



## **New and Emerging Science on Hexavalent Chromium/Other Topics**

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U.S. EPA IRIS Public Science Meeting

April 24, 2019

Comments on behalf of the American Chemistry Council

# Topics to Discuss

## 1. Question regarding the status of a published 2017 study with direct relevance to MOA and risk assessment

- Thompson et al. (2017) Assessment of the mutagenic potential of hexavalent chromium in the duodenum of Big Blue® rats. *Toxicology and Applied Pharmacology* 330: 48-52.

## 2. Availability of new study with direct relevance to MOA and risk assessment

- Aoki et al. (2019) Mutant frequency is not increased in mice orally exposed to sodium dichromate. *Food Safety*. In press.

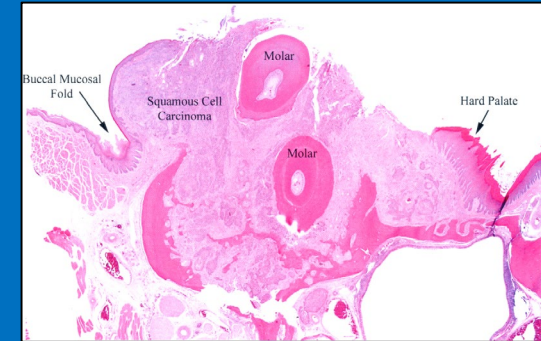
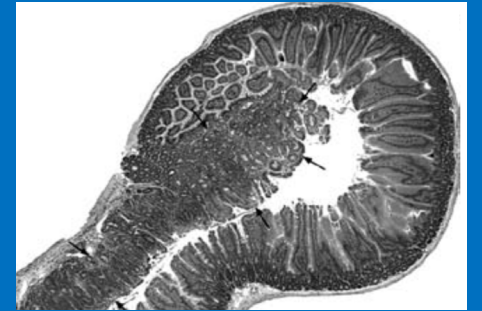
# NTP Cr(VI) Bioassay (2008)

## NTP Cr(VI) drinking water study

- 5 to 180 ppm in drinking water
- Rare tumors appeared late in the study

Mice: adenomas and carcinomas of small intestine ( $\geq 30$  ppm)

Rats: SCC in oral cavity (180 ppm)



# Importance of Target Tissue Mode of Action Research

## Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005):

### 1.3.4 Dose-response Assessment

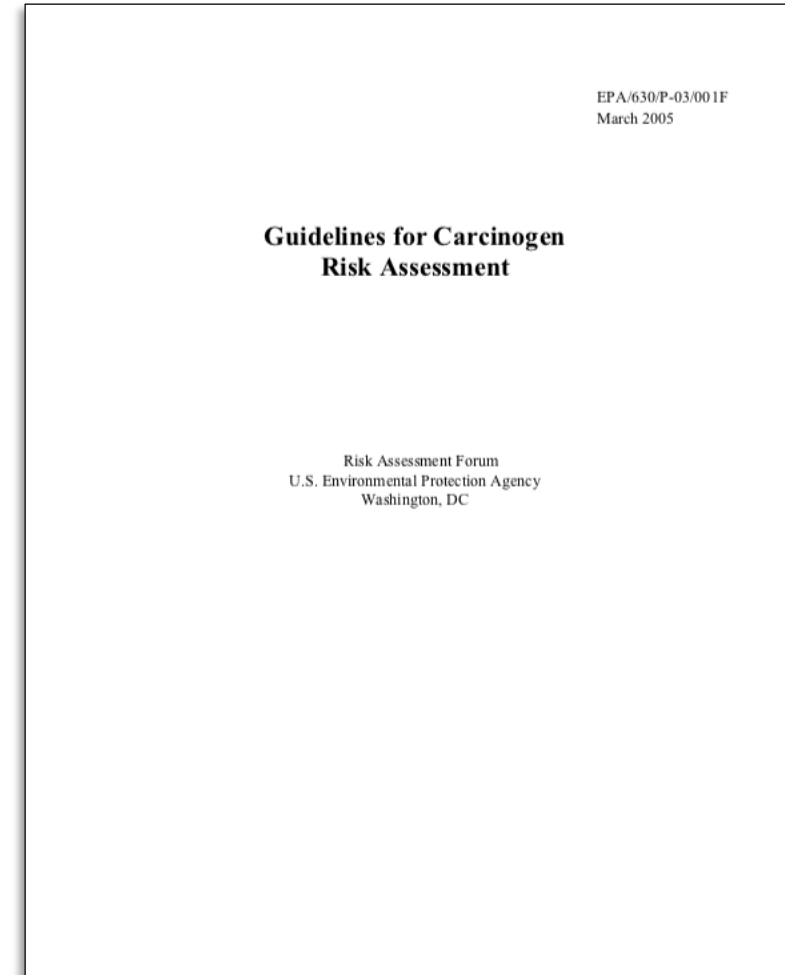
- The approach to dose-response assessment for a particular agent is based on the conclusion reached as to its potential mode(s) of action for each tumor type.

