Updating the BBDR Model for Formaldehyde

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Presentation to the US EPA
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1:00 to 2:00 PM

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Outline

- BBDR modeling
  - Data-based, exposure to response
- Updates to the CIIT model
  - CFD
  - Adduct dosimetry
  - Labeling index data
  - Historical controls
  - Initiated cells
- Summary & conclusions

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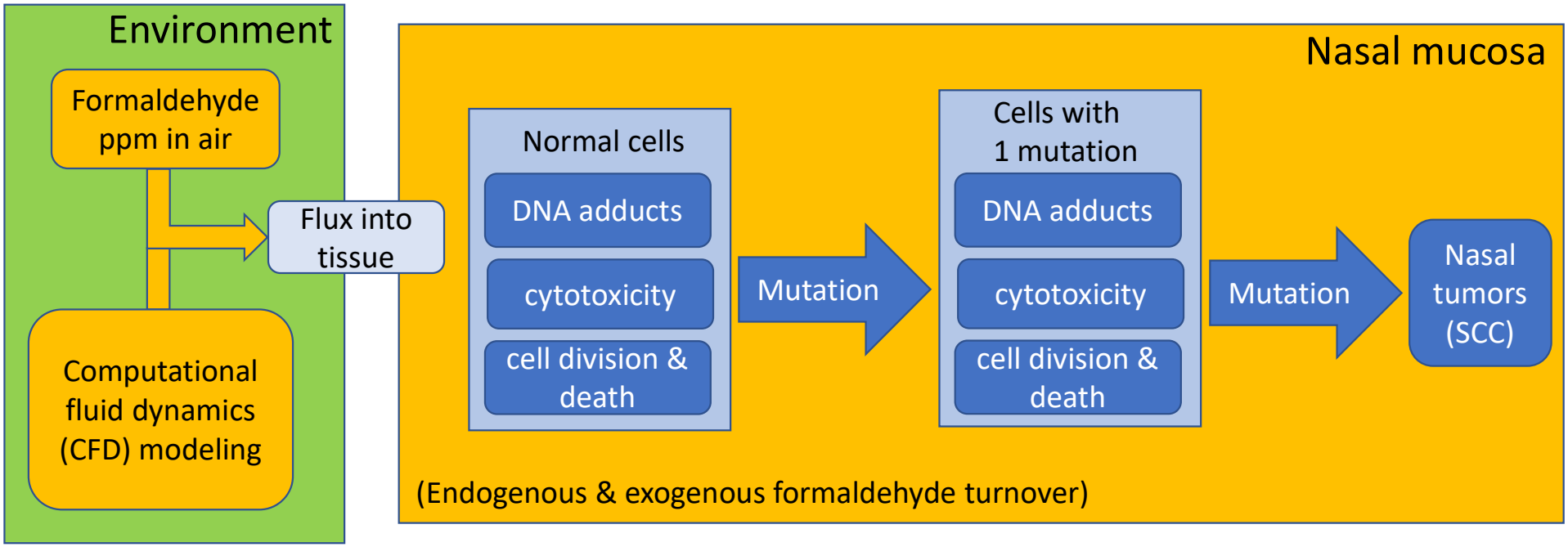
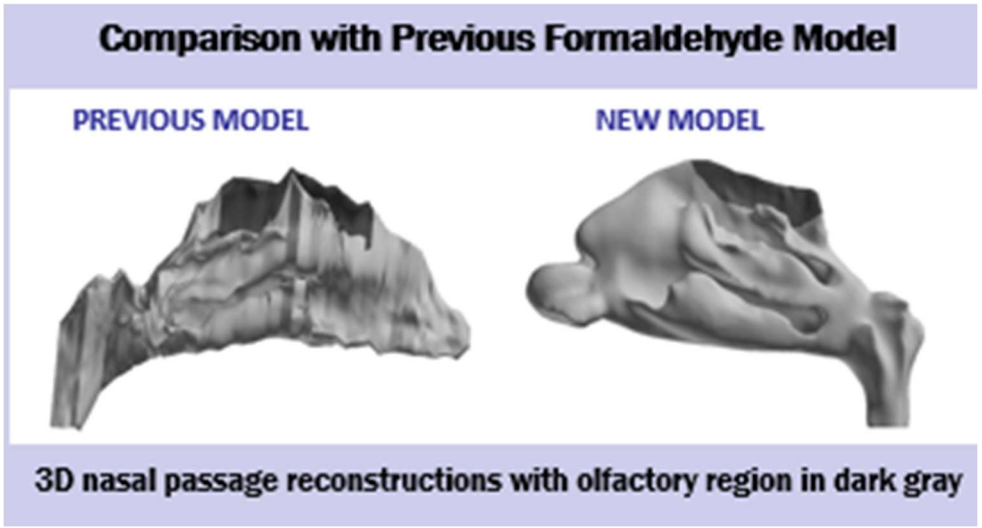
BBDR: exposure to response



CFD, 20 years ago vs today

- CIIT BBDR used FIDAP CFD software – Julie Kimbell
  - 15% mass balance error
- 2022 uses Fluent CFD software – Jeff Schroeter, ARA
  - Minimal mass balance error



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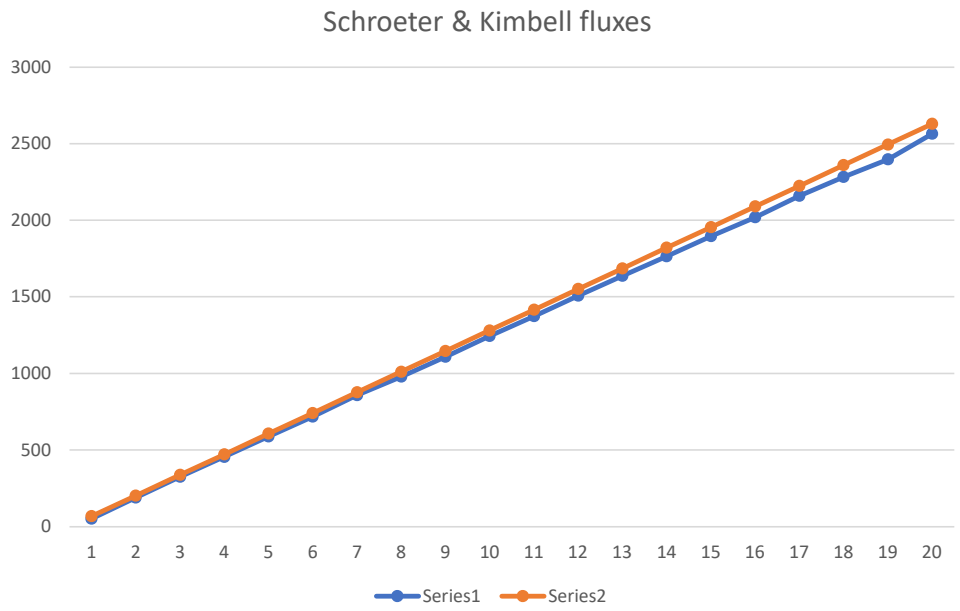
CFD modeling: Rat nasal flux bins



Bin #	Kimbell	Schroeter	S/K
1	50.8	67.4	1.33E+00
2	189.6	202.2	1.07E+00
3	325.0	337.1	1.04E+00
4	455.5	471.9	1.04E+00
5	588.4	606.7	1.03E+00
6	718.1	741.6	1.03E+00
7	858.2	876.4	1.02E+00
8	978.2	1011.2	1.03E+00
9	1108.8	1146	1.03E+00
10	1245.0	1280.9	1.03E+00
11	1374.3	1415.7	1.03E+00
12	1507.6	1550.5	1.03E+00
13	1636.5	1685.4	1.03E+00
14	1764.0	1820.2	1.03E+00
15	1895.6	1955	1.03E+00
16	2019.3	2089.9	1.03E+00
17	2158.8	2224.7	1.03E+00
18	2282.8	2359.5	1.03E+00
19	2397.5	2494.3	1.04E+00
20	2564.4	2629.2	1.03E+00

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Rat nose: CFD prediction of flux into tissue

Lateral view of rat nasal passage, nostrils at left, colored by formaldehyde flux rate (Kimbell et al., Toxicol. Sci. 64, 111 – 121, 2001). Simulation conducted at 576 ml/min.

