



June 19, 2018

Kristina Thayer, Ph.D.  
Director, Integrated Risk Information System (IRIS)  
National Center for Environmental Assessment  
USEPA Headquarters  
Ariel Rios Building 1200 Pennsylvania Avenue, N.W.  
**Mail Code:** 8601P  
Washington, DC 20460

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

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,

Following up on my correspondence from March 21, 2018 and April 30, 2018, the American Chemistry Council's (ACC) Hexavalent Chromium Panel (Panel) has concerns about how the IRIS program will incorporate the large toxicogenomics dataset sponsored by the Panel into the assessment of hexavalent chromium [Cr(VI)]. The mode of action (MOA) researchers communicated with Dr. Lyle Burgoon, formerly at EPA, from 2014 – 2016 concerning this Cr(VI) toxicogenomics dataset, and in my last correspondence I requested a meeting with EPA to discuss the following concerning use of the dataset to inform the MOA for tumors observed in a 2-year rodent cancer bioassay:

1. A timeline of events relevant to the Cr(VI) genomics data;
2. An explanation for the varying number of microarrays available through different online data repositories; and
3. A general findings comparison between published analyses.

Since the IRIS program has declined my request for a meeting, we are submitting this information into the docket for the Cr(VI) IRIS assessment.



**Timeline of events relevant to Cr(VI) genomics data**

Table 1 summarizes the timeline of events surrounding the Cr(VI) genomics data and clarifies any potential discrepancies between data repositories over time and differences in analysis strategies used in different publications.

**Table 1. Timeline summarizing events involved in the Cr(VI) genomics dataset.**

DATE	EVENT	RELEVANT WEBSITE <sup>1</sup>
2012	Two studies were published using: <ol style="list-style-type: none"> <li>1. Mouse duodenum and jejunum data (Kopec et al. 2012a)</li> <li>2. Mouse and rat duodenum and jejunum data (Kopec et al. 2012b).</li> </ol> Data from manuscripts were deposited in dbZach, an internal data management system that is compliant with the Minimum Information About a Microarray Experiment (MIAME) standard (Burgoon et al. 2006).	dbZach
2014	Data were provided online through Cr6study.info. Data included: <ol style="list-style-type: none"> <li>1. <u>qRT-PCR data used in the Kopec (2012a,b) publications</u></li> <li>2. <u>Raw genomics microarray data used in the Kopec (2012a,b) publications</u> <ul style="list-style-type: none"> <li>• All raw microarray data (as .gpr files) for the mice and rat, oral palate, duodenum, and jejunum (day 8 and 91), alongside a metadata file</li> </ul> </li> <li>3. <u>Genomics analysis code used in the Kopec (2012a,b) publications</u> <ul style="list-style-type: none"> <li>• Note that this analysis included data from both array dyes (Cy3 and Cy5) and data were processed using in-house code and algorithms, which are provided in Cr6study.info, and include:               <ul style="list-style-type: none"> <li>○ SAS code used to analyze microarray data (note: input files with appropriate tags referred to in the code were not originally provided – see 2018 update)</li> <li>○ R code to calculate P1(t) statistics</li> </ul> </li> </ul> </li> <li>4. <u>Genomics analysis statistical results used in the Kopec (2012a,b) publications</u> <ul style="list-style-type: none"> <li>• Excel worksheets containing all array probesets and their corresponding fold change values and P1(t) statistical results for the rat and mouse, duodenum and jejunum, at day 8 and 91</li> </ul> </li> </ol>	Cr6study.info
APRIL 2016	A labeling error was identified in the raw genomics data for the rat within the files in Cr6study.info.	Cr6study.info



DATE	EVENT	RELEVANT WEBSITE <sup>1</sup>
	<ul style="list-style-type: none"> <li>Specifically, incorrect probeset identifiers were included in the rat raw array data files (.gpr files). These identifiers were corrected, and Dr. Burgoon was notified of this edit via email on January 8, 2016 and April 5, 2016 (see ATTACHMENT A)</li> <li>This labeling error had no effect on the analyses or interpretation reported in Kopec et al. (2012b)</li> </ul>	
<b>AUGUST 2016</b>	ToxStrategies received a request from Stiven Foster at the US EPA to access data from the Cr6study.info website. Access was granted on August 10, 2016 (see ATTACHMENT A).	Cr6study.info
<b>SEPTEMBER 2016</b>	<p>All raw and processed array files were uploaded into the NCBI's Gene Expression Omnibus (GEO) repository. These data included:</p> <ul style="list-style-type: none"> <li>All raw microarray files</li> <li>Processed array data, consisting of quantile normalized expression data derived from the Cy3 array signal. Note: these processed array data were updated in 2016 and differ from those used in the Kopec (2012a,b) publications. Updated results from these data were published (Thompson et al. 2016, Rager et al. 2017, described below)</li> </ul> <p>Data were uploaded alongside a reference to the Thompson et al. (2016) publication (final publication on November 2016, below)</p>	GEO
<b>NOVEMBER 2016</b>	A study was published using the mouse and rat palate data (Thompson et al. 2016), using the updated array processing strategy provided in GEO.	GEO
<b>MAY 2017</b>	A study was published using the mouse duodenum data (Rager et al. 2017), using the updated array processing strategy provided in GEO.	GEO
<b>FEBRUARY 2018</b>	The GEO posting was updated to include additional citation information, referencing Rager et al. (2017).	GEO
<b>FEBRUARY 2018</b>	The link to the raw microarray files was temporarily not working through Cr6study.info. This link was corrected.	Cr6study.info
<b>FEBRUARY 2018</b>	<p>More data were provided to further support the analysis conducted in the Kopec (2012a,b) publications.</p> <ul style="list-style-type: none"> <li>To detail, the original SAS code used in the genomics statistical analysis was originally provided in the 2014 data upload. This update added the specific input files that were used to execute the SAS code.</li> </ul>	Cr6study.info



<sup>1</sup> website URLs are Cr6study.info (<https://cr6study.info>), dbZach (<http://dbzach.fst.msu.edu/>), GEO (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE87262>).

