Pharmacokinetics of Formaldehyde and the Impact of Endogenous Levels on Uptake

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NAS Report on the EPA Risk Assessment for Formaldehyde

Endogenous formaldehyde. Humans and other animals produce formaldehyde through various biologic pathways as part of normal metabolism. Thus, formaldehyde is normally present at low concentrations in all tissues, cells, and bodily fluids. Although there is some debate regarding interpretation of the analytic measurements, formaldehyde has been measured in exhaled breath and is most likely present normally at a concentration of a few parts per billion. The endogenous production of formaldehyde complicates the assessment of the risk associated with formaldehyde inhalation and remains an important uncertainty in assessing the additional dose received by inhalation, particularly at sites beyond the respiratory tract.

Usefulness of various models. Computational fluid dynamics (CFD) models have been developed to help to predict the dose to nasal tissues from inhaled formaldehyde. EPA fairly evaluated the models and sources of uncertainty but did not use the models to extrapolate to low concentrations. The committee concludes that the models would be useful for that purpose and recommends that EPA use the CFD models to extrapolate to low concentrations, include the results in the revised IRIS assessment, and explain clearly its use of CFD modeling approaches.

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 the human data, the committee recommends that EPA use the BBDR model for formaldehyde in its cancer assessment, compare the results with those described in the draft assessment, and discuss the strengths and weaknesses of each approach.

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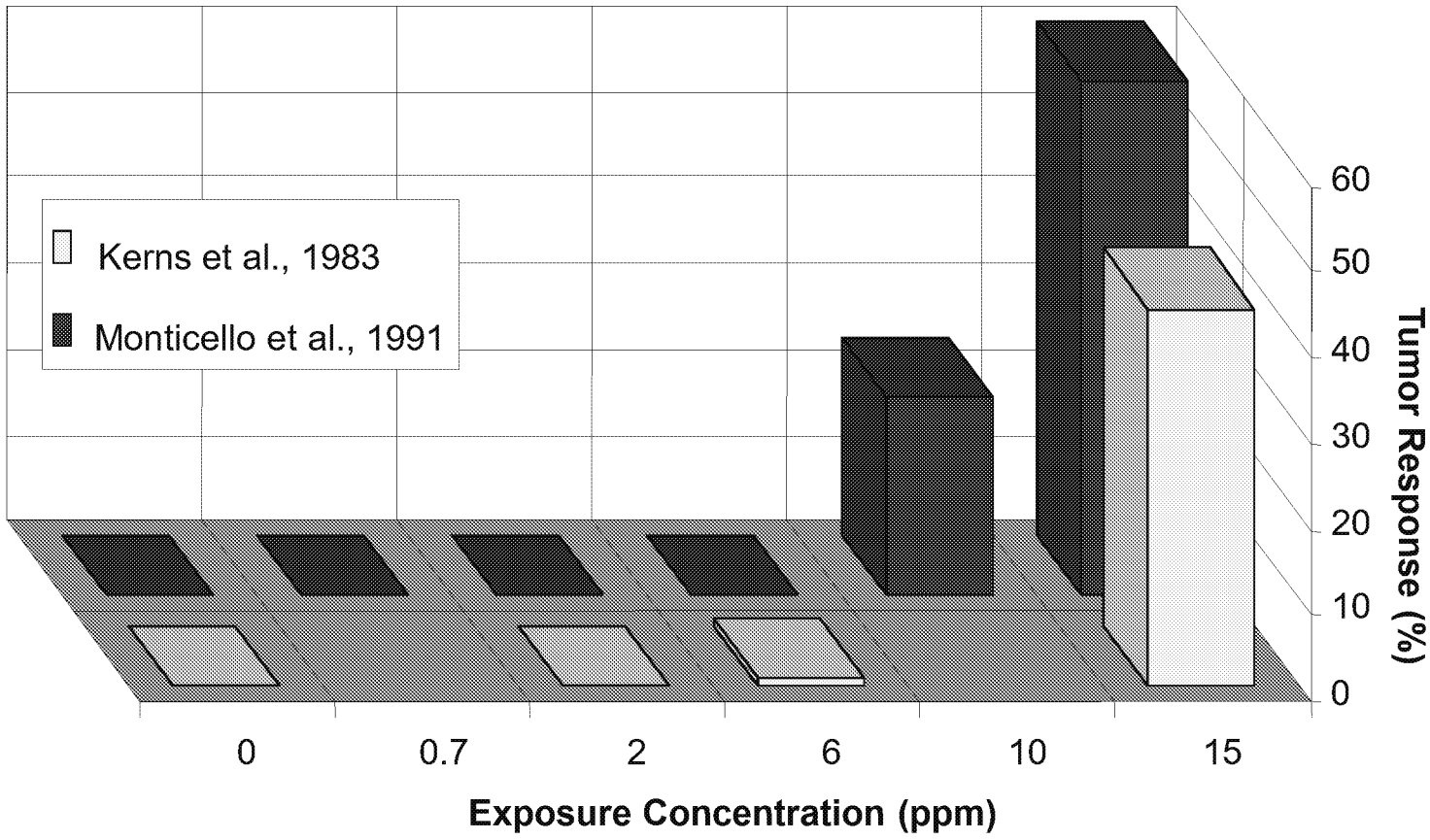
Yes, formaldehyde caused tumors in the rat nose