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DNA adducts

- Endogenous formaldehyde
- dG monoadducts
  - Swenberg, Lu
- DPX
  - Heck, Casanova

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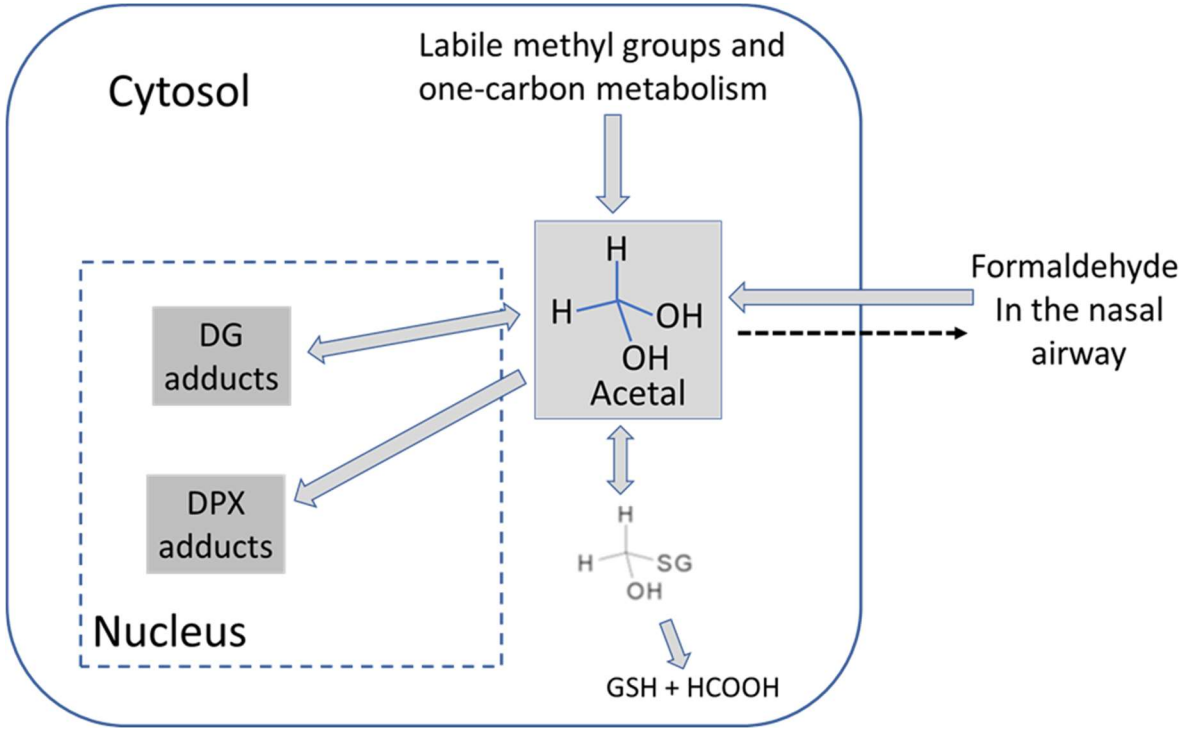
DNA adduct modeling



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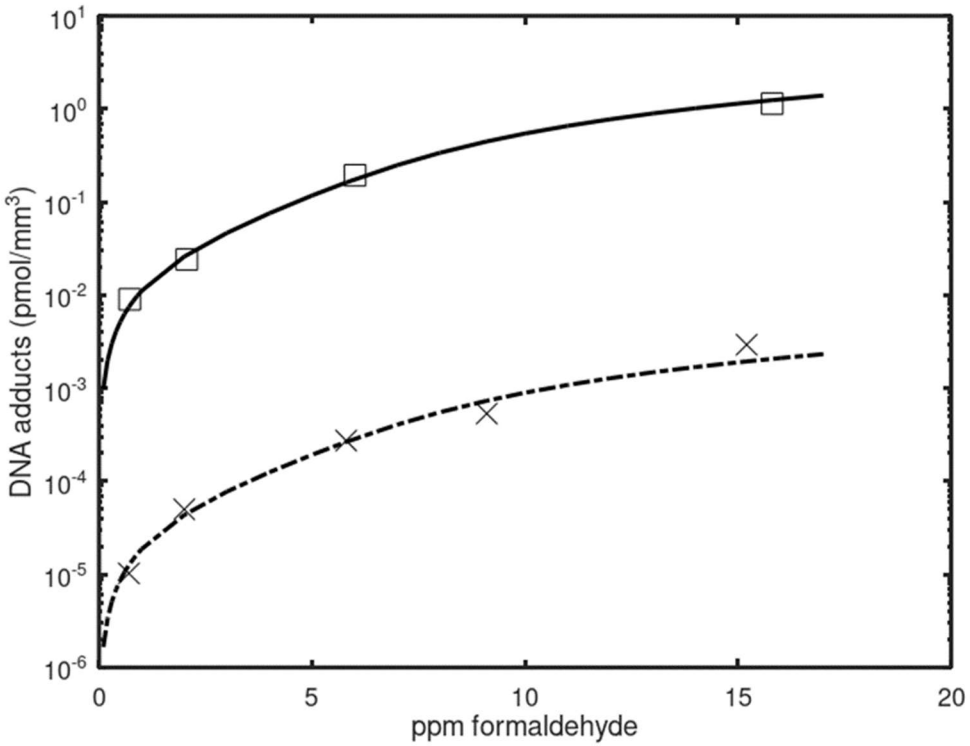
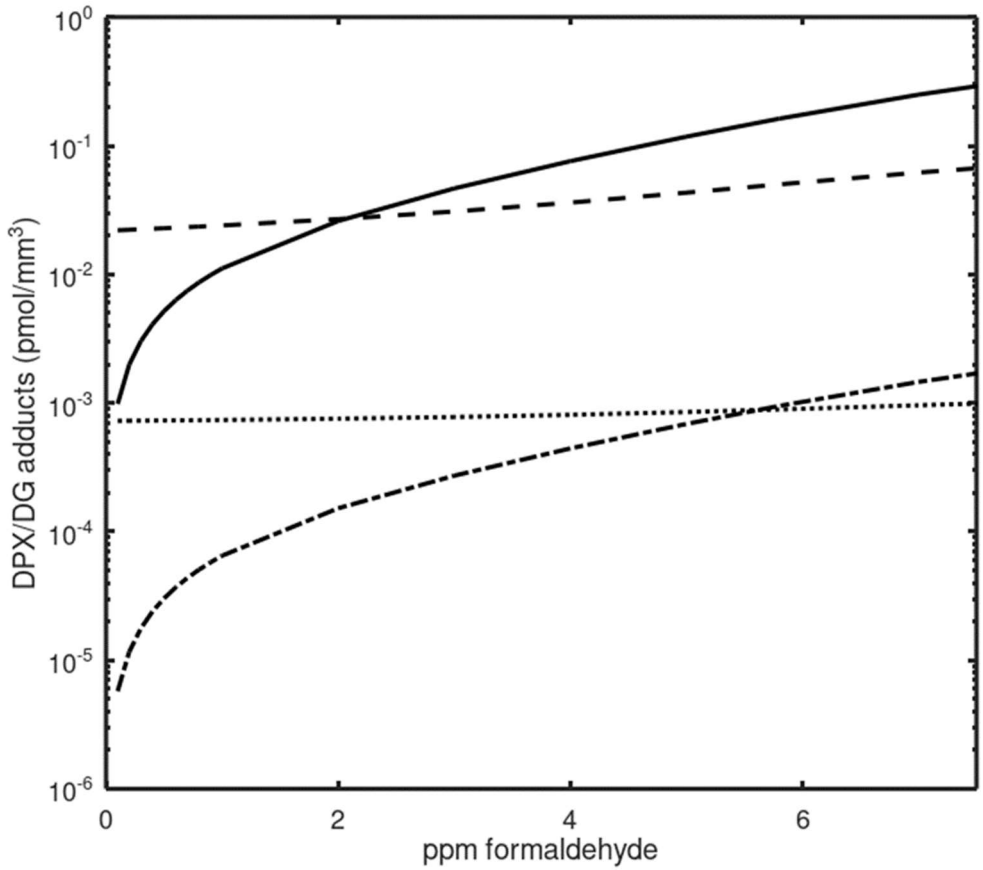
dG and DPX exogenous dose-response



