Science Question 8: Definitions

Chad Thompson, Ph.D.

ToxStrategies, Inc.

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Definitions of Genotoxicity & Mutagenicity

For this assessment, the IRIS Program is considering using the following definitions found in the EU Technical Guidance on Risk Assessment (1996)…

Comments:

- **What is meant by "for this assessment"?**
  - **Do the definitions differ across assessments?**
  - **Does EPA intend to adopt these definitions formally?**
  - **Has EPA considered whether these definitions conflict with *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005)**

- **The proposed definitions can be found in Section 3.10 of EU guidance document (2003)[*], which contains important information and recommendations for considering the genotoxicity and mutagenicity of a chemical…**

[*]European Commission. (2003) Technical guidance document in support of commission directive 93/67/EEC on risk assessment for new notified substances and commission regulation (EC) No 1488/94 on risk assessment for existing substances, Part I.

Section 3.10: EU 2003 Guidance Document*

1. "Evaluation of genotoxicity test data should be made with care. Regarding 'positive' findings, responses may be generated only at highly toxic/cytotoxic concentrations, and the presence or absence of a dose-response relationship should be considered."

2. "In vitro tests are particularly useful for gaining an understanding of the potential mutagenicity of a substance…Animal tests will…be needed, however, for the clarification of positive findings…"

3. "Following a positive result in an in vitro mammalian cell mutagenicity test, adequately conducted somatic cell in vivo testing is required to ascertain if this potential can be expressed in vivo."

4. "Select adequate somatic cell in vivo test, primarily on basis of systemic availability of the test substance:
   1. adequate systemic availability:
   - Micronucleus test (pref. for in-vitro clastogens and/or aneugens)

   2. lack of adequate systemic availability:
   - studies with tissues at initial sites of contact, e.g. in vivo comet assay; gene mutation with transgenic mice"

Can also do MN in GI tissue

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γ-H2AX staining and MN in duodenum (O'Brien et al., 2013)

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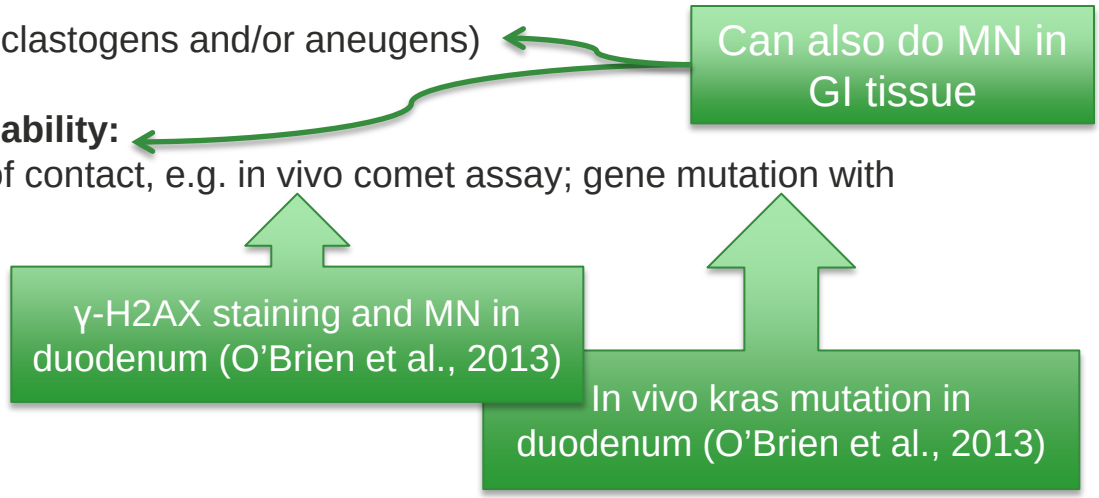

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Big Blue rat OECD guideline study in rat oral mucosa

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In vivo kras mutation in duodenum (O'Brien et al., 2013)

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