

# **Understanding the Health Risks Associated with Formaldehyde Exposure**

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The Hamner Institutes for Health Sciences

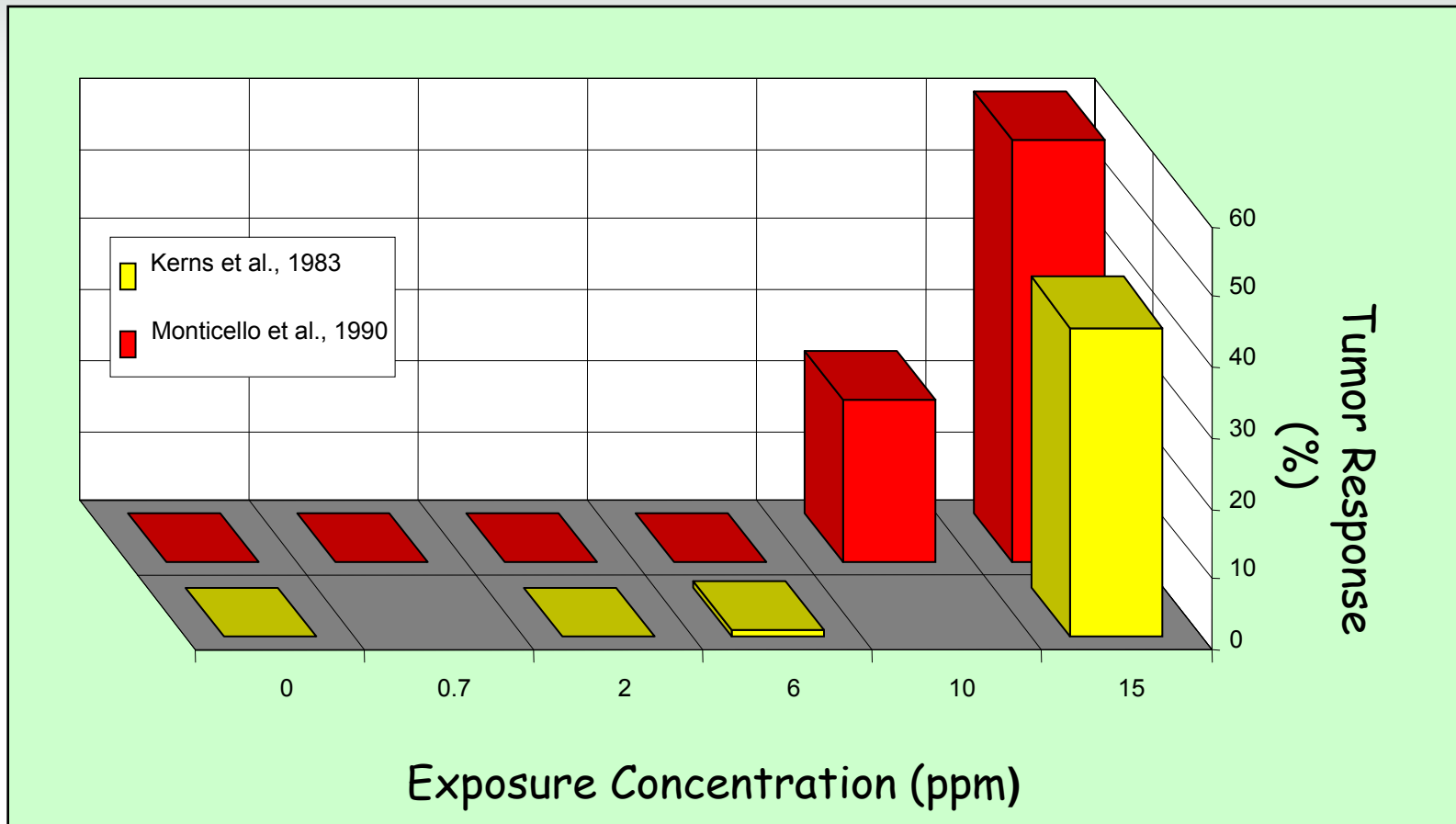
# *Health Effects of Inhalation Exposure to Formaldehyde*

- Noncancer effects
  - Acute irritation (eyes, nose, throat) above 1 ppm
  - Chronic irritation above 0.1 ppm
  - "Safe concentrations"
    - ATSDR: 0.008 ppm
    - Germany: 0.1 ppm
- Cancer
  - Animal evidence: Nasal tumors in rats at 6 ppm and above
  - Human evidence: uncertain
  - Cancer risk estimates at 0.1 ppm
    - EPA (1991): ~ 1/1000
    - Health Canada (2001): less than 1/10,000,000
    - Germany (2006): "safe"

