Tox Strategies

Hexavalent Chromium New and Emerging Science and Other Comments:
IRIS Public Meeting SR Protocol

Deborah Proctor
Managing Principal Health Scientist
Orange County, California
Consultant to EPRI and American Chemistry Council

New Transcriptomic Analysis—Rager et al. 2019 *Toxicology Letters*

Transcriptomic analysis to assess mechanisms underlying lung cancer associated with Cr(VI)

- Identify biological pathways consistently modulated by Cr(VI) using compilation of published transcriptomic data
- Assess epigenetic regulators and transcriptomic responses
- Results:
  - Pathway enrichment identified commonly modulated genes, cytotoxicity and cell proliferation highly enriched, general suppression of DNA damage repair
  - Alterations predicted to be by DNA methylation, histone modifications and micro RNAs

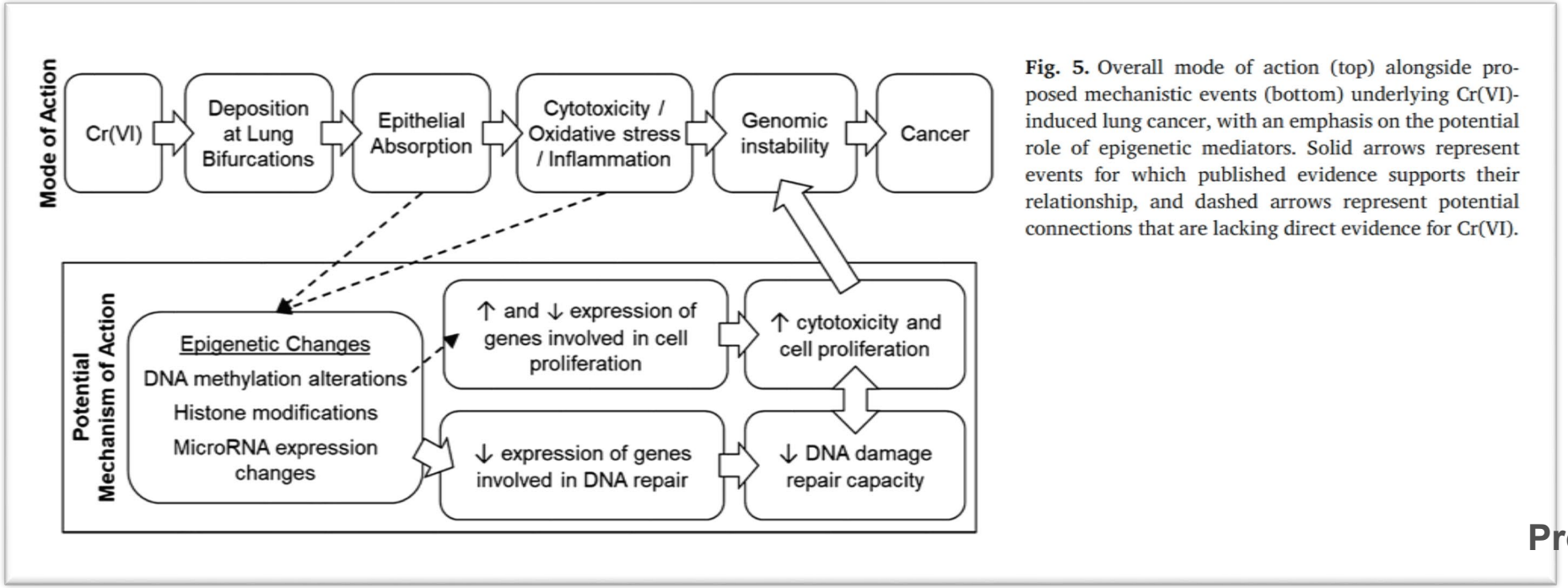


Fig. 5. Overall mode of action (top) alongside proposed mechanistic events (bottom) underlying Cr(VI)-induced lung cancer, with an emphasis on the potential role of epigenetic mediators. Solid arrows represent events for which published evidence supports their relationship, and dashed arrows represent potential connections that are lacking direct evidence for Cr(VI).