### 2.4.3.1 Description of the Hypothesized Mode of Action

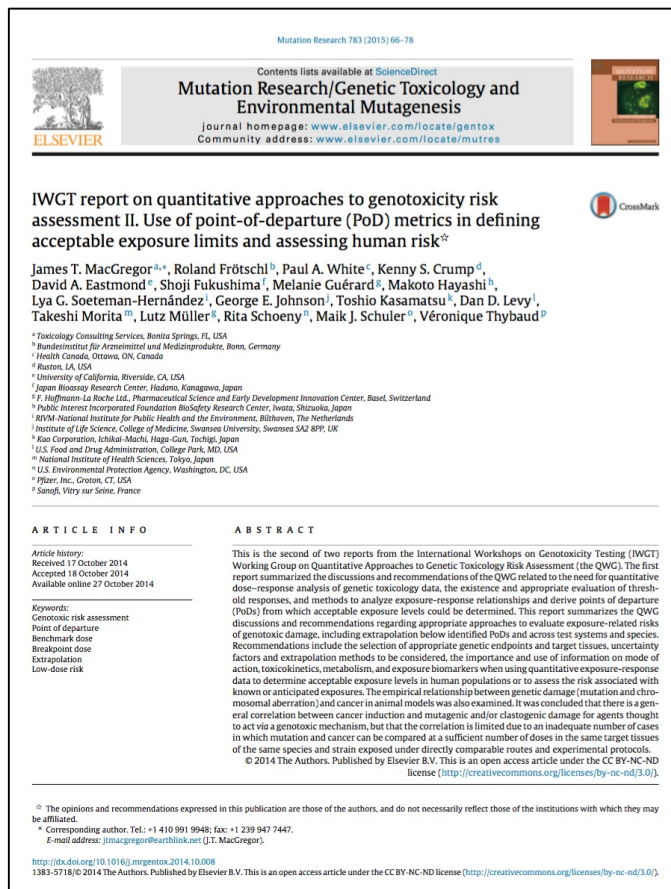
- For each tumor site, the mode of action analysis begins with a description of the hypothesized mode of action and its sequence of key events.

### 3.3.1 Choosing an Extrapolation Approach

- The approach for extrapolation below the observed data considers the understanding of the agent's mode of action at each tumor site (see Section 2.4)

