

Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460
EPA-HQ-OAR-2020-0312
FRL-7887-03-OAR

**Comments on Integrated Review Plan for the National Ambient Air
Quality Standards for Lead.
Volume 3: Planning Document for Quantitative Exposure/Risk Analyses**

Our comments are specific to the planned approach for modeling IQ decrement in young children. The United States Environmental Protection Agency (EPA) describes newly available information on this technical area in Section K of Table 2-3 and associated text in Volume 3 of the Integrated Review Plan for the National Ambient Air Quality Standards for Lead (IRP). EPA has not provided adequate detail to allow for critical review of the plan for modeling IQ decrements in young children, and the available information suggests the plan may not be robust enough to support a reliable dose-response analysis. Specific items EPA should consider are outlined below.

June 12, 2023

1. Section K of Table 2-3 in the IRP refers to both Lanphear et al. 2005, 2019 and Crump et al. 2013, but fails to mention Van Landingham et al. 2020 which analyzed the same data as Lanphear and Crump but including confounding variables (variables with interaction with the BPb variable). Van Landingham et al. 2020 raises concerns about the modeling in the low exposure range. Their analysis shows that "confounders influence IQ estimates in a quantifiable way that may exceed or at least obscure previously reported effects of blood lead on IQ with blood lead levels below 5 µg/dL; however, limitations in the datasets make predictions of the low dose dose/response analysis questionable". The Van Landingham et al. 2020 analysis should be mentioned in this section. Email correspondence with EPA epidemiologists regarding the Van Landingham et al. 2020 publication, and associated correspondence with the Journal *Critical Reviews in Toxicology* regarding the submission of an erratum for the publication are included as attachments to these comments.
2. There is no mention of the fact that by reducing the data used for the Concentration-Response (C-R) function to just the Boston and Rochester data from the Lanphear cohort, the sample size is reduced from over 2100 records to less than 500. In addition, depending on the covariates and or confounders used, the actual number of records that will be used in the analysis could reduce to less than 300. If it is further reduced by using only those records with blood lead (BPb) less than 5 µg/dL, depending on the BPb measurement used (peak, concurrent, etc.) this could reduce the data even further – to something less than 140 records (determined using last measured BPb). What does the EPA have to say about the reduction of sample size and the effect the reduced sample size will have on the confidence bounds and on predictions made by the function?

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3. Besides the modeling being linear, what can the EPA tell us about the functional form of the planned model?
 - a. What covariates are the EPA planning on using in the linear regression?
 - b. Are possible confounders (covariates that have an interaction with the BPb that effects the IQ) to be used in the modeling?
4. Which of the measured IQ estimates will be used in the modeling? The Boston data has IQ data at age 10. Is that considered to be outside the range of values to be used due to an age above 7?
5. Does the EPA plan on using site specific variables to account for differences in Home Scores and alcohol use during pregnancy as Crump *et al.* 2013 did? Or will separate normalization of the Home Scores be done as Lanphear *et al.* 2005 did?
6. Does the EPA plan on providing the details on the model and the data used so that it could be reproduced by others?

Yours sincerely,

Cynthia Van Landingham

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Rosalind Schoof, PhD, DABT

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Attachments:

Attachment 1: EPA Email Correspondence RE: Van Landingham et al. 2020

Attachment 2: Critical Reviews in Toxicology Errata Email Correspondence RE: Van Landingham et al. 2020

Attachment 1

EPA Email Correspondence RE: Van Landingham et al. 2020

From: [Cynthia Van Landingham](#)
To: [Julia Tyr](#), [Rosalind A. Schoof](#), [Cris Williams](#)
Subject: FW: Van Landingham et al. 2020
Date: Thursday, June 8, 2023 1:36:17 PM
Attachments: [image001.png](#)
[image002.png](#)
[image003.png](#)

See below, EPA is putting the e-mail stating they can match our results in Van Landingham et al. 2020 in the docket

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From: Coffman, Evan <Coffman.Evan@epa.gov>
Sent: Thursday, June 8, 2023 3:33 PM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>
Subject: RE: Van Landingham et al. 2020

Hi Cynthia,

Thanks for checking in on this. Yes, we will submit this conversation to the docket.