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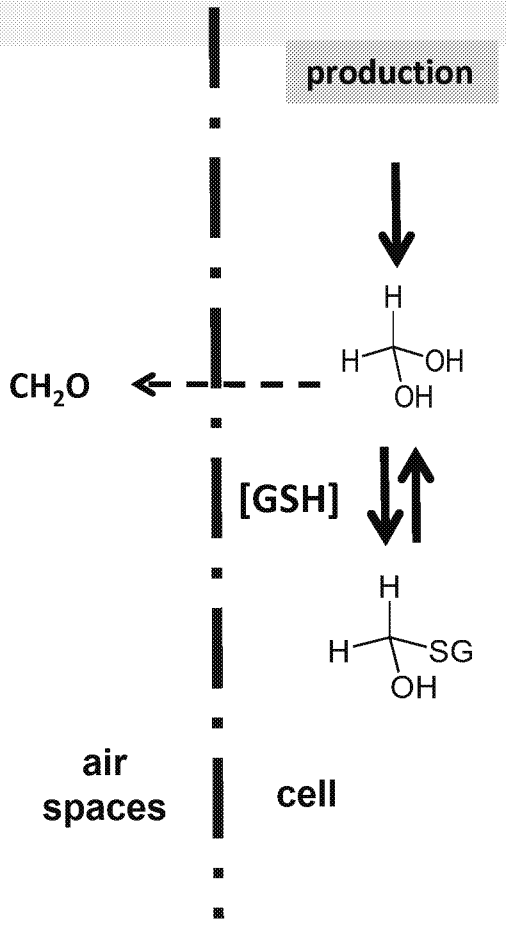
But formaldehyde is an endogenous metabolite present in all cells



- Formaldehyde is formed in cells by normal metabolic processes
- Formaldehyde complexes with glutathione to form hydroxymethylglutathione
- Total tissue formaldehye in the nasal mucosa in rats, in the absence of any inhalation exposure, was 0.42 ± 0.09 mM (12,600 ppb)
- Human exhaled air formaldehyde concentration: ~ 1 ppb (Riess et al. 2010)

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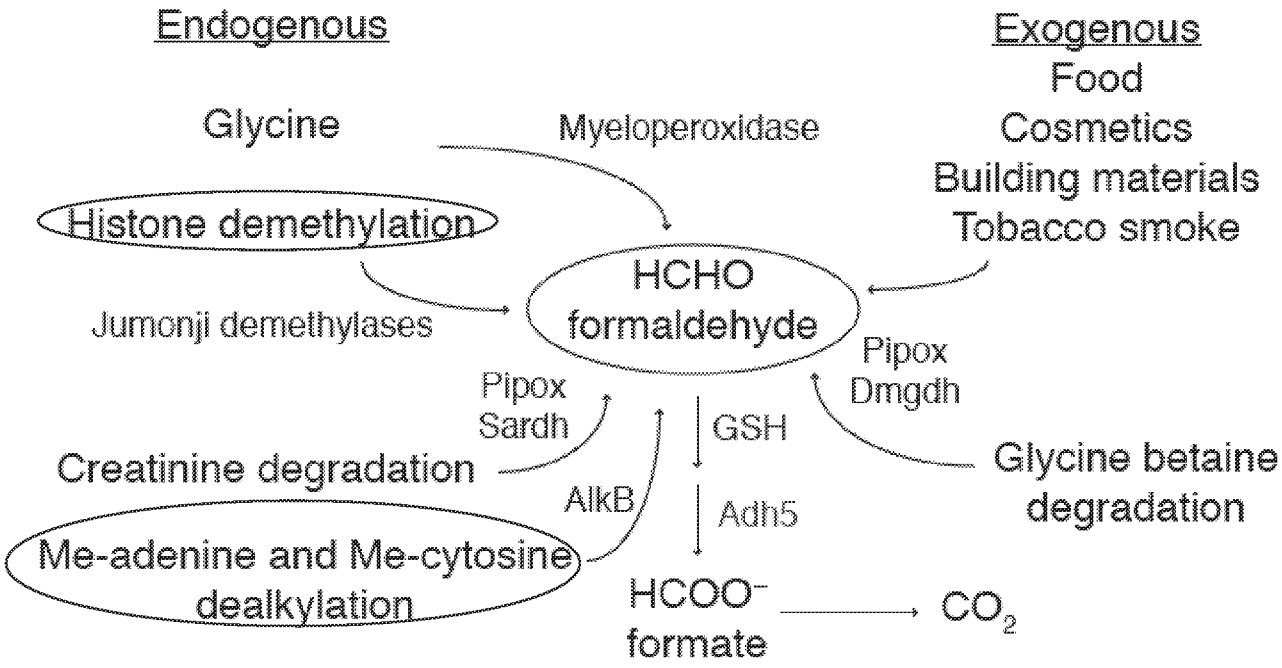
Sources of Endogenous Formaldehyde



