Author’s response to reviews

Title: Intelligence gain and social cost savings attributable to environmental lead exposure reduction strategies since the year 2000 in Flanders, Belgium

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Author’s response to reviews:

Dear editor, dear reviewers,

We are grateful to the reviewers for the extensive review of our manuscript. The comments of the reviewers helped further improve the manuscript. Please find below our responses to each of the points raised. Where appropriate, new pieces of text have been copied to this response report.

Warm regards

Reviewer 1

Reviewer's report:

This is an interesting assessment of cost saving attributable to environmental lead exposure reduction since the early 2000s in Flanders, Belgium

The results are relevant for other countries of the Western EU region as well, and I recommend publication in Environmental Health after essential revisions. The present
version is not sufficiently clear; explanations and presentation need to be greatly improved, so the reader can follow the calculations.

1) I would suggest to revise the title. First, using societal costs might be misleading for the reader who would expect more than the current estimates. Only productivity loss due to IQ decrease was included in the calculation, I would rather use social costs (even only partial social costs were estimated, as the authors discussed in the manuscript). Second, why the authors did not use Flanders region in Belgium? West (or Western?) EU region, might not be precise enough.

In response to the reviewers comment #1, the title has been reformulated to:

Intelligence gain and social cost savings attributable to environmental lead exposure reduction strategies since the year 2000 in Flanders, Belgium

In addition, the manuscript text has been edited accordingly at different places.

2) Background

I find that section as a mix of background and methods, since population studied is partially included in that section. This results in very short "background" per se. It will be all the more relevant to explicitly show some lead exposure findings in other European countries, with the same strategies implemented. The authors should then explain the importance such a study on adolescent exposures and economic evaluation of prevention, when lead can be associated with other factors, such as socio-economic status, smoking and other environmental factors.

We agree that this interesting information to include. We included now reference to other studies in Europe that assessed BLL in children our teenagers. The FLEHS studies are unique in the aspect that they follow the population already since 2003. As such the reduction in exposure cannot be clearly shown for the other countries. Hence it has been decided to not include details on the exposure levels for all studies but just the references, as it would be too complicated for the reader to compare different age categories and different sampling periods across countries.

Lines 38 to 57: some of the population studied should be moved within the method section, this will avoid some redundancy.

We agree with the reviewer that the methods section is better suited. The paragraph has been rewritten and a large part has been integrated into methods section “5.3. blood lead level distribution”.

Please find herewith a copy of the revised paragraph based on comment #2:

Furthermore, lead exposure has been associated with socio-economic status, smoking and other environmental factors. Targeted prevention strategies focusing on those factors shall be considered to further reduce exposure. Lead has been monitored extensively in European children and teenagers over the last years, through assessment of blood lead levels (BLL) in countries such as Belgium [8], Croatia [9], Czech Republic [10], Germany [11], Hungary
[12], Kosovo [13], Poland [14,15], Slovakia [9], Slovenia [9], and Sweden [9]. Within the framework of the Flemish Environment and Health Studies (FLEHS), BLL has been monitored in teenagers between 2003 and 2014 in Flanders, Belgium [8]. Based on those data, we assessed the IQ gain and cost savings that can be attributed to reductions in lead exposure over the last decade.

Methods

Some improvements are required. See below for more details.

3) I understand that "detailed information on the selection of the study population and recruitment (…) has been described elsewhere, lines 44-46. However, it would be much easier for the reader to have some of that information, for instance sampling weights, and adjustments made. Only couple of additional lines will be sufficient.

FLEHS I had a different sampling strategy as compared to FLEHS II and III. For FLEHS II and III, the number of participants per province was proportional to the number of inhabitants of that province; while FLEHS I was sampled in nine areas in Flanders. To better clarify, we introduced a few sentences to section 5.1 (Study Population) and a sentence to 5.3 (BLL distribution) in response to reviewers comment #3:

Section 5.1:

… In FLEHS II and III, a representative sample of the general Flemish adolescent population of respectively 210 and 208 participants was recruited by a two stage sampling design with the five districts of Flanders as primary sampling units and schools as secondary sampling units. The number of participants per province was proportional to the number of inhabitants of that province. To account for seasonal variation, recruitment was spread over one year with no recruitment of adolescents during examination periods and summer holidays (June, July, August).