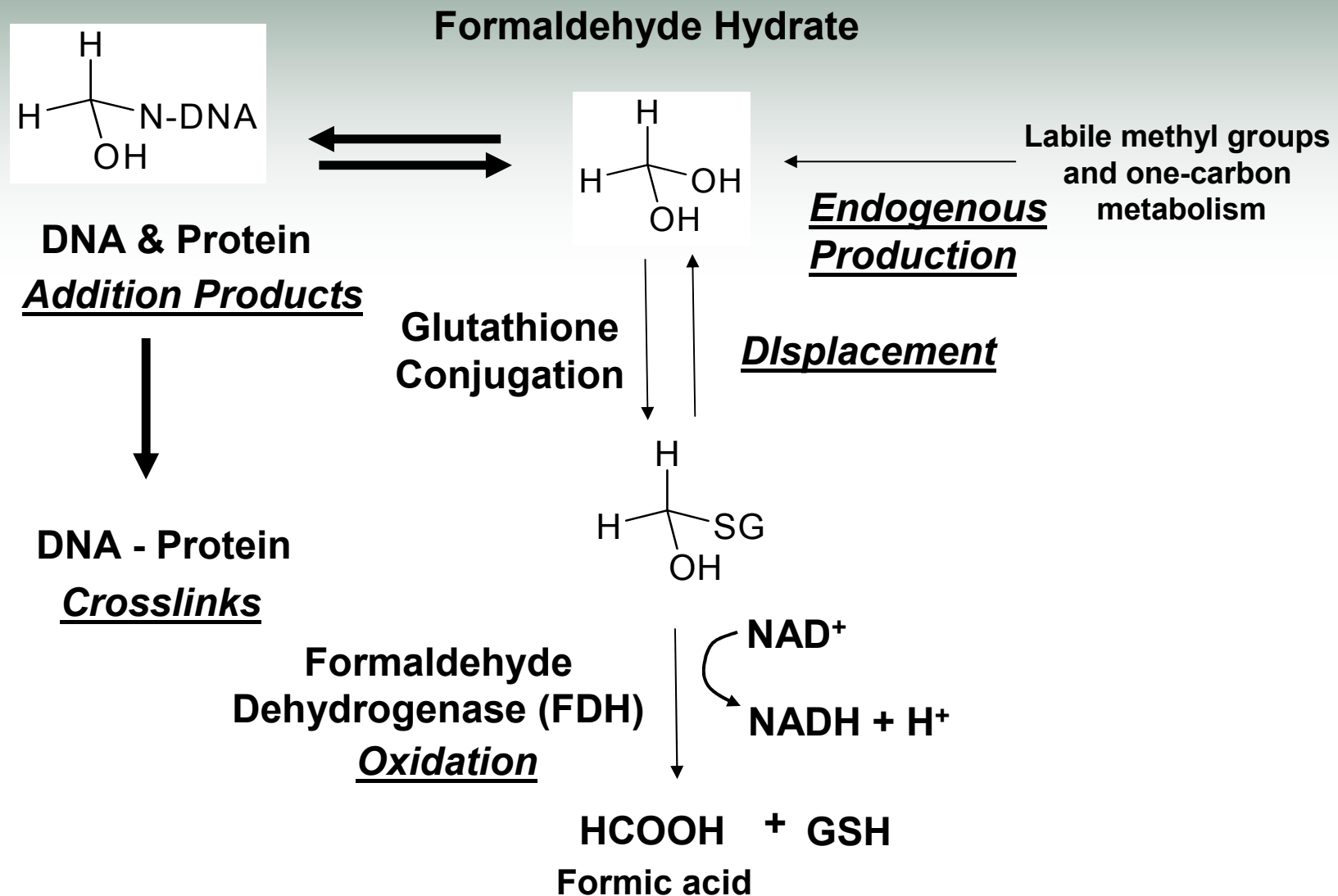
# *Health Effects of Inhalation Exposure to Formaldehyde*

- Why are the cancer risk estimates so different?
- - Conservative default approaches are used when the scientific data on a chemical is incomplete
  - Chemical-specific approaches are used in place of the default when the necessary data are available
  - Over time, the scientific data on formaldehyde carcinogenicity has increased dramatically
    - Studies of how formaldehyde causes cancer in the rodent
    - Development of a biological model of formaldehyde carcinogenicity
    - Studies on the effects of formaldehyde on cells

