

Keith Fluegge

From: Keith Fluegge <keithfluegge@iher.org>
Sent: Monday, August 17, 2015 1:20 PM
To: 'PLOS ONE'
Cc: [REDACTED]
Subject: RE: PLOS ONE Decision: PONE-D-15-02750R2 - [EMID:94243ae13eda7bd6]
Importance: High
Follow Up Flag: Follow up
Flag Status: Flagged
Tracking: Recipient Read
'PLOS ONE'
[REDACTED] Read: 8/17/2015 1:34 PM

Dear PLOS ONE,

As a response to the post-acceptance rejection, I respectfully request that you reconvene the editorial staff, including the Academic Editor (cc'd), whom you consulted to generate this last-minute decision to consider and assess the following point-by-point responses from the authors of the manuscript (shown in red in your original message). Thank you for your consideration.

Kind regards,
keith

From: [REDACTED] **On Behalf Of** PLOS ONE
Sent: Monday, August 17, 2015 5:51 AM
To: Keith R Fluegge
Subject: PLOS ONE Decision: PONE-D-15-02750R2 - [EMID:94243ae13eda7bd6]

PONE-D-15-02750R2
Glyphosate Use Predicts ADHD Hospital Discharges in the Healthcare Cost and Utilization Project Net (HCUPnet): A Two-Way Fixed-Effects Analysis
PLOS ONE

Dear Mr. Fluegge,

I am writing concerning your submission to PLOS ONE entitled "Glyphosate Use Predicts ADHD Hospital Discharges in the Healthcare Cost and Utilization Project Net (HCUPnet): A Two-Way Fixed-Effects Analysis", for which you have recently received an Accept decision. As part of the checks our editorial team

complete on accepted manuscripts, we identified concerns regarding your study design along with issues relating to an undeclared competing interest and a change in authorship. In light of these concerns, we further consulted the Academic Editor and also sought additional advice on the manuscript from another member of the editorial board. Your manuscript has also been assessed by the editorial staff, including the Deputy Editor and a Senior Editor.

During our assessment, we identified several substantial concerns regarding the methodology and reporting of the study in your submission. Following careful consideration of the manuscript and the advice we have received from our further consultation, we have concluded that it does not meet PLOS ONE's publication criteria (in particular #3 and #4 at <http://journals.plos.org/plosone/s/criteria-for-publication>) and must be rejected. The advice we have received noted the following concerns about the analyses and the interpretation of the results:

1) The manuscript does not link children to exposures. The authors generate state estimates of herbicide use, but it is not clear how this was done and the validity of the exercise. It is also not clear that the people classified as cases of ADHD were ever exposed.

A strength of the study is that the healthcare seeking population being used is NOT restricted to children. The population pool takes into account adult ADHD (those receiving the diagnosis as children and then experience symptoms as adults). The USGS absolutely encourages use of the county estimates as state totals (please read the citation, where they say it almost VERBATIM), as opposed to using county data since the data, in the aggregate, may be more accurate. This is not a dose-dependent study. In fact, it would be nearly **impossible**, not to mention **unethical**, to do such a study given the hypotheses made.

(2) The authors did not actually establish that their data represents prevalent cases of ADHD for two reasons. One is that they use hospital discharge data. This does not reflect how many people had ADHD, but rather how many people who used the hospital were discharged with this diagnosis. Changes in this number could reflect changes in prevalence, changes in service provision, or changes in how likely health care providers were to note the diagnosis in charts over time, regardless of actual prevalence, which would be impossible to disambiguate. Second, the authors reported that they used a clinical classification software diagnosis category that includes attention-deficit, conduct, and disruptive behavior disorder. These are very different diagnoses, but they seem to have been lumped all together and used as a variable for ADHD. Why should this grouping of diagnoses be considered to represent ADHD alone? What proportion of these were ADHD? Related to this, ADHD is not a condition that typically requires hospitalization. Were these inpatient hospitalizations? Were they psychiatric? Were they then primarily conduct disorders (not ADHD)? It would not seem that they necessarily even had diagnoses of ADHD.

