March 21, 2018

By email (thayer.kris@EPA.gov) and submission to EPA Docket Nos. EPA-HQ-ORD-2014-0313 and EPA-HQ-ORD-2010-0540

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RE: Draft IRIS Assessment of Hexavalent Chromium (Chromium VI)
Docket ID Nos. EPA-HQ-ORD-2014-0313 and EPA-HQ-ORD-2010-0540

Dear Dr. Thayer,

We recently learned from the EPA Office of Water that a draft IRIS assessment of hexavalent chromium (Cr(VI)) is expected to be publicly released by the end of 2018. To that end, we want to ensure that the IRIS office has been briefed on the most recent findings and publications by the Cr(VI) mode of action (MOA) study researchers, is familiar with all aspects of the MOA research, and considers the findings of this research, including the Cr(VI) genomics dataset, during the development of the toxicological review for oral exposure to Cr(VI). Thus, on behalf of the Hexavalent Chromium Panel of the American Chemistry Council (ACC), I write to request a stakeholder meeting as soon as possible to present an overview of the most recent publications by the MOA study researchers, including

- an integration of mechanistic and pharmacokinetic information to derive an oral reference dose and margin-of-exposure values for Cr(VI),
- an analysis of Eastmond's ten factors for considering the mode of action of Cr(VI)-induced gastrointestinal tumors in rodents, and
- a recovery study comparing the duodenal histopathology in mice following exposure to Cr(VI), captan, and folpet.

Additionally, we wish to review important information relevant to the Cr(VI) genomics dataset that was communicated to Dr. Lyle Burgoon prior to his departure from EPA.[1]

[1] This letter follows our most recent correspondence to EPA's IRIS program on October 16, 2017 and April 27, 2017, our February 4, 2016, correspondence to Vincent Cogliano, and an August 10, 2016 meeting between ACC, the MOA study researchers, and EPA's IRIS staff working on the Cr(VI) assessment.

I will be following up to schedule a meeting as soon as possible with you and other appropriate staff to discuss this information in detail. If you have any questions, please contact me at eileen_conneely@americanchemistry.com or at Ex. 6

Sincerely,

Eileen Conneely

Eileen Conneely, M.P.H., J.D.
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Attachment 1: Hexavalent Chromium Research MOA Study Published Papers
as of March 20, 2018.

cc:
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Attachment 1. Cr(VI) MOA Study Published Papers (updated March 20, 2018)

Overview

The Cr(VI) Mode of Action (MOA) Research Study was designed to understand how hexavalent chromium [Cr(VI)] in drinking water is associated with carcinogenesis in rats and mice. The project involved investigators from multiple institutions and conducted two 90-day drinking water studies, using the same mouse (B6C3F1) and rat (Fisher 344) strains used in the NTP study. The in-life portions of the study (i.e., the exposure, macro- and microscopic examinations, and some biochemical analyses) were conducted at the same research facility, Southern Research, that conducted the NTP study to further minimize inter-study variability. Histological lesions, biochemical analyses, toxicogenomic analyses, pharmacokinetic analyses, and mutational analyses were examined in the target tissues of interest, i.e., the small intestine and oral mucosa, of the mice and rats. In addition, in vitro cell culture studies were conducted to further inform the Cr(VI) MOA. The Cr(VI) MOA Research Study used the same concentrations of Cr(VI) in drinking water as the NTP study and also included lower Cr(VI) concentrations, which are more indicative of possible environmental exposures, such as U.S. drinking water.

See http://cr6study.info/ for more information on the MOA research.
Technical Contacts: ToxStrategies, Dr. Mark Harris (281-394-1567) or Dr. Chad Thompson (281-769-2195).

Publications (all open access)

1) Thompson, C.M., L.C. Haws, M.A. Harris, N.M. Gatto, and D.M. Proctor. 2011. Application of the U.S. EPA Mode of Action Framework for Purposes of Guiding Future Research: A Case Study Involving the Oral Carcinogenicity of Hexavalent Chromium. *Toxicological Sciences*. 119(1): 20-40. Manuscript: http://toxsci.oxfordjournals.org/content/119/1/20.full.pdf+html?sid=896b4c7e-b535-4884-aa79-261ecc512de8; Supplemental data: http://toxsci.oxfordjournals.org/content/119/1/20/suppl/DC1

2) Thompson, C.M., D.M. Proctor, L.C. Haws, C.D. Hébert, S.D. Grimes, H.G. Shertzer, A.K. Kopec, J.G. Hixon, T.R. Zacharewski, and M.A. Harris. 2011. Investigation of the Mode of Action Underlying the Tumorigenic Response Induced in B6C3F1 Mice Exposed Orally to Hexavalent Chromium. *Toxicological Sciences*. 123(1): 58-70. Manuscript: http://toxsci.oxfordjournals.org/content/123/1/58.full.pdf+html?sid=d185e9e8-71d0-415b-9e2d-97ca5844207c; Supplemental data: http://toxsci.oxfordjournals.org/content/123/1/58/suppl/DC1