Endogenous & exogenous dose-response



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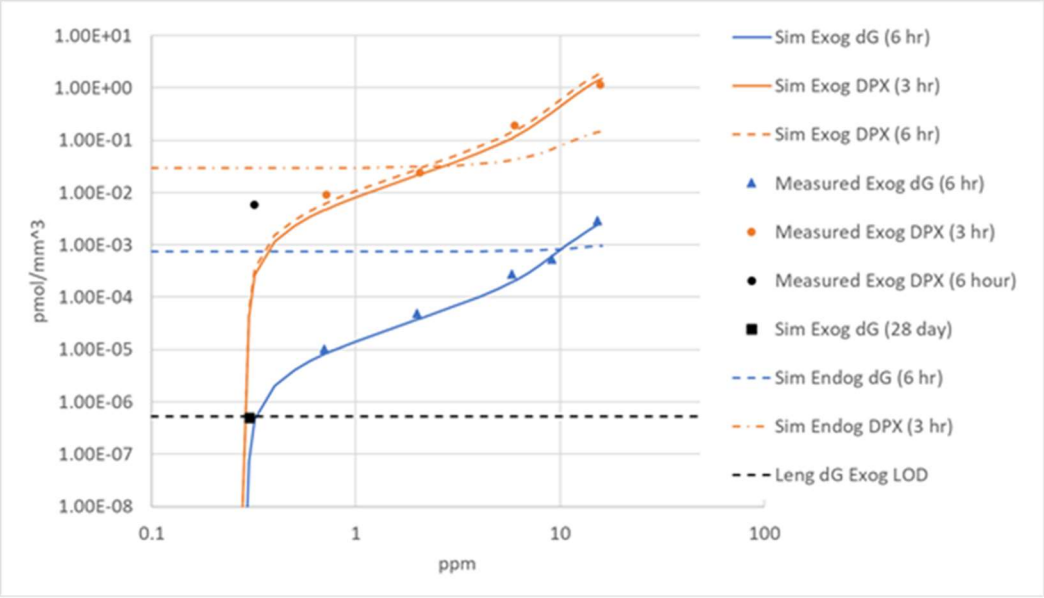
dG adduct dose-response



- No dG adducts seen at 0.3 ppm and lower (Leng et al., 2019)
- Inhaled formaldehyde reacts with mucus, cell membrane and cytoplasm before reaching DNA in nucleus.

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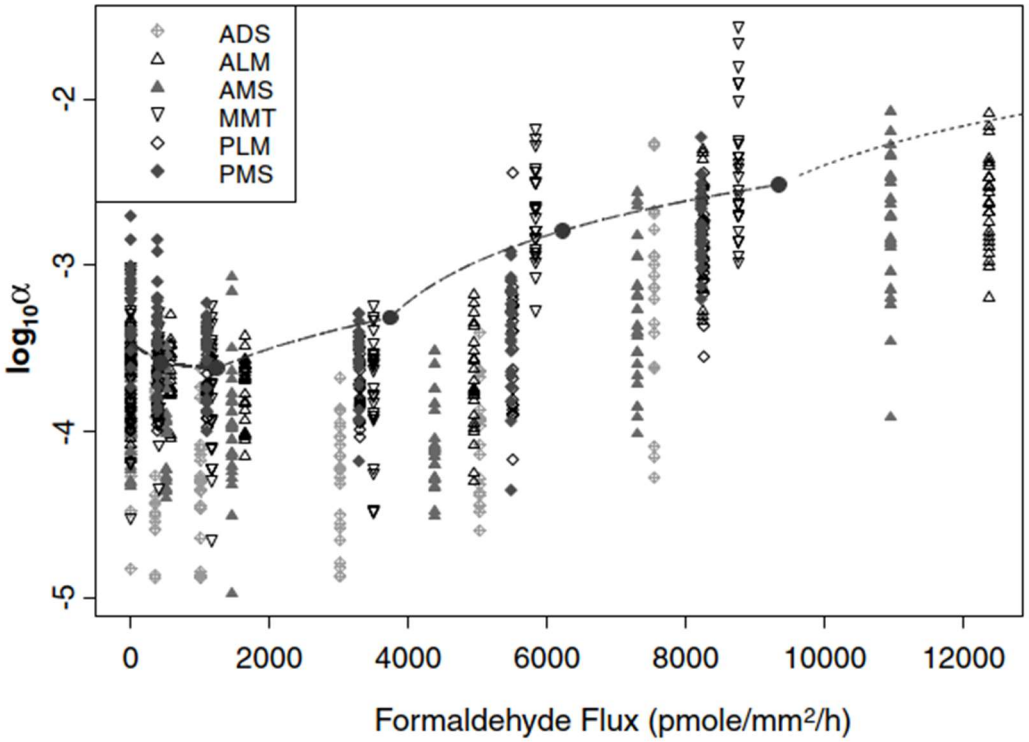
Nasal epithelial labeling index