Section 5.3:

The data of FLEHS I were weighed to correct for unequal sample sizes in the eight geographical areas spread over Flanders.

4) I found the text in lines 19 and 59 pretty confusing. Your choice of Lanphear et al (2005) study should be more straightforward. For instance, a loss of 1.9 IQ points was associated with an increase from 10 to 20 µg/dL, so that not all children with a blood lead level greater than 10 would be expected to incur such a loss, as you stated further based on your Figure 1.

In our initial paragraph we included the dose response function reported by Canfield (2003) and the one reported by Lanphear (2005). The one reported by Lanphear is based on pooled analysis of 7 cohort. We now noticed that the cohort that was used in the publication of Canfield (2003) – the Rochester cohort - was considered in the pooled analysis of Lanphear (2005). At the time of the pooled analysis, data of the children at 6 years old were considered;
while the original publication of Canfield used data at 5 years old. As we can consider this as an update, we decided to not include the separate publication of Canfield anymore, and only include the estimates derived from the pooled analysis by Lanphear in our manuscript. As such, the paragraph has been rewritten significantly.

Line 4-5, page 11 the findings from Figure 1, were based on your estimates? For the last interval, as shown in Figure 1, I would suggest to write 20 µg/dL and 30 µg/dL, instead of ≥ 20 µg/dL.

Figure 1 is a visual presentation of the dose response functions from literature. In this case the linear-log dose response curve by Lanphear, and the linear-interval relationship by Gould. We adapted the text to “and ≥ between 20 and 30 µg/dL”, instead of ≥ 20 µg/dL.

In the following paragraph lines 25 to 41, you refer to Gilbert and Weiss' argument in 2006, of using a 2 µg/dL level for action. At that level, since it is below 10µg/dL, did you use a linear relationship or a log linear relationship?

Both models were applied above the cut-off of 2µg/dL, as visualised in figure 1. The linear-log model has been applied for the main conclusions, the linear-interval relationship has been applied as a sensitivity analysis. We added a clarification in the text.

Lines 39-40, why did you estimate the IQ loss per 100,000, this is a bit confusing. Do you mean for a population of 100,000 individuals, to make uniformed your different sampled populations?

Indeed, we express the results per 100,000 individuals to enable comparison between the campaigns.

Perhaps the 5.4 paragraph could be revised to make it clearer. You'll adjust the result section accordingly (see below)

Please find herewith a copy of revised section 5.4:

We focused on the study of Lanphear et al. (2005) [7] as it covered the low exposure range, it was based on international pooled analysis of 7 cohorts (total N = 1333), and the data had been obtained from children followed from birth or infancy until 5-10 years of age.

They established a linear-log inverse relationship between IQ and BLL, in which a doubling in BLL was associated with a decrease in IQ of 1.88 points (95% CI: 1.16-2.59). The linear-log relationship implies that, for a given absolute increase in blood lead, the associated IQ loss is higher in the low level range. A statistical re-evaluation of the data used confirmed that the effect was higher in the low level range and that the conclusions were robust [21]. Based on the linear-log relationship proposed by Lanphear, Gould et al. suggested in 2009 that a uniform decrease (i.e. linear relationship) may be assumed over three ranges, i.e. for BLL between 2 and 10 µg/dL; between 10 and 20 µg/dL; and between 20 and 30 µg/dL [22]. The estimated decrease in IQ points for an increase in BLL with 1 µg/dL was equal to 0.54 (95% CI: 0.34-0.75); 0.19 (95% CI: 0.12-0.26); 0.11 (95% CI: 0.07-0.15) for blood levels between respectively 2 and 10 µg/dL; 10 and 20 µg/dL; and between 20 and 30 µg/dL. There
is little difference in the linear-log and the linear-interval dose response relationship at higher exposure levels. However, the linear-interval dose response relationship is more conservative in the lower dose range (blood lead level below 10 µg/dL), as visualised in figure 1.

5) Page 10: lines 25-26, what do you mean by "a clear dose-response relationship has been demonstrated from 2 µg/dL onwards, we estimated IQ loss to BLL above this threshold". You did no longer differentiate based on different sub-levels, as based on Figure 1?