### Explanation for varying numbers of arrays on different websites

The number of array samples included at Cr6study.info, representing the analysis published in the Kopec et al. (2012a,b) publications, differs slightly from the number of array samples included in the GEO repository, representing the analyses published in the recent publications (Rager et al. 2017, Thompson et al. 2016). Specifically, the arrays in **Table 2** were excluded from the GEO repository.

**Table 2. Arrays that are included in Cr6study.info but excluded in the GEO repositories.**

GPR file	Species, Tissue, and Duration Group	Array Components <sup>1</sup>	Note
4417.gpr	Mouse duodenum day 91	Cy3 signal: animal ID 3426, control Cy5 signal: animal ID 3401, exposed at 4 mg/L dose	Duplicate
4418.gpr	Mouse duodenum day 91	Cy3 signal: animal ID 3401, exposed at 4 mg/L dose Cy5 signal: animal ID 3426, control	Duplicate
4451.gpr	Mouse duodenum day 91	Cy3 signal: animal ID 3416, exposed at 14 mg/L dose Cy5 signal: animal ID 3426, control	Technical replicate
4452.gpr	Mouse duodenum day 91	Cy3 signal: animal ID 3421, exposed at 60 mg/L Cy5 signal: animal ID 3426, control	Technical replicate
4453.gpr	Mouse duodenum day 91	Cy3 signal: animal ID 3409, exposed at 170 mg/L Cy5 signal: animal ID 3425, control	Technical replicate
4454.gpr	Mouse duodenum day 91	Cy3 signal: animal ID 3400, control Cy5 signal: animal ID 3404, exposed at 520 mg/L	Technical replicate

<sup>1</sup> Note that data from the Cy3 and Cy5 dye signals were used in the Kopec et al. (2012a,b) publications; while analyses only focused on data from the Cy3 dye signal in the Rager et al (2017) and Thompson et al. (2016) publications to minimize potential dye bias / interference issues.

These arrays in Table 2 were excluded from the GEO repository, reflective of the more recent Rager et al. (2017) publication, because these arrays represented duplicated data or technical replicates. Specifically, chip scan data in array IDs 4417 and 4418 were identified as duplicated data; thus both of these arrays were removed from the analysis. Array IDs 4451, 4452, 4453, and 4454 represented technical replicate arrays used for internal quality purposes. These arrays measured gene expression profiles of samples from animals that were already accounted for by



other arrays. Neither the Kopec et al. nor the Rager et al. analyses included technical replicate arrays.

The biological replicates were explained in the Rager et al. (2017) publication in the methods section:

*“RNA samples were assessed in biological triplicate in all dose groups (0, 0.03, 4, 14, 60, 170, and 520 mg/l SDD at day 8 and day 91) except for the 4 mg/l SDD exposure group from day 91, which was analyzed in biological duplicate due to potential microarray quality issues.”*

The arrays that were removed due to duplicate issues or represented technical replicates were excluded from the data in the GEO repository, to be consistent with the Rager et al. (2017) publication. The number of biological replicates used in this analysis is detailed in Table 3. All array data, including duplicate data/technical replicates, are included in Cr6study.info.

**Table 3. Biological replicate numbers in the GEO database, reflective of the array analysis in Rager et al. (2017).**

Duration Group	Species, Tissue	Dose (mg/L sodium dichromate dihydrate)							Total
		0	0.3	4	14	60	170	520	
8 days	Mouse, duodenum	3	3	3	3	3	3	3	21
91 days	Mouse, duodenum	3	3	2 <sup>1</sup>	3	3	3	3	20

<sup>1</sup> Note that the analyses conducted by Kopec et al. (2012a,b) contained one more biological replicate in this dose group.

### General comparison between publication findings

Genomics data analysis methods and standards have evolved over time. Thus, the data processing and statistical methods differed between the original publications using the Cr(VI) genomics data in the mouse duodenum (Kopec et al. 2012a,b) and more recent, updated publication (Rager et al. 2017); however, overall general findings remained consistent despite these varying approaches. For example, Kopec et al. 2012a, which focused on the mouse intestinal responses, identified genes involved in oxidative stress and cytotoxicity with altered expression, representing early key events. Other pathways noted as enriched included those involved in cell cycle, lipid metabolism, and immune response. Pathways involved in DNA repair were also noted in the day 8 results, including the nucleotide excision repair pathway, which did not show enrichment at day 91 (Kopec et al. 2012a). Similarly, Kopec et al. (2012b) noted pathways relevant to oxidative stress, immune response, protein synthesis, cell cycle/cell growth and proliferation, and DNA damage and repair in the mouse and rat duodenum and jejunum.

Similar results were apparent in the Rager et al. (2017) analysis focusing on the mouse duodenum, with pathways involved in cell stress and injury, cell death, and cell growth, proliferation and



development involved in early key events that were also sustained in the day 91 results. The nucleotide excision repair pathway was also identified as enriched in the day 8 results, but not the day 91 results; and it was noted that this pathway included eight genes showing increased expression associated with Cr(VI), all of which were involved in general DNA transcription and cell cycle signaling. Pathways involved in metabolism and immune response were also identified as enriched, similar to Kopec et al. (2012a). **In summary, analysis strategies have evolved over time surrounding the use of the Cr(VI) genomics data; still, general findings have remained consistent despite varying approaches.**

In conclusion, the raw and processed Cr(VI) genomics data are provided online, and the methods used to analyze these data have evolved over time to parallel ongoing advances in genomics-based assessments. This robust data set provides important information that can be used to further understand the MOA of Cr(VI). We have been fully transparent about the research conducted, including making the raw genomics data as well as other raw data available to EPA and other scientists.

If you have any questions, please contact me at [eileen\\_conneely@americanchemistry.com](mailto:eileen_conneely@americanchemistry.com) or at 202-249-6711.