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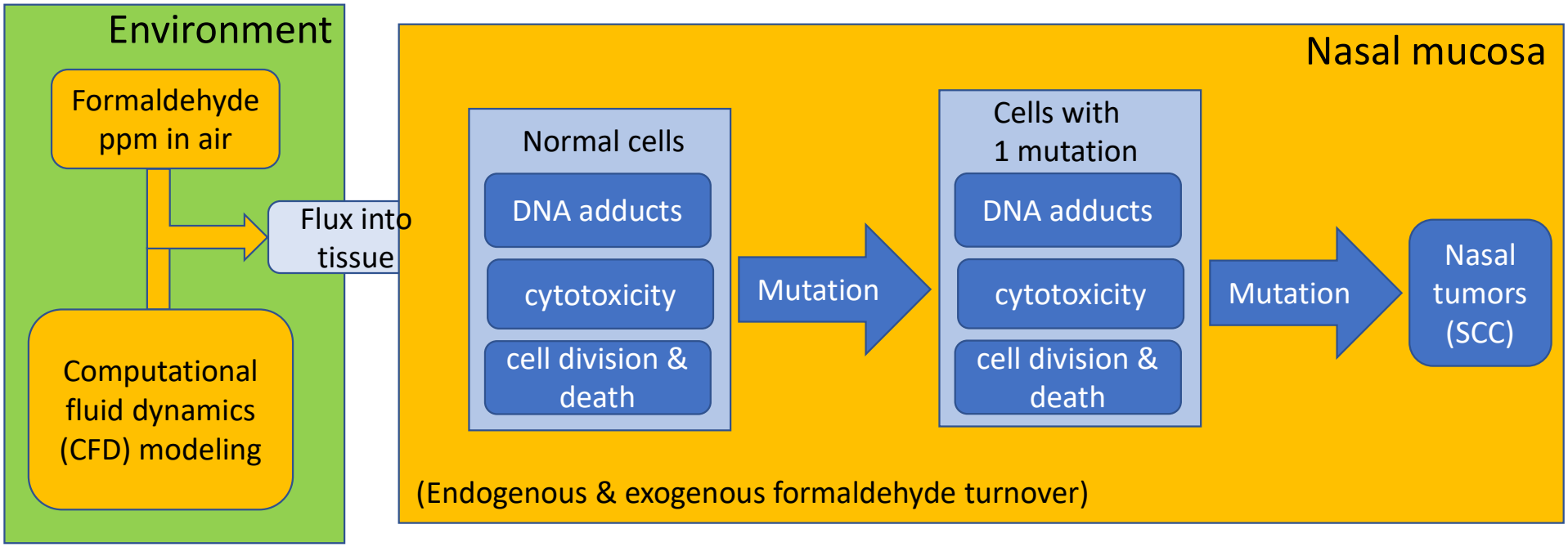
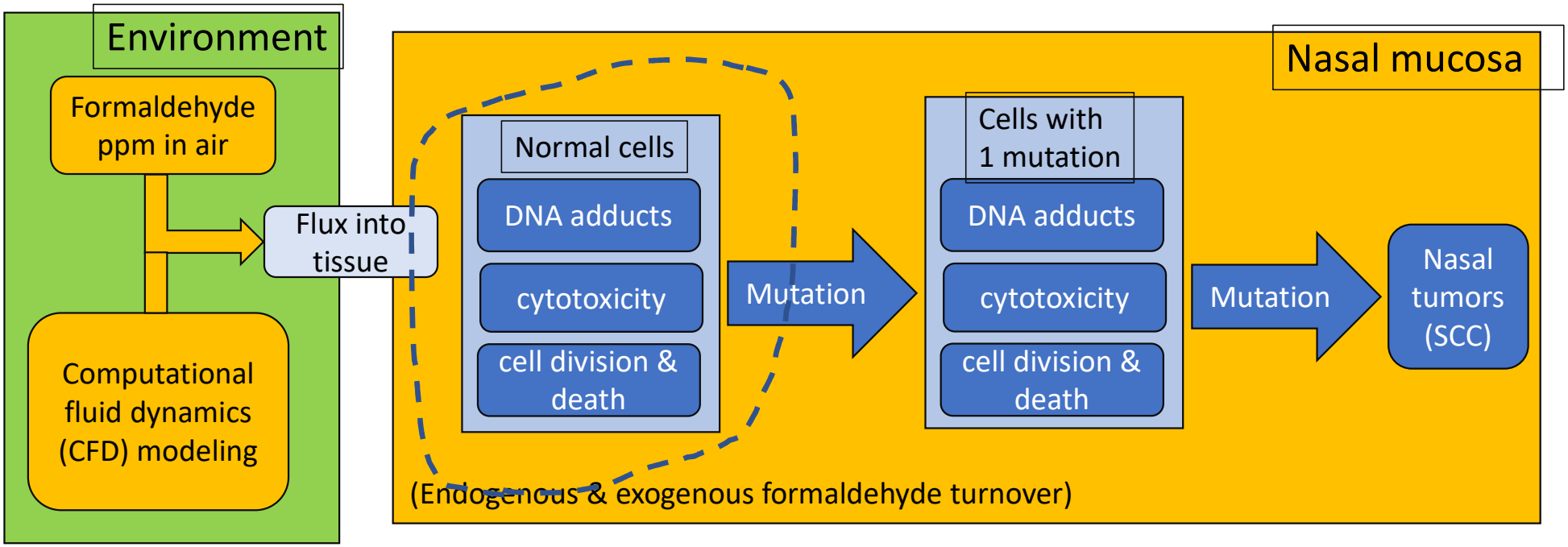
Risk Analysis 28, 907-923, (2008)
PMID: 18564991 PMCID: PMC2719764 DOI: 10.1111/j.1539-6924.2008.01083.x