The ADHD diagnoses were based on ICD (International Classification of Disease)-9 diagnoses. We did not focus on only one diagnoses in our fixed effects analysis (BUT DID IN OUR NATIONAL CDC FINDINGS, USING 314.01 – attention-deficit hyperactivity disorder), but we used the clinical classification software for ADHD (which is part of the mental disorders), which comprises a grouping of diagnoses, including conduct disorder, attention deficit without hyperactivity and with hyperactivity, etc., for example. All of the diagnoses included in the ADHD classification were listed in Supplementary Table 1. These were diagnoses made by a medical professional. Literature shows that ADHD DOES necessitate further psychiatric hospitalizations, and by including more diagnoses, we have introduced replication and increased our population (N).

These steps should be considered **STRENGTHS** and not weaknesses of the methodology.

(3) Even if the authors did establish that herbicide use precedes ADHD increases, there are many other things that likely do, as well. They have not ruled out a very large number of other possible explanations.

We have **NOT** ruled out other possible explanations; in fact, we have actually **TESTED** for them (4 OTHER KNOWN ASSOCIATIONS, IN ADDITION TO OTHER HERBICIDES) or identified their absence as a limitation (as in the case of lead, phthalates, improved diagnostics, greater public awareness, etc)!

We have established that glyphosate use predicts ADHD hospitalization discharges (based upon ICD-9 diagnoses). There are many other variables that could be at play, however, and the authors test for these other variables in ALL models. Model 1: we used other variables with KNOWN associations with ADHD. We included the significant variables (which replicate previous work by others, and we **CITE** these works) in our Model 1. We also included these variables in Model 2. We tested for an additional variable in Model 3 that could be acting as a proxy for the variable of interest. We further add in our discussion several other variables that are not accounted for in the modeling but could be exerting an effect.

(4) The lack of a clear pathway from hypotheses to variables to model to results, along with the very large dataset and the very large number of analyses presented suggests that there is a high risk of generating false positive results.

The modeling and the hypothesizing is VERY specific. We hypothesized that glyphosate may be exerting an effect on ADHD, and we sought to test this hypothesis very specifically. Model 1 does this. We wanted to know if this relationship depended on land use, and we revealed that it did. In Model 3, we wanted to know if glyphosate was acting as a proxy for some other closely related input, and we did. All datasets used in the study have been used in the scientific literature before, including the USGS and HCUPNET.

A criticism of the scientific databases or the number of very targeted analyses done does **NOT** at all warrant a post-acceptance rejection.

(5) The authors' finding on the state of Nebraska is difficult to interpret. The authors highlight that an increase in glyphosate use in Nebraska by over 3 million kg was related to a 0.18% increase in all listed ADHD hospital discharges. However, a 0.18% increase is not one that is meaningful or realistically detectable for medical disorders given the sort of gross level data that is being used.

If this is difficult to understand, this paragraph can be removed. The authors sought to highlight Nebraska specifically, since the state (along with Minnesota) had a much higher proportion of ADHD diagnoses and discharges (as a % of total mental disorders) than other states, which is a finding that would go unnoticed if raw values were used, as you have suggested in (6).

This paragraph alone is **not** enough to warrant a post-acceptance rejection of the manuscript, however.

(6) The authors present much of their work in terms of percent changes and proportions. However, these are not meaningful without understanding raw values, and it is not clear what is meant by some of the findings. Were the percentages and proportions that were presented throughout the article actually entered in models as such?

Absolutely. The use of proportions in health-services research is extremely critical because, not only have we identified an important link that should be published, we have done so showing that ADHD has been increasing as a percentage of all mental health disorders in the U.S. healthcare seeking population. The methodology therefore has important policy implications. Raw data excludes this context.

It has been widely suggested that glyphosate affects a number of mental disorders, which is why we sought to express the data as a proportion to understand what mental disorders were actually increasing in the U.S. healthcare seeking population. The same analogy can be applied to genetic analysis. Gene A might be increasing under a certain drug treatment, but if Gene B is also increasing, does that possibly negate the effect of the drug on Gene A? Quite possibly. Our methodology has taken into consideration glyphosate's possible effect on other mental disorders without having to add a ton more independent variables and risk overfitting or unnecessarily complicating data analysis (i.e., drug's impact on Gene B), making our analyses MORE meaningful than it would otherwise be with raw values (i.e., drug impact on Gene A possibly has something to do with Gene B, for which you did not account, if simply using raw values of Gene A and B.) It is often why efficiency-corrected (ΔCt) values are used in qPCR, for example.