Sincerely,

*Eileen Conneely*

Eileen Conneely, M.P.H., J.D.  
Director, Chemical Products & Technology Division  
American Chemistry Council

Attachment A: Email communication on updates to Cr6study.info genomics data

cc: C. Gibbons, [gibbons.catherine@epa.gov](mailto:gibbons.catherine@epa.gov)  
A. Sasso, [sasso.alan@epa.gov](mailto:sasso.alan@epa.gov)  
R. Yamada, [yamada.richard@epa.gov](mailto:yamada.richard@epa.gov)  
J. Orme-Zavaleta, [orme-zavaleta.jennifer@epa.gov](mailto:orme-zavaleta.jennifer@epa.gov)  
T. Bahadori, [bahadori.tina@epa.gov](mailto:bahadori.tina@epa.gov)  
E. Ohanian, [ohanian.edward@epa.gov](mailto:ohanian.edward@epa.gov)



ATTACHMENT A

**Email communication on  
updates to Cr6study.info  
genomics data**

**Subject:** Cr(VI) raw microarray data

**Date:** Thursday, March 13, 2014 at 12:37:11 PM Central Daylight Time

**From:** Apple-Mail=\_405249D0-D0F5-4909-96A9-35F59E23F6BE Mark Harris boundary=

**To:** Burgoon.Lyle@epa.gov

**CC:** Rusty Thomas, Tim Zacharewski, Gibbons.Catherine@epa.gov, Chad Thompson, Deb Proctor

Lyle: as I mentioned in the meeting on Monday, the data will be posted to our new Cr(VI) MOA website before SOT. Once the site is live I will send you all a link to it. You will be able to download the genomics data at that time.

The approach and methods that were used to analyze the data are adequately described in the Kopec papers. Our use of the genomics data to support the Mode of Action can be found in our Critical Reviews in Toxicology paper. Links to these Open Access papers can be found at the web page below:

[http://www.toxstrategies.com/publications/CRVI\\_MOA\\_study.htm](http://www.toxstrategies.com/publications/CRVI_MOA_study.htm)

mark

**From:** "Burgoon, Lyle" <[Burgoon.Lyle@epa.gov](mailto:Burgoon.Lyle@epa.gov)>

**Date:** March 12, 2014 at 8:43:16 AM CDT

**To:** "[cthompson@toxstrategies.com](mailto:cthompson@toxstrategies.com)" <[cthompson@toxstrategies.com](mailto:cthompson@toxstrategies.com)>

**Cc:** "[tzachare@msu.edu](mailto:tzachare@msu.edu)" <[tzachare@msu.edu](mailto:tzachare@msu.edu)>, "Gibbons, Catherine" <[Gibbons.Catherine@epa.gov](mailto:Gibbons.Catherine@epa.gov)>

**Subject:** Cr(VI) raw microarray data

Dr. Thompson,

It was nice seeing you and Dr. Harris (via video) at Monday's meeting @ NCEA HQ. I was quite pleased to hear Ms. Mason state that ACC expected the researchers would share their data and results with NCEA.

I'm following up on our discussion from Monday and am requesting access to all of your raw microarray data, as well as your analyzed data that supports the conclusions in your papers. In addition, it would be helpful if you could also supply us with the analysis code that was used, any protocols used for the analyses, and any other supporting documentation that may help us understand how the assays and analyses were performed.

For clarity, I am using the MIAME definition of <sup>3</sup>raw data<sup>2</sup>, and my request for the additional information is in line and keeping with the MIAME standard, which can be found here:

<http://www.mged.org/Workgroups/MIAME/miame.html>.

To facilitate data transfer, I can set-up an EPA-based FTP site where you can upload the data.

Thanks again for presenting your latest results to us, and I look forward to receiving the data.

Cheers,

Lyle

Lyle D. Burgoon, Ph.D  
National Center for Environmental Assessment  
Chief, Hazardous Pollutant Assessment Group (Acting)  
US Environmental Protection Agency  
Phone: 919.541.7808  
Fax: 919.685.3473  
Cell: **Ex. 6**

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**Mark Harris, Ph.D.**  
Principal Health Scientist

23123 Cinco Ranch Blvd, Suite 220  
Katy, TX 77494

Direct Dial: **Ex. 6**  
Houston Office: (281) 712-2062 Ext **Ex. 6**  
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fax: (832) 218-2756  
Email: [mharris@toxstrategies.com](mailto:mharris@toxstrategies.com)  
Website: <http://www.toxstrategies.com>

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**Subject:** Cr(VI) MOA Study Website

**Date:** Monday, March 24, 2014 at 8:34:03 AM Central Daylight Time

**From:** Apple-Mail=\_B33E4A44-0724-416B-A519-C1B4A7F9AE29 Mark Harris boundary=

**To:** Burgoon.Lyle@epa.gov

**CC:** Tim Zacharewski, Gibbons.Catherine@epa.gov, Chad Thompson, Rusty Thomas

Lyle: our Cr(VI) MOA study website is live. You can access it at [www.cr6study.info](http://www.cr6study.info)

Under the Study Data tab you can register to download data. Once registered, you will receive a password to access the data download portion of the site.

Not all of the genomics data you requested has been posted. Things that are not posted yet are:

1. Analysis Code
2. QRT-PCR data

These items will be added in the next few weeks.

mark

--

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### Mark Harris, Ph.D.

Principal Health Scientist

-----  
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Katy, TX 77494

Direct Dial: **Ex. 6**  
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Email: [mharris@toxstrategies.com](mailto:mharris@toxstrategies.com)  
Website: <http://www.toxstrategies.com>

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**Subject:** Re: Cr(VI) MOA Study Website  
**Date:** Thursday, April 3, 2014 at 3:07:45 PM Central Daylight Time  
**From:** Mark Harris  
**To:** Burgoon, Lyle  
**CC:** Gibbons, Catherine, Vandenberg, John, Flowers, Lynn

I will have to talk to our legal folks about this.

Back in touch shortly.

mark

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Principal Health Scientist

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Email: [mharris@toxstrategies.com](mailto:mharris@toxstrategies.com)  
Website: <http://www.toxstrategies.com>

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On Apr 3, 2014, at 2:59 PM, Burgoon, Lyle <[Burgoon.Lyle@epa.gov](mailto:Burgoon.Lyle@epa.gov)> wrote:

Hi Mark,

We cannot access the data at this time due to our inability to agree to the Terms and Conditions associated with data access found here: <http://cr6study.info/study-data/terms-and-conditions/>

Specifically, we request that ToxStrategies delete the indemnification clause in the Terms and Conditions. As written, the Agency cannot agree to the terms as it would be a violation of the Anti-Deficiency Act (i.e., making a commitment to an unknown future cost is a direct violation of the Anti-Deficiency Act).