BBDR: Normal cell division rates



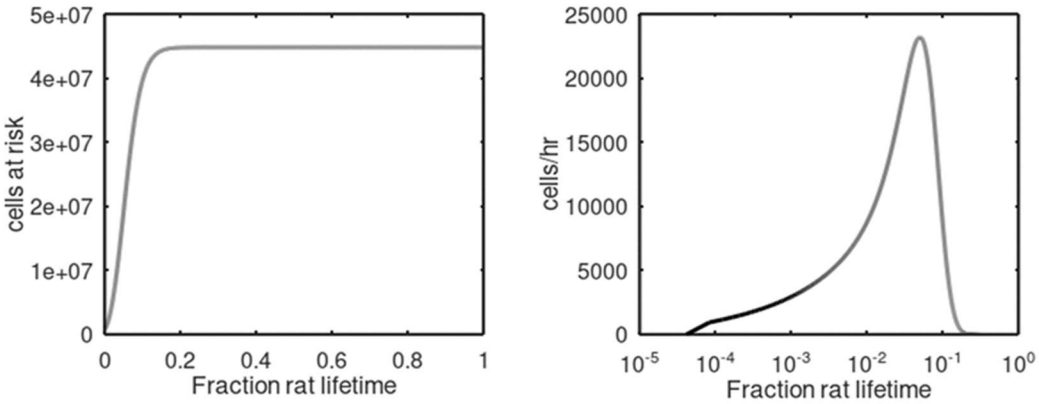
BBDR: Normal cell division rates

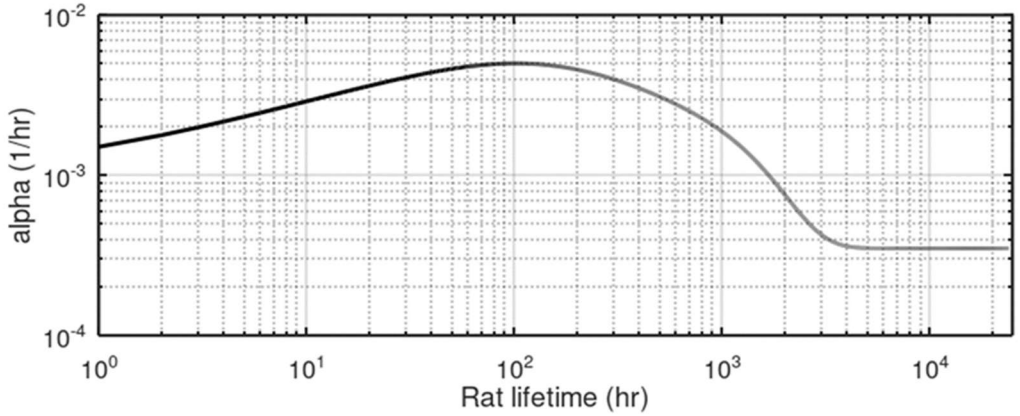


Rat nasal mucosal cells and cell division

Inputs

- Body weight growth curve
- Number of cells at risk in nasal epithelium





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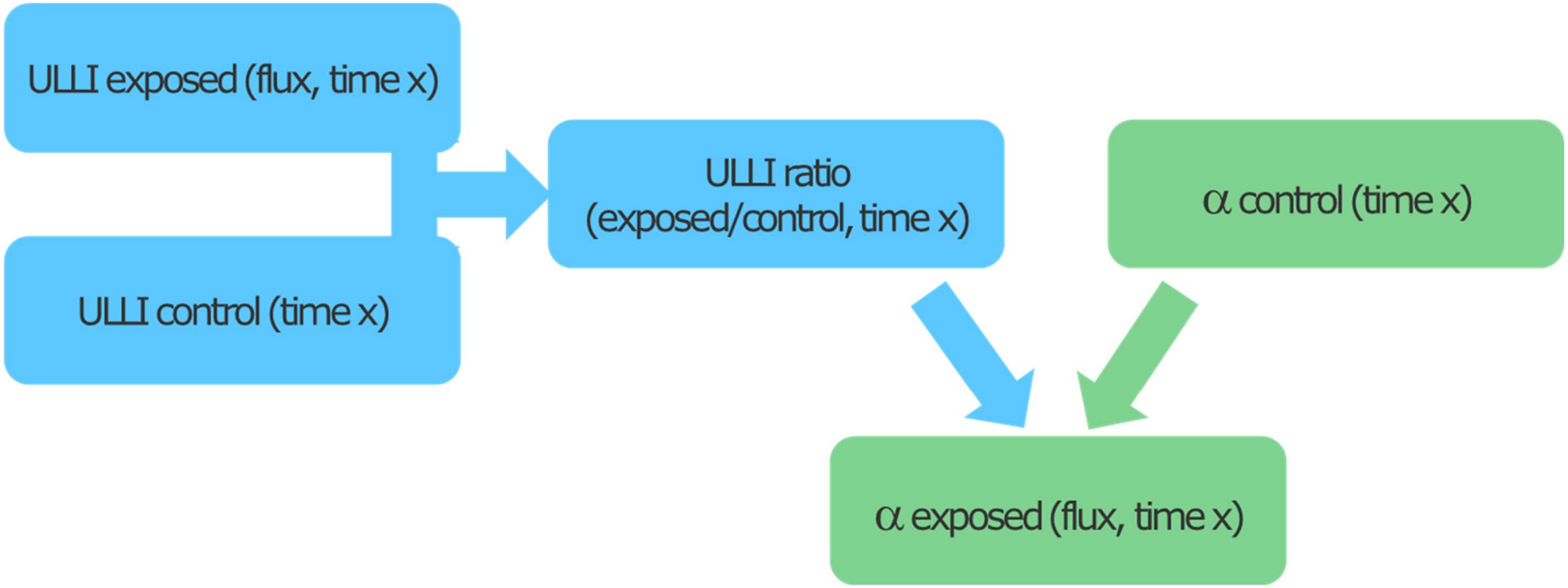
Effect of formaldehyde inhalation on rate of cell division



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Division rate as a function time and exposure

Age (hr)	Flux (pmol/mm^2/hr)					
	0	530	1515	4544	7574	11360
1	1.505E-03	1.505E-03	1.505E-03	1.505E-03	1.505E-03	1.505E-03
10	2.894E-03	2.894E-03	2.894E-03	2.894E-03	2.894E-03	2.894E-03
25	3.867E-03	3.867E-03	3.867E-03	3.867E-03	3.867E-03	3.867E-03
50	4.617E-03	4.617E-03	4.617E-03	4.617E-03	4.617E-03	4.617E-03
75	4.915E-03	4.915E-03	4.915E-03	4.915E-03	4.915E-03	4.915E-03
102	4.994E-03	4.994E-03	4.994E-03	4.994E-03	4.994E-03	4.994E-03
500	3.099E-03	3.099E-03	3.099E-03	3.099E-03	3.099E-03	3.099E-03
1000	1.878E-03	1.878E-03	1.878E-03	1.878E-03	1.878E-03	1.878E-03
1512	1.165E-03	1.165E-03	1.165E-03	1.165E-03	1.165E-03	1.165E-03
1536	1.139E-03	8.109E-04	1.261E-03	5.448E-03	7.954E-03	7.571E-03
1608	1.067E-03	1.132E-03	8.249E-04	1.148E-02	1.457E-02	1.918E-02
1729	9.572E-04	7.244E-04	1.012E-03	1.016E-02	1.768E-02	2.138E-02
2520	5.293E-04	4.600E-04	6.323E-04	3.608E-03	1.054E-02	1.367E-02
3696	3.700E-04	4.190E-04	4.838E-04	4.133E-04	2.025E-03	3.313E-03
5880	3.501E-04	2.285E-04	2.059E-04	1.711E-04	8.199E-04	1.652E-03
10248	3.500E-04	1.996E-04	1.860E-04	1.781E-04	5.899E-04	1.790E-03
14616	3.500E-04	3.208E-04	1.754E-04	2.433E-04	1.049E-03	1.459E-03
19031	3.500E-04	1.632E-04	1.496E-04	8.181E-05	1.135E-04	4.894E-04
19032	3.500E-04	3.500E-04	3.500E-04	3.500E-04	3.500E-04	3.500E-04
30000	3.500E-04	3.500E-04	3.500E-04	3.500E-04	3.500E-04	3.500E-04

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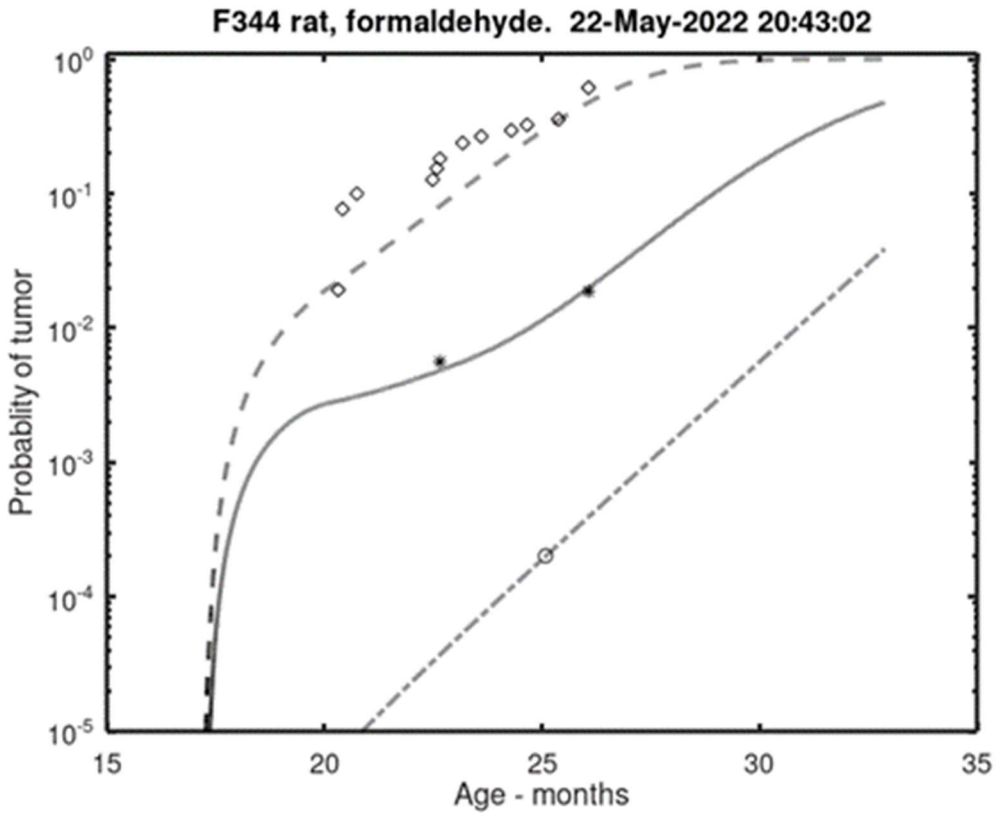
Historical controls

