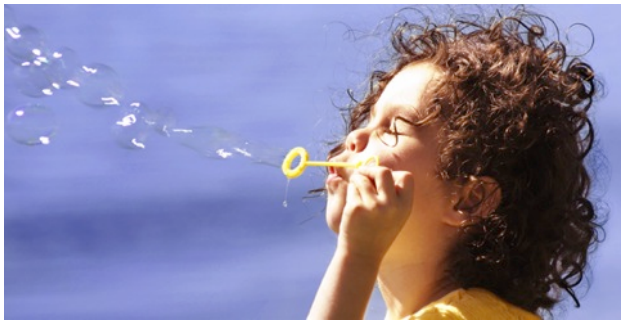
Endogenous Chemical Risk Assessment: Formaldehyde as a Case Example





Beyond Science & Decisions WEBINAR

November 2, 2012

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Consideration of Background in Dose-Response Assessments

- Dose-response models should fully address background disease processes and exposures (NAS 2009).
- What special modeling considerations and data are needed when the chemical of concern is an environmental contaminant in air, drinking water, food or consumer products (for example, foods, pharmaceuticals, cosmetics) and is also present endogenously?

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?
  - Alternative dose-response approaches
  - Use of PBPK/BBDR modeling approaches

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

Case Study: Formaldehyde

- How can we accurately assess the risk of exogenous formaldehyde in the presence of a substantial background of endogenous formaldehyde?
- What is needed to conduct a dose-response assessment considering “background” concentrations present in biological systems?

Case Study: Formaldehyde

- Research underway to quantify endogenous production and investigate quantitative approaches for dose-response modeling
  - Biological Data
    - Characterization of endogenous versus exogenous DNA adducts following inhalation exposure to formaldehyde in rats and nonhuman primates
  - Alternative Dose-Response Approaches
    - New “bottom up” approach (Starr and Swenberg 2012) that provides a completely independent reality check on any kind of "standard" top-down risk extrapolation from high dose animal or human cancer data.
  - PBPK/BBDR modeling
    - Conolly et al. (2003, 2004) models available but do not consider endogenous production.

Development of Biological Data to address endogenous compounds

- *Formaldehyde*: Analytical approach developed that incorporates the use of radiolabeled exogenous inhaled formaldehyde with measurements of harvested DNA adducts (Lu et al. 2011; Moeller et al. 2011).
  - DNA adducts have been widely used as a molecular dosimeter to better reflect the internal dose of a genotoxic chemical in target tissues following exposure.

Development of Biological Data to address endogenous compounds

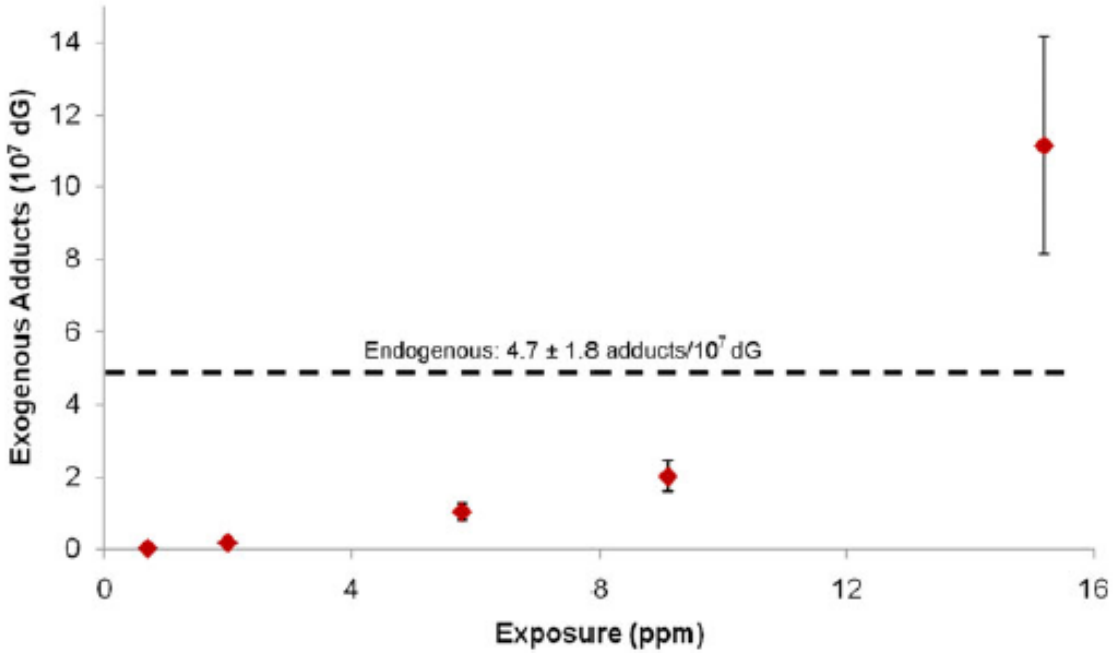


FIG. 2. Molecular dosimetry of N^2-hydroxymethyl-dG adducts in rats exposed to formaldehyde.