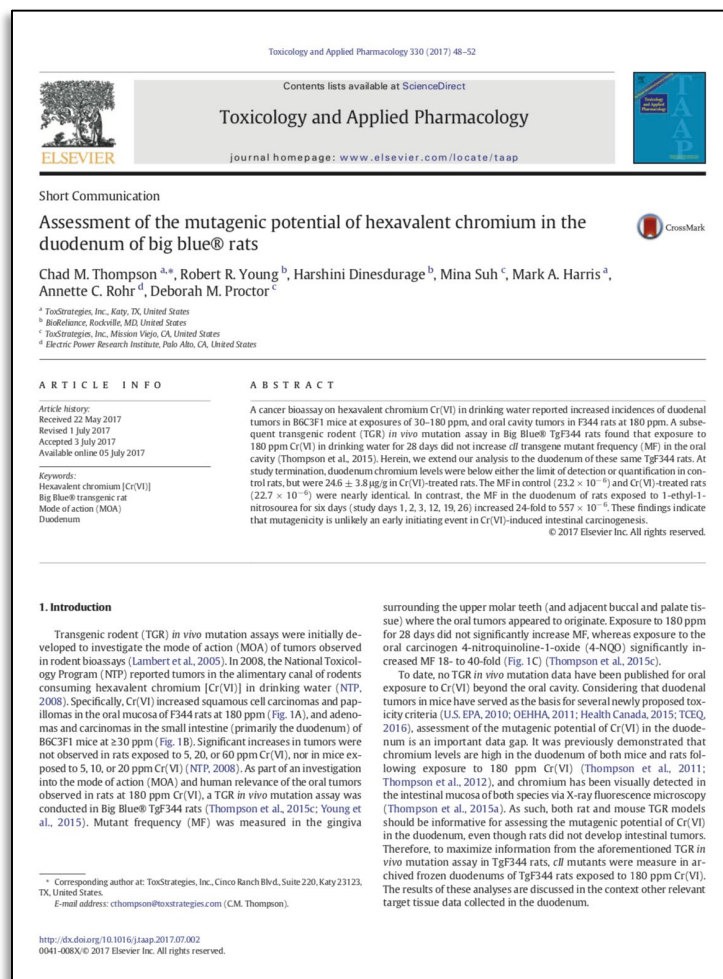


# Recommendations for In Vivo Genotoxicity Assays



- ✓ Ideally at site of carcinogenic action
- ✓ Ideally in tissue with high dosimetry (e.g. site of contact)
- ✓ Ideally conducted in a proliferative tissue

# Question Regarding In Vivo TGR Mutation Assay in EPA's SR



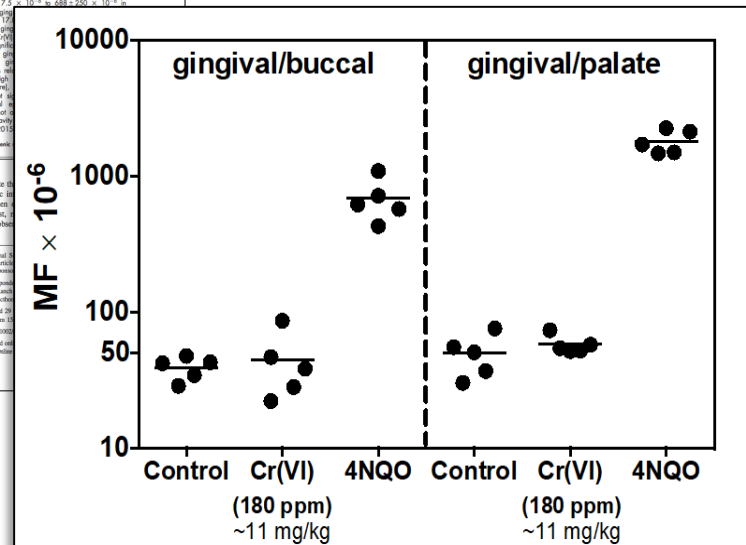
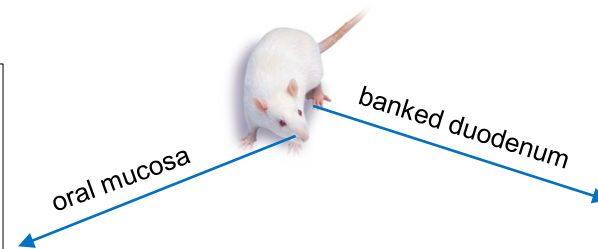
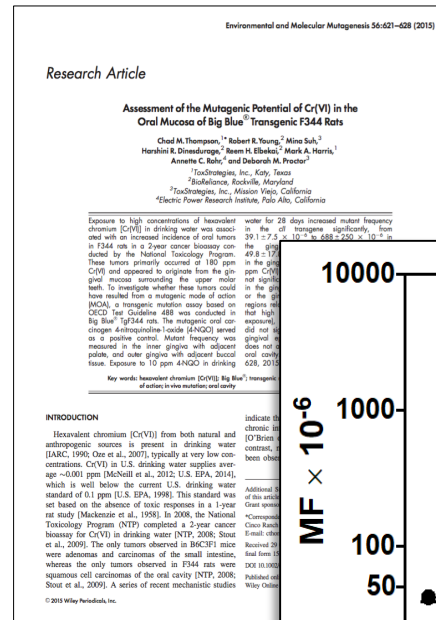
## Tags IRIS

- [Chromium VI](#)  
[Not in Lit Search](#)  
[Lit Search Updates](#)  
[May 2017 to May 2018](#)

