

# *Endogenous Formation: Implications for Formaldehyde Carcinogenicity*



Beyond Science & Decisions

May 28, 2013



# *Endogenous Compounds in Dose-Response Assessments*

- Consideration of the effects of exposures that add to background processes or endogenous concentrations when attempting to characterize the shape of the dose-response curve in the low-dose region (e.g., linear versus nonlinear) (NAS 2009).
  - *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.

# *Development of New Analytical Methods*

- Provide very sensitive and highly accurate quantitative data that allow evaluation of endogenous levels that were not readily available in the past.
  - Includes use of stable isotope exposures, measurement of DNA damage from common pathways such as oxidative stress and inflammation.
- Mutation data for low exposures are being addressed, rather than the previous Hazard Identification studies that utilized high doses.
  - Will decrease uncertainty and address the contribution of these effects through appropriate dose–response modeling procedures.

# *Challenges with Endogenous Compounds*

- Development of methods are needed to quantify endogenous production and differentiate compounds present from endogenous production versus exogenous exposure.
- Once methods developed and results obtained, how to incorporate results into the dose–response assessment?
- Can exogenous exposure increase endogenous levels sufficiently to create biological perturbations that culminate in detectable adverse effects?

# *Case Study: Formaldehyde*

- Endogenously present compound
  - an essential metabolic intermediate in all living cells
- Numerous exogenous sources
  - vehicle emissions, building materials, and tobacco smoke, as well as through metabolism of foods, chemicals and drugs
- Concerns related to potential to cause to carcinogenic health effects in humans:
  - Nasopharyngeal
  - Lymphohematopoietic/Leukemias

# *National Academy of Sciences*

- *“...formaldehyde is an endogenous compound and that this finding complicates assessments of the risk posed by inhalation of formaldehyde. This committee emphasizes that the natural presence of various concentrations of formaldehyde in target tissues remains an important uncertainty with regard to assessment of the additional dose received by inhalation.”*

# *Questions Related to Formaldehyde Dose-Response Assessment*

- How can we accurately assess the risk of exogenous formaldehyde at low air concentrations (ppb range) in the presence of a substantial background of endogenous formaldehyde (exhaled breath concentrations ranging from 1–73 ppb)?
- What is needed to conduct a dose–response assessment considering the “background” concentrations that are always present in biological systems?
- If a specific marker is used to differentiate endogenous from exogenous exposure, can this be a biomarker of exposure or a biomarker of effect (related to the mode of action)?

## *Case Study: Formaldehyde*

- Recent research results for formaldehyde provide as an example of methods for quantifying endogenous production
  - Work by Swenberg and colleagues (Lu et al. 2011, 2012, Moeller et al. 2011) provides an accurate characterization of endogenous versus exogenous DNA adducts following inhalation exposure to formaldehyde in rats and nonhuman primates.



# *Case Study: Formaldehyde*

- Recent dose–response assessments provide an example of how these results can be incorporated into dose–response modeling
  - New “bottom up” approach (Starr and Swenberg 2013) provides an alternative to the "standard" top–down risk extrapolation from high dose animal or human cancer data.
- Recent modeling efforts provide an evaluation of impact on target tissue dosimetry
  - Initial findings (Schroeter et al. 2013) from the incorporation of endogenous concentrations of formaldehyde into BBDR modeling (Conolly et al. 2003; 2004) demonstrate the significant impact of endogenous concentrations when characterizing the dose–response curve in the low concentration region.

# *Additional Questions to be Addressed*

- Characterizing endogenous production of formaldehyde and consideration of these concentrations in conducting dose-response assessment may assist in addressing other issues raised in the Science and Decisions (NRC 2009)
  - Variability
  - Mode of Action
- Remaining Questions:
  - Polymorphisms in metabolic pathways
  - Potential for endogenous formaldehyde to cause effects
- Results to these questions may be relevant to understanding the impact of individual and cell type variability in characterizing the shape of the dose-response curve in the low concentration region.

# *Case Study: Endogenous Formaldehyde*

- **Quantifying Endogenous Levels** – James Swenberg
- **Incorporation in Dose–Response Modeling** – Thomas Starr
- **Impact on Target Tissue Dosimetry (CFD/BBDR Modeling)** – Jeffry Schroeter