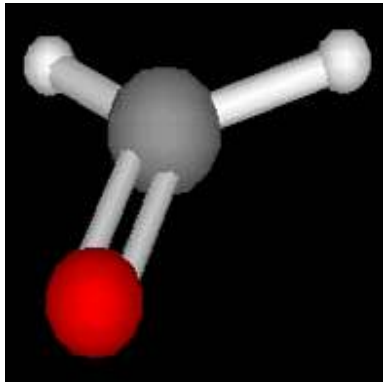
# *Formaldehyde causes nasal cancer in rats...*



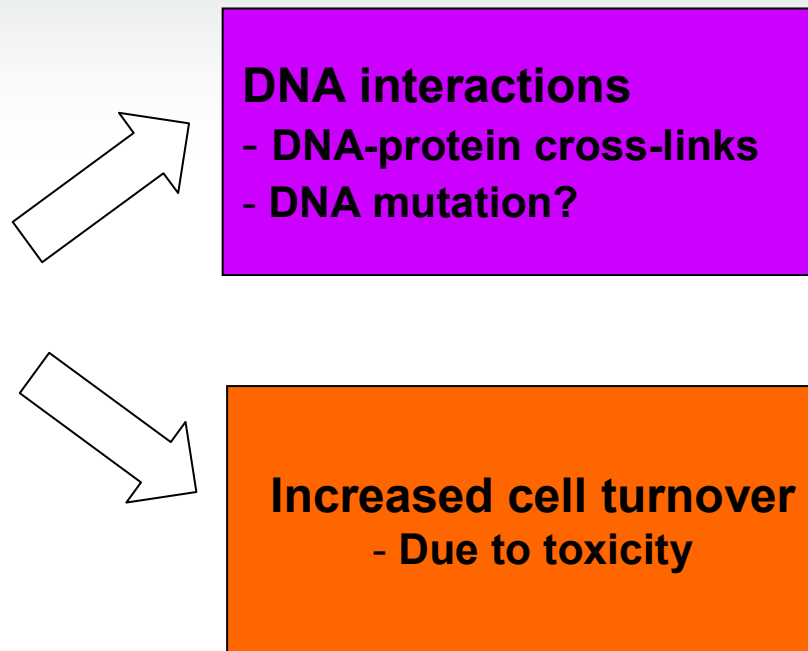
...but it's a normal constituent of cells