From Swenberg et al. (2011)

N2-hydroxymethyl-dG Adducts in Monkeys Exposed Twice for 6 hrs to 2 ppm CH2O

Tissue	Endogenous Adducts at 30 hrs	Exogenous Adducts at 30 hrs	Exogenous Adducts at Steady-State
Nasal Epithelium Mean ± se Lower 95% Bound	 2.49 ± 0.23 2.11	 0.25 ± 0.020	 2.21 ± 0.18
Bone Marrow Mean ± se Lower 95% Bound	 17.5 ± 1.31 15.34	 < 0.00103[a]	 <0.00912[a]

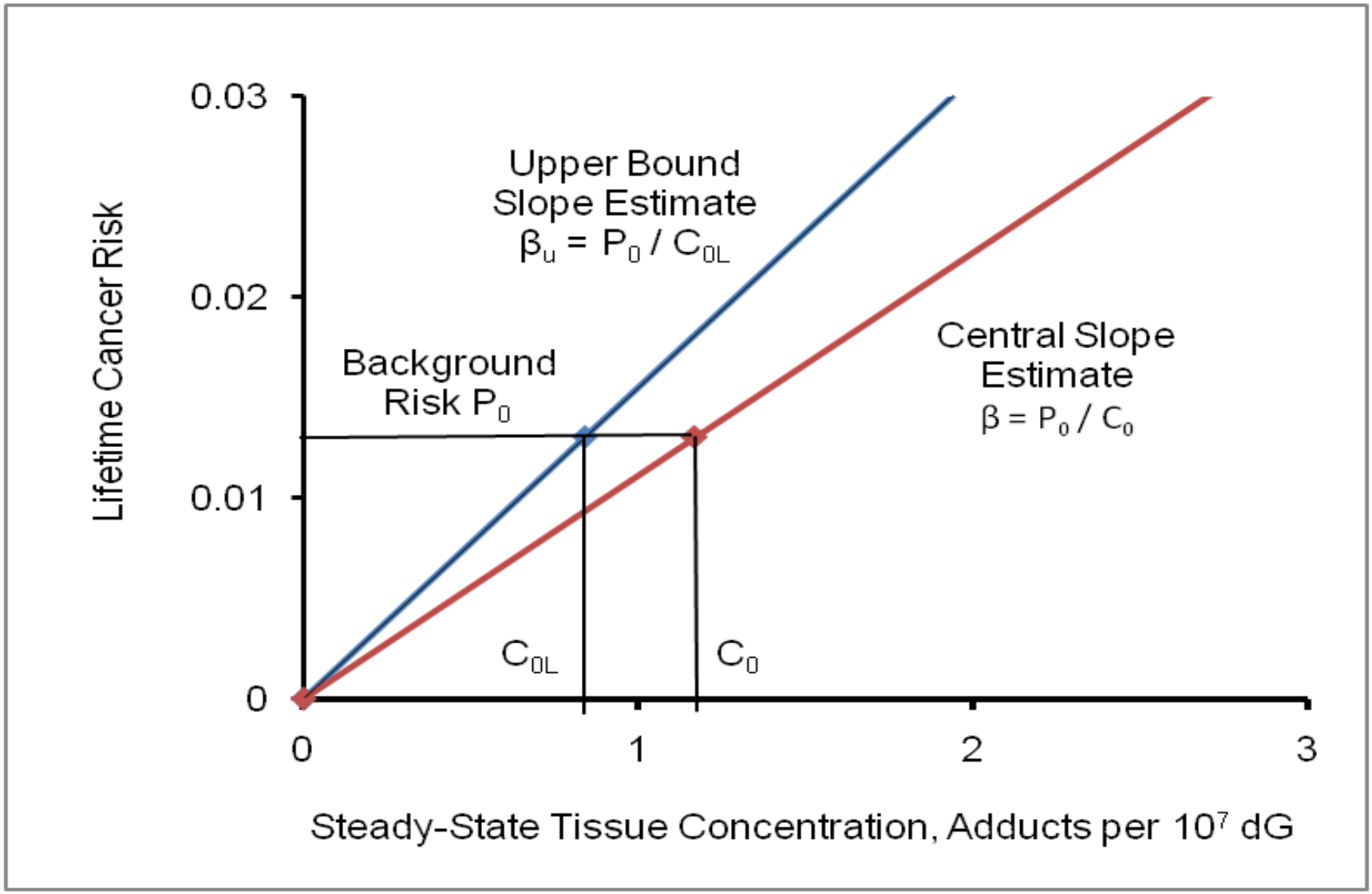
a: no exogenous adducts were detected in bone marrow; upper limit estimate based on the detection limit reported in Moeller et al. (2011).