Best,
Evan

Classification: Confidential

From: Cynthia Van Landingham <cvanlandingham@ramboll.com>
Sent: Wednesday, June 7, 2023 4:18 PM
To: Coffman, Evan <Coffman.Evan@epa.gov>
Subject: RE: Van Landingham et al. 2020

Evan, since our original e-mails concerning reproducing the results in Van Landingham et al. 2020 were put into the record (EPA-HQ-ORD-2020-0701-0005.pdf), will this conversation regarding the errata and you now being able to reproduce our results also be added?

Regard, Cynthia

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From: Coffman, Evan <Coffman.Evan@epa.gov>
Sent: Thursday, May 18, 2023 7:59 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>; Kirrane, Ellen <Kirrane.Ellen@epa.gov>
Cc: Rosalind A. Schoof <rschoof@ramboll.com>
Subject: RE: Van Landingham et al. 2020

Hi Cynthia,

Thank you for clarifying the discrepancy in the results. I can confirm that I was able to reproduce the results in Table S4 with the updated interaction coefficients. We would appreciate it if you could keep us up to date on the status of the errata.

As you previously noted, the draft ISA was already released (March 31st), but there is an opportunity to [provide input](#) to our advisory committee (the Clean Air Scientific Advisory Committee) via oral and/or written comments. Relevant comments to CASAC include identification of studies that were not included in the draft ISA.

Thanks again for taking the time to respond to our inquiry.

Best,
Evan

From: Cynthia Van Landingham <cvanlandingham@ramboll.com>
Sent: Monday, May 15, 2023 1:19 PM
To: Kirrane, Ellen <Kirrane.Ellen@epa.gov>
Cc: Rosalind A. Schoof <rschoof@ramboll.com>; Coffman, Evan <Coffman.Evan@epa.gov>
Subject: RE: Van Landingham et al. 2020

Ellen and Evan,
Sorry for the delay but it took me a while to track this down. As I think I told you in an earlier e-mail, the actual calculations were made using a feature in SAS that allows you to add records to your dataset used in the regression with no dependent variable value (in this case IQ) but with all the independent variables you want to use in the model (e.g. means for all the variables as specified in the paper or variations on those means). SAS does not use this record in the fitting process but does give a prediction for the dependent variable based on the model fit to the rest of the data and the values for lead and the covariates specified in the records added that have no observed value for the dependent variable. This is how I got the prediction for the IQ when varying the covariates, and also the values when varying the blood lead. To get the amount from a change of 1 in the lead, I subtracted the predicted values for lead of 1 from that for lead of 0 when all the covariates set at mean values.

The problem that you discovered came from the fact that I made an error in what is listed in Table 10 for the two values highlighted below.

Variable	Model 3 - linear model		Model 4 - log-linear Ln (BPb b-1) model	
	Variable value	Variable for interaction with BPb (confounder x BPb)	Variable value	Variable for interaction with BPb (confounder x ln(BPb b-1))
BPb	-0.1247		-4.945	
Mother's IQ	0.296	-0.0023587	0.383	-0.0003
Mother's education level	0.517	-0.0087	0.3967	-0.0051
HOME score	0.4745	0.0023	0.3789	0.0437

The value for the confounder x BPB listed for Mother's IQ and Mother's education level should be -0.00087 and -0.00704, respectively. This only effects this table, since I performed the operation as described above for the actual calculations in Tables 7,8,9,11 and 12 and the Supplemental Tables S4 and S5. I think that you will find that the values in Table S4 and Table 11 will be correct if you use these parameter values in the equations - with small differences that can happen considering rounding/truncation of the variable values or means reported in the paper versus the more compete values used inside the SAS process. This "error" does not affect our conclusions in the paper.

Sorry for any confusion that this caused and I will be sending an errata to the journal to correct this.