# *Cancer Risk Assessment Considerations for Formaldehyde*



*Dosimetry*

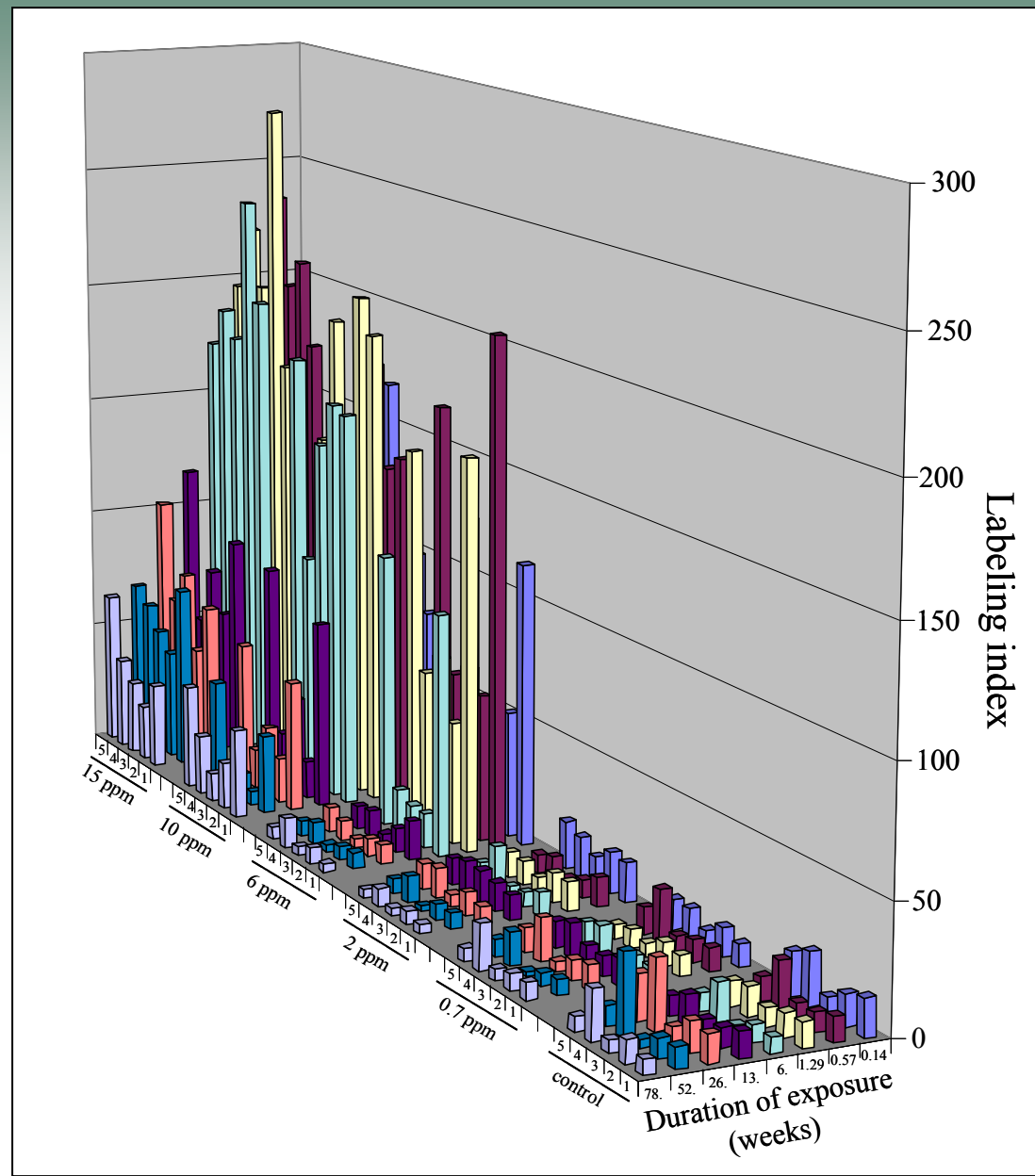


*Modes of action*

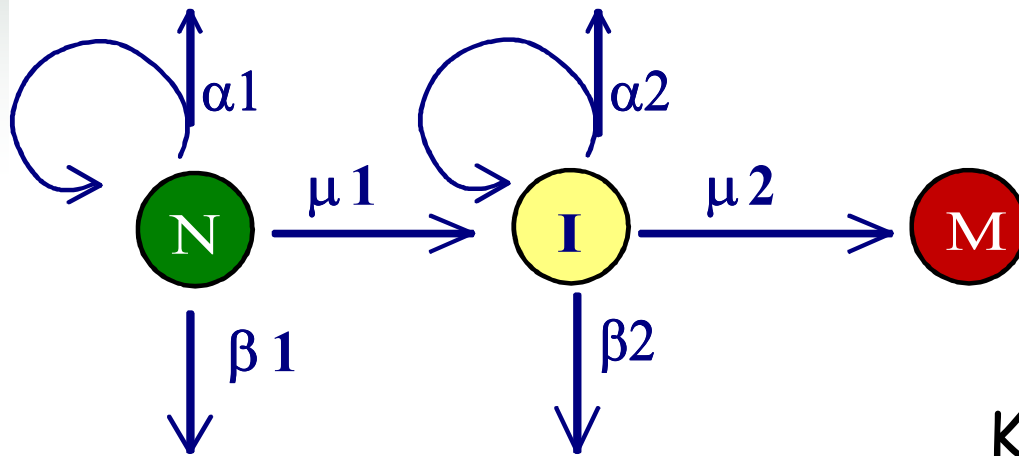


*Effects*

Formaldehyde tumors occur at high inhaled concentrations (above 2 ppm) where severe toxicity leads to increased cell division to replace dead cells



