Endogenous Formation: Implications for Formaldehyde Carcinogenicity



Beyond Science & Decisions

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Endogenous Compounds in Dose-Response Assessments

- *Understanding the potential effects and concentrations of an endogenously present compound are critical in characterizing the shape of the dose-response curve in the low-dose region (e.g., linear versus nonlinear).*
  - *Threshold-like dose-response curves* – depending upon the magnitude of the background concentrations and toxic response.
  - *Linear dose-response curves* – if a detectable background level of toxicity occurs and the exogenous exposure adds to or augments the background toxicity process, assuming no adaptive responses.

Endogenous Concentrations of Formaldehyde

- Measuring concentrations resulting from endogenous production versus exogenous exposure is a challenge, especially in the case of formaldehyde which is a reactive compound
  - Recent studies employing stable isotope-labeled formaldehyde have differentiated between formaldehyde DNA adducts of endogenous and exogenous origin.
  - DNA adducts have been used as molecular dosimeters to reflect the internal dose of a genotoxic chemical in target tissues following exposure.

Endogenous Concentrations of Formaldehyde

- Adducts focused upon as a biomarker of exposure for inhalation exposure to formaldehyde (dG adducts) are considered to be mildly pro-mutagenic (not potent) and a key event in the initiation of mutations that lead to carcinogenesis.
- Preliminary data (Moeller et al. 2013) suggest that some of the dG adducts may be breakdown products of DNA-protein crosslinks (DPX), which are considered as key events in understanding the mode of action for potential carcinogens (USEPA 2010).
- Although it is recognized that not every adduct leads to a mutation that leads to tumors, the initial BBDR and "bottom up" approaches made the conservative assumption that the adducts were quantitatively related to tumor development.

Endogenous Concentrations in Dose-Response Assessment

- Results from DNA adduct studies provide an alternate characterization of exposure that can be incorporated into dose-response assessments for the potential carcinogenicity of formaldehyde.
  - There may be an inflection point for a dose response curve where the exogenous adducts increases nonlinearly above the endogenous level, or there may be a linear increase with data points that are not significantly different from controls at lower doses.
  - The point at which the adducts increase above the background adducts is where the presence of exogenous concentrations begin to drive the biology that results in effects.

Dose-Response Models: Endogenous compounds

- Traditionally applied empirical dose-response models, such as the Multistage model, are based on statistical fits to the tumor dose-response in the observable range.
- These models are then used to extrapolate downward to environmentally relevant external exposure concentrations.
- With endogenously present compounds, modeling approaches, such as the “bottom up” approach, are needed to incorporate endogenously present concentrations that are critical for characterization the low-dose region.

Current Case Study: Formaldehyde

- Recent research on specific formaldehyde DNA adducts can be incorporated into dose-response modeling as biomarkers of exposure for both endogenous and exogenous formaldehyde.
- The application of this information into two methods for estimating the dose-response curve (bottom up and BBDR) can provide the potential impact on the shape of the dose-response curve in the low concentration region.

Target Tissue Dosimetry

- Even without the implementation of the fluid BBDR model for formaldehyde, the CFD modeling conducted to date demonstrates the importance of understanding the target tissue dosimetry in the low concentration range.
  - The presence of endogenous formaldehyde had no effect on nasal uptake at high exposure concentrations (> 500 ppb). However, as exogenous exposure decreased, the presence of endogenous formaldehyde reduced nasal tissue uptake of inhaled exogenous formaldehyde, most notably at concentrations < 10 ppb.
  - At lower exogenous exposure concentrations, the concentration gradient between air and tissue is greatly reduced due to the presence of endogenous formaldehyde in nasal tissues, leading to reduced tissue uptake.
  - These results further demonstrate the importance in understanding endogenous concentrations of a compound, such as formaldehyde, in characterizing the shape of the dose response curve in the low dose region.

Strengths

- Use of biomarkers, such as specific DNA adducts, which are closer to the critical "target tissue" concentrations than is the corresponding external exposure concentration.
- Reliance on a highly sensitive and accurate method that differentiates between exogenous and endogenous concentrations.
- Approaches for the measurement of exposure biomarkers and application of the "bottom up" approach can be extended to other compounds.
- CFD modeling has been conducted to investigate the impact of the presence of endogenous formaldehyde on the site-specific absorption of exogenous formaldehyde in the nasal cavities of rats, monkeys, and humans.

Limitations

- Assumption of a linear dose-response relationship for the bottom up approach restricts it to bounding low-dose cancer risks. It may not be appropriate for bounding risks in the observable response range, where nonlinear processes can dominate the dose-response relationship, or for developing "best" or central estimates of risks.
- Pharmacokinetic assumptions are required to convert the quantified biomarkers of exposure (DNA adducts) obtained in short-term animal studies to corresponding estimates arising from continuous lifetime exposures in humans.
- Potential variability in the endogenous concentrations present in humans has not yet been quantified, although interanimal variation in endogenous concentrations has been quantified and employed in the current approach.

Data Needed for Approach

- Biomarkers of exposure that are plausibly linked to either the noncarcinogenic or carcinogenic process to characterize the endogenously present concentrations, as well as the contributions arising from exogenous exposure.
- PK and, possibly, CFD/BBDR models to characterize the target tissue dosimetry associated with endogenous and exogenous exposure.
- Incorporation of data into the ‘bottom up” approach and interpretation of results.

Science and Decisions Issues

- **Address background exposures and responses?**
  - This case study demonstrates for an endogenously present compound the impact of endogenous and exogenous exposure on target tissue dosimetry and upper bounds on the dose-response curve in the low concentration region.
- **Work practically?**
  - The bottom up approach is a relatively easy method to apply, as long as the critical data are available.

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