Please let me know what action you are willing to take as soon as possible. As you are aware,

time is of the essence with respect to the Cr(VI) IRIS Assessment. Your prompt attention to this matter is appreciated.

Thanks,

Lyle

Lyle D. Burgoon, Ph.D  
Chief, Hazardous Pollutant Assessment Group (Acting)  
National Center for Environmental Assessment  
US Environmental Protection Agency  
Phone: 919.541.7808  
Fax: 919.685.3473  
Cell: **Ex. 6**

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**From:** Mark Harris [mailto:mharris@toxstrategies.com]  
**Sent:** Monday, March 24, 2014 9:34 AM  
**To:** Burgoon, Lyle  
**Cc:** Tim Zacharewski; Gibbons, Catherine; Chad Thompson; Thomas, Russell  
**Subject:** Cr(VI) MOA Study Website

Lyle: our Cr(VI) MOA study website is live. You can access it at [www.cr6study.info](http://www.cr6study.info)

Under the Study Data tab you can register to download data. Once registered, you will receive a password to access the data download portion of the site.

Not all of the genomics data you requested has been posted. Things that are not posted yet are:

1. Analysis Code
2. QRT-PCR data

These items will be added in the next few weeks.

mark

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Principal Health Scientist

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**Subject:** Terms and Conditions Modified

**Date:** Monday, April 7, 2014 at 12:23:08 PM Central Daylight Time

**From:** Apple-Mail=\_54682036-6E73-4A57-B537-DA70B702C164 Mark Harris boundary=

**To:** Burgoon, Lyle

We modified the terms and conditions for the US Government for our website <http://cr6study.info>. The additional text is: If you are a United States Government entity, the indemnification provision of the Terms and Conditions is hereby waived. Your liability for any breach of the Terms and Conditions, or any claim arising from the Terms and Conditions, shall be determined under the Federal Tort Claims Act, or other governing authority.

mark

---

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Cell: [redacted] **Ex. 6**  
fax: (832) 218-2756  
Email: [mharris@toxstrategies.com](mailto:mharris@toxstrategies.com)  
Website: <http://www.toxstrategies.com>

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**Subject:** Website

**Date:** Monday, April 7, 2014 at 3:43:02 PM Central Daylight Time

**From:** Apple-Mail=\_5CAFA6EE-E253-474E-8737-E357CC0E69C7 Mark Harris boundary=

**To:** Burgoon, Lyle

We have also posted the genomics analysis code to the website today. Only thing remaining is the QRT-PCR info which is still being assembled.

mark

---

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Principal Health Scientist

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fax: (832) 218-2756  
Email: [mharris@toxstrategies.com](mailto:mharris@toxstrategies.com)  
Website: <http://www.toxstrategies.com>

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**Subject:** T&C - how does this  
**Date:** Wednesday, April 23, 2014 at 2:09:01 PM Central Daylight Time  
**From:** Apple-Mail=\_1704D469-54A7-4A17-9C82-0F0AADD0DE20 Mark Harris boundary=  
**To:** Burgoon, Lyle  
**Attachments:** Revised Cr6 Website Terms.docx

Lyle: I got some revised T&C language from the attorneys today. See attached in Tracked Changes. If this works let me know and I will get the website updated.

Also, if these words don't work, can you ask the attorney reviewing this to suggest some words that would work for the US government?

thanks

mark

---

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Principal Health Scientist

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**Subject:** Re: T&C - how does this

**Date:** Tuesday, April 29, 2014 at 7:28:32 AM Central Daylight Time

**From:** Apple-Mail=\_3480B4DA-5FF4-4C62-AE8C-422044ED03FF Mark Harris boundary=

**To:** Burgoon, Lyle

Lyle: the website has been updated with this revised language. Also, we have added the QRT-PCR data that we received from Tim.

mark

---

## Note New Address ToxStrategies, Inc.

Innovative Solutions > Sound Science

**Mark Harris, Ph.D.**  
Principal Health Scientist

23123 Cinco Ranch Blvd, Suite 220  
Katy, TX 77494

Direct Dial: **Ex. 6**  
Houston Office: (281) 712-2062 Ext. **Ex. 6**  
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fax: (832) 218-2750  
Email: [mharris@toxstrategies.com](mailto:mharris@toxstrategies.com)  
Website: <http://www.toxstrategies.com>

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On Apr 28, 2014, at 10:08 AM, Burgoon, Lyle <[Burgoon.Lyle@epa.gov](mailto:Burgoon.Lyle@epa.gov)> wrote:

Hi Mark,

Thanks for working with us that language meets our needs. Sorry for the delay was out sick last week.

Cheers,

Lyle

Lyle D. Burgoon, Ph.D  
Chief, Hazardous Pollutant Assessment Group (Acting)  
National Center for Environmental Assessment  
US Environmental Protection Agency  
Phone: 919.541.7808  
Fax: 919.685.3473

Cell: **Ex. 6**

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---

**From:** Mark Harris [<mailto:mharris@toxstrategies.com>]

**Sent:** Wednesday, April 23, 2014 3:09 PM

**To:** Burgoon, Lyle

**Subject:** T&C - how does this

Lyle: I got some revised T&C language from the attorneys today. See attached in Tracked Changes. If this works let me know and I will get the website updated.