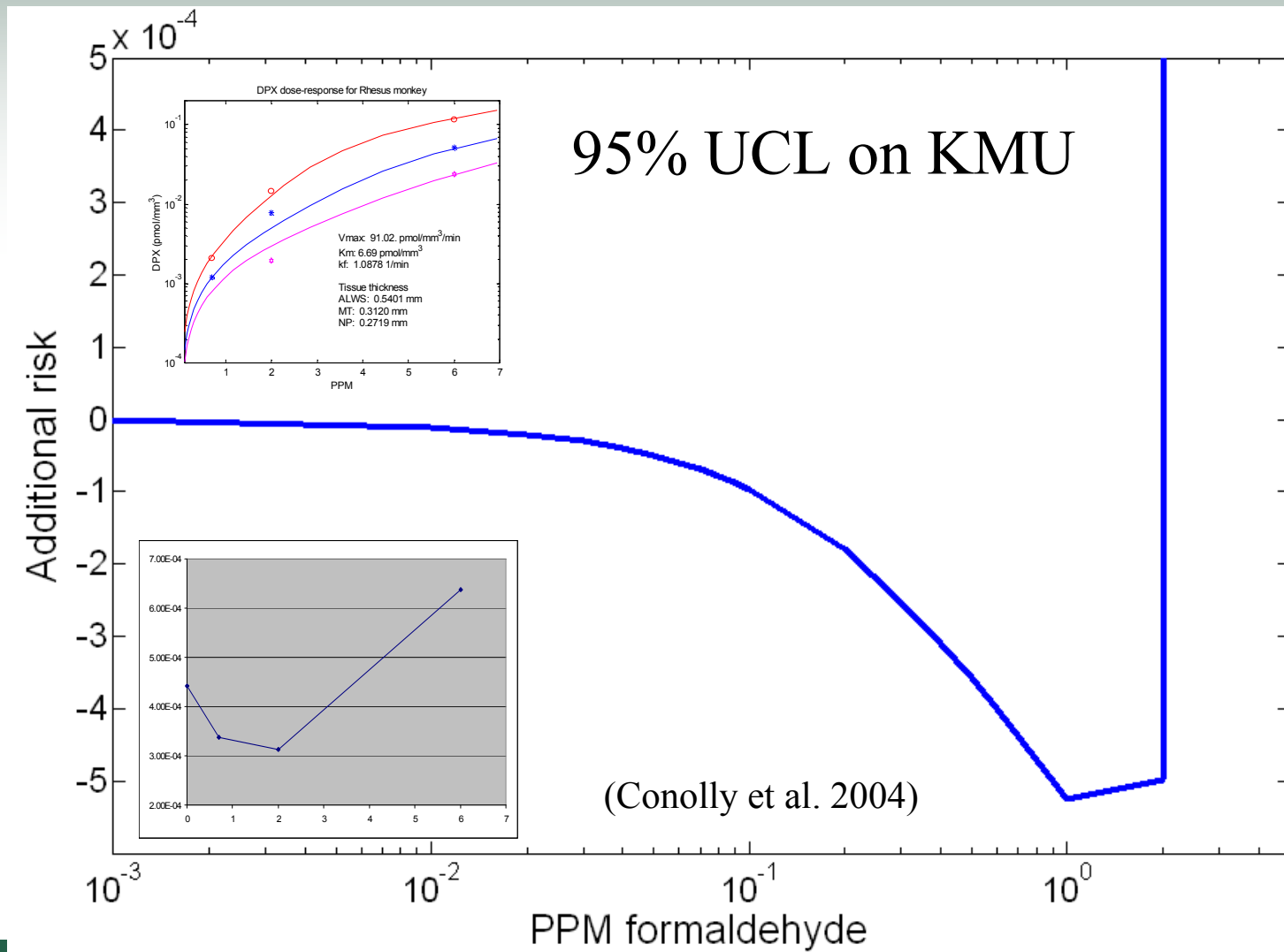
# CIIT Formaldehyde Cancer Model (Conolly et al. 2004)



A Biologically Motivated Model for Cancer

Key Capability:  
Describes the  
Interaction of  
Mutation and Cell  
Division

# dose-response of cell replication predicts decreased risk at low concentrations



# Summary

## 1999 CIIT Clonal Growth Risk Assessment

- Predicted either no additional risk, or a much smaller level of risk than previous assessments
- Consistent with mechanistic database
  - No evidence of direct (point) mutagenicity
  - Evidence of high-concentration effects on cell replication

# Response to 1999 CIIT Clonal Growth Risk Assessment

- **International acceptance**
  - Health Canada
  - WHO
  - MAK Commission (Germany)
  - Australia