Apologies for confusion, we did use the different sub-levels as visualized in Figure 1. The text has been rewritten for better understanding and readability.

We estimated IQ loss above the threshold of 2 µg/dL as dose response estimates are lacking in the lower dose region. Furthermore, 2µg/dL is considered as a relevant action level for BLL, as was already argued by Gilbert and Weiss in 2006 to lower the CDC action level to 2 µg/dL [23]. We applied the linear-log dose response function to derive our main conclusions, the linear-interval dose response function was used as a sensitivity analysis.

6) Assuming a non-economist reader, I would suggest to be more explicit in the economic estimates of IQ loss. What do you mean by a "Belgian estimate" of the lifetime value of a one IQ point”? Did you adjust for Purchaser power parity (PPP) for Belgium? It is not clear for which year your estimates were made. I would suggest to use a recent year and update for inflation the 2008 value, and state it is a present value.

We added clarification on the estimate, indeed it was adjusted for purchasing power for Belgium. Furthermore, we adjusted it for inflation. All calculations have been adapted accordingly.

Overall, I would recommend to write a specific paragraph on the economic estimates since your study wants to show the economic saving associated with the reduction of lead exposure on adolescents. Explain what costs are included, how they were estimated, and what costs were not included and the reasons of doing so. This would prevent you to refer to methods in the results or in the discussion sections (see Lines 2 to 21 page 15 in the discussion)

A separate section has been introduced: “5.5. Estimation of social costs attributable to blood lead levels above 2 µg Pb/dL “

The following text has been introduced as paragraph 5.5 in response to reviewer comment #6:

Social costs of IQ decrement were valued by calculating lifetime earning loss per person. We used the estimated lifetime value of 1 IQ point reported by Bellanger et al. [24] as a basis. In this publication, the authors used the life time value of 1 IQ point that was calculated for France in 2008 based on data from the US by Pichery et al. [25] (€ 17,363) and adjusted it for differences in purchasing power to derive an estimate for other countries. As such, the Belgian lifetime value of 1 IQ point was estimated at € 16,458. Based on the harmonised index of consumer prices (https://ec.europa.eu/eurostat/web/hicp/data/database) this value was adjusted for inflation, which results in an estimated lifetime value of 1 IQ point of € 19,464 for Belgium in 2018.
It shall be noted that this estimate is mainly based on studies carried out in the United States [22,27], so we assumed that differences in lifetime incomes are the same in Europe which is not necessarily true. Adjustment for differences in purchasing power parity has been included to take this issue partially into account. As we focused on lifetime earnings only, our estimate is probably an underestimate of the total benefits of Pb control. We did not consider direct medical costs linked to treatment or interventions for children with neurodevelopmental disorders, costs related to special education or additional years of schooling for children as a consequence of these disorders [24]. Furthermore, our estimate is an underestimate of total costs attributable to Pb exposure, as we did not consider e.g. cardiovascular effects.

7) Results of great interest were found. But, again, I find the text in lines 19 to 49 not easy to read. Results should be presented as results, and not as mix of methods and results. Since Table 1 will be included in the text, the reader will have the findings, so it might not be necessary to repeat information from Table 1, extensively. Overall the result section has to be revised and summarized. For instance, there is no need to "repeat during the second sampling (line 33) and line 40, during the third sampling, just refer to the first, second and third samples.

In response to reviewer comment #7, the paragraph has been significantly rewritten:

For each of the sampling periods, the estimated IQ loss attributable to blood lead levels above 2 µg Pb/dL is summarized by table 1. Based on the linear-log dose response function [7], IQ loss per 100,000 individuals was estimated at 94,280 IQ points (95% CI: 58,427-130,138) for FLEHSI; 14,993 IQ points (95% CI: 9,289-20,698) for FLEHSII; and 976 IQ points (95% CI: 604-1,347) for FLEHSIII. This translates into associated social costs that were nearly 100 fold reduced between 1st and 3rd cycle, i.e. from € 1,835 million to € 19 million per 100,000 individuals. When using the linear-interval dose response function as sensitivity analysis, the estimates for the 3 cycles were respectively 32%, 50%, and 54% lower.