Study not in HERO

Project funded by EPRI

New Systematic Review and Meta Analysis for Stomach Cancer —Suh et al. 2019 *Critical Reviews in Toxicology*

Assess risk of mortality and morbidity from stomach cancer in humans and animals exposed to Cr(VI)

- Published protocol in PROSPERO
- Critical appraisal of internal validity and qualitative integration by NTP OHAT approach
- Only human occupational data could be assessed in meta analysis
- Meta RR of 1.08 (95% CI: 0.96-1.21) with all studies, excluding those with high risk of bias resulted in meta RR of 1.03 (95% CI: 0.84-1.26)
- Combining streams of evidence per OHAT, Cr(VI) does not pose a stomach cancer hazard in humans

OHAT Framework: Step 6 - Translate Confidence Ratings into Level of Evidence of Health Effects					Application of OHAT to Cr(VI)-Stomach Cancer Evidence Base		OHAT Framework: Step 7 - Integrate Evidence to Develop Hazard Identification Conclusions	Cr6-Stomach Cancer Evidence Base	
Confidence in the Body of Evidence		*Direction of effect or no effect*		*Level of Evidence for Health Effect*	*Human Data*	*Animal Data*		Effect/No Effect Level of Evidence by Stream	Overall
(++++) High	➡	Health effect/ No effect	➡	High	Low to moderate confidence in body of evidence demonstrating "no effect" between Cr(VI) exposure and stomach cancer (primarily supported by no increased risk in meta-analyses)	High confidence in the body of evidence demonstrating "no effect" between Cr(VI) ingestion and stomach cancer	Health Effects: • Known to be a hazard • Presumed to be a hazard • Suspected to be a hazard • Not classifiable to be a hazard No Effect • Not identified to be a hazard; inadequate to determine hazard to humans	Human: not identified/not classifiable to be a hazard to humans	Not identified to be stomach cancer hazard to humans
(+++) Moderate	➡	Health effect/ No effect	➡	Moderate					
(++) Low	➡	Health effect/ No effect	➡	Low				Animal: not identified to be a hazard	
(+) Very low or no evidence identified	➡	Health effect/ No effect	➡	Inadequate					

Figure 6. Application of the NTP OHAT (2015) framework of systematic review and evidence integration for developing hazard identification conclusions.

Study not in HERO

Project funded by EPRI

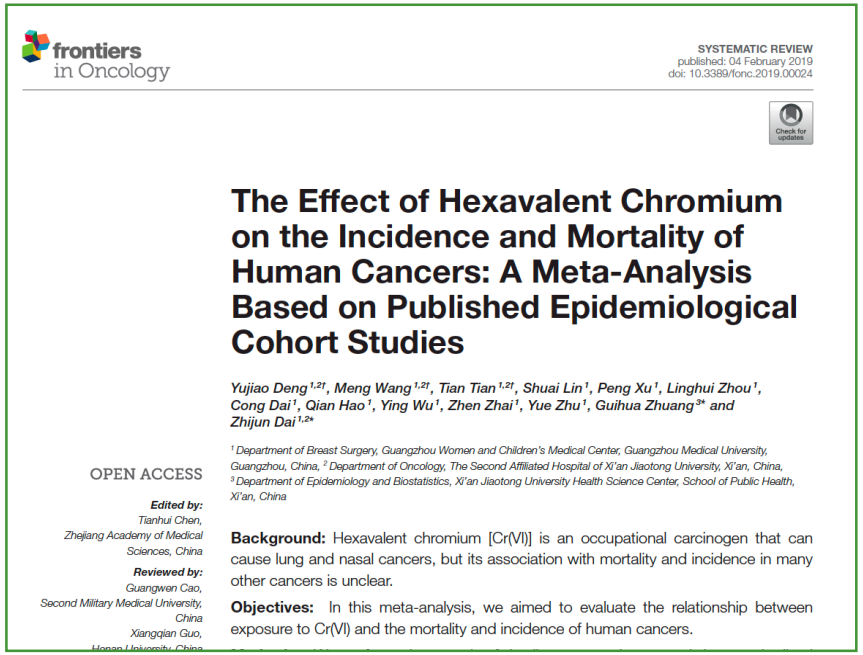
New Systematic Review and Meta Analysis of Occ Epi—Deng et al. 2019 *Frontiers in Oncology*