# *Hamner Studies on Formaldehyde \**

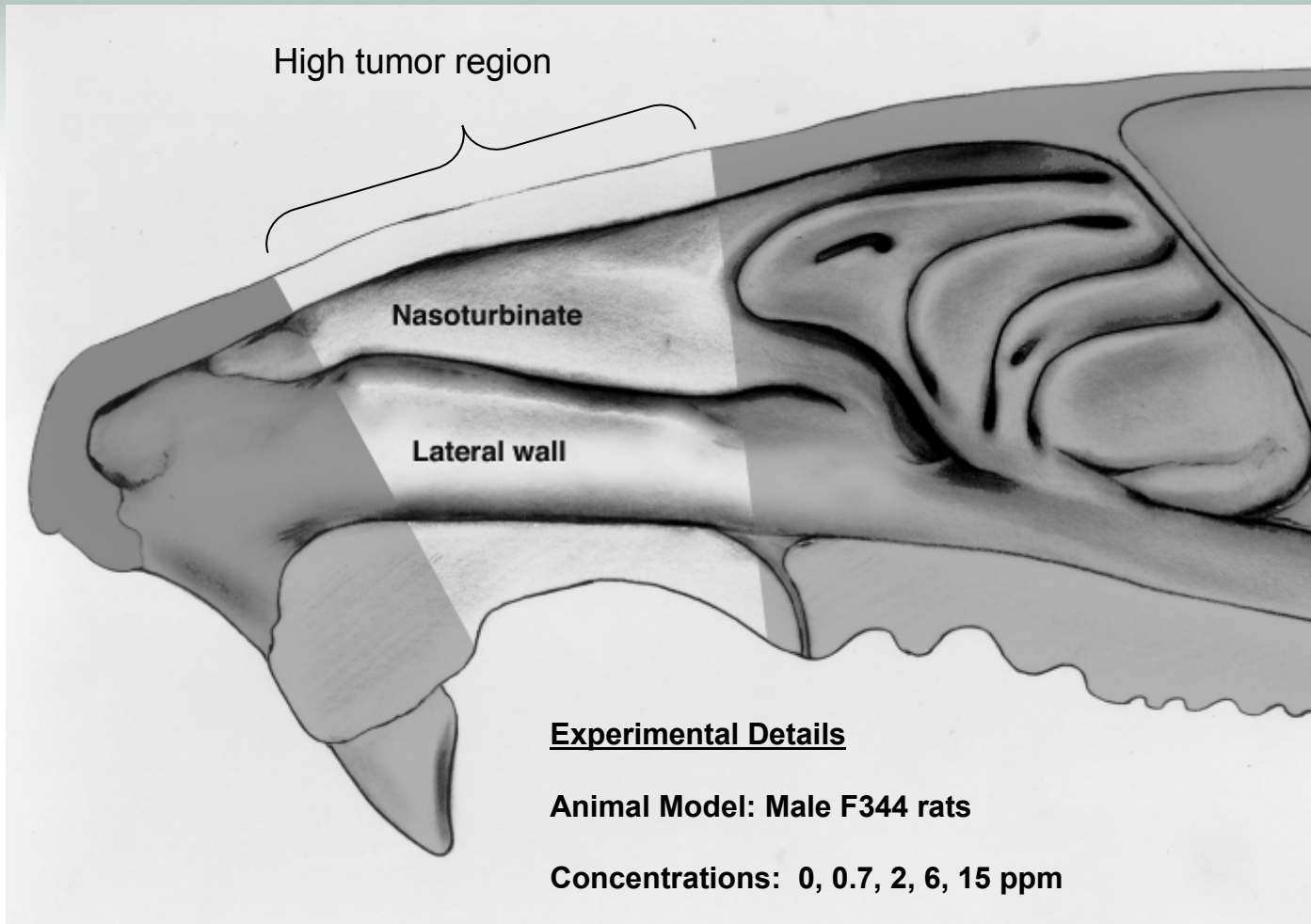
## *Goals*

- Improve the scientific basis for conducting a biologically realistic risk assessment for formaldehyde
- Illuminate the modes of action for cancer and noncancer effects
- Develop additional data to refine the quantitative dose-response relationships
- Evaluate impact of data and model uncertainties on the estimation of human risk

\* Studies supported by the Formaldehyde Council, Inc.



# How Did We Apply Genomic Technology to Formaldehyde?



## Experimental Details

**Animal Model: Male F344 rats**

**Concentrations: 0, 0.7, 2, 6, 15 ppm**

**Time Points: 6 hr, 5 d, and 19 d**

## Genomic Markers Changed by Exposures

Sampling Time	0.7	2.0	6.0	15.0 ppm
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<b>6 hrs</b>	<b>0</b>	<b>1</b>	<b>42</b>	<b>773</b>
<b>1 day</b>	<b>0</b>	<b>0</b>	<b>0</b>	
<b>5 days</b>	<b>0</b>	<b>15</b>	<b>28</b>	
<b>8 days</b>	<b>0</b>	<b>0</b>	<b>9</b>	
<b>19 days</b>	<b>0</b>	<b>0</b>	<b>48</b>	