3) Thompson, C.M., D.M. Proctor, M. Suh, L.C. Haws, C.D. Hébert, J.F. Mann, H.G. Shertzer, J.G. Hixon, and M.A. Harris. 2011. Comparison of the Effects on Hexavalent Chromium in the Alimentary Canal of F344 rats and B6C3F1 Mice Following Exposure in Drinking Water: Implications for Carcinogenic Modes of Action. *Toxicological Sciences.* 125(1): 79-90. Manuscript: http://toxsci.oxfordjournals.org/content/125/1/79.full.pdf+html?sid=d7c79f9a-4b38-46d1-953e-81449fd02eae; Supplemental data: http://toxsci.oxfordjournals.org/content/125/1/79/suppl/DC1

4) Thompson, C.M., D.M. Proctor, and M.A. Harris. 2012. Duodenal GSH/GSSG Ratios in Mice Following Oral Exposure to Cr(VI). *Toxicological Sciences.* 126(1): 287-288. Letter to Editor: http://toxsci.oxfordjournals.org/content/126/1/287.full.pdf+html

5) Kopec, A.K., S. Kim, A.L. Forgacs, T.R. Zacharewski, D.M. Proctor, M.A. Harris, L.C. Haws, and C.M. Thompson. 2012. Genome-wide gene expression effects in B6C3F1 mouse intestinal epithelia following 7 and 90 days of exposure to hexavalent chromium in drinking water. *Toxicology and Applied Pharmacology.* 259(1): 13-26. Manuscript: http://www.sciencedirect.com/science/article/pii/S0041008X11004480;

6) Kopec, A.K., C.M. Thompson, S. Kim, A.L. Forgacs, and T.R. Zacharewski. 2012. Comparative toxicogenomic analysis of oral Cr(VI) exposure effects in rat and mouse small intestinal epithelia. *Toxicology and Applied Pharmacology*. 262(2): 124-138. http://www.sciencedirect.com/science/article/pii/S0041008X12001731

7) Thompson, C.M., J.G. Hixon, D.M. Proctor, L.C. Haws, M. Suh, J.D. Urban, and M.A. Harris. 2012. Assessment of Genotoxic Potential of Cr(VI) in the Mouse Duodenum: An In Silico Comparison with Mutagenic and Nonmutagenic Carcinogens Across Tissues. *Regulatory Toxicology and Pharmacology*. 64(1): 68-76. http://www.sciencedirect.com/science/article/pii/S0273230012001134?v=s5

8) Proctor, D., M. Suh, L.L. Aylward, C.R. Kirman, M.A. Harris, C.M. Thompson, H. Gürleyük, R. Gerads, L.C. Haws, and S.M. Hays. 2012. Hexavalent Chromium Reduction Kinetics in Rodent Stomach Contents. *Chemosphere*. 89 (5): 487-493. http://www.sciencedirect.com/science/article/pii/S0045653512005978.

9) Thompson, C.M., Y. Federov, D.D. Brown, M. Suh, D.M. Proctor, L. Kuriakose, L.C. Haws, and M.A. Harris. 2012. Assessment of Cr(VI)-Induced Cytotoxicity and Genotoxicity Using High Content Analysis. *PLoS ONE*. 7(8): e42720. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0042720

10) Kirman, C.R., S.M. Hays, L.L. Aylward, M. Suh, M.A. Harris, C.M. Thompson, L.C. Haws, and D.M. Proctor. 2012. Physiologically Based Pharmacokinetic Model for Rats and Mice Orally Exposed to Chromium. *Chemico-Biological Interactions*. 200(1): 45-64. http://www.sciencedirect.com/science/article/pii/S0009279712001548?v=s5

11) Thompson, C.M., D.M. Proctor, M. Suh, L.C. Haws, C.R. Kirman, and M.A. Harris. 2013. Assessment of the Mode of Action Underlying Development of Rodent Small Intestinal Tumors Following Oral Exposure to Hexavalent Chromium and Relevance to Humans. *Critical Reviews in Toxicology*. 43(3): 244-274. http://informahealthcare.com/doi/abs/10.3109/10408444.2013.768596

12) Kirman, C.R., L.L. Aylward, M. Suh, M.A. Harris, C.M. Thompson, L.C. Haws, D.M. Proctor, W. Parker, and S.M. Hays. 2013. Physiologically Based Pharmacokinetic Model for Humans Orally Exposed to Chromium. *Chemico-Biological Interactions.* 204(1): 13-27. http://www.sciencedirect.com/science/article/pii/S0009279713000823