Also, if these words don't work, can you ask the attorney reviewing this to suggest some words that would work for the US government?

thanks

mark

--

## Note New Address

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-----  
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**Subject:** cr6study.info

**Date:** Friday, September 18, 2015 at 12:51:30 PM Central Daylight Time

**From:** Mark Harris

**To:** lyle.d.burgoon@usace.army.mil

Lyle: you should have received an approval for access to the data via email. If you have any issues downloading data just let me know. I did not realize you had changed jobs. Good luck with the new position. Why is the Army interested in Cr(VI)?

mark

--

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Linkedin: <http://www.linkedin.com/in/toxstrategiesharris>

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**Subject:** Re: [EXTERNAL] cr6study.info  
**Date:** Friday, September 18, 2015 at 3:40:14 PM Central Daylight Time  
**From:** Mark Harris  
**To:** Burgoon, Lyle D ERD-MS

Lyle: that is good to know about being able to collaborate on future projects. You never know when a client will ask for such analyses.

One question – is it relatively straightforward to engage you all for a project? Meaning, if something came up, could the paperwork being done relatively quickly to get going?

mark

---

**From:** "Burgoon, Lyle D ERD-MS"  
**Date:** Friday, September 18, 2015 at 3:35 PM  
**To:** Mark Harris  
**Subject:** Re: [EXTERNAL] cr6study.info

Hey Mark,

Thanks. The Army has no interest in chromium (thankfully). However, EPA is in the process of contracting with the Army to reanalyze the data. So, in preparation for that, we requested the data.

On a side note, in my new federal job I'm soft money, and we operate like a consulting company. So if in the future you need CompTox or toxicogenomic support, let me know. We can accept funds from companies for collaborative work.

If you want to chat sometime, my number is

**Ex. 6**

Cheers,

Lyle

Lyle D. Burgoon, PhD  
Environmental Laboratory  
US Army Engineer Research and Development Center  
Research Triangle Park, NC

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

---

**From:** Mark Harris  
**Sent:** Friday, September 18, 2015 1:51 PM  
**To:** Burgoon, Lyle D ERD-MS  
**Subject:** [EXTERNAL] cr6study.info

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LinkedIn: [Blockedhttp://www.linkedin.com/in/toxstrategiesharris](http://www.linkedin.com/in/toxstrategiesharris)

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**Subject:** Re: [EXTERNAL] cr6study.info  
**Date:** Friday, January 8, 2016 at 5:04:08 PM Central Standard Time  
**From:** Burgoon, Lyle D ERD-MS  
**To:** Mark Harris

Thanks for the heads up, Mark.

Have a nice weekend.

Lyle D. Burgoon, PhD  
Environmental Laboratory  
US Army Engineer Research and Development Center  
Research Triangle Park, NC

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

---

**From:** Mark Harris  
**Sent:** Friday, January 8, 2016 6:02 PM  
**To:** Burgoon, Lyle D ERD-MS  
**Subject:** Re: [EXTERNAL] cr6study.info

---

Lyle: we were doing some work on the Cr(VI) genomics data and noticed an error in the rat data (some probe ID's were mislabeled). The actual data is correct - just the labels are wrong. This doesn't impact our publications but does impact the data available for download from our Cr(VI) study website. MSU is fixing and I will alert you when we update the files.

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---

**From:** "Burgoon, Lyle D ERD-MS" <Lyle.D.Burgoon@usace.army.mil>  
**Date:** Friday, September 18, 2015 at 3:50 PM  
**To:** Mark Harris <mharris@toxstrategies.com>  
**Subject:** Re: [EXTERNAL] cr6study.info

Army moves paperwork pretty quick. If I know it's coming, I can grease the skids. If you have a tight turnaround on paperwork approval needed my lab director can expedite and maybe 1-2weeks we should be able to turn it around. Unless it's after July 31, then it might take longer bc of the backlog at contracts.

Lyle D. Burgoon, PhD  
Environmental Laboratory  
US Army Engineer Research and Development Center  
Research Triangle Park, NC

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

---

**From:** Mark Harris  
**Sent:** Friday, September 18, 2015 4:40 PM  
**To:** Burgoon, Lyle D ERD-MS  
**Subject:** Re: [EXTERNAL] cr6study.info

Lyle: that is good to know about being able to collaborate on future projects. You never know when a client will ask for such analyses.

One question – is it is relatively straightforward to engage you all for a project? Meaning, if something came up, could the paperwork being done relatively quickly to get going?

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**From:** "Burgoon, Lyle D ERD-MS"  
**Date:** Friday, September 18, 2015 at 3:35 PM  
**To:** Mark Harris  
**Subject:** Re: [EXTERNAL] cr6study.info

Hey Mark,

Thanks. The Army has no interest in chromium (thankfully). However, EPA is in the process of contracting with the Army to reanalyze the data. So, in preparation for that, we requested the data.

On a side note, in my new federal job I'm soft money, and we operate like a consulting company. So if in the future you need CompTox or toxicogenomic support, let me know. We can accept funds from companies for collaborative work.

If you want to chat sometime, my number is

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Cheers,

Lyle

Lyle D. Burgoon, PhD  
Environmental Laboratory

US Army Engineer Research and Development Center  
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**From:** Mark Harris  
**Sent:** Friday, September 18, 2015 1:51 PM  
**To:** Burgoon, Lyle D ERD-MS  
**Subject:** [EXTERNAL] cr6study.info

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Lyle: you should have received an approval for access to the data via email. If you have any issues downloading data just let me know. I did not realize you had changed jobs. Good luck with the new position. Why is the Army interested in Cr(VI)?

mark

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**Subject:** Re: [EXTERNAL] cr6study.info

**Date:** Tuesday, April 5, 2016 at 2:42:13 PM Central Daylight Time

**From:** Burgoon, Lyle D ERD-MS

**To:** Mark Harris

Hey Mark,

Not started yet, but thanks for the update. Once I get cranking if I have questions I'll let ya know.

Cheers,

Lyle

Lyle D. Burgoon, PhD  
Environmental Laboratory  
US Army Engineer Research and Development Center  
Research Triangle Park, NC

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

---

**From:** Mark Harris  
**Sent:** Tuesday, April 5, 2016 2:09 PM  
**To:** Burgoon, Lyle D ERD-MS  
**Subject:** Re: [EXTERNAL] cr6study.info

---

Lyle: just touching base. Have you done anything with the data – the labels are all fixed in the raw data.

