

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

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**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<sup>®</sup> 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 (≥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 <u>each tumor type</u>.

### 2.4.3.1 Description of the Hypothesized Mode of Action

 For <u>each tumor site</u>, 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 <u>at</u> <u>each tumor site</u> (see Section 2.4)



### Recommendations for In Vivo Genotoxicity Assays

N	Contens lists available at ScienceDirect Autation Research/Genetic Toxicology and Environmental Mutagenesis
IWGT report on qua	ntitative approaches to genotoxicity risk f point-of-departure (PoD) metrics in defining
acceptable exposure James T. MacGregor <sup>a,*</sup> , Ro David A. Eastmond <sup>e</sup> , Shoj Uva G. Soeteman-Hernány	limits and assessing human risk* pland Frötschl <sup>b</sup> , Paul A. White <sup>c</sup> , Kenny S. Crump <sup>4</sup> , I Fukushima <sup>4</sup> , Melanie Guérard <sup>8</sup> , Makoto Hayash <sup>1b</sup> , Jey: George F. Johnson J. Teshio Kasamatuk <sup>1b</sup> , Dan D. Lewi <sup>1</sup>
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RIVM-National Institute for Public Health a Institute of Life Science, College of Medicin <sup>6</sup> Kao Corporation, Ichikai-Machi, Hago-Gun U.S. Food and Drug Administration, College <sup>79</sup> National Institute of Health Sciences, Toky U.S. Environmental Protection Agency, Wa <sup>9</sup> Fjärer, Inc., Groon, CT, USA <sup>8</sup> Sanofi, Vitry sur Seine, France	- Savanne (Antoneu, Bullowen, IV, Nederlandaus) - Savanne (Savanne Sub WP, UK Forley, Japan Forley, J. J. Japan
RYM-Horitonal Institute for Public Health in Institute of IJ6-Senex, College of Medicin, 'Kao Corporation, Ichikai-Machi, Haga-Cui U.S. Ford and Drux Administration, College 'Mational Institute of Health Sciences, Toky U.S. Environmental Potection Agency, Wa 'Pfizer, Inc., Groton, CT, USA 'Sanoff, Vitry sur Seine, France ARTICLE INFO	a dhe Lavorouninette, Builhoven, The Netherinands Summar University, Sommar Sch 2019, UK Farle, KD, USA Jogan A B S T R A C T
RIVA-National Institute for Public Health a Hindhard gif US-cost College of Medical U.S. Food and Drug Administration, College With State (Health Science, Topical U.S. Food and Drug Administration, College With Environmental Protection Agency, We "Jear, Inc., Costou, Classification, Classification, College With Science, Classification, Classificati	a die Larvorannet, Billhoven, IIA Verfarinansis Troffel, Joegen Troffel, Joegen Joegen ABSTRACT ABSTRACT ABSTRACT This is the second of two reports from the International Workshops on Genotoxicity Testing (IWCT) Working Group on Quantitative Approaches to Genetic Toxicology Risk Assessment (the QWC). The first report summarized the discussions and recommendations of the QWC related to the need for quantitative doss-response analysis of genetic toxicology data, the existence and appropriate evaluation of thread
ARVA Astenia Institute for Public Health A Minister of UK Sector College of Health Similar U.S. Food and Drug Administration, College V.S. Food and Drug Administration, College Network (1996) (1997) (1997) (1997) (1997) U.S. Food and Drug Administration, College Network (1997) (1997) (1997) (1997) (1997) (1997) AR TILLE INFO ARTICLE INFO ARTICLE INFO ARTICLE INFO ARTICLE OF AND	and detail former, Bullhover, IR Netherlands Tochell, Jagon Part, MJ, OSA Jagon Magner, DC, LGM AB S T R A C T A B S T R A C T This is the second of two reports from the International Workshops on Genotoxicity Testing (IWCT) Working Group on Quantitative Approaches to Genetic Toxicology Biak Assessment (the QWG). The first report summarized the discussions and recommendations of the QWC related to the need for quantitative dose-response analysis of genetic toxicology data, the existence and appropriate evaluation of thresh- old responses, and methods to analyze exposure-response relationslips and derive points of departure (PDD) from which acceptable exposure levels could be determined. This report summarizes the QWC of genotoxic damage, including extrapolation below itentified PDDs and across test systems and specifics, Recommendations include the selection of appropriate genetic endpoints and target toxies, and extrapolation methods to be considered, the importance and use of information on mode of actions toxicokinetics, metabolism, and exposure biomarkers when using quantitative exposure response and aberration) and cancer in namian Model was also examined. It was concluded that there is a gene- morsonia description cancer induction and mutagenic adjoir classion induction of Cases in which matiation and classer in thread bode was also examined. It was accouncided that there is a gene- morsonia description cancer in anism. But that the correlation is limited due to an inadequate number of Cases in which matiation and classer in thread body was also examined. It was accouncided that there is a gene- morsonia description construction and promoted does in the mater application and examples in the promoted does in the mater applications and the construction and advection. Construction construction compared in the construction of does in the agreents thought to act via agenotoxic mechanism, but that the correlation is limited due to an inadequate number of Cases in which matinform and canc

- ✓ Ideally at site of carcinogenic action
- $\checkmark$  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



2016), assessment of the mutagenic potential of Cr(VI) in the duode-B6C3F1 mice at ≥30 ppm (Fig. 1B). Significant increases in tumors were not observed in rats exposed to 5, 20, or 60 ppm Cr(VI), nor in mice exchromium levels are high in the duodenum of both mice and rats folposed to 5, 10, or 20 ppm Cr(VI) (NTP, 2008). As part of an investigation lowing exposure to 180 ppm Cr(VI) (Thompson et al., 2011; into the mode of action (MOA) and human relevance of the oral tumors observed in rats at 180 ppm Cr(VI), a TGR in vivo mutation assay was the intestinal mucosa of both species via X-ray fluorescence microscopy conducted in Big Blue® TgF344 rats (Thompson et al., 2015c; Young et (Thompson et al., 2015a). As such, both rat and mouse TGR models al., 2015). Mutant frequency (MF) was measured in the gingiva should be informative for assessing the mutagenic potential of Cr(VI) in the duodenum, even though rats did not develop intestinal tumors

target tissue data collected in the duodenum.

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num is an important data gap. It was previously demonstrated that Thompson et al., 2012), and chromium has been visually detected in Therefore, to maximize information from the aforementioned TGR in vivo mutation assay in TgF344 rats, cll mutants were measure in archived frozen duodenums of TgF344 rats exposed to 180 ppm Cr(VI) The results of these analyses are discussed in the context other relevant



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

### The 2017 TGR Study Has Important MOA Information



2017



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

#### 2019



The contents of this article reflect solely the view of the author(s). Suggested citation: Yasunobu Aoki, Michiyo Matsumoto, Michi Matsumoto, Kenichi Masumura, Takehiko Nohmi. Mutant Frequency is not Increased in Mice Orally Exposed to Sodium Dichromate. Food Safety: 2019; \*\* (\*\*) \*\*-\*\*. doi: 10.14252/foodsafetyfscj.2018014

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Cr(VI), ppm

Cr(VI), ppm

0

20

### 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)

Hexaval anthropogu [IARC, 19 centrations age ~0.00 which is standard o set based rat study.]

- **Duodenal MN assays** 
  - Neg after 7 and 90 days of exposure
- Duodenal y-H2AX immunostaining •
  - No diff from controls at 7 and 90 days of exposure •
- kras codon 12 GAT MF in duodenum ۰
  - 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 •