# Comparison Between Genomic Dose Response and Tumor Response

## Formaldehyde Time Course

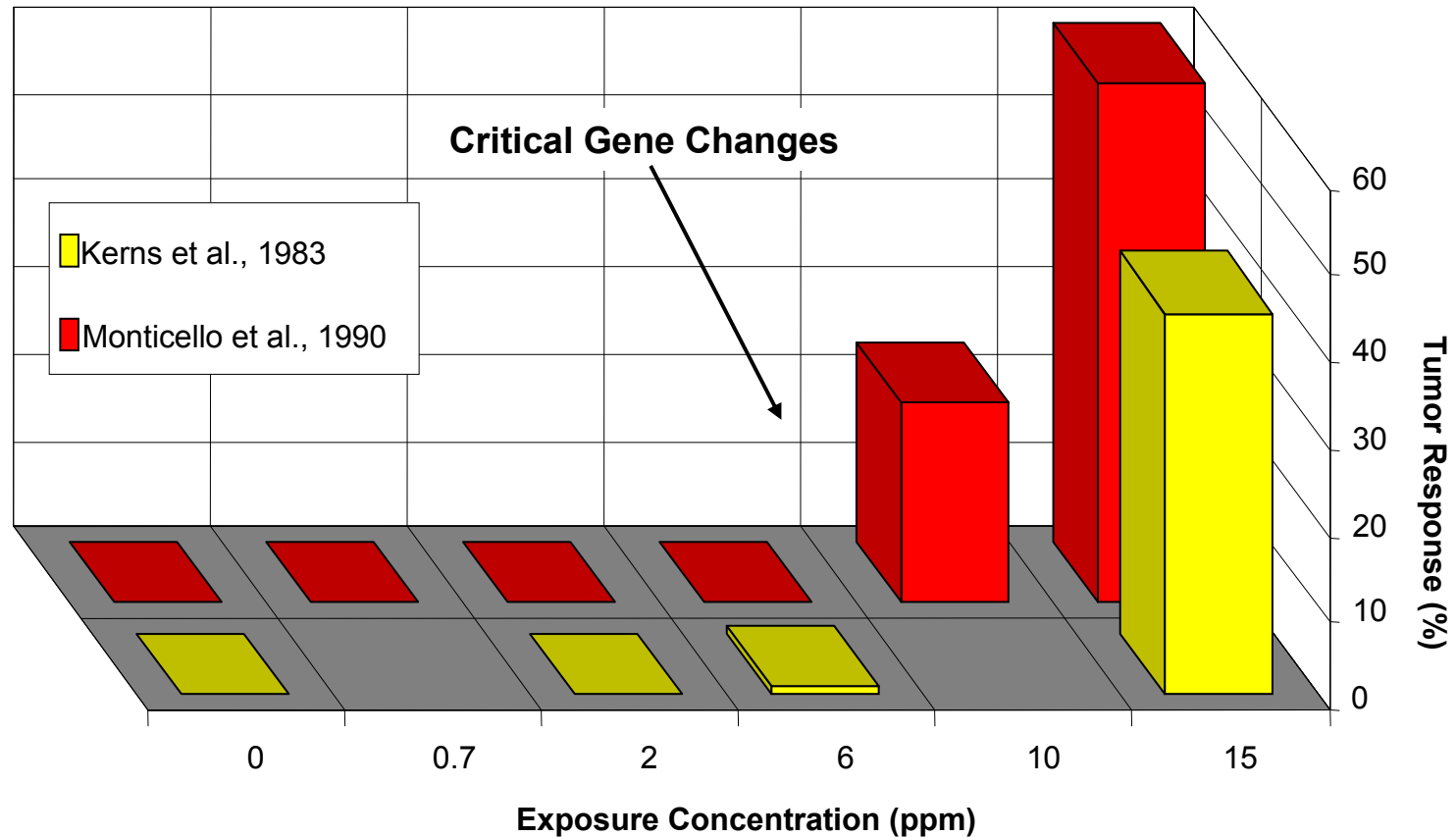
		Time Point											
		6 hr				5 day				19 day			
		Mean (ppm)	SD	Min (ppm)	Count	Mean (ppm)	SD	Min (ppm)	Count	Mean (ppm)	SD	Min (ppm)	Count
Lowest Response Categories													
Protein Import into Nucleus	GO:0000059	2.02	0.34	1.53	4								
Complement Activation, Alternative	GO:0006957					1.58	0.28	1.37	3				
Positive T-cell Selection	GO:0043368									1.18	0.17	1.02	3
Selected Categories Related to Carcinogenicity													
Positive Regulation of Cell Proliferation	GO:0008284	7.82	4.26	0.64	100	7.52	3.78	0.63	114	6.85	3.90	0.57	137
Response to DNA Damage Stimulus	GO:0006974	6.82	4.07	0.64	103	7.12	3.79	0.84	105	6.57	3.73	0.70	124
Inflammatory Response	GO:0006954	7.61	4.64	0.86	100	8.16	3.78	0.79	132	7.15	4.03	0.49	140