Trust all is well.

mark

--

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**Mark Harris, Ph.D.**  
Principal Health Scientist

---

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**From:** "Burgoon, Lyle D ERD-MS" <Lyle.D.Burgoon@usace.army.mil>

**Date:** Friday, January 8, 2016 at 5:04 PM

**To:** Mark Harris <mharris@toxstrategies.com>

**Subject:** Re: [EXTERNAL] cr6study.info

Thanks for the heads up, Mark.

Have a nice weekend.

Lyle D. Burgoon, PhD  
Environmental Laboratory  
US Army Engineer Research and Development Center  
Research Triangle Park, NC

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**To:** Burgoon, Lyle D ERD-MS

**Subject:** Re: [EXTERNAL] cr6study.info

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Lyle

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Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

**From:** Mark Harris  
**Sent:** Friday, September 18, 2015 1:51 PM  
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**Subject:** Re: Cr(VI) raw microarray data

**Date:** Thursday, March 13, 2014 at 12:39:33 PM Central Daylight Time

**From:** Burgoon, Lyle

**To:** Mark Harris

Thanks, Mark; looking forward to the data. If you're going to SOT, safe travels.

Cheers,

Lyle

---

**From:** Mark Harris <mharris@toxstrategies.com>

**Sent:** Thursday, March 13, 2014 1:37:10 PM

**To:** Burgoon, Lyle

**Cc:** Thomas, Russell; Tim Zacharewski; Gibbons, Catherine; Chad Thompson; Deborah Proctor

**Subject:** Cr(VI) raw microarray data

Lyle: as I mentioned in the meeting on Monday, the data will be posted to our new Cr(VI) MOA website before SOT. Once the site is live I will send you all a link to it. You will be able to download the genomics data at that time.

The approach and methods that were used to analyze the data are adequately described in the Kopec papers. Our use of the genomics data to support the Mode of Action can be found in our Critical Reviews in Toxicology paper. Links to these Open Access papers can be found at the web page below:

[http://www.toxstrategies.com/publications/CRVI\\_MOA\\_study.htm](http://www.toxstrategies.com/publications/CRVI_MOA_study.htm)

mark

**From:** "Burgoon, Lyle" <Burgoon.Lyle@epa.gov>

**Date:** March 12, 2014 at 8:43:16 AM CDT

**To:** "cthompson@toxstrategies.com" <cthompson@toxstrategies.com>

**Cc:** "tzachare@msu.edu" <tzachare@msu.edu>, "Gibbons, Catherine" <Gibbons.Catherine@epa.gov>

**Subject:** Cr(VI) raw microarray data

Dr. Thompson,

It was nice seeing you and Dr. Harris (via video) at Monday's meeting @ NCEA HQ. I was quite pleased to hear Ms. Mason state that ACC expected the researchers would share their data and results with NCEA.

I'm following up on our discussion from Monday and am requesting access to all of your raw microarray data, as well as your analyzed data that supports the conclusions in your papers. In addition, it would be helpful if you could also supply us with the analysis code that was used,

any protocols used for the analyses, and any other supporting documentation that may help us understand how the assays and analyses were performed.

For clarity, I am using the MIAME definition of "raw data", and my request for the additional information is in line and keeping with the MIAME standard, which can be found here: <http://www.mged.org/Workgroups/MIAME/miame.html>.

To facilitate data transfer, I can set-up an EPA-based FTP site where you can upload the data.

Thanks again for presenting your latest results to us, and I look forward to receiving the data.

Cheers,

Lyle

Lyle D. Burgoon, Ph.D  
National Center for Environmental Assessment  
Chief, Hazardous Pollutant Assessment Group (Acting)  
US Environmental Protection Agency  
Phone: 919.541.7808  
Fax: 919.685.3473  
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**Subject:** Re: Cr(VI) raw microarray data

**Date:** Monday, March 17, 2014 at 9:40:37 AM Central Daylight Time

**From:** Burgoon, Lyle

**To:** mharris@toxstrategies.com

**CC:** tzachare@msu.edu, Gibbons, Catherine, cthompson@toxstrategies.com

Hi Mark,

I have read the Kopec, et al papers again, at your suggestion. Reading them reaffirms that we absolutely need to have the analysis code in order to understand what exactly was done. Per the MIAME standard (Minimum Information About a Microarray Experiment: [http://www.mged.org/Workgroups/MIAME/miame\\_2.0.html](http://www.mged.org/Workgroups/MIAME/miame_2.0.html)):

The essential laboratory and data processing protocols are usually described in the journal methods section. It is sufficient to simply reference the standard experimental or data processing protocols, such as MAS5 or RMA. However, if a protocol depends on parameters that can be varied, their values should be provided. If novel or non-standard data processing protocols are used, these should be described in sufficient detail to allow the user to understand what exactly has been done in the experiment and how the data have been analysed to reach the conclusions of the study.

In the case of the Kopec, et al papers, the analysis protocols used are non-standard data processing methods. As far as I can tell, these methods are commonly used in Dr. Zacharewski's laboratory; however, they are not commonly used elsewhere. The Eckel, et al 2005 and Eckel, et al 2004 papers describe analysis methods used in the Kopec, et al papers that require parameterization or changes to the code in order to work properly. Thus, it is critical for us to see the code in order to understand how the data were treated. Without the code we will be unable to understand how you came to draw the hypotheses you did in the Kopec, et al and subsequent papers. Without this understanding, we cannot interpret your results.

As MIAME is a community standard, first adopted several years ago by many prominent journals, you can see that this request is not unusual.

Likewise, we need to have the rawest form of the data possible for the QRT-PCR analyses, which Kopec, et al have used to support their microarray data. At a minimum, this would include any spreadsheets or text files of the data from the ABI machine, detailing all of the mathematical manipulations of the data from prior to standardization, through normalization, ratio calculation, and statistical analysis. Note: I couldn't find any details on how the statistical analysis of the QRT-PCR was performed, nor can I find a reference for how the standard errors of a ratio were calculated.

We may have additional data requirements and needs as we dig into the toxicogenomics data further, and we look forward to working with you in obtaining the information we need to better understand these studies.

