

Mutagenic Modes of Action for Cancer and Default Low Dose Linear Extrapolation

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In 2005, the European Food Safety Authority (EFSA, 2005) recommended a margin of exposure (MOE) approach in their Scientific Opinion on "A Harmonised Approach for Risk Assessment of Substances which are both Genotoxic and Carcinogenic". A revision of this opinion is currently underway, in response to a request from the EFSA Scientific Committee (SC) to:

- o clearly define terminology (Terms of Reference 1) (TOR 1)
- o provide comprehensive guidance incorporating advances in the development and interpretation of MOEs (Terms of Reference 2), and
- o extend the guidance to non-cancer critical effects (Terms of Reference 3)

In the earlier opinion, EFSA (2005) recommended an MOE of > 10,000 for genotoxic carcinogens based on uncertainties related only to hazard.

Reconsideration of the early opinion takes into account considerable subsequent advancement in a number of critical areas. This includes technical advances in characterizing effects at lower levels of biological organization and the associated documentation of pathways/networks of key events [adverse outcome pathways] for mutation and chromosome aberration and chemical specific mutagenic modes of action (MOAs) for cancer. It also addresses additional experience in the consideration of uncertainty and variability in both exposure and hazard in tiered approaches in interpreting the adequacy of margins of exposure to protect human health.

The status of consideration of these evolving areas and potential implications relevant to the assumption of low dose linear extrapolation for carcinogens acting via a mutagenic mode of action will be addressed.