Not all Systematic Reviews follow Guidelines

- Claims to have used PRISMA-P, but no evidence of an *a priori* protocol
- No risk of bias assessment, although NOS scores provided, but with no description of how they were reached
- Significant quality control issues readily apparent to knowledgeable reviewer

Importance of Selecting and Correctly Executing Inclusion/Exclusion Criteria

- Deng included overlapping populations from many studies (e.g., Painesville cohort included multiple times)
- Not excluding studies with confounding exposures such as asbestos
- Use of Fixed Effects Model over Random Effects Model
- Heterogeneity not adequately addressed (large I^2 values, many at >80%)



frontiers in Oncology

SYSTEMATIC REVIEW
published: 04 February 2019
doi: 10.3389/fonc.2019.00024

Check for updates

The Effect of Hexavalent Chromium on the Incidence and Mortality of Human Cancers: A Meta-Analysis Based on Published Epidemiological Cohort Studies

Yujiao Deng[1,2†], Meng Wang[1,2†], Tian Tian[1,2†], Shuai Lin[1], Peng Xu[1], Linghui Zhou[1], Cong Dai[1], Qian Hao[1], Ying Wu[1], Zhen Zhai[1], Yue Zhu[1], Guihua Zhuang[3] and Zhijun Dai[1,2*]*

[1] Department of Breast Surgery, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China, [2] Department of Oncology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [3] Department of Epidemiology and Biostatistics, Xi'an Jiaotong University Health Science Center, School of Public Health, Xi'an, China

OPEN ACCESS

Edited by:
Tianhui Chen,
Zhejiang Academy of Medical Sciences, China

Reviewed by:
Guangwen Cao,
Second Military Medical University, China
Xiangqian Guo,

Background: Hexavalent chromium [Cr(VI)] is an occupational carcinogen that can cause lung and nasal cancers, but its association with mortality and incidence in many other cancers is unclear.

Objectives: In this meta-analysis, we aimed to evaluate the relationship between exposure to Cr(VI) and the mortality and incidence of human cancers.

Study in HERO

Deng et al. reports significant increased risk of stomach cancer incidence, contrary to findings of Suh et al. (2019), because large study of cement workers included in one and excluded in other. Excluded in Suh because of stated co-exposure to asbestos, arsenic and radiation.

How will Published Systematic Reviews and Meta-Analyses be Used by EPA in the Assessment?

Meta analyses review data, but provide new quantitative data from the analysis presented

- No PECO criteria for assessment in protocol
- Inclusion/Exclusion criteria are critical to the outcome, especially for Cr(VI)-exposed worker studies because of the wide spectrum of possible exposures, co-exposures to lung carcinogens, and lack of clarity in some studies as to the forms of Cr exposure
- Lack of clarity as to what is included and considered, and what is not in EPA's SR protocol

Systematic reviews are a significant effort when performed thoughtfully and rigorously executed

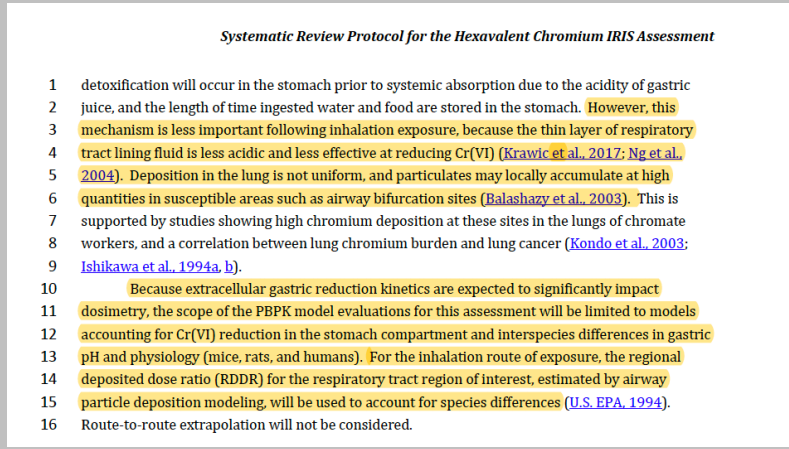
- Applaud EPA's efforts in this regard!
- How can the Agency judge and use what already exists in the literature?
- Its not clear if/how they will be used in the protocol, recommend assessing systematic reviews and meta-analyses that meet established criteria to expedite process.