Thanks,

Lyle

Lyle D. Burgoon, Ph.D  
Chief, Hazardous Pollutant Assessment Group (Acting)  
National Center for Environmental Assessment  
US Environmental Protection Agency  
Phone: 919.541.7808

Fax: 919.685.3473

Cell: **Ex. 6**

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**From:** Mark Harris <[mharris@toxstrategies.com](mailto:mharris@toxstrategies.com)>

**Sent:** Thursday, March 13, 2014 1:37:10 PM

**To:** Burgoon, Lyle

**Cc:** Thomas, Russell; Tim Zacharewski; Gibbons, Catherine; Chad Thompson; Deborah Proctor

**Subject:** Cr(VI) raw microarray data

Lyle: as I mentioned in the meeting on Monday, the data will be posted to our new Cr(VI) MOA website before SOT. Once the site is live I will send you all a link to it. You will be able to download the genomics data at that time.

The approach and methods that were used to analyze the data are adequately described in the Kopec papers. Our use of the genomics data to support the Mode of Action can be found in our Critical Reviews in Toxicology paper. Links to these Open Access papers can be found at the web page below:

[http://www.toxstrategies.com/publications/CRVI\\_MOA\\_study.htm](http://www.toxstrategies.com/publications/CRVI_MOA_study.htm)

mark

**From:** "Burgoon, Lyle" <[Burgoon.Lyle@epa.gov](mailto:Burgoon.Lyle@epa.gov)>

**Date:** March 12, 2014 at 8:43:16 AM CDT

**To:** "[cthompson@toxstrategies.com](mailto:cthompson@toxstrategies.com)" <[cthompson@toxstrategies.com](mailto:cthompson@toxstrategies.com)>

**Cc:** "[tzachare@msu.edu](mailto:tzachare@msu.edu)" <[tzachare@msu.edu](mailto:tzachare@msu.edu)>, "Gibbons, Catherine" <[Gibbons.Catherine@epa.gov](mailto:Gibbons.Catherine@epa.gov)>

**Subject:** Cr(VI) raw microarray data

Dr. Thompson,

It was nice seeing you and Dr. Harris (via video) at Monday's meeting @ NCEA HQ. I was quite pleased to hear Ms. Mason state that ACC expected the researchers would share their data and results with NCEA.

I'm following up on our discussion from Monday and am requesting access to all of your raw microarray data, as well as your analyzed data that supports the conclusions in your papers. In addition, it would be helpful if you could also supply us with the analysis code that was used, any protocols used for the analyses, and any other supporting documentation that may help us understand how the assays and analyses were performed.

For clarity, I am using the MIAME definition of "raw data", and my request for the additional information is in line and keeping with the MIAME standard, which can be found here: <http://www.mged.org/Workgroups/MIAME/miame.html>.

To facilitate data transfer, I can set-up an EPA-based FTP site where you can upload the data.

Thanks again for presenting your latest results to us, and I look forward to receiving the data.

Cheers,

Lyle

Lyle D. Burgoon, Ph.D  
National Center for Environmental Assessment  
Chief, Hazardous Pollutant Assessment Group (Acting)  
US Environmental Protection Agency  
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## Note New Address

### ToxStrategies, Inc.

Innovative Solutions > Sound Science

#### Mark Harris, Ph.D.

Principal Health Scientist

---

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Katy, TX 77494

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Houston Office: (281) 212-2062

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fax: (832) 218-2756

Email: [mharris@toxstrategies.com](mailto:mharris@toxstrategies.com)

Website: <http://www.toxstrategies.com>

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**Subject:** RE: Cr(VI) MOA Study Website  
**Date:** Thursday, April 3, 2014 at 2:59:52 PM Central Daylight Time  
**From:** Burgoon, Lyle  
**To:** Mark Harris  
**CC:** Gibbons, Catherine, Vandenberg, John, Flowers, Lynn

Hi Mark,

We cannot access the data at this time due to our inability to agree to the Terms and Conditions associated with data access found here: <http://cr6study.info/study-data/terms-and-conditions/>

Specifically, we request that ToxStrategies delete the indemnification clause in the Terms and Conditions. As written, the Agency cannot agree to the terms as it would be a violation of the Anti-Deficiency Act (i.e., making a commitment to an unknown future cost is a direct violation of the Anti-Deficiency Act).

Please let me know what action you are willing to take as soon as possible. As you are aware, time is of the essence with respect to the Cr(VI) IRIS Assessment. Your prompt attention to this matter is appreciated.

Thanks,

Lyle

Lyle D. Burgoon, Ph.D  
Chief, Hazardous Pollutant Assessment Group (Acting)  
National Center for Environmental Assessment  
US Environmental Protection Agency  
Phone: Ex. 6  
Fax: 919.685.3473  
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**From:** Mark Harris [mailto:mharris@toxstrategies.com]  
**Sent:** Monday, March 24, 2014 9:34 AM  
**To:** Burgoon, Lyle  
**Cc:** Tim Zacharewski; Gibbons, Catherine; Chad Thompson; Thomas, Russell  
**Subject:** Cr(VI) MOA Study Website

Lyle: our Cr(VI) MOA study website is live. You can access it at [www.cr6study.info](http://www.cr6study.info)

Under the Study Data tab you can register to download data. Once registered, you will receive a password to access the data download portion of the site.

Not all of the genomics data you requested has been posted. Things that are not posted yet are:

1. Analysis Code
2. QRT-PCR data

These items will be added in the next few weeks.

mark

---

## Note New Address ToxStrategies, Inc.

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**Mark Harris, Ph.D.**  
Principal Health Scientist

-----  
23123 Cinco Ranch Blvd, Suite 220  
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Email: [mharris@toxstrategies.com](mailto:mharris@toxstrategies.com)  
Website: <http://www.toxstrategies.com>

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**Subject:** RE: T&C - how does this

**Date:** Monday, April 28, 2014 at 10:08:36 AM Central Daylight Time

**From:** Burgoon, Lyle

**To:** Mark Harris

Hi Mark,

Thanks for working with us – that language meets our needs. Sorry for the delay – was out sick last week.