Cynthia

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From: Kirrane, Ellen <Kirrane.Ellen@epa.gov>
Sent: Tuesday, May 9, 2023 3:03 PM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>
Cc: Rosalind A. Schoof <rschoof@ramboll.com>; Coffman, Evan <Coffman.Evan@epa.gov>
Subject: RE: Van Landingham et al. 2020

Dear Cynthia,

Thank you for your response to my request for clarification on your 2020 paper titled, "The effect of confounding variables in studies of lead exposure and IQ." I pasted your most recent email into the email chain from August 2022. Please note that I intended to copy Evan Coffman, the project lead for the Pb ISA, on the February 6, 2022 email but inadvertently left him off my response. He is copied now.

I reached out to Evan when I initially read your paper because I did not follow some of its underlying logic and conclusions. In his effort to better understand the paper he reproduced your site specific results in Table S5, but was not able to

To take the simplest example from Table S4, the paper states that “for 1 ug/dL BPb, the estimate for change in IQ is -0.203 for the linear model [...] when the confounders are set at an average”. This result corresponds to the linear model results for the 1 ug/dL BPb column and the 0 row for each of the confounders. We used the following equation, average confounder values, and regression coefficients to reproduce the result, but got a different number:

$$\text{Change in IQ} = \text{BPb} \times (\text{B1} + (\text{B2} \times \text{maternal IQ}) + (\text{B3} \times \text{maternal education}) + (\text{B4} \times \text{HOME Score}))$$

Maternal IQ: 88.89

Maternal education: 11.12

HOME score: 34.49

BPb (B1): -0.1247

Maternal IQ intxn (B2): -0.0023587

Maternal education intxn (B3): -0.0087

HOME Score intxn (B4): 0.0023

Thus, holding all confounders fixed at 0, the change in IQ estimated for a BPb of 1 ug/dL =

$$\text{BPb} \times (\text{B1} + (\text{B2} \times \text{maternal IQ}) + (\text{B3} \times \text{maternal education}) + (\text{B4} \times \text{HOME Score}))$$
$$1 \times (-0.1347) + (-0.0023587 \times 88.89) + (-0.0087 \times 11.12) + (0.0023 \times 34.49)$$
$$(-0.1247 - 0.2097 - 0.0967 \pm 0.079327)$$

-0.35

The full set of results are pasted below. Please let us know if you can offer any clarification.

Best regards,

Ellen F. Kirrane (she/her/hers)

Senior Epidemiologist

U.S. EPA CRHEA

U.S. EPA CPHE
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From: Cynthia Van Landingham cyanlandingham@ramboll.com

Sent: Tuesday, May 2, 2023 6:23 PM

To: Kirrane, Ellen Kirrane.Ellen@epa.gov

Cc: Rosalind A. Schoof rschoof@ramboll.com

Subject: RF: Van Landingham et al. 2020

Ellen

We communicated last year regarding the analyses in Van Landingham et al. 2020 and your ability to reproduce some of the values reported. I am checking back with you as to whether you completed your analysis. I have seen the draft ISA for lead and noted that our paper was not referenced in that document. Was it not included as you could not reproduce the results or was there some other reason that it was not included. If you are having problems reproducing, maybe I can help you with that. Let me know you would like to discuss this.

Regards, Cynthia

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From: Cynthia Van Landingham <cvanlandingham@ramboll.com>
Sent: Monday, February 6, 2023 4:04 PM
To: Kिरrane, Ellen <Kिरrane.Ellen@epa.gov>
Subject: Re: Van Landingham et al. 2020

Sorry. I am semi retired. I will try to get back into my code next week to see if my answer below changes. All calculations were done in SAS using its ability to provide predictive values as part of the fitting process. Average value's were used for all variables either overall sires or specific to each site to get predictions with BPB values of 0 and 1. The difference provides the reported results.

From: Kिरrane, Ellen <Kिरrane.Ellen@epa.gov>
Sent: Monday, February 6, 2023 2:48:41 PM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>
Subject: RE: Van Landingham et al. 2020

Dear Dr. Van Landingham,

This is to follow up on the email of August 2 below seeking clarification on your paper. I am looping in Evan Coffman who is leading the Lead ISA team.

Best regards,

Ellen

From: Cynthia Van Landingham <cvanlandingham@ramboll.com>
Sent: Tuesday, August 2, 2022 12:51 PM
To: Kिरrane, Ellen <Kिरrane.Ellen@epa.gov>
Subject: Re: Van Landingham et al. 2020

Sorry, I am on vacation this week but will get back to you next week. But my memory says I calculated those as the difference of the predicted values.