Applaud use of PBPK modeling of GI, Recommend considerations for inhalation

Agency has focused PBPK modeling efforts exclusively on oral exposure without transparent review of options for modeling the lung as well

- Information exists to model kinetics and tissue dose in the lung, similar to GI
  - MODELS: O'Flaherty 2001 lung model and lung particle deposition models exist
  - DATA: Individual-level data for worker exposures and ADME for lung from animal models exists
- **Why needed?** Linear extrapolation of risks from former chromate producing industry workers may result in unrealistic risk estimates at current environmental exposures which are ~ million times lower in concentration
- Support for non-mutagenic MOA and non-linearity in low dose range:
- Both animal and human data support that lung cancer is associated with high exposures that caused respiratory irritation and tissue damage
  - Dose-rate effect in animals and humans
  - Evidence supports tissue dose is a key dose metric with less soluble (more persistent) forms of Cr(VI) exerting greater carcinogenic potential
- Consideration of approach used by TCEQ 2014
- **We are currently working on producing reduction rate data for lung epithelial lining fluid to support modeling and MOA**

Discussed in Proctor et al. 2014 *Toxicology*

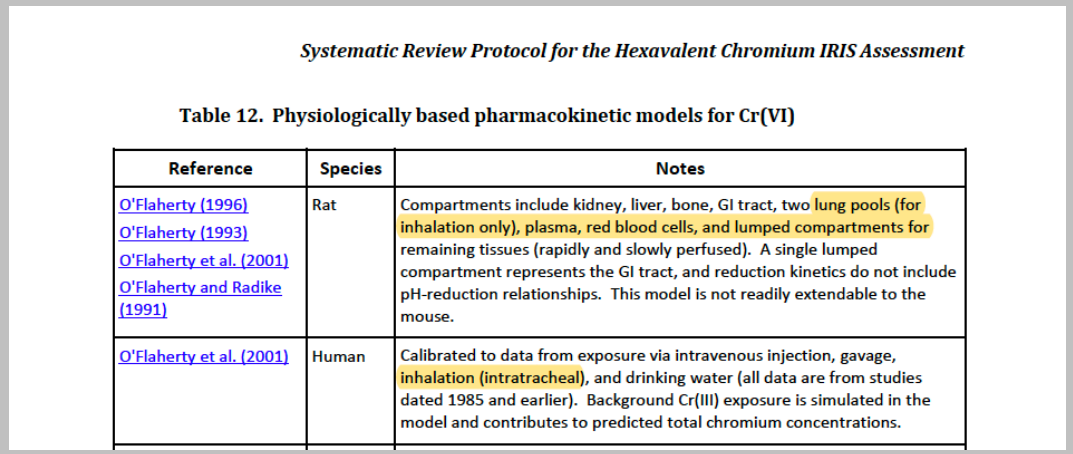


Systematic Review Protocol for the Hexavalent Chromium IRIS Assessment

detoxification will occur in the stomach prior to systemic absorption due to the acidity of gastric juice, and the length of time ingested water and food are stored in the stomach. However, this mechanism is less important following inhalation exposure, because the thin layer of respiratory tract lining fluid is less acidic and less effective at reducing Cr(VI) (Krawic et al., 2017; Ng et al., 2004). Deposition in the lung is not uniform, and particulates may locally accumulate at high quantities in susceptible areas such as airway bifurcation sites (Balashazy et al., 2003). This is supported by studies showing high chromium deposition at these sites in the lungs of chromate workers, and a correlation between lung chromium burden and lung cancer (Kondo et al., 2003; Ishikawa et al., 1994a, b).

Because extracellular gastric reduction kinetics are expected to significantly impact dosimetry, the scope of the PBPK model evaluations for this assessment will be limited to models accounting for Cr(VI) reduction in the stomach compartment and interspecies differences in gastric pH and physiology (mice, rats, and humans). For the inhalation route of exposure, the regional deposited dose ratio (RDDR) for the respiratory tract region of interest, estimated by airway particle deposition modeling, will be used to account for species differences (U.S. EPA, 1994).