Nuclear

(Rosado et al., 2011)

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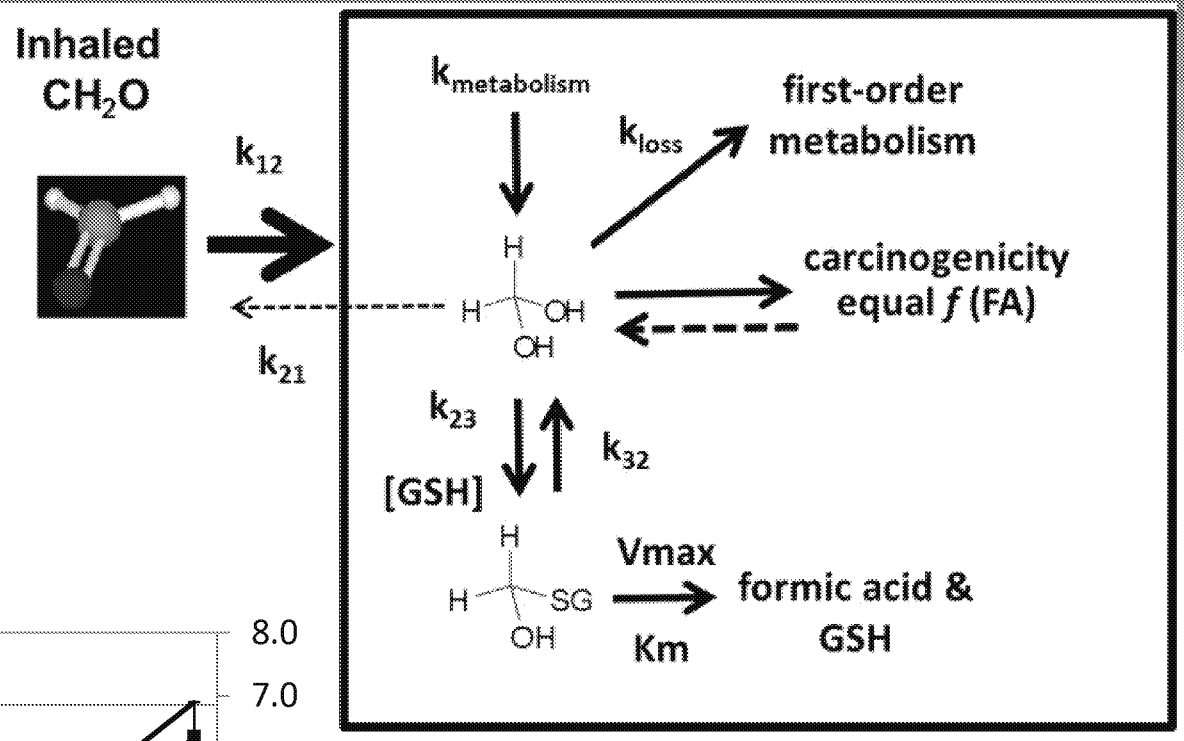
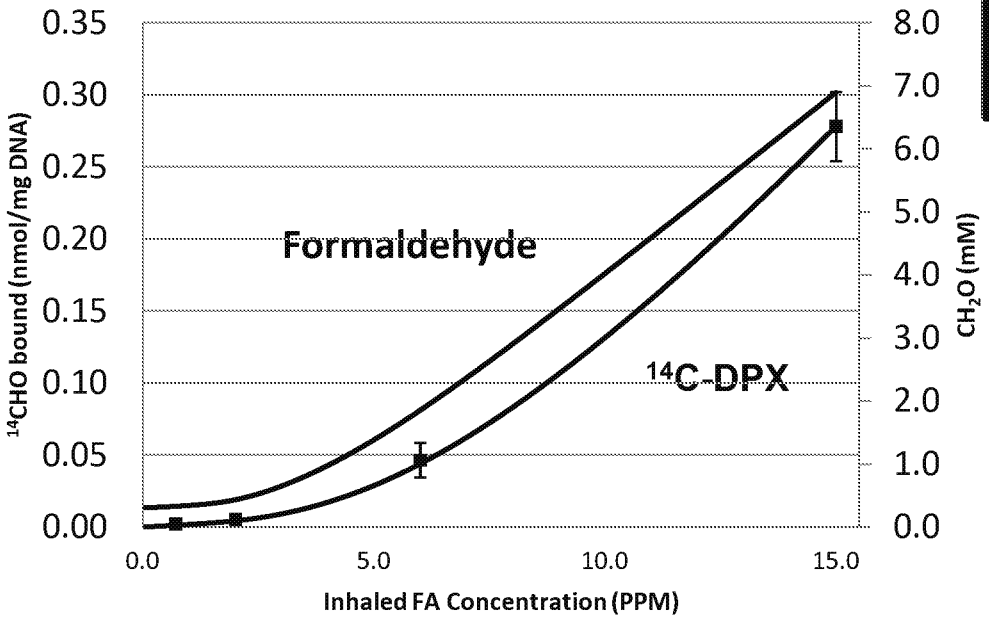
Andersen et al. 2010:

