Definitions of Mutagenicity and Genotoxicity

Nancy Beck, PhD, DABT
October 30, 2014
EPA October Bimonthly Meeting

American® Chemistry Council

Definitions of Mutagenicity and Genotoxicity

Genotoxicity encompasses mutagenicity; however:

- What is the context for the use of these definitions?
  - Is EPA suggesting use of only the definitions or also EU implementation?
- Is EU 2006 guidance document outdated?

This information is critical to an informed and constructive discussion.

Context Matters

- How will EPA use these definitions?
  - How will EPA interpret words like “potentially” and “provide indication” in the genotoxicity definition?
  - Determination of genotoxicity should be based on a weighing of all evidence, not a one test threshold.
  - Will EPA have data requirements like the EU?
  - Assumptions of linearity may be inappropriate for genotoxicity and mutagenicity; dose-response and consideration of mode of action are important.
    - Thresholds must be recognized as plausible for both genotoxicity and mutagencity.

Context Matters (2)

- How will EPA use these definitions?
  - 2005 Cancer Guidelines focus on the presumption of linearity when there is evidence that a chemical or its metabolite is DNA-reactive and/or has the ability to bind DNA.
    - How will EPA treat indirect mutagens?
  - A genotoxic mode of action is not the same as mutagenic mode of action. However, is there such a thing as a genotoxic mode of action? Genotoxic markers are not typically heritable.
    - DNA adducts are biomarkers of exposure and not equivalent to a mutation-- not necessarily an adverse effect.
    - See Abertini & Sweeney 2007, Crit Rev. in Tox.; Jarabek et al., 2009, Crit Rev in Tox.; Pottenger et al., 2014, Crit. Rev. in Tox.; Johnson et al., 2014, Cancer Prevention Research.

Mutagenic MOA

"… ***to establish a mutagenic MOA, it should not be enough to establish that a carcinogen is a mutagen, even if that mutagenicity is supported by a pile of hazard ID data. This amounts only to a high-order WOE evaluation of mutagenic potential.*** In this reviewer's opinion, the important part of a MOA evaluation is connecting the mutations induced by the agent with the specific tumors that it produces. This will require types of data not typically employed for mutagenic hazard ID. These types of data could include, but should not be limited to:

a. An analysis of the temporality (and dose response) of in vivo mutation induction, along with the induction of cytotoxicity, apoptosis, compensatory cell proliferation, changes in gene expression, hormonal status (etc.) in comparison with the production of preneoplastic lesions and then tumors in the target tissues for tumors.

b. Mutational spectra analysis of the mutations caused by the adducts formed by the agent in comparison with the mutations found in the oncogenes and tumor suppressor genes that are causative of the tumors;.."

Dr. Heflich, FDA/NCTR, 2008, Commenting on EPA's draft Framework for Determining a Mutagenic MOA.

Can a Genotoxic Mode of Action Exist?

- Genotoxicity is a process.
  - Sometimes, but rarely, leading to mutation induction.
    - When there is a mutation, it is a mutagenic mode of action.
    - This can be direct or indirect
  - If it doesn’t progress to a mutation, there is no biological effect. A mode of action must have an endpoint.

OECD Genetic Toxicology Testing Guidance

- OECD is updating guidelines and accepted tests. (see: http://www.oecd.org/env/ehs/testing/TG_List_EN_Jul_2013.pdf).

- Certain OECD genetox test guidelines were deleted in 2014 including:
  - *in vitro* SCE assays (mammals)
  - *in vitro* UDS assays (mammals)

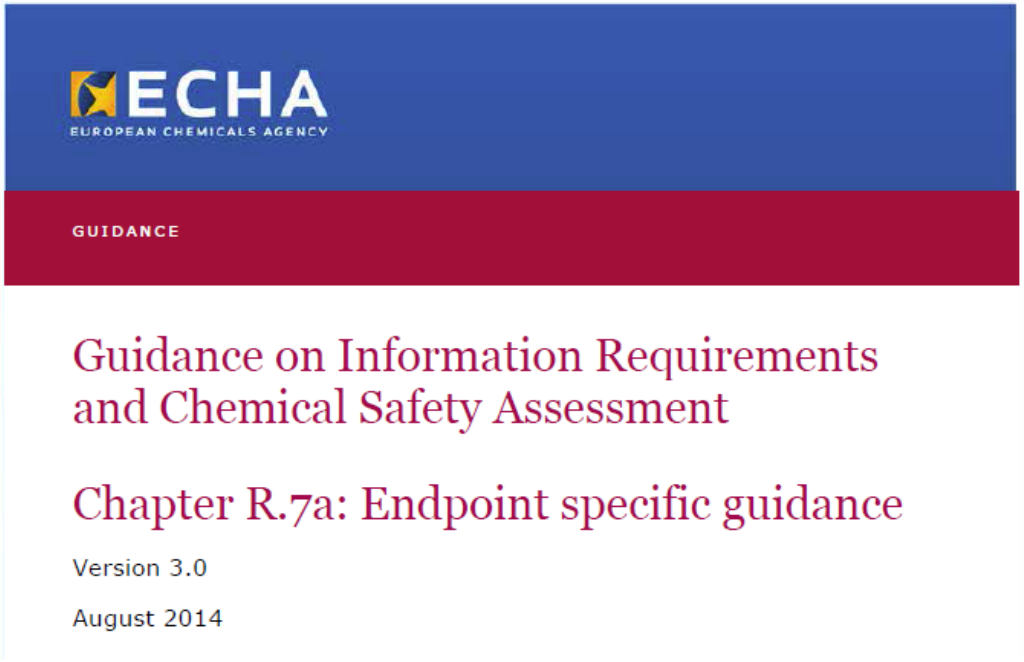
- These changes are not reflected in the EU Guidance. Does this matter to EPA?

Is 1996 EU Guidance Outdated?

- August 2014 release from ECHA

http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf

  - More expansive definition of mutagenicity: recognizing mutagenicity, includes gene mutation, clastogenicity and aneugenicity.
  - More detailed discussion of sources and evaluation of data



Questions and Discussion