Cheers,

Lyle

Lyle D. Burgoon, Ph.D  
Chief, Hazardous Pollutant Assessment Group (Acting)  
National Center for Environmental Assessment  
US Environmental Protection Agency  
Phone: 919.541.7808  
Fax: 919.685.3473  
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**From:** Mark Harris [mailto:mharris@toxstrategies.com]  
**Sent:** Wednesday, April 23, 2014 3:09 PM  
**To:** Burgoon, Lyle  
**Subject:** T&C - how does this

Lyle: I got some revised T&C language from the attorneys today. See attached in Tracked Changes. If this works let me know and I will get the website updated.

Also, if these words don't work, can you ask the attorney reviewing this to suggest some words that would work for the US government?

thanks

mark

---  
**Note New Address**  
**ToxStrategies, Inc.**  
Innovative Solutions > Sound Science

**Mark Harris, Ph.D.**  
Principal Health Scientist

---

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**Subject:** Re: [EXTERNAL] cr6study.info

**Date:** Friday, September 18, 2015 at 3:35:41 PM Central Daylight Time

**From:** Burgoon, Lyle D ERD-MS

**To:** Mark Harris

Hey Mark,

Thanks. The Army has no interest in chromium (thankfully). However, EPA is in the process of contracting with the Army to reanalyze the data. So, in preparation for that, we requested the data.

On a side note, in my new federal job I'm soft money, and we operate like a consulting company. So if in the future you need CompTox or toxicogenomic support, let me know. We can accept funds from companies for collaborative work.

If you want to chat sometime, my number is Ex. 6

Cheers,

Lyle

Lyle D. Burgoon, PhD  
Environmental Laboratory  
US Army Engineer Research and Development Center  
Research Triangle Park, NC

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

---

**From:** Mark Harris  
**Sent:** Friday, September 18, 2015 1:51 PM  
**To:** Burgoon, Lyle D ERD-MS  
**Subject:** [EXTERNAL] cr6study.info

---

Lyle: you should have received an approval for access to the data via email. If you have any issues downloading data just let me know. I did not realize you had changed jobs. Good luck with the new position. Why is the Army interested in Cr(VI)?

mark

--

**ToxStrategies, Inc.**  
Innovative Solutions > Sound Science

**Mark Harris, Ph.D.**  
Principal Health Scientist

---

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**Subject:** Re: [EXTERNAL] cr6study.info

**Date:** Friday, September 18, 2015 at 3:50:25 PM Central Daylight Time

**From:** Burgoon, Lyle D ERD-MS

**To:** Mark Harris

Army moves paperwork pretty quick. If I know it's coming, I can grease the skids. If you have a tight turnaround on paperwork approval needed my lab director can expedite and maybe 1-2weeks we should be able to turn it around. Unless it's after July 31, then it might take longer bc of the backlog at contracts.

Lyle D. Burgoon, PhD  
Environmental Laboratory  
US Army Engineer Research and Development Center  
Research Triangle Park, NC

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

---

**From:** Mark Harris

**Sent:** Friday, September 18, 2015 4:40 PM

**To:** Burgoon, Lyle D ERD-MS

**Subject:** Re: [EXTERNAL] cr6study.info

---

Lyle: that is good to know about being able to collaborate on future projects. You never know when a client will ask for such analyses.

One question – is it is relatively straightforward to engage you all for a project? Meaning, if something came up, could the paperwork being done relatively quickly to get going?

mark

---

**From:** "Burgoon, Lyle D ERD-MS"

**Date:** Friday, September 18, 2015 at 3:35 PM

**To:** Mark Harris

**Subject:** Re: [EXTERNAL] cr6study.info

Hey Mark,

Thanks. The Army has no interest in chromium (thankfully). However, EPA is in the process of contracting with the Army to reanalyze the data. So, in preparation for that, we requested the data.

On a side note, in my new federal job I'm soft money, and we operate like a consulting company. So if in the future you need CompTox or toxicogenomic support, let me know. We can accept funds from companies for collaborative work.

If you want to chat sometime, my number is: Ex. 6

Cheers,

Lyle

Lyle D. Burgoon, PhD  
Environmental Laboratory  
US Army Engineer Research and Development Center

Research Triangle Park, NC

Sent from my BlackBerry 10 smartphone on the Verizon Wireless 4G LTE network.

---

**From:** Mark Harris  
**Sent:** Friday, September 18, 2015 1:51 PM  
**To:** Burgoon, Lyle D ERD-MS  
**Subject:** [EXTERNAL] cr6study.info

---

Lyle: you should have received an approval for access to the data via email. If you have any issues downloading data just let me know. I did not realize you had changed jobs. Good luck with the new position. Why is the Army interested in Cr(VI)?

mark

--

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Principal Health Scientist

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**Subject:** New user registration for Cr(VI) MOA Study

**Date:** Wednesday, August 10, 2016 at 1:16:17 PM Central Daylight Time

**From:** CrVI MOA Study

**To:** mharris@toxstrategies.com

The following user registered for Cr(VI) MOA Study (and is pending approval)

username: sfoster  
email: [foster.stiven@epa.gov](mailto:foster.stiven@epa.gov)

First Name: Stiven  
Last Name: Foster  
Company: USEPA  
Position: Toxicologist  
Address 1: 1200 Pennsylvania Ave, NW  
Address 2: MC-5103T  
City: Washington  
State: DC  
Zip: 20460  
Country: USA  
Day Phone: 202-566-1911  
Plans for Data Use: Evaluation of finding for consideration in EPA efforts.  
TOS: agree

This user registered here:  
<http://cr6study.info/register/>

**Ex. 6**

-----  
This is an automated message from Cr(VI) MOA Study  
Please do not reply to this address

**Subject:** (none)

**Date:** Wednesday, August 10, 2016 at 1:19:59 PM Central Daylight Time

**From:** Mark Harris

**To:** foster.stiven@epa.gov

I have activated your access to the raw data. If you have any problems accessing the data let me know.

Mark

--

ToxStrategies, Inc.  
Innovative Solutions > Sound Science

Mark Harris, Ph.D.  
Principal Health Scientist

-----  
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