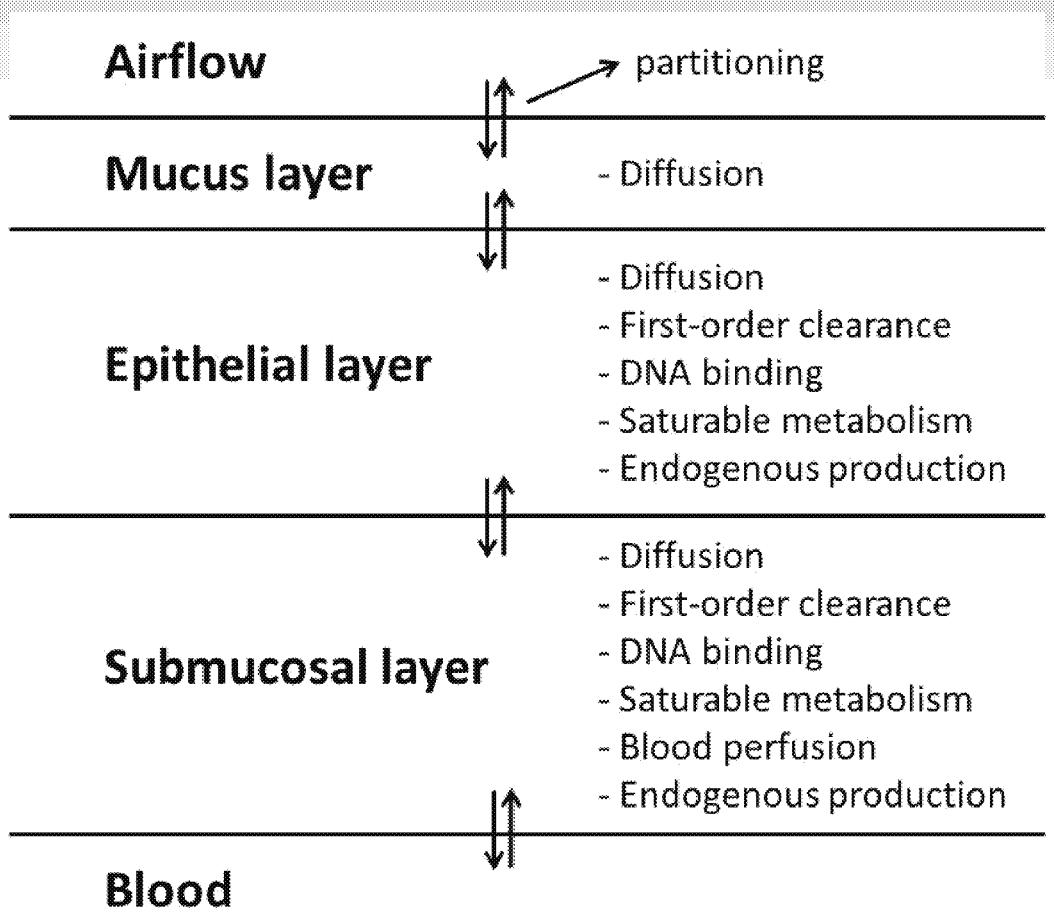
Used ^{14C}-DPX-data for formaldehyde in the nose to infer tissue levels of formaldehyde





- **Goal 1: to apply Andersen et al. model to re-estimate nasal uptake using CFD modeling.**

Adaptation of CFD model to describe endogenous formaldehyde (Schroeter et al. 2013)