Alternative Dose-Response Approaches

"Bottom Up" Approach Features

- Upper bound on lifetime cancer risks without using high dose data from animal bioassays or epidemiology studies
- Suitable for chemicals present in the body as a result of normal endogenous processes, e.g., metabolism
- Conservative:
  - Assumes linearity at low doses
  - All background risk attributed to background, i.e., endogenous, exposure
  - Upper 95% confidence bound risk estimates derived for steady-state exogenous exposure
- Provides a completely independent "reality check" on extrapolations from high-dose data

Bottom-Up Approach Elements



Bottom Up Approach

- Nasopharyngeal cancer: the bottom-up UCL95 risk estimate is 29.8-fold lower than the top-down estimate of 1.1%

- Lymphohematopoietic/Leukemias: based on the detection limit for DNA adducts, the bottom-up UCL95 risk estimate is 14,615-fold lower than the top-down estimate of 5.7%

- These large discrepancies suggest that the top-down approach may be overly conservative

PBPK/BBDR Models: Formaldehyde

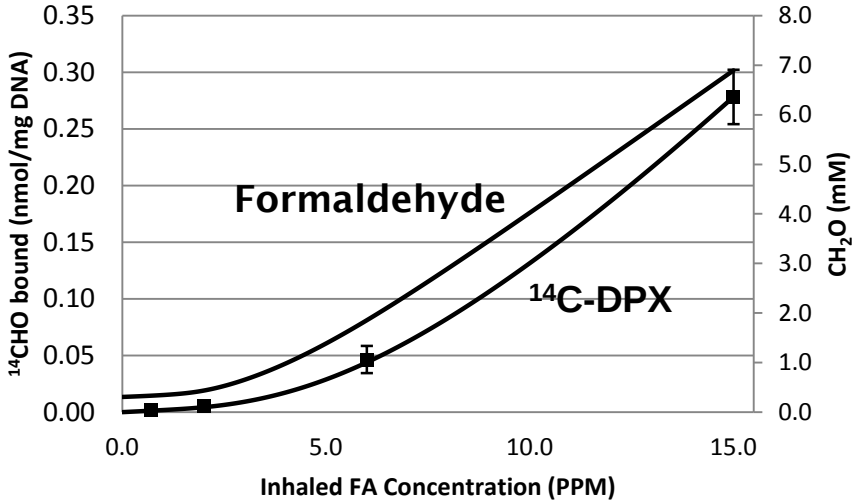
- **NAS (2010)** – *"Given that the BBDR model for formaldehyde is one of the best-developed BBDR models to date, the positive attributes of BBDR models generally, and the limitations of human data, the committee recommends that EPA use the BBDR model for formaldehyde…"*

  - Conolly et al. (2003, 2004) – CFD/BBDR formaldehyde models for the rat and the human.
  - Available models do not consider endogenous production of formaldehyde.

PBPK/BBDR Models: Formaldehyde

Andersen et al. (2010)

Used ^{14C}-DPX-data with formaldehyde in the nose to infer tissue levels of FAcetal



Lu et al. (2010) have group have measured exogenous and endogenous adducts

Table 1. Formaldehyde-Induced N^2-Hydroxymethyl-dG Adducts in the Nasal Epithelium of Rats Exposed to [$^{13}CD_2$]-Formaldehyde for 6 h

exposure (ppm)	endogenous dG adduct (adducts/10^7 dG)	exogenous dG adducts (adducts/10^7 dG)
0.7 ± 0.2	3.62 ± 1.33[a]	0.039 ± 0.019
2.0 ± 0.1	6.09 ± 3.03[b]	0.19 ± 0.08
5.8 ± 0.5	5.51 ± 1.06[c]	1.04 ± 0.24
9.1 ± 2.2	3.41 ± 0.46	2.03 ± 0.43
15.2 ± 2.1	4.24 ± 0.92	11.15 ± 3.01

