Science Question 7: *In Vivo* Mutagenicity/Genotoxicity—Oral Cavity MOA

Key Points

1. **We conducted a Big Blue transgenic rat mutation study to examine whether Cr(VI) acts by a mutagenic MOA in rat oral tissues [EPRI Funded]**
2. **Study is finished; paper has been submitted for peer-review**

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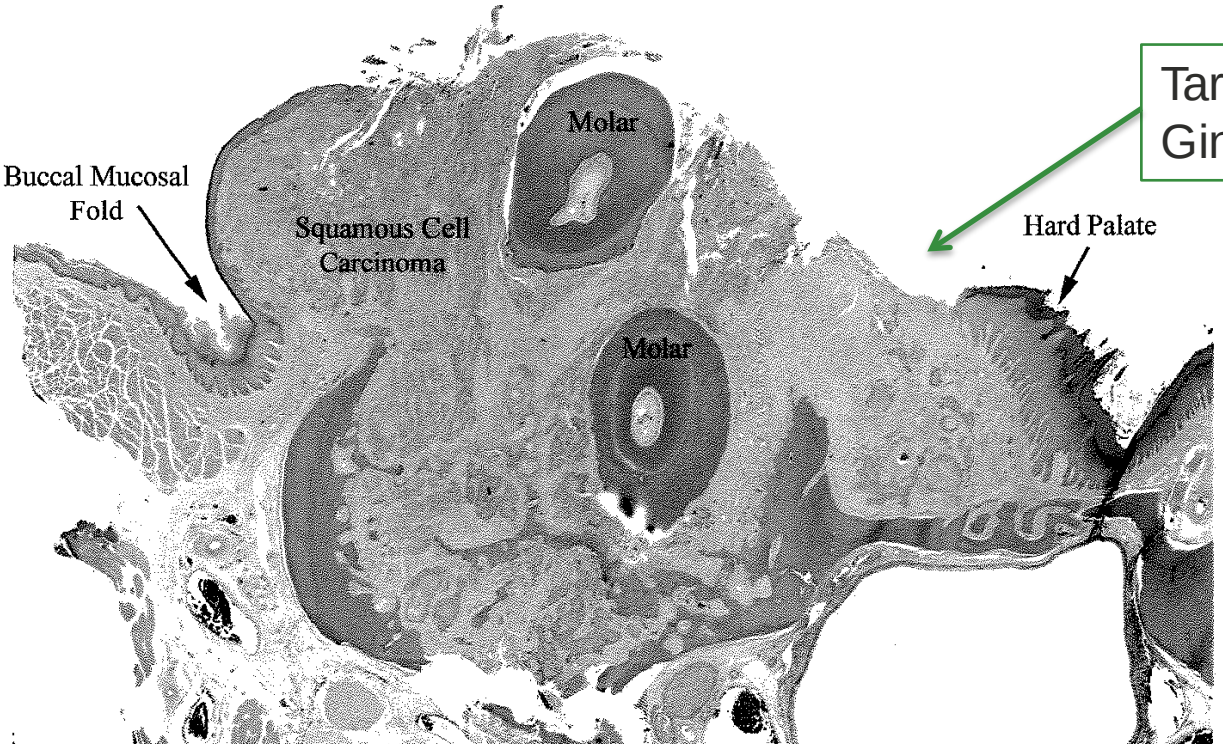
ToxStrategies

Transgenic Mutation Study in Big Blue Transgenic Rats

- **ToxStrategies and BioReliance conducted OECD 488, GLP-compliant transgenic mutation assays in Big Blue rats**
- **Study Objective: Examine the mutagenicity of Cr(VI) in the rat oral mucosa to inform the MOA**