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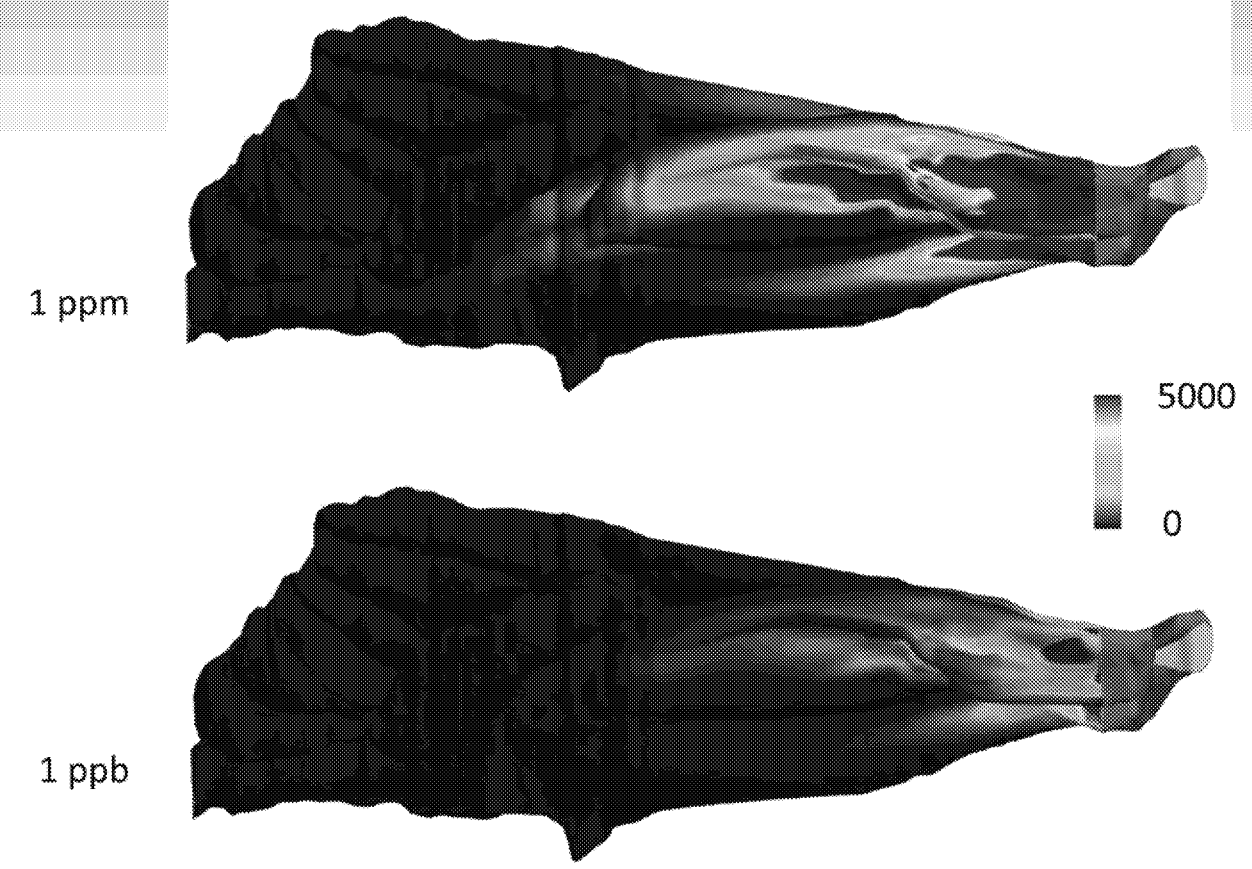
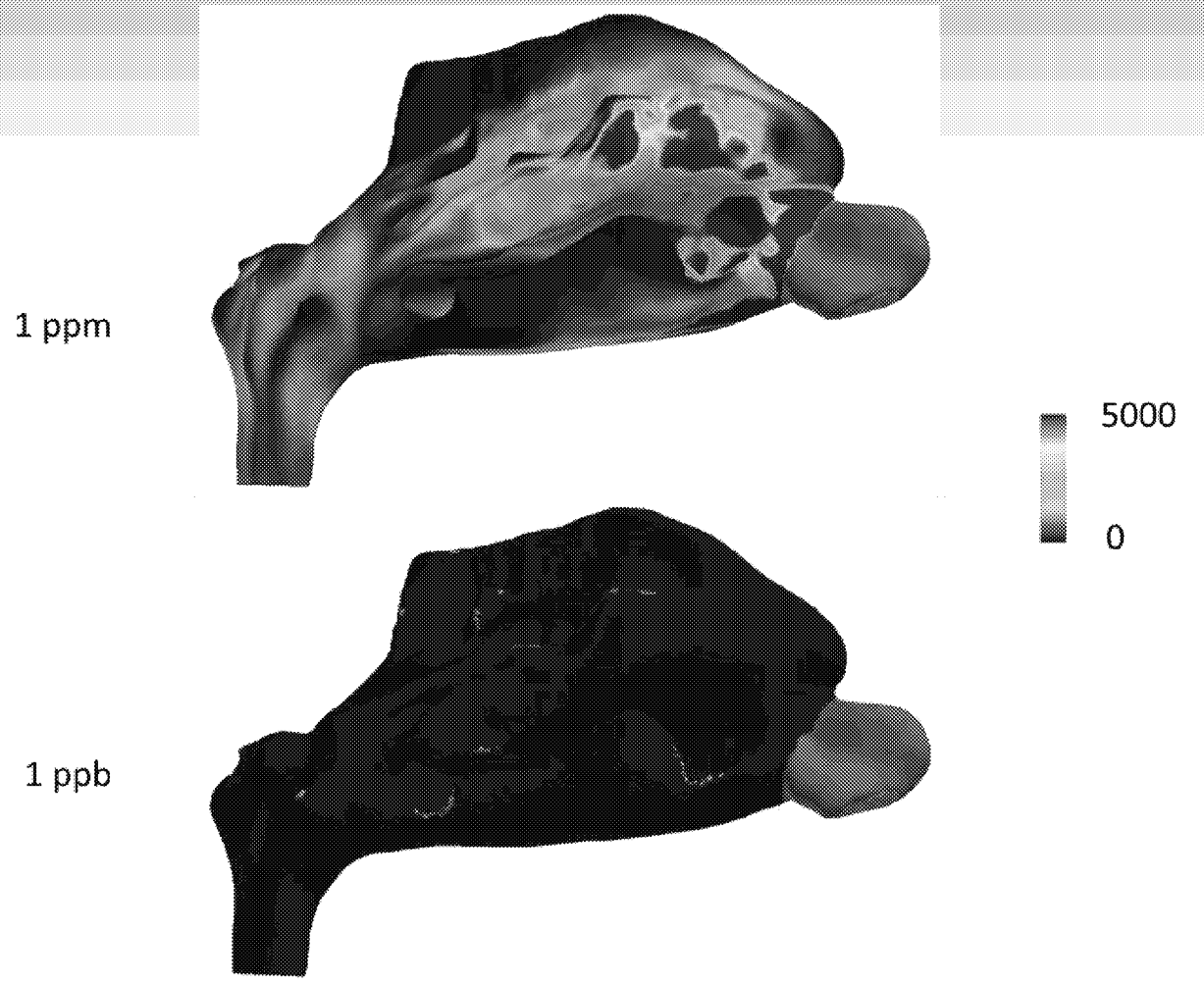
CFD modeling of formaldehyde uptake in the rat