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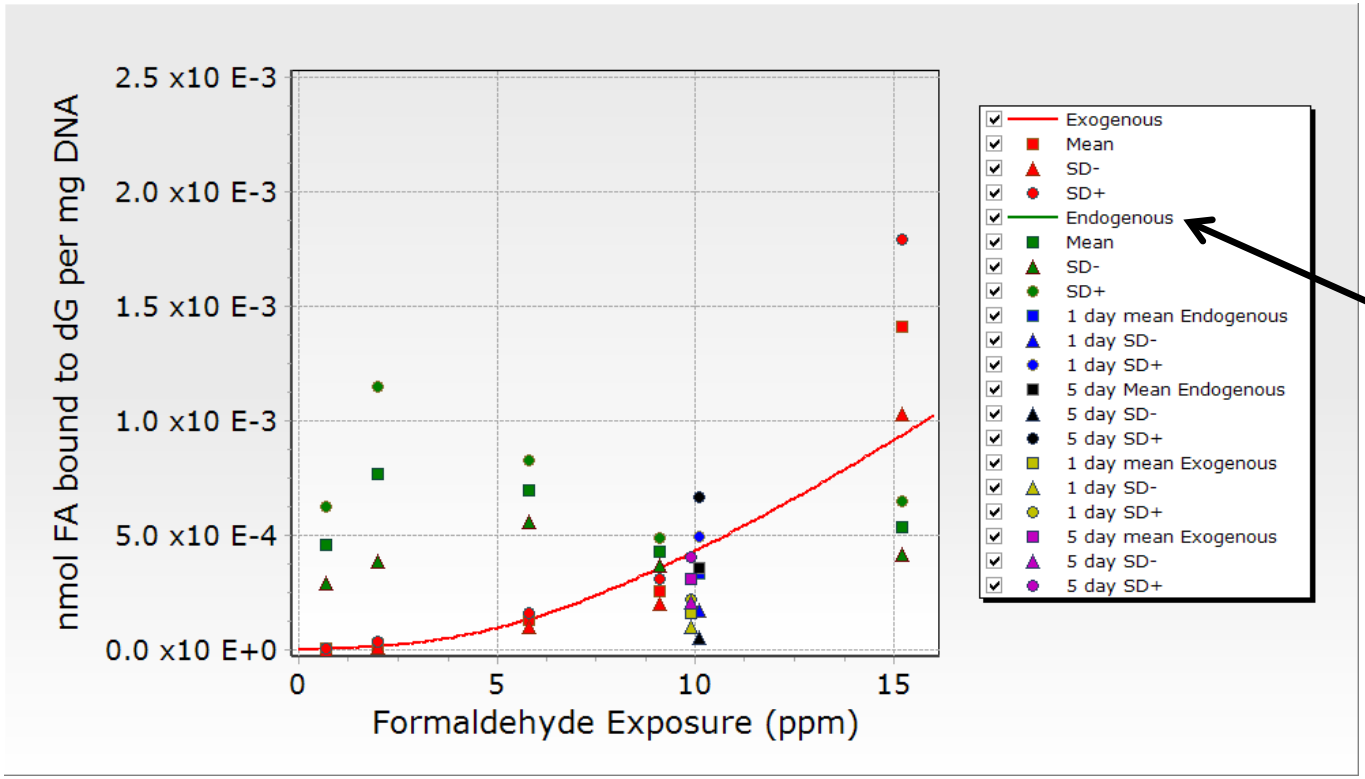
Original Model of Endogenous Formaldehyde

- Andersen et al. (2010) model prediction of endogenous and exogenous formaldehyde binding after 6 hour exposure to labeled formaldehyde



At first glance not a bad fit but…

Where is the endogenous?

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Original Model of Endogenous Formaldehyde