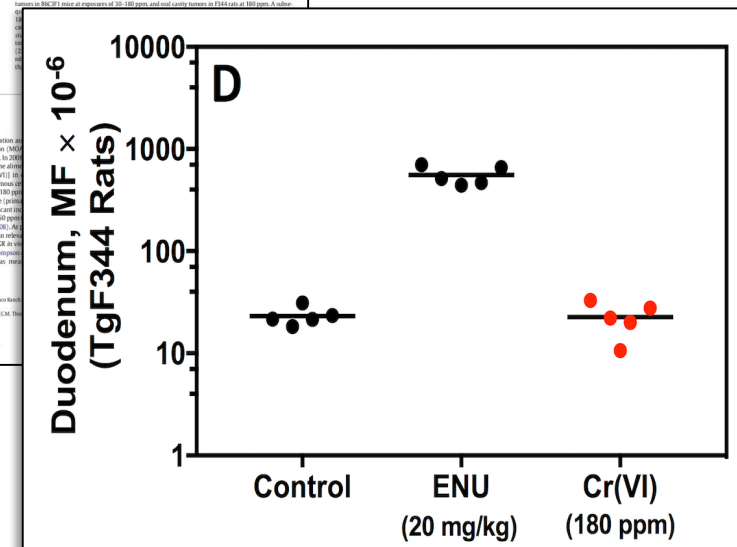
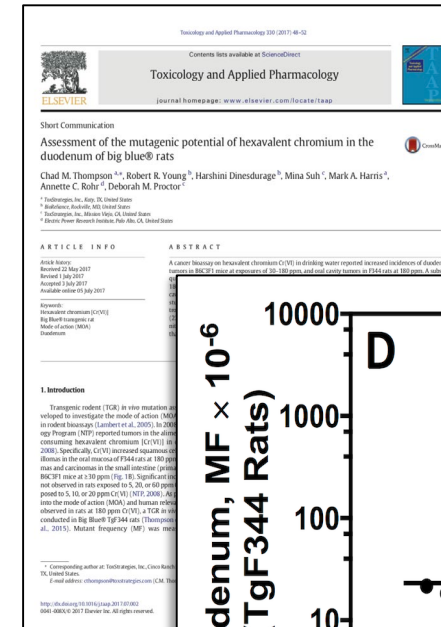
No additional tags (e.g., potentially relevant).