CFD modeling of formaldehyde uptake in the human



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Uptake of formaldehyde in the rat, monkey, and human nose with endogenous formaldehyde added to the CFD model:

Exposure concentration (ppb)	Nasal Uptake (%)		
	Rat	Monkey	Human
≥ 1000	99.4	86.5	85.3
500	99.3	86.5	85.3
100	98.6	86.5	84.7
50	97.8	86.3	83.9
10	91.3	84.1	77.1
5	83.1	81.7	68.3
1	17.5	42.8	n/a*

* at 1 ppb, the predicted formaldehyde concentration exiting the nasal tissue in the human was greater than the exposure concentration (net efflux)

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

- **Goal 2: to extend Andersen et al. model to describe Lu et al. data.**

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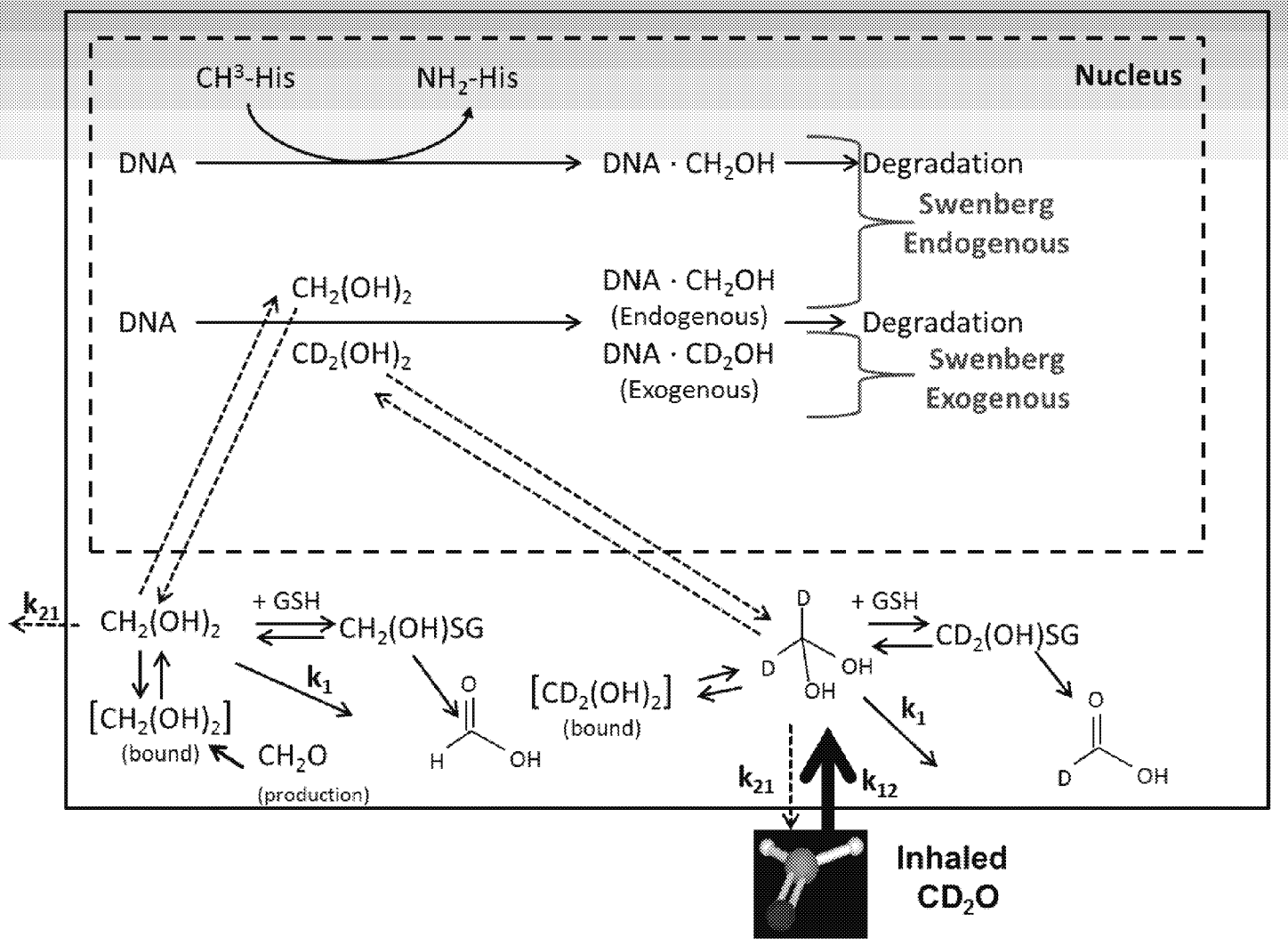
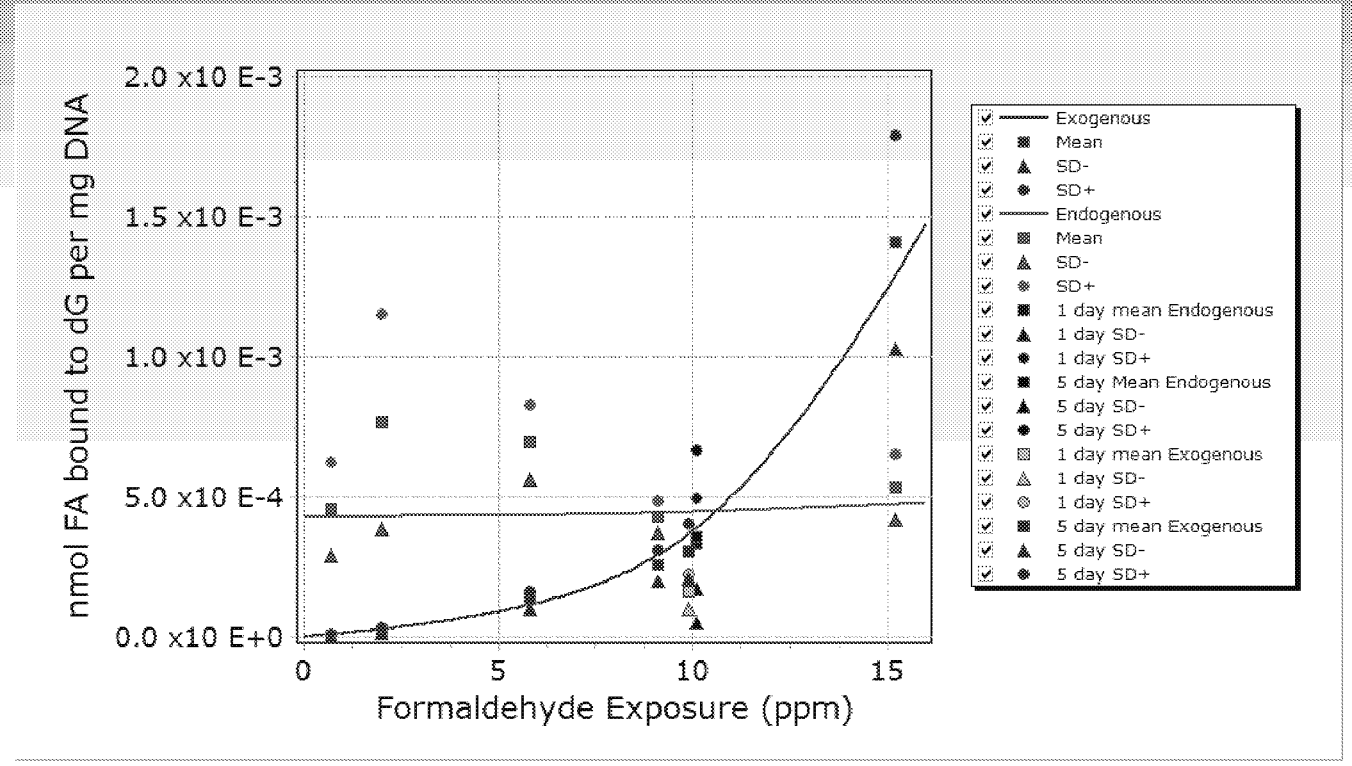
Revised pharmacokinetic model of endogenous formaldehyde