**BMD for cell labeling index: 4.9 ppm**

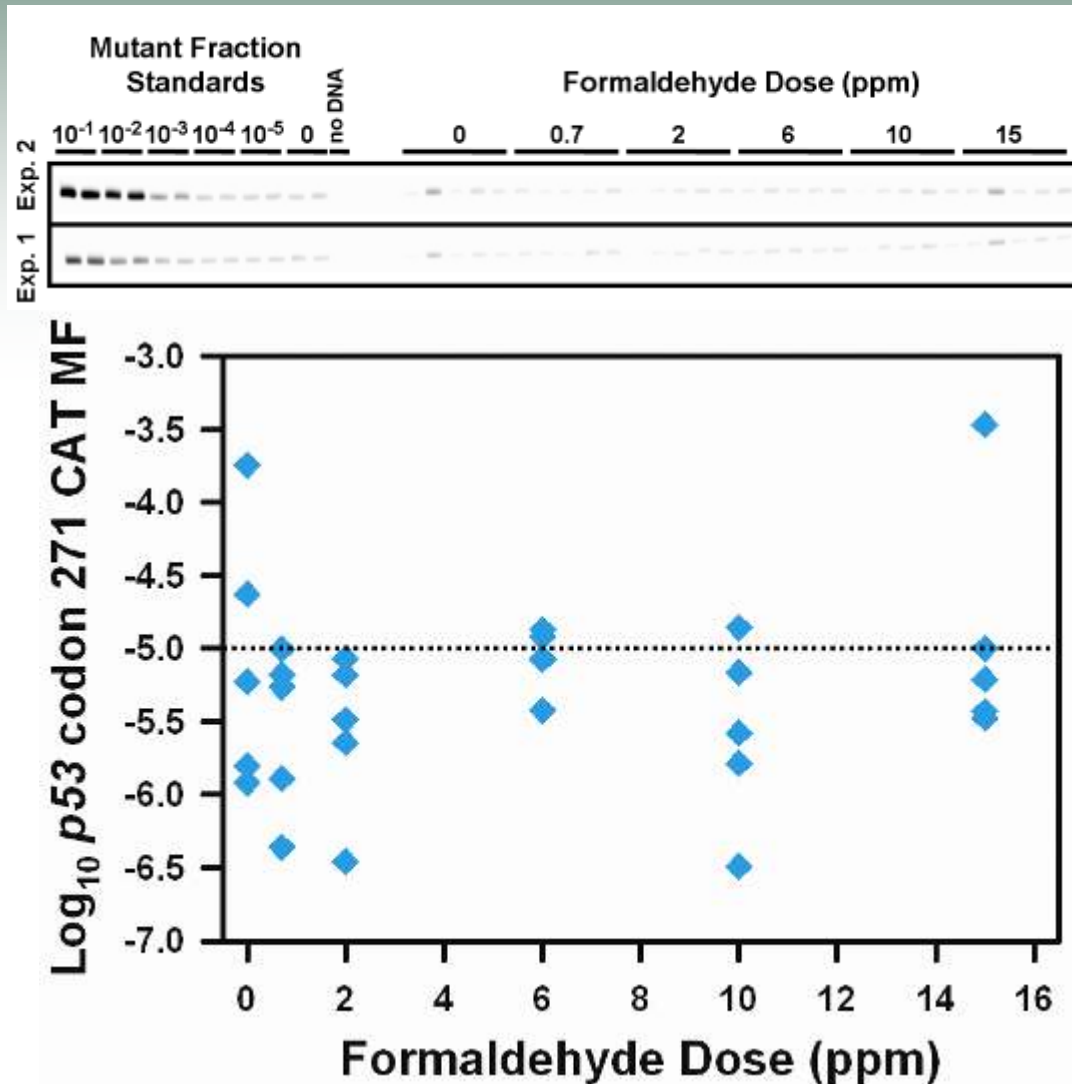
**BMD for tumors: 6.4 ppm**

(Schlosser, Risk Anal., 2003)

# Comparison Between Transcriptomic Dose Response and Tumor Response



# Analysis of Mutation Frequency in p53 and K-ras Oncogenes



- NCTR analysis
- Found no increase in p53 or K-ras mutations after 90 days of exposure to formaldehyde at up to 15 ppm
- Demonstrates lack of mutagenic activity in vivo at carcinogenic concentrations

# Conclusions

- Genomic analysis supports the lack of human relevance of tumors at concentrations with severe tissue damage ( $> 6$  ppm)
- Mutation analysis shows no evidence of mutagenic activity at concentrations that are clearly toxic and tumorigenic
- Results provide mechanistic support for threshold for cancer and for the modeling results of Conolly et al. 2004
- Recommendation: avoid irritating exposures (greater than 0.1 ppm)