13) O'Brien, T.J., H. Ding, M. Suh, C.M. Thompson, B.L. Parsons, M.A. Harris, L.C. Haws, W.A. Winkelman, J.C. Wolf, J.G. Hixon, A.M. Schwartz, M.B. Myers, L.C. Haws, and D.M. Proctor. 2013. Assessment of K-*Ras* mutant frequency and micronucleus incidence in the mouse duodenum following 90-days of exposure to Cr(VI) in drinking water. *Mutation Research.* 754: 15-21. http://www.sciencedirect.com/science/article/pii/S1383571813000752

14) Thompson, C.M., C.R. Kirman, D.M. Proctor, L.C. Haws, M. Suh, S.M. Hays, and M.A. Harris. 2014. A Chronic Oral Reference Dose for Hexavalent Chromium—Induced Intestinal Cancer. *Journal of*

Applied Toxicology. 34: 525-536. http://onlinelibrary.wiley.com/doi/10.1002/jat.2907/pdf; Supplemental Information: http://onlinelibrary.wiley.com/store/10.1002/jat.2907/asset/supinfo/jat_2907_Supplemental%20Material_Appendices.docx?v=1&s=64762ef5f64f32afac1581e845f27ebcc9eeed1e

15) Suh, M., C.M. Thompson, C.R. Kirman, M.C. Carakostas, L.C. Haws, M.A. Harris, and D.M. Proctor. 2014. High Concentrations of Hexavalent Chromium in Drinking Water Alter Iron Homeostasis in F344 Rats and B6C3F1 Mice. *Food and Chemical Toxicology.* 65: 381-388. Manuscript: http://www.sciencedirect.com/science/article/pii/S027869151400012X; Supplemental data: http://www.sciencedirect.com/science/MiamiMultiMediaURL/1-s2.0-S027869151400012X/1-s2.0-S027869151400012X-mmc1.docx/271257/FULL/S027869151400012X/5820684ed005bb81f0302625060aa258/mmc1.docx

16.) Thompson, C.M., J. Seiter, M.A. Chappell, R.V. Tappero, D.M. Proctor, M. Suh, J.C. Wolf, L.C. Haws, R. Vitale, L. Mittal, C.R. Kirman, S.M. Hays, and M.A. Harris. 2015. Synchrotron-Based Imaging of Chromium and c-H2AX Immunostaining in the Duodenum Following Repeated Exposure to Cr(VI) in Drinking Water. *Toxicological Sciences.* 143(1): 16-25. http://toxsci.oxfordjournals.org/content/early/2014/10/31/toxsci.kfu206.full.pdf+html

17) Thompson, C.M., J.C. Wolf, R.H. Elbekai, M.G. Paranjpe, J.M. Seiter, M.A. Chappell, R.V. Tappero, M. Suh, D.M. Proctor, A. Bichteler, L.C. Haws, and M.A. Harris. 2015. Duodenal crypt health following exposure to Cr(VI): micronucleus scoring, γ-H2AX immunostaining, and synchrotron X-ray fluorescence microscopy. *Mutation Research.* 789-790, 61-66. http://www.sciencedirect.com/science/article/pii/S1383571815001205

18) Cullen, J.M., J.M. Ward, and C.M. Thompson. 2015. Reevaluation and classification of duodenal lesions in B6C3F1 mice and F344 rats from 4 studies of hexavalent chromium in drinking water. *Toxicologic Pathology.* 44(2): 279-289. http://tpx.sagepub.com/content/early/2015/11/13/0192623315611501.full.pdf

19) Thompson, C.M., A. Bichteler, J. Rager, M. Suh, D. Proctor, L. Haws, and M. Harris. 2016. Comparison of In Vivo Genotoxic and Carcinogenic Potency to Augment Mode of Action Analysis: Case Study with Hexavalent Chromium, *Mutation Research.* 800-801: 28-34. http://www.sciencedirect.com/science/article/pii/S1383571815300334

20) Thompson, C.M., J.E. Rager, M. Suh, C.L. Ring, D.M. Proctor, L.C. Haws, R.C. Fry, and M.A. Harris. 2016. Transcriptomic responses in the oral cavity of F344 rats and B6C3F1 mice following exposure to Cr(VI): Implications for risk assessment. *Environmental and Molecular Mutagenesis.* 57(9): 706-716. http://onlinelibrary.wiley.com/doi/10.1002/em.22064/epdf

21) De Flora, S., A. Camoirano, R.T. Micale, S. La Maestra, V. Savarino, P. Zentilin, E. Marabotto, M. Suh, and D.M. Proctor. 2016. Reduction of hexavalent chromium by fasted and fed human gastric fluid. I. Chemical reduction and mitigation of mutagenicity. *Toxicology and Applied Pharmacology.* 306: 113-119. http://www.sciencedirect.com/science/article/pii/S0041008X16301788?via%3Dihub