Modeling of Endogenous Formaldehyde



Simulation of endogenous (green) and exogenous (red) formaldehyde binding to dG in rat nasal tissue after a single 6 hour exposure to labeled formaldehyde concentrations of 1, 2, 6, 10 and 15 ppm (Lu et al. 2010)

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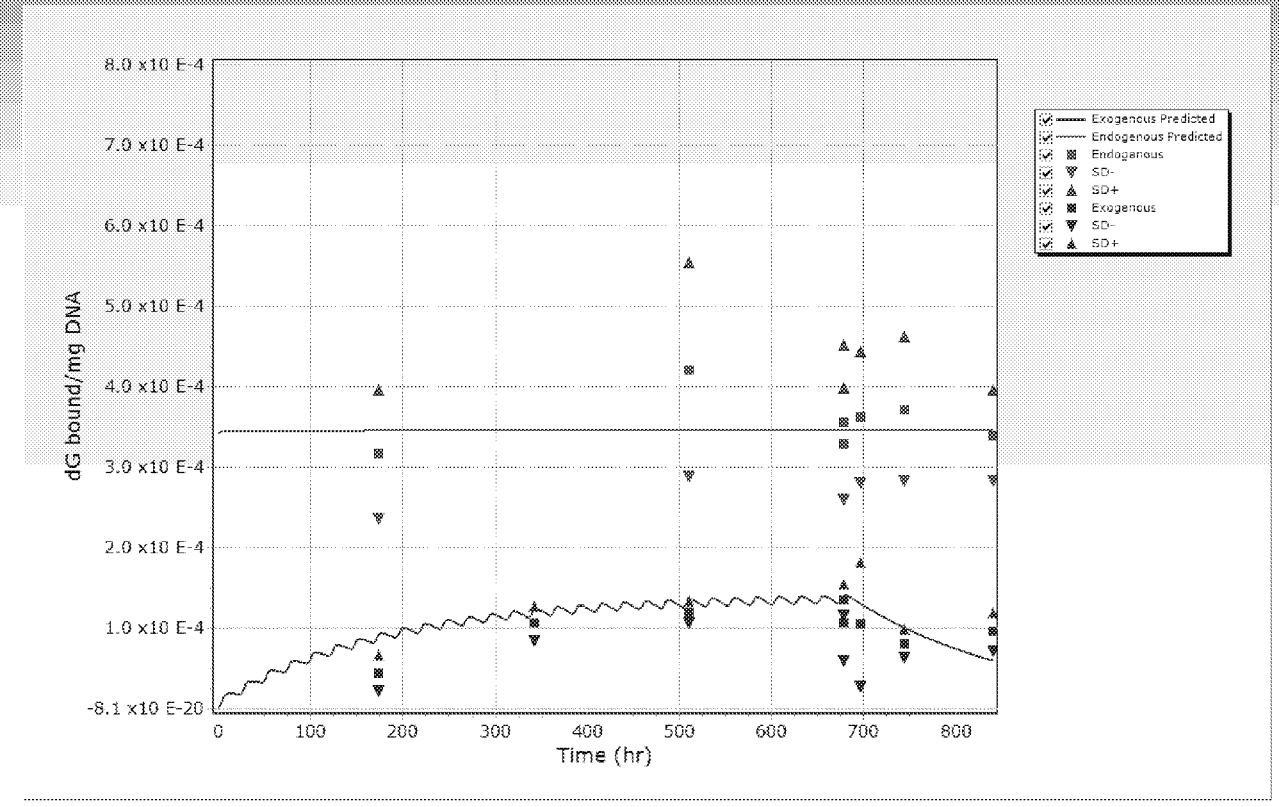
Modeling of Endogenous Formaldehyde



Model simulation of endogenous (green) and exogenous (red) formaldehyde binding to dG in rat nasal tissue during and after 28 day exposure to 2 ppm formaldehyde 6 hr/d, 5 d/wk (Swenberg, unpublished)

Modeling of Endogenous Formaldehyde

Risk Assessment Applications

- Re-estimate human risk using new CFD predictions for nasal uptake in rat and human
- Incorporate endogenous model into formaldehyde BBDR model (Conolly et al. 2003, 2004)
- Evaluate plausibility of IRIS risk estimates in view of endogenous formaldehyde concentrations

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