has late onset (>65 years)
 - Uncommon in children

- USEPA guidelines: adjustment for early life susceptibility necessary only for:
 - Chemicals with specific data showing increased susceptibility to cancer at early life stages
 - Mutagenic chemicals
- Since no evidence of early life susceptibility and DMA not mutagenic, FQPA safety factor adjustment not warranted

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