Target Tissue: Gingival Epithelium

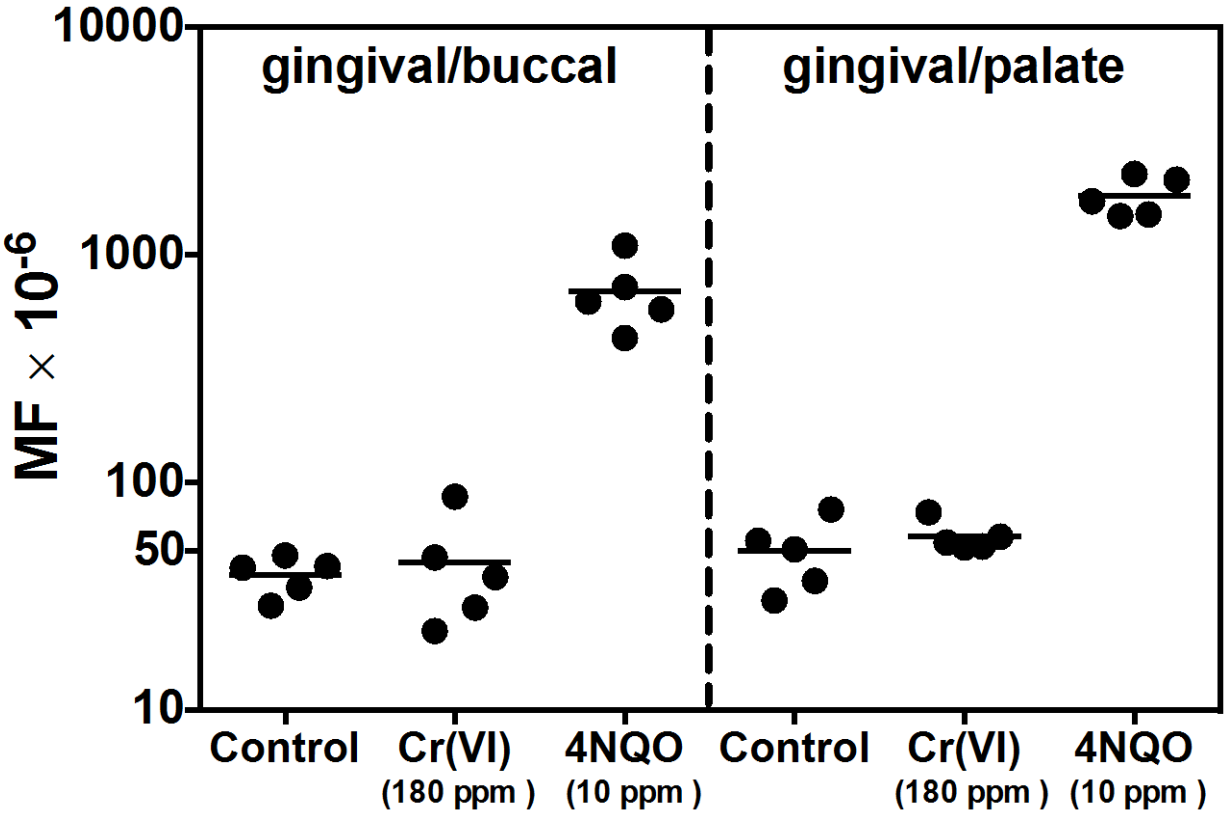
Rat oral cavity squamous cell carcinoma
Source: NTP 2008

Study Design

- **Transgenic Big Blue Rats (TgF344)**
- **Dosing**
  - Control: Bottled water
  - Positive control: 10 ppm 4-Nitroquinoline-N-oxid (4NQO) in drinking water
  - Cr(VI): 180 mgCr(VI)/L as sodium dichromate dihydrate in drinking water
- **OECD 488 Dosing protocol**
  - 28 days of dosing followed by 3 days to fix mutations
  - 5 animals per exposure group

Results of 28-Day Big Blue Assay in Rat Oral Cavity

- **Positive Control (4NQO) is strongly mutagenic**
- **Cr(VI) did not increase mutation frequency over that of controls**



Findings & Conclusions

- **Mutation Frequency for Cr(VI) exposed rats was consistent with water controls**
- **Results argue against a mutagenic MOA in rat oral cavity**
- **Support indirect mechanisms such as those reported in Suh et al. (2014)**
  - Questions as to whether rat oral tumors are relevant – High-dose effect
  - One or multiple possible factors are observed at high dose
    - Effects on iron homeostasis (toxicogenomic analyses, Fe levels in tissues and bone marrow)
    - Decreased water intake, mild dehydration
    - Effects on salivary production or saliva chemistry