From: Kिरrane, Ellen <Kिरrane.Ellen@epa.gov>
Sent: Tuesday, August 2, 2022 11:46:40 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>
Subject: Van Landingham et al. 2020

Dear Dr. Van Landingham,

I am writing to you as the corresponding author for the paper titled, "The effect of confounding variables in studies of lead exposure and IQ." Could you please explain how you calculated the estimated change in IQ for 1 microgram per dL BPb for both the linear and the loglinear models to obtain -0.203 and -2.36, respectively (Tables 11 and S4.) We are not able to obtain these results by using equation 1 and substituting the non site-specific results in table 10. I apologize if I missed something in the paper.

Best regards,

Ellen F. Kिरrane, Ph.D. | Senior Epidemiologist | she/her/hers | U.S. EPA Center for Public Health and Environmental Assessment (CPHEA) | Integrated Health Assessment Branch | Tel: 919 541-1340 | 109 TW Alexander Drive | Research Triangle Park, NC 27709

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Attachment 2

**Critical Reviews in Toxicology Errata Email Correspondence
RE: Van Landingham et al. 2020**

From: [Jesse Denson Hesch](#)
To: ITXC-peerreview@journals.tandf.co.uk
Cc: [Cynthia Van Landingham](#); roger.o.mcclellan@att.net
Subject: Re: RE: Question #TrackingId:15202799
Date: Wednesday, May 31, 2023 10:06:37 AM
Attachments: [Corrected Table 10.docx](#)

Hello Josie,

Dr. Landingham would like to submit an erratum for the manuscript listed below published in CRT in 2020. The attached Word file has the corrected table.

In detail: Two values reported in Table 10 for Model 3 were reported incorrectly (linear model for the interaction variables for Mother's IQ and Mother's education level. Instead of the reported values of -0.0023587 and -0.0087, the values for the confounder × BPB listed for Mother's IQ and Mother's education level should be -0.00087 and -0.00704, respectively).

Cynthia Van Landingham , William G. Fuller & Rosalind A. Schoof (2020) The effect of confounding variables in studies of lead exposure and IQ, Critical Reviews in Toxicology,

50:9, 815-825, DOI: 10.1080/10408444.2020.1842851

Please let me know if you have any questions.

Best,
Jesse

On Wed, May 31, 2023 at 8:43 AM <ITXC-peerreview@journals.tandf.co.uk> wrote:

Thanks Marissa.

Hi Jesse and Roger,

Could you please let know what the issue is as I couldn't follow the email trail properly.

All best,

Josie

Josie Brown
Production Editor

My working hours are Tuesday-Friday 8:30 - 4:30 GMT

Critical Reviews In Toxicology

From: Marissa.nania@gwinc.com

Sent: 22-05-2023 07.00 PM

To: evanlandingham@ramboll.com, services@heschconsulting.com

Cc: roger.o.mcclellan@att.net

Subject: RE: RE: Question

Hello Josie,

Hope you are well!

I am forwarding the below author correction for their already-published article. Would you kindly be able to assist them with this issue?

Thank you and please let me know if you have further queries or concerns.

Best,

Marissa

Marissa Nania - Journal Editorial Office

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Critical Reviews In Toxicology

From: cvanlandingham@ramboll.com

Sent: 17-05-2023 10:33 AM

To: ITXC-peerreview@journals.tandf.co.uk, services@heschconsulting.com

Cc: roger.o.mcclellan@att.net

Subject: RE: RE: Question

Marissa, Thanks for your instructions. The information you requested is below.

The mistake made was in two values reported in Table 10 for Model 3 – linear model for the interaction variables for Mother's IQ and Mother's education level. Instead of the reported values of -0.0023587 and -0.0087, the values for the confounder × BPB listed for Mother's IQ and Mother's education level should be -0.00087 and -0.00704, respectively. The attached Word file has the corrected table.