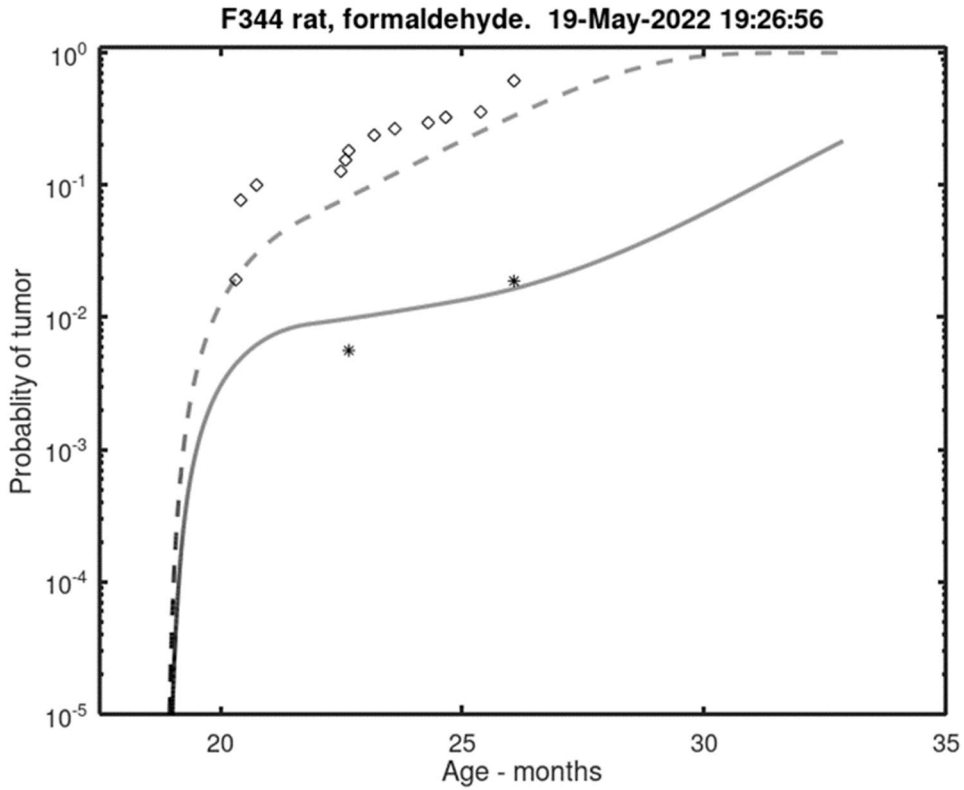
- CIIT BBDR
  - 13 controls
  - Inhalation + oral gavage
- Revised BBDR
  - 1 or none
  - Inhalation only

Single inhalation control is problematical



Cytotoxicity only, no mutagenic effect of adducts

- cytotoxicity creates a mutagenic environment



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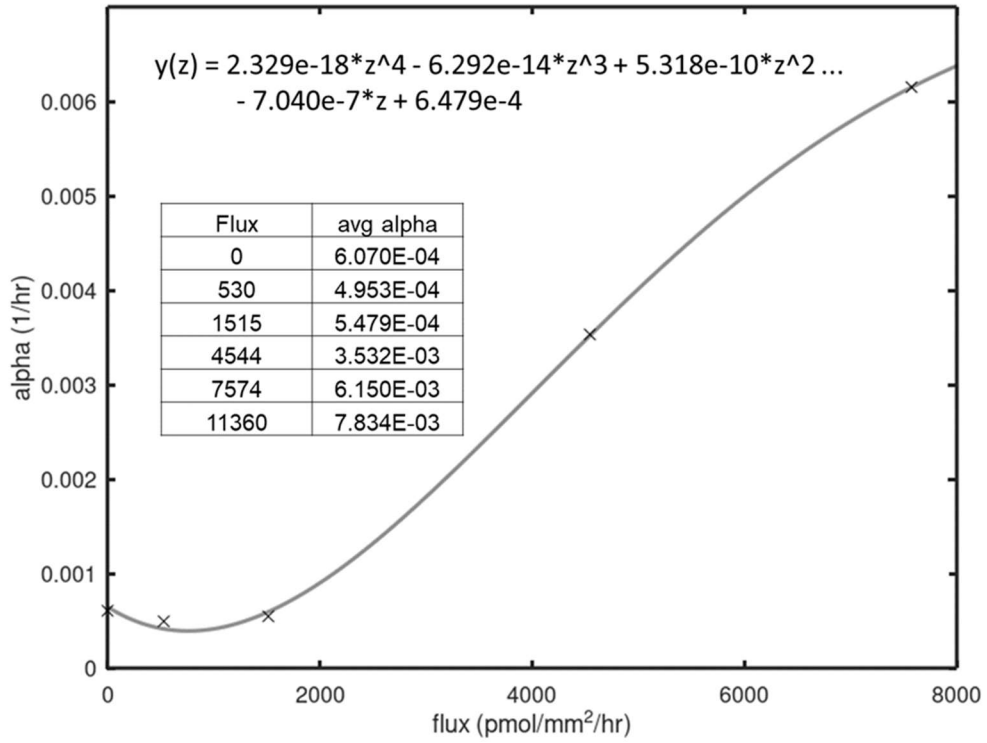
Cytotoxicity when division rate curve inflects upward. Cytotoxic-inflammatory environment is mutagenic (see mesothelioma literature)



Flux	avg alpha
0	6.070E-04
530	4.953E-04
1515	5.479E-04
4544	3.532E-03
7574	6.150E-03
11360	7.834E-03

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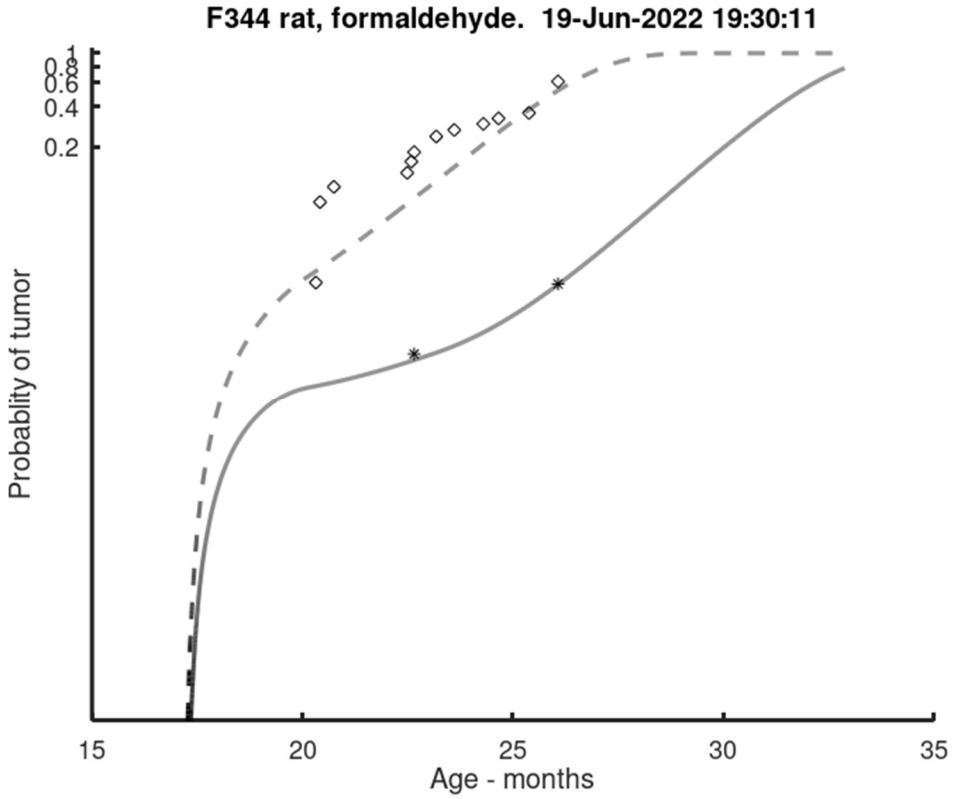
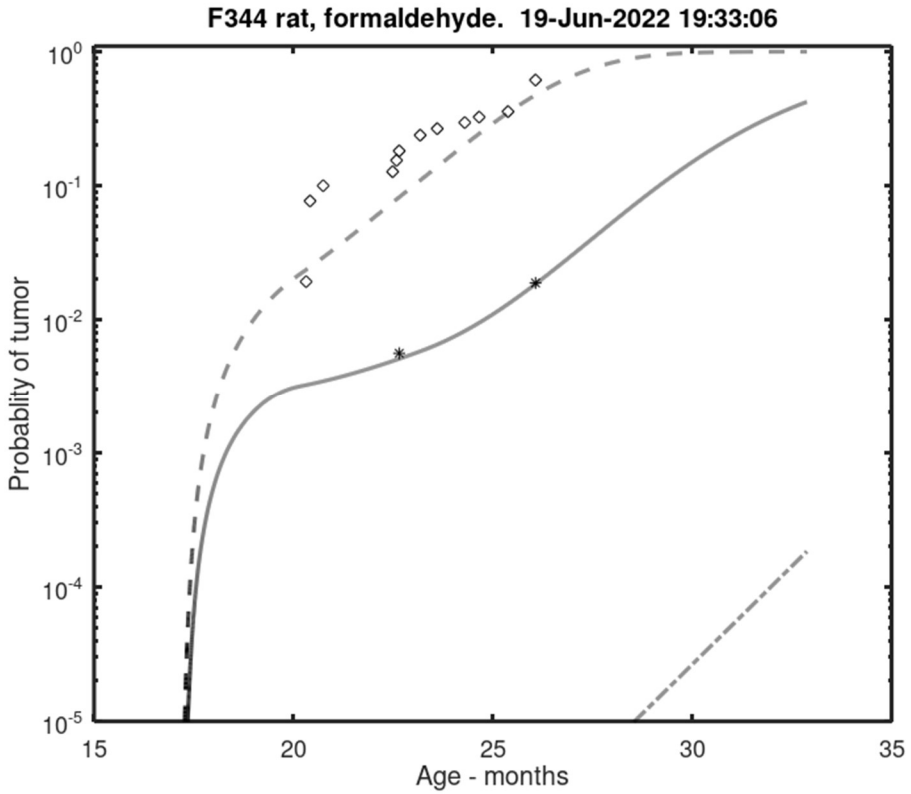
Cytotoxicity only, no mutagenic effect of adducts