So, is it sound science to exclude such an important context in health services research? If your recommendation were to hold in genetic analysis, it would pass review at all. **How can the PLOS ONE editors justify different methodological standards?**

(7) The authors seem to premise this work on the idea that ADHD prevalence has increased since 2007. They state that there has been a sharp increase in ADHD prevalence in the US beginning in 2007. They cite CDC data that compares 2003 and 2007 and indicates that there was a 22% increase in those 4 years. However, this increase did not begin in 2007, it occurred between 2003 and 2007. Furthermore, other studies show that the prevalence of ADHD has been increasing going back even farther in time, including back into the early 1990s (see, for example, Boyle et al., Pediatrics, 2011; Atladóttir et al., Arch Pediatr Adolesc Med, 2007; Robinson et al., CNS Drugs, 2002).

The increase in ADHD was shown, scientifically, to be increasing beginning in 2007. It does not mean that the increase started then, and our discussion takes this explicitly into account. Our discussion reveals that something changed in glyphosate use around the 2006 timeframe (i.e., the increase occurred between 2003 and 2007). **Indeed, the patent that we cite was originally filed in August 2003!!** So, we fully understand the limitations of the CDC report and have ACTIVELY acknowledged and incorporated it in our interpretation. To say otherwise is a clear indication you have not read the paper at all and do not understand, for example, that we have robustly shown that glyphosate may be acting as a proxy for some other agricultural input, like soil nitrogen cycling (which we have cross-validated with other government databases).

(8) The support for the authors' hypotheses, in many cases, is not clear. For instance, in the introduction, the authors hypothesize that glyphosate and genetically modified corn could be driving the increase in ADHD prevalence. Why this herbicide and this crop among all others? Triple-stacked corn was introduced onto the market in 1997, well after the increase in ADHD prevalence was underway. The introduction describes many different proposed pathways that the authors suggest might be related to linking this herbicide and this crop to ADHD, but it isn't clear why specifically these of all others.

We say that glyphosate and triple-stacked corn are functionally related, and of course they are. In the introduction, the authors highlight two possible mechanisms, using the scientific literature, as to how each could physiologically contribute to the development of ADHD (glyphosate through inhibition of CYP enzymes and Bt through an enteric/neural crosstalk with excess histamine production). The increase in ADHD was underway in 1997, which is why we wanted to test if there was a relationship or not. We reasonably suspected a null result given ADHD was increasing before the introduction of BT maize. Importantly, if the physiological mechanisms presented in the Introduction were contributing to ADHD, we would **NOT** expect

the relationship to depend on land use, as it did. Therefore, we tacitly downplayed these earlier mechanisms, in favor of the findings revealed by Model 3. This is all very carefully and directly explained.

In addition to the above, we also feel that the declaration of competing interests supplied for the submission was incomplete. PLOS defines a competing interest as “anything that interferes with, or could reasonably be perceived as interfering with, the full and objective presentation, peer review, editorial decision-making, or publication of research or non-research articles”. We note that you are affiliated at The Institute of Health and Environmental Research Inc (IHER) which describes its mission as being a “not-for-profit research institute with an interest in genetically modified (GM) organisms, particularly those destined for food”. We feel that this information should have been declared as a competing interest. For more details of our competing interest policy, see <http://journals.plos.org/plosone/s/competing-interests>.

This is **NOT** accurate. The Institute of Health and Environmental Research Inc (IHER) is a U.S. based non-profit. Our mission statement, submitted and confirmed to the Internal Revenue Service for 501(c)3 status (which the authors can supply for further review, if necessary) reads as follows:

“The Institute of Health and Environmental Research, Incorporated (IHER) is an independently operated, 501(c)(3) organization in the United States. The Institute works toward the following goals: the betterment of environmental health and well-being by protecting natural ecosystems and fostering sustainable and environmentally friendly agricultural systems; the improvement of public health through the prevention and control of disease and illness; understand the links between human and environmental health.”