Route-to-route extrapolation will not be considered.



Systematic Review Protocol for the Hexavalent Chromium IRIS Assessment

Table 12. Physiologically based pharmacokinetic models for Cr(VI)

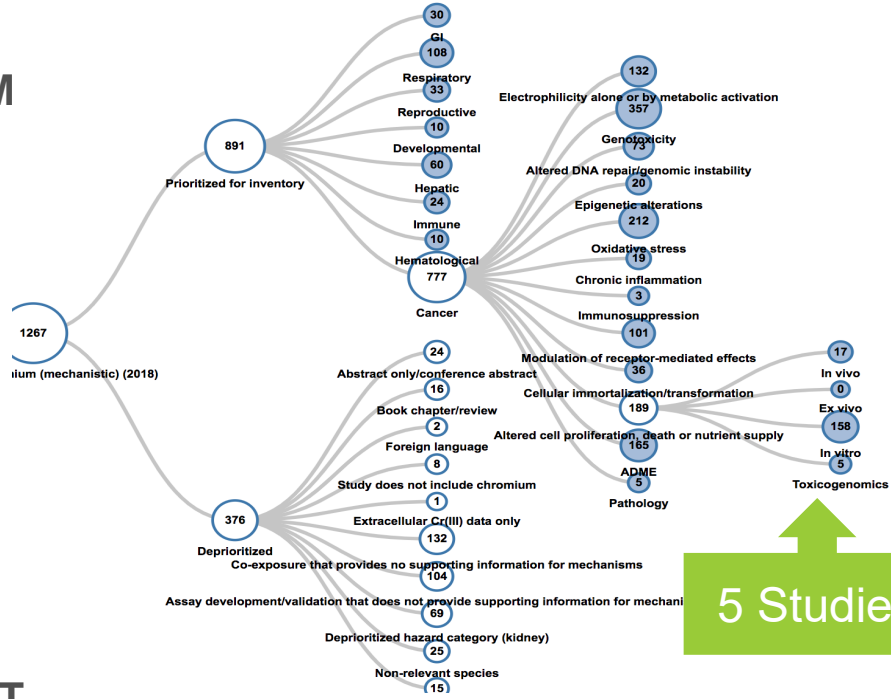
Reference	Species	Notes
O'Flaherty (1996) O'Flaherty (1993) O'Flaherty et al. (2001) O'Flaherty and Radike (1991)	Rat	Compartments include kidney, liver, bone, GI tract, two lung pools (for inhalation only), plasma, red blood cells, and lumped compartments for remaining tissues (rapidly and slowly perfused). A single lumped compartment represents the GI tract, and reduction kinetics do not include pH-reduction relationships. This model is not readily extendable to the mouse.
O'Flaherty et al. (2001)	Human	Calibrated to data from exposure via intravenous injection, gavage, inhalation (intratracheal), and drinking water (all data are from studies dated 1985 and earlier). Background Cr(III) exposure is simulated in the model and contributes to predicted total chromium concentrations.

Lack of transparency on categorization and inclusion/exclusion of studies

The number of studies in HAWC has changed from the time that the protocol was released for comment