The Effect of Confounding Variables in Studies of Lead Exposure and IQ

Corresponding author: Cynthia Van Landingham; cvanlandingham@ramboll.com;
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From: ITXC-peerreview@journals.tandf.co.uk <ITXC-peerreview@journals.tandf.co.uk>

Sent: Wednesday, May 17, 2023 11:19 AM
To: Cynthia Van Landingham <cvanlandingham@ramboll.com>;
services@heschconsulting.com
Cc: roger.o.mcclellan@att.net
Subject: Re: RE: Question #TrackingId:15202799

Hello All,

Thank you for your email!

I confirm any corrections to an already-published paper can be forwarded to the Production Team for handling.

Kindly reply to this email with the full article title, the corresponding author name and email address, and a file attachment with the corrected table. This information will be forwarded to the Production Team, who will make the necessary correction to your published article.

Please let me know if you have further queries or concerns.

Best,

Marissa

Marissa Nania - Journal Editorial Office

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Critical Reviews In Toxicology

From:cvanlandingham@ramboll.com

Sent:17-05-2023 09:42

To:services@heschconsulting.com,Marissa.nania@gwinc.com

Cc:roger.o.mcclellan@att.net

Subject:Re: RE: Question

Thanks for your reply. I have not heard from Marissa and I am not sure that I understand what you mean when you say it must be like submitting a new manuscript. Do I have to change the one table and submit the original manuscript as accepted or do I submit a letter to the editor detailing the errata (which is only 2 values listed in Table 10)? Could you be more specific about what is needed?

Thanks, Cynthia

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From: Jesse Denson Hesch <services@heschconsulting.com>

Sent: Monday, May 15, 2023 7:00 PM

To: Cynthia Van Landingham <cvanlandingham@ramboll.com>

Cc: roger.o.mcclellan@att.net; Marissa Nania <itxc-peerreview@journals.tandf.co.uk>

Subject: Re: Question

Dear Cynthia and Roger,

I'm not exactly sure how to submit an errata, but my guess is that you can submit it through the ScholarOne system as if you were submitting a new manuscript. Hopefully, Marissa will be able to confirm.

Best,

Jesse

On Mon, May 15, 2023 at 3:01 PM Cynthia Van Landingham
<cvanlandingham@ramboll.com> wrote:

Thanks Roger. I will look for communication from Jessie and/or Marissa. I am sorry to hear about Mildred. I know you will miss her.

Regards, Cynthia

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From: roger.o.mcclellan@att.net <roger.o.mcclellan@att.net>

Sent: Monday, May 15, 2023 3:57:44 PM

To: Cynthia Van Landingham <cvanlandingham@ramboll.com>

Cc: Jesse Denson Hesch <services@heschconsulting.com>; Marissa Nania <itxc-peerreview@journals.tandf.co.uk>; Roger McClellan <roger.o.mcclellan@att.net>

Subject: Re: Question

Cynthia;

It was great to hear from you although I wish it did not concern a problem. By copy of this e-mail I am asking two of my colleagues to assist you with advice on how to prepare a communication concerning an errata. Marissa is part of the T and F team. Jesse is now my assistant replacing my long time assistant, Mildred Morgan, who. passed away last April at age 92 years. She had along productive and enjoyable life. You probably had some contact with her over the more than a half century she worked with me.

If you ever have any questions related to Critical Reviews in Toxicology or my publications feel free to contact Jesse who works from her home in Colorado Springs.

I hope you will have another review paper to submit to Critical Reviews in Toxicology in the near future It is always a pleasure to publish papers you have authored or co-authored.

Best regards,

Roger

On Monday, May 15, 2023 at 01:02:09 PM PDT, Cynthia Van Landingham
<cvanlandingham@ramboll.com> wrote:

Hello Roger,

Long time sine we have talked. Unfortunately, I need to report an errata in my 2020 paper (citation below). The mistake was a transcription mistake in two values reported in Table 10 and does not affect any of the rest of the document including the supplemental tables.

Cynthia Van Landingham , William G. Fuller & Rosalind A. Schoof (2020) The

effect of confounding variables in studies of lead exposure and IQ, Critical Reviews in Toxicology,

50:9, 815-825, DOI: 10.1080/10408444.2020.1842851

I cannot seem to find the instructions on how to submit and errata to Critical Reviews in Toxicology. Can you help me?

Regards, Cynthia

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