# The 2017 TGR Study Has Important MOA Information

2015

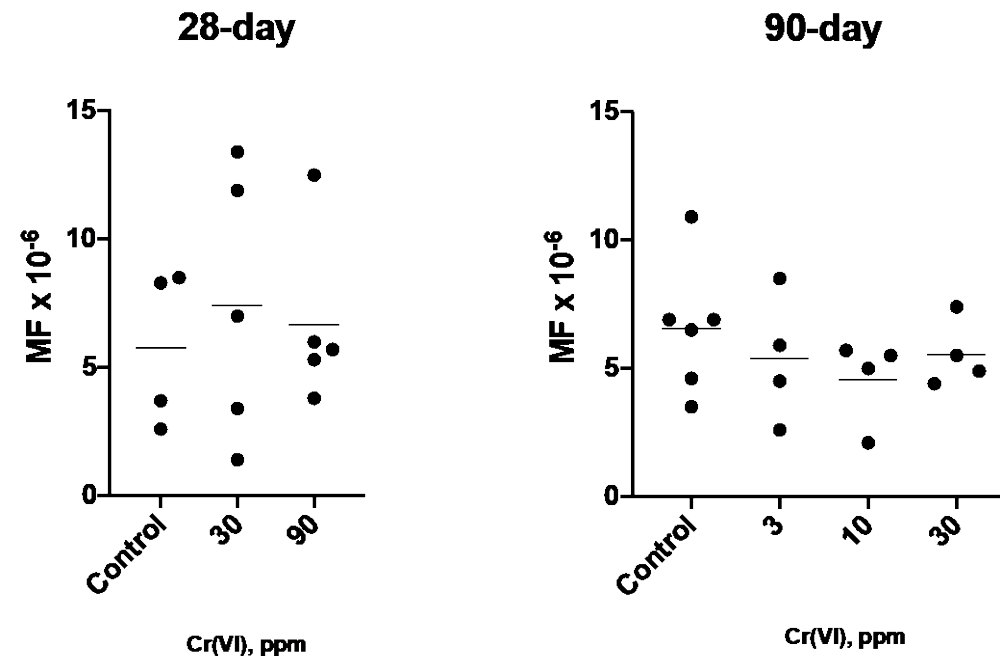


2017

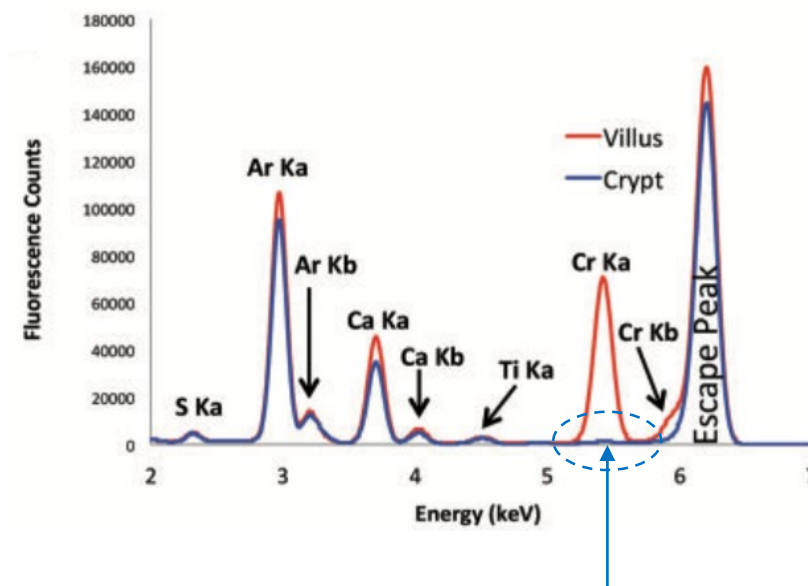
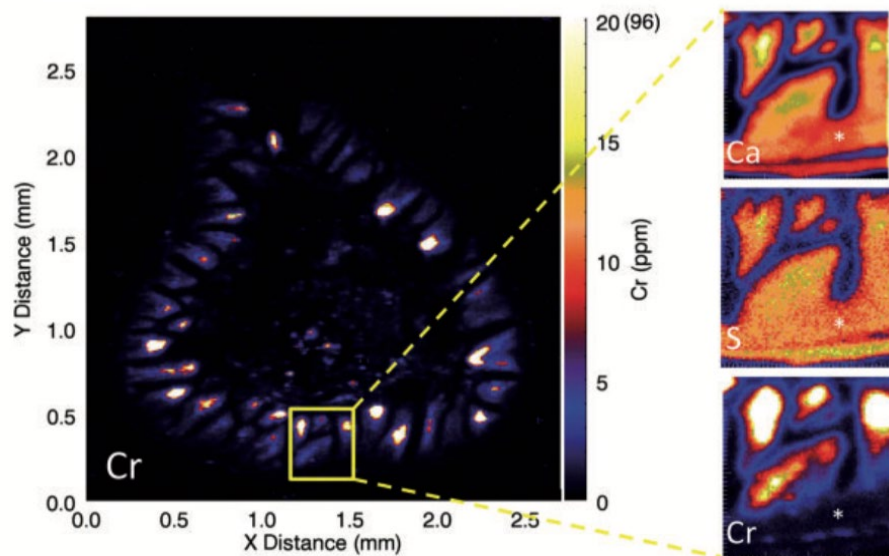


# New TGR Mutation Assay in Small Intestine of *gpt* Delta Mice

2019



# Negative Genotoxicity is Consistent with Lack of Cr in Crypts



Source: Thompson et al. (2015) Tox Sci 143, 16.

# In Vivo Genotoxicity Assays in Target Tissue (2013-2019)

- **Duodenal MN assays**
  - Neg after 7 and 90 days of exposure
- **Duodenal  $\gamma$ -H2AX immunostaining**
  - No diff from controls at 7 and 90 days of exposure
- ***kras* codon 12 GAT MF in duodenum**
  - Neg after 90 days of exposure
- **Duodenal TGR assays**
  - Neg in Big Blue rats after 28 days of exposure
  - Neg in *gpt* delta mice after 28 & 90 days exposure
- **XRF microscopy**
  - Cr detected in villi (not crypt)
- **Oral mucosa mutation assay**
  - Neg in Big Blue rats after 28 days of exposure