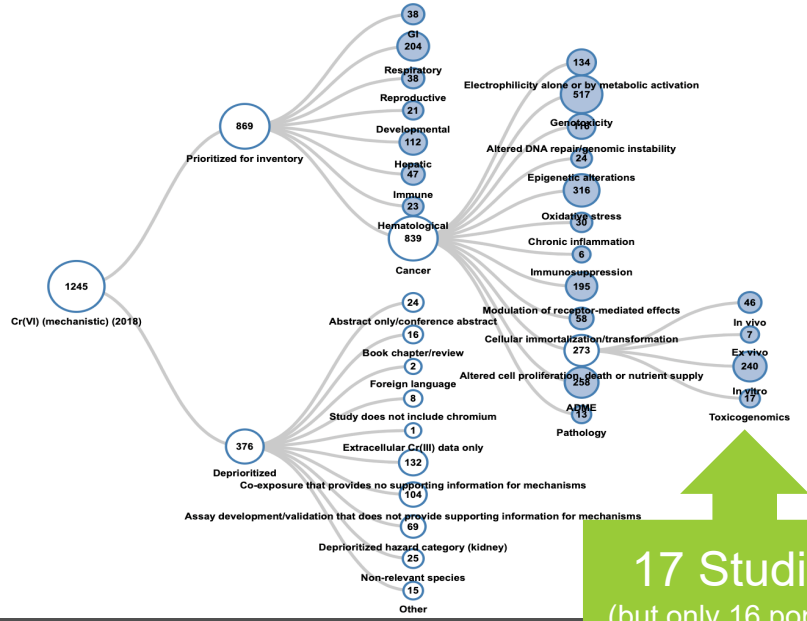
- **How will mechanistic studies be reviewed (no PECO)?**
- **When we download the Endnote library from HERO, there are no tags**
- **Lit search says through 5/2018 but there are 2019 papers in HERO, some papers included, some not…why?**
- **Download links on EPA-designated HAWC site do not populate studies**
- **How can the public comment on this?**

When Released in M



5 Studies

Yesterday at 5 pm PST



17 Studies
(but only 16 populate in visualization tool)

"PECO-P"?

- **Agree with PBPK modeling being used in the risk assessment, but it is not conventionally part of PECO**
- **Should PBPK be listed as a PECO element?**
- **What is the "evidence" to be assessed?**
- **If PBPK, then why not mechanistic data too?**
- **If PBPK, they why not Modes of Action?**
- ➢ **How will mechanistic and mode of action data be assessed/scored?**

Table 5. Populations, exposures, comparators, and outcomes (PECO) criteria

PECO element	Evidence
Populations	**Human:** Any population and life stage (occupational or general population, including children and other potentially sensitive populations). **Animal:** Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages).
Exposures	**Human:** Any exposure to Cr(VI), including occupational exposures, via oral or inhalation routes. Exposures by the inhalation and oral routes may be assessed based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental or occupational-setting measures (e.g., air, water, dust levels), or job title or residence. Some relevant forms of compounds containing Cr(VI) (18540-29-9) are listed below: • Chromic acid (H_2CrO_4 [7738-94-5] and $H_2Cr_2O_7$ [13530-68-2]) • Salts of the chromate (CrO_4^{2-}) and dichromate ($Cr_2O_7^{2-}$) anions: Sodium chromate (7775-11-3), sodium dichromate (10588-01-9), sodium dichromate dihydrate (7789-12-0), potassium chromate (7789-00-6), potassium dichromate (7778-50-9) • Chromium(VI) trioxide (commonly referred to as chromium oxide [1333-82-0]) • Calcium chromate (13765-19-0) **Animal:** Any exposure to Cr(VI) via oral or inhalation routes based on administered dose or concentration. Cr(VI) may be administered orally via gavage or ad libitum in diet or drinking water. Cr(VI) may be administered by inhalation via whole-body or nose-only systems. Relevant forms of Cr(VI) are listed above. Animal studies involving exposures to mixtures will be included only if they include exposure to Cr(VI) alone.
Comparators	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of Cr(VI), or exposure to Cr(VI) for shorter periods of time. **Animal:** A concurrent control group exposed to vehicle-only treatment or an untreated control.
Outcomes	All cancer outcomes are considered; noncancer health outcomes are considered for the following potential target systems: respiratory, GI, hepatic, hematological, immunological, reproductive, or developmental effects. As discussed above, EPA anticipates that a systematic review for other health effect categories (e.g., nephrotoxicity, neurotoxicity) will not be undertaken unless a significant amount of new evidence is identified.
PBPK models	Studies describing PBPK models for Cr(VI) will be included.

Big Picture Comments

- The elephant in the room (more specifically in the protocol) is that there is no information about how mechanistic data and mode of action analysis will be reviewed, considered/scored, included/excluded.....I believe that is the most important issue for public comment
- There are several challenges that are recognized with the proposed systematic review for Cr(VI), and the protocol specifically, which make it incredibly frustrating to review and provide comments….It's not clear and not transparent
- Recommend that the the Agency focus review on mechanistic data in target tissue, mode of action, dose-response and risk assessment to reach a quantitative evaluation as expeditiously as possible