22) Kirman, C.R., M. Suh, S.M. Hays, H. Gurleyuk, R. Gerads, S. De Flora, W. Parker, S. Lin, L.C. Haws, M.A. Harris, and D.M. Proctor. 2016. Reduction of hexavalent chromium by fasted and fed human gastric fluid. II. Ex vivo gastric reduction modeling. *Toxicology and Applied Pharmacology.* 306: 120-133. http://www.sciencedirect.com/science/article/pii/S0041008X16301764?via%3Dihub

23) Rager, J.E., C.L. Ring, R.C. Fry, M. Suh, D.M. Proctor, L.C. Haws, M.A. Harris, and C.M. Thompson. 2017. High-throughput screening data interpretation in the context of in vivo transcriptomic

responses to oral Cr(VI) exposure. *Toxicological Sciences.* 158(1): 199-212. https://academic.oup.com/toxsci/article-lookup/doi/10.1093/toxsci/kfx085

24) Kirman, C.R., M. Suh, D.M. Proctor, and S. Hays. 2017. Improved physiologically based pharmacokinetic model for oral exposures to chromium in mice, rats, and humans to address temporal variation and sensitive populations. *Toxicology and Applied Pharmacology.* 325: 9-17. http://www.sciencedirect.com/science/article/pii/S0041008X17301370?via%3Dihub

25) Thompson, C.M., M. Suh, D.M. Proctor, L.C. Haws, and M.A. Harris. 2017. Ten factors for considering the mode of action of Cr(VI)-induced gastrointestinal tumors in rodents. *Mutation Research.* 823: 45-57. https://www.sciencedirect.com/science/article/pii/S1383571817301365

26) Thompson, C.M., J. Wolf, A. McCoy, M. Suh, D.M. Proctor, C. Kirman, L.C. Haws, and M.A. Harris. 2017. Comparison of toxicity and recovery in the duodenum of B6C3F1 mice following treatment with intestinal carcinogens captan, folpet, and hexavalent chromium. *Toxicologic Pathology.* 45(8): 1091-1101. http://journals.sagepub.com/doi/10.1177/0192623317742324

27) Thompson, C.M., C.R. Kirman, S. Hays, M. Suh, S. Harvey, J.E. Rager, L.C. Haws, and M.A. Harris. 2018. Integration of mechanistic and pharmacokinetic information to derive oral reference dose and margin-of-exposure values for hexavalent chromium. *Journal of Applied Toxicology.* 38: 351-365. https://onlinelibrary.wiley.com/doi/full/10.1002/jat.3545

Papers on Cr6 Supported by sponsors other than ACC

28) Proctor, D.M., M. Suh, S.L. Campleman, and C.M. Thompson. 2014. Assessment of the mode of action for hexavalent chromium-induced lung cancer following inhalation exposures. *Toxicology*. 325: 160-179. http://www.sciencedirect.com/science/article/pii/S0300483X14001681

29) Thompson, C.M., R.R. Young, M. Suh, H. Dinesdurage, R.H. Elbekai, M.A. Harris, A.C. Rohr, and D.M. Proctor. 2015. Assessment of the mutagenic potential of Cr(VI) in the oral mucosa of Big Blue® transgenic F344 rats. *Environmental and Molecular Mutagenesis*. 56: 621-628. http://onlinelibrary.wiley.com/doi/10.1002/em.21952/abstract

30) Young, R.R., C.M. Thompson, H.R. Dinesdurage, R.H. Elbekai, M. Suh, A.C. Rohr, and D.M. Proctor. 2015. A robust method for assessing chemically induced mutagenic effects in the oral cavity of transgenic Big Blue(R) rats. *Environmental and Molecular Mutagenesis.* 56: 629-636. http://onlinelibrary.wiley.com/doi/10.1002/em.21951/abstract

31) Proctor, D.M., M. Suh, L. Mittal, S. Hirsch, R.V. Salgado, C. Bartlett, C. Van Landingham, A. Rohr, and K. Crump. 2016. Inhalation cancer risk assessment of hexavalent chromium based on updated mortality for Painesville chromate production workers. *Journal of Exposure Science and Environmental Epidemiology*. 26: 224-231. http://www.nature.com/jes/journal/vaop/ncurrent/full/jes201577a.html

32) Thompson, C.M., R.R. Young, H. Dinesdurage, M. Suh, M.A. Harris, A.C. Rohr, and D.M. Proctor. 2017. Assessment of the mutagenic potential of hexavalent chromium in the duodenum of Big Blue® rats. *Toxicology and Applied Pharmacology* 330: 48-52. http://www.sciencedirect.com/science/article/pii/S0041008X1730282X