In fact, many of our publications do **not** relate to genetically modified organisms at all. We perform work in tuberculosis research, skin cancer, and psychology. We have publications in Cancer Epidemiology Biomarkers and Prevention, Photochemistry & Photobiology, Journal of Evaluation in Clinical Practice, and Public Health Nursing, etc. It is our regret that you have conflated the work of an organization in Australia with the same name. We are not affiliated with that organization in any way: we are governed by differing tax laws and have completely independent operations, and this disclaimer can be made if is not already clear in the disclosure both in the affiliation and the website cited in the manuscript.

Furthermore, the authors have declared their affiliation with all relevant organizations. We have even cited the organization’s website in the manuscript for further information for readers. We have made every effort to disclose every single possible interest, affiliation, grant support, etc. To say otherwise is to admit that you have not read the manuscript in its entirety.

Finally, we have concerns about the request from the senior author, Stephanie Seneff, to be removed from the paper after it had gone through review, and about the contents of the appendix being added to the Discussion after the manuscript was accepted for publication. While we appreciate that you indicated that you wished to include this information in the Discussion section, the Academic Editor did not have a chance to consider this material in the context of the full manuscript during the review process and has expressed concerns about the late addition of this commentary.

Both of these critiques have nothing to do with the authors remaining on the manuscript or the content contained within the manuscript. Stephanie Seneff attributed her decision to her “psychological “ problems regarding her prior publications, some of which were in the process of being reclassified or retracted

(including prior work detailing a relationship between glyphosate, vaccines, and autism). She stated that she found nothing inherently wrong with the manuscript. I am happy to provide her email to me, which states exactly that. She said the exact same thing to Mr. David Accame as well (dated June 16, 2015) I have that email and would gladly share it if asked to do so. Furthermore, I expressed a concern to Geoff Hamm (cc'd) that Stephanie Seneff was attempting to integrate the findings of the current manuscript **ERRONEOUSLY** in to her presentations at her website. I asked her to refrain from doing so if she did not do so in a way that supported the findings of the manuscript. In essence, Dr. Seneff has a very real reason not to be a part of this work or see it published in any form, for it falsifies many of her theory-based papers.

The inclusion of Appendix A into the main manuscript was made **AT THE REQUEST** of the reviewers! The request could not be accommodated while Dr. Seneff was an author on the paper because she did not agree with the writing. (again because it did not support her glyphosate, vaccines, autism theory). Once Dr. Seneff removed herself as author, I sought to add this content, which had been reviewed by all reviewers as the Appendix A, at the request of reviewers/editors! Additionally, I contacted Mr. David Accame BEFORE the manuscript was editorially accepted, and he indicated that he informed the academic editor that there were changes that needed to be made in light of the authorship withdrawal of Stephanie Seneff from the manuscript. Again, this occurred **BEFORE** (almost two weeks) editorial acceptance on June 29, 2015, further indicating that the authors did **EVERYTHING** in their power to keep everyone informed during this very unusual review and before any final editorial decisions were made.

In light of the above concerns, we are rescinding the Accept decision and rejecting your manuscript. This decision was reached based on extensive discussion among PLOS ONE staff editors, and in consultation with both the Academic Editor who handled the manuscript and another editorial board member, as mentioned above.

None of the aforementioned reasons constitutes a sound reason to accept and then reject this manuscript. In fact, most of the suggestions are ethically questionable or wholly scientifically unreliable! The scientifically rigorous approach we have used and reported in the manuscript uses **MORE THAN TEN** scientifically validated databases. All hypotheses are directly tested using proven methodological standards, and all the findings are supported with **OVER 100 HIGH-QUALITY CITATIONS.**

In light of our very sound rebuttal, the authors respectfully request that the PLOS ONE editors carefully reevaluate their position on this post-acceptance rejection, which has occurred **TWO days** before the original date of publication on August 19, 2015. It is highly questionable and a huge detriment to scientific advancement on the issues of ADHD and autism and their underlying etiologies.

Therefore, the authors of the work ask that publication be granted on the original date indicated of August 19, 2015.

We appreciate that this unexpected news will be very disappointing, and we are sorry that the concerns outlined above were not identified earlier.

Sincerely,

A black rectangular box redacting the signature of the sender.