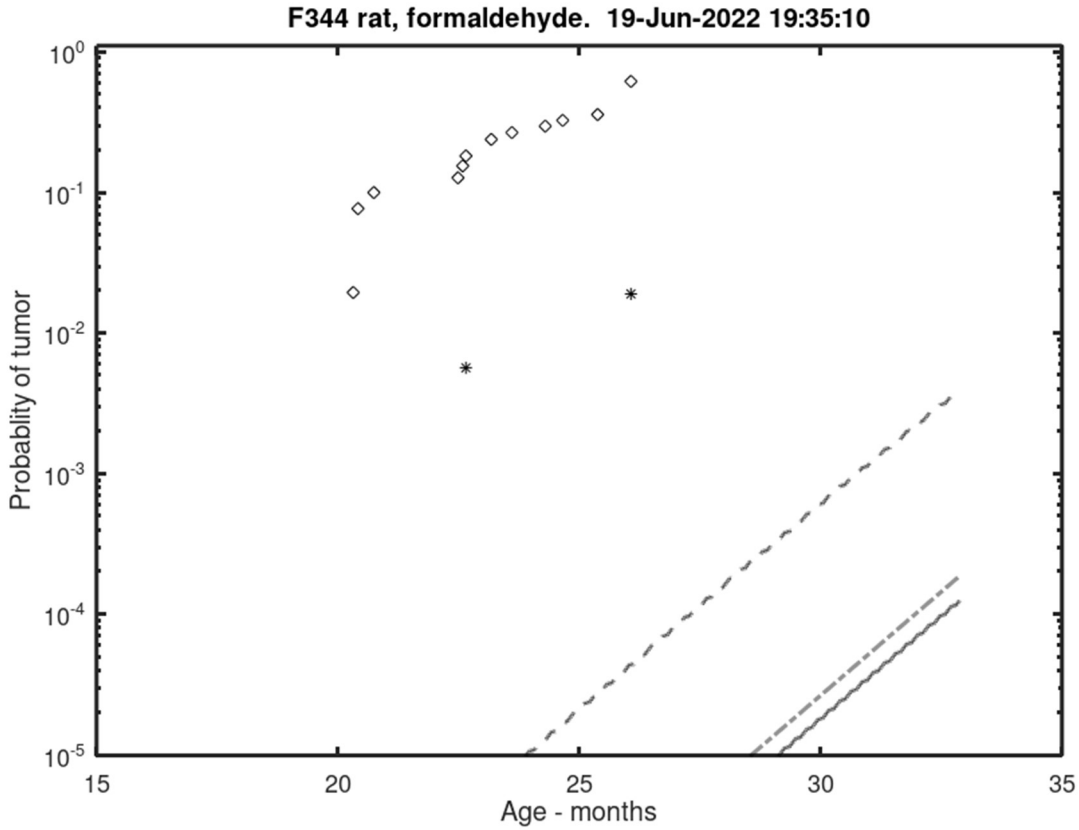
- cytotoxicity creates a mutagenic environment



Small degree of adduct mutagenicity, tumor response driven by cytotoxicity



Same small degree of adduct mutagenicity, but with no mutagenicity due to cytotoxicity