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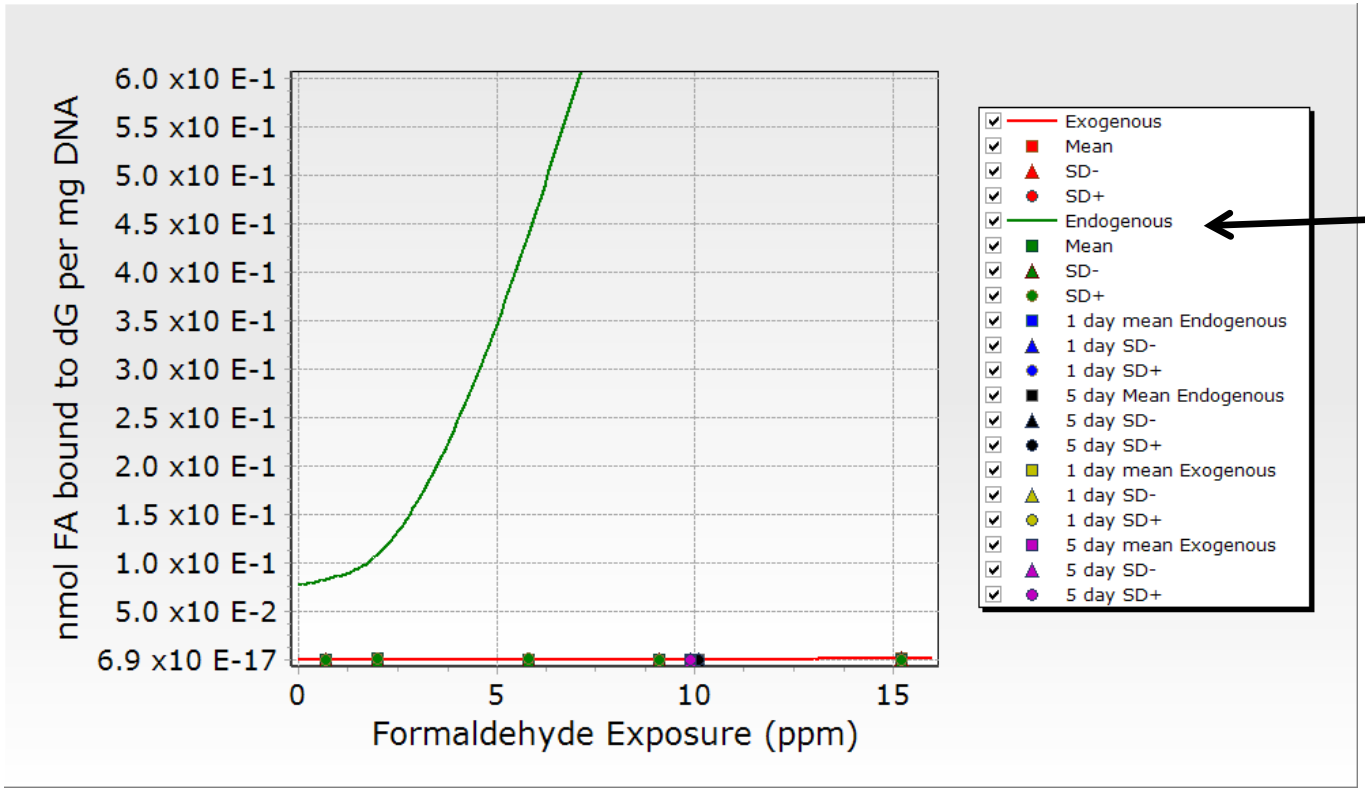

orders of magnitude higher

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Adaptation of BBDR model to describe endogenous formaldehyde

Uptake of formaldehyde in the rat nose with the endogenous formaldehyde added to the CFD model

Exposure Concentration (ppm)	Nasal Uptake (%)
1.0	99.4
0.1	98.6
0.01	91.3
0.001	17.5

Refinement of Formaldehyde BBDR Model

Ultimate Goals

- Add description of endogenous formaldehyde to BBDR model and recalibrate against original data, as well as new data from Swenberg et al.
- Evaluate alternative assumptions/approaches to characterize range of plausible risk estimates.
- Evaluate the compatibility of low-dose linear risk estimates with endogenous tissue concentrations.
- Evaluate impact of data and model uncertainties on the estimation of human risk.

Questions

- What issues need to be addressed related to the application and acceptance of alternative approaches (e.g.,"bottom" up approach)?
- What additional data or documentation are needed for a complex model, such as the BBDR model, for it to be more informative to a formaldehyde assessment?

- As a framework for other endogenous chemicals:
  - Can this approach be developed for other chemicals with endogenous production?
  - What types of information are needed to make PBPK/BBDR models useful to inform chemical assessments for endogenous chemicals?
  - Provide input on the key considerations and factors that you would expect EPA to include when discussing the comparison of the PBPK/BBDR with alternative approaches.
  - When evaluating the model results to those derived from the application of EPA's Mode of Action Guidelines, what are the key factors that should influence the comparison?
  - How should BBDR models incorporate background cancer rates?

Full Case Study: Spring 2013

- **Development of Biological Data** – James Swenberg
- **Alternative Dose-Response Approaches ("Bottom Up" Model)** – Thomas Starr
- **Progress on the CFD/BBDR Model** – Robinan Gentry