Initiated cells

- Simplified mathematical description
- I cell parameter values

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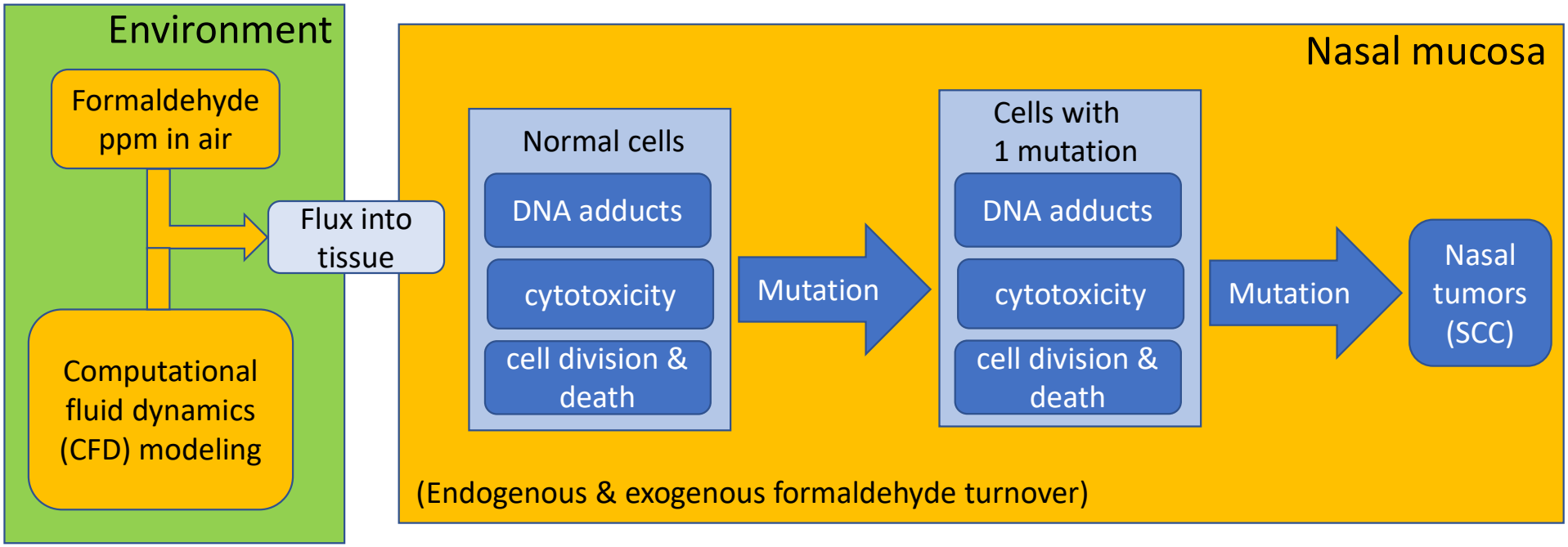
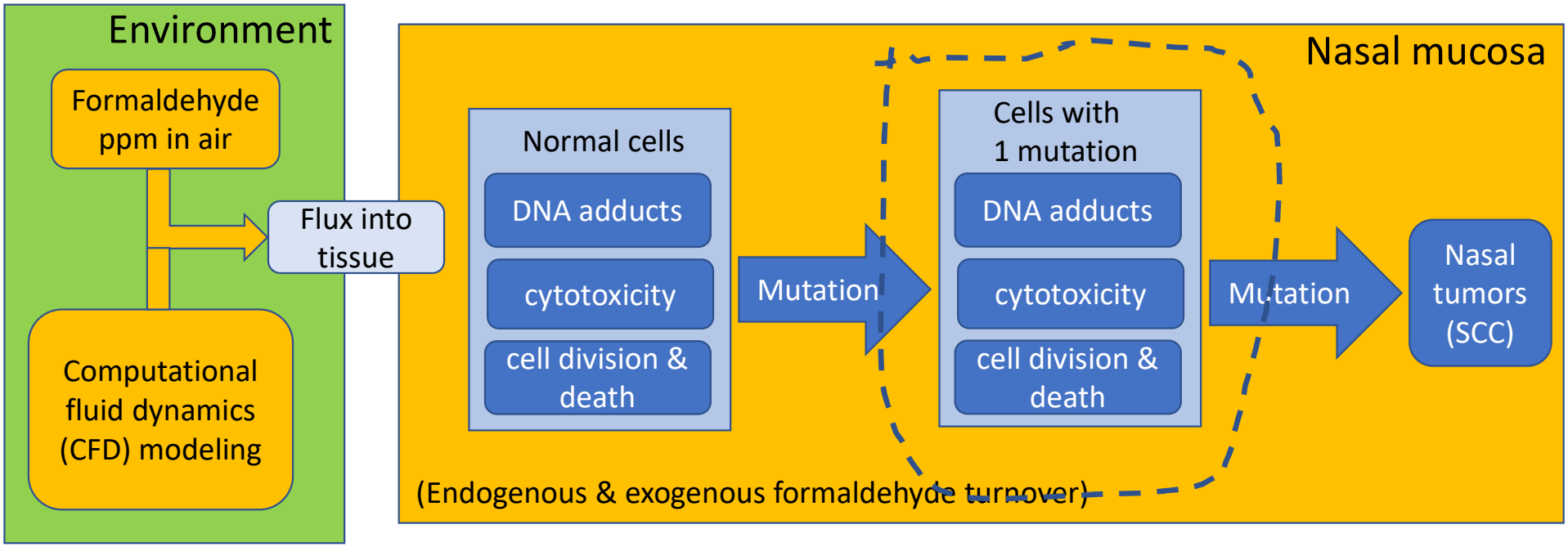
BBDR: Initiated cells



BBDR: Initiated cells



Growth of initiated cells (CIIT BBDR)

- Complicated description:
- Adjustment to I cell div rate a function of flux of formaldehyde:
  - p.multf = c.multb - c.multfc.*max(p.rbN - divrate(1), 0);
  - p.rbI = p.rbN.*p.multf

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Growth of initiated cells (New BBDR)

- p.rbI = p.rbN + c.gai; %I cells have fixed growth advantage c.gai
- p.rdI = p.rbN;

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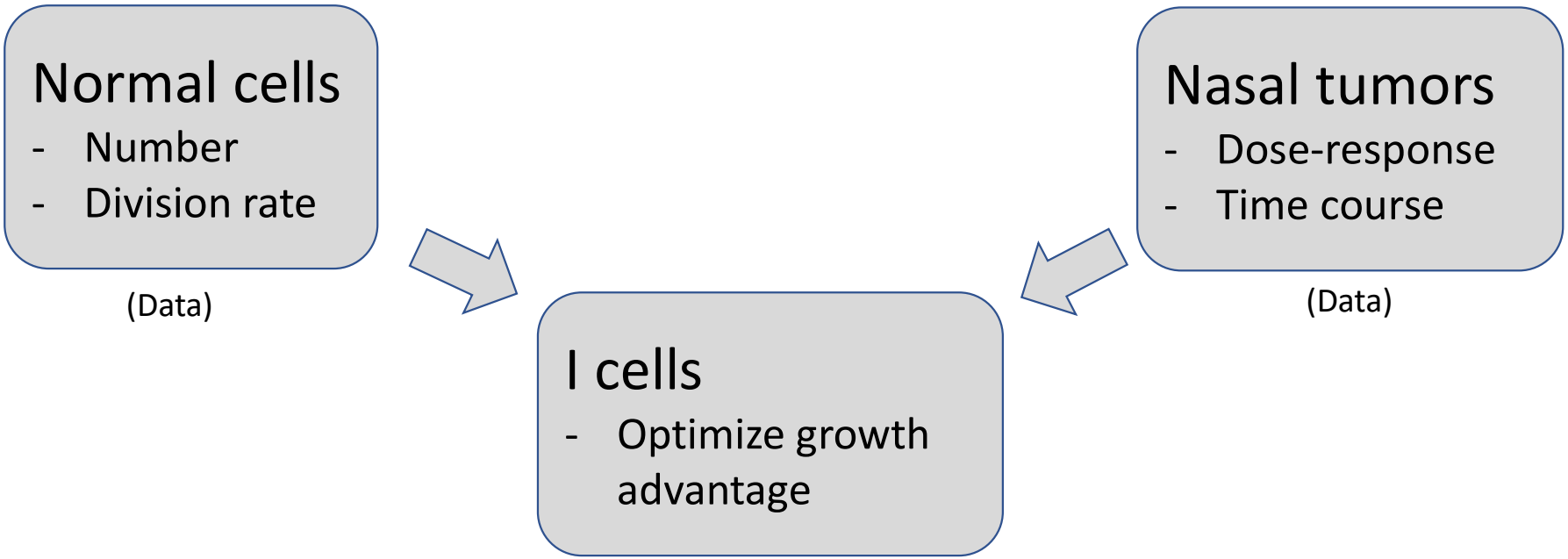
Initiated cell division rate is optimized – value is constrained by normal cell and tumor data



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Summary and Conclusions

- Critiques of CIIT BBDR model are addressable
- CFD
  - Refined technology, but new predictions of flux into tissue very similar to the CIIT CFD modeling
- Adduct dosimetry
  - Account for exogenous and endogenous adducts
  - dG and DPX
  - dG data show threshold at 0.3 ppm

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Summary and Conclusions

- Labeling index data
  - No longer translate injection data into equivalent pump data
  - Control division rate calculated from BW growth curve
  - Age and flux dependent 2-D table of division rates

- Historical controls
  - Lack of control nasal tumors implies bioassay tumors are due to cytotoxicity and associated inflammation. This is not a low dose linear process.
  - If a small degree of low dose linear adduct mutagenicity is used that is consistent with lack of observed control tumors, bioassay tumor response is still driven by cytotoxicity.

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Summary and Conclusions

- Initiated cells
  - Simplified mathematical description of growth advantage
  - Extensive datasets for normal cells and for tumors tightly constrain parameter values for initiated cells. Value used in the BBDR model is optimized by maximizing the likelihood of the tumor and survivor data.

Manuscripts

- Two manuscripts describing the revised rat BBDR modeling
  - Adduct dosimetry
    - In review at Toxicological Sciences
  - Rat BBDR
    - Manuscript to be submitted later this summer

- No plans at present for development of a revised human BBDR model.

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Questions?