8) Line 53, the sentence should be in the method section if not in the section yet. In the result section, the reader should have the results of the simulation that are presented in Table 2. Also check the consistency of the simulation period are 2015 to 2029 line 56-58 and 2014 - 2027 line 7 on the following page.

In response to reviewer comment #8, the sentence has been adapted to:

In table 2, the estimated IQ loss - attributable to BLL above 2 µg/dL - between 2000 and 2014 is compared with the estimated IQ loss that is expected between 2015 and 2029 for the Flemish population.

As there was already a sentence on this in the methods, we did not copy it to the methods to avoid duplication.

The inconsistency in line 56-58 has been corrected

9) Table 2 see title of col BLL ≥2 , this should be proportion of population?
The title of the respective column has been adapted to “Proportion population BLL ≥ 2 µg/dL (%)

10): It would be helpful if the authors could lead the reader through the
Tables 1 and 2, clarifying how the various calculations were carried out. This could be done in a footnote.

For the methodology of the calculations we prefer to refer to the methods section.

11) Discussion:

The results of the study should be summarized (lines 3 to 27)

Line 3 to 27 has been reduced to the following text in response to comment #11:

This study provides the estimated IQ gain and cost savings that can be attributed to reductions in lead exposure over the last decade in Flanders, a West-European region, based on adolescent BLL levels that were measured in 2003-2014 that showed a clear decrease in BLL over time [8]. The cost attributable to BLL exposure above 2 µg/dL decreased by nearly 100 fold over 10 years. Simulating the IQ decrement for the period between 2000 and 2014 and comparing it with the period from 2015-2029 the health and economic benefit in Flanders attributable to Pb reduction strategies has been estimated at respectively 368,687 IQ points (95%CI: 228,476-508,909) and € 7,176 million (95%CI: 4,447-9,9905). The economic estimates are strongly influenced by the shape of the dose response curve.

12) The added value of the study should be introduced.

The added value has been added to the conclusion section in response to comment #12:

The results are relevant for other countries of the Western EU region as well. The approach can be used to estimate the impacts of many environmental policies.

13) As above mentioned, lines 2 to 21 should be better placed in a specific paragraph in the method section. And in the discussion, it would be good to emphasize that the authors have only considered a subset of societal costs that are the most important part of costs in this type of estimates. And maybe authors could refer to studies where those other costs were estimated, to discuss their own results that are conservative. Also, using IQ value has some limitation that authors should report.

In response to the reviewer comment #13, line 2-21 has been integrated in the methods section. The results section now only includes the following text.

Our study underestimates the total costs of Pb exposure, as only the value of IQ decrement was considered based on lifetime earnings.
14) Line 28, page 16, I totally agree with the authors, he difference in BLL between children and adolescents have to be taken into account in the estimates. Would this be possible to show how, even no precision model between the two populations is apparently available.

In response to the reviewer comment #14, we have provided more details on the difference between children and adults based on a report from Health Canada. The difference in geomean between children and adults was 11% and 19% for Canada and the US respectively.

In 2013, Health Canada published detailed BLL statistics over different age groups for Canada (2007-2009, Canadian Health Measures Survey (CHMS)) and the US (2007 – 2009, NHANES) [29]. For Canada, the geometric mean BLL was 11% lower in teenagers (12 – 19 years) as compared to children (6 – 11 years), i.e. 0.90 µg/dL in children and 0.80 µg/dL in teenagers. The 95th percentile was 1.95 µg/dL in children and 1.64 µg/dL in teenagers. For the US, the difference in the geometric mean and 95th percentile between children and teenagers was slightly higher, i.e. 19% (0.988 in children compared to 0.800 µg/dL in teenagers) and 24% (2.5 µg/dL in children compared to 1.9 µg/dL in teenagers) respectively. These findings indicate that our results based on BLL in adolescents of 14-15 years old likely underestimate the actual impact of lead on IQ in the population.

Minor edits among many other typos not reported below

- Some quotation marks appear in the manuscript for instance

Abstract : line 35

Background: line 8

The question marks in the Abstract (line 35) and Background (line 8) have been removed.

- Background: Line 18-19 to be revised

Line 18-19 has been revised to: It shall be emphasized that Even the effects of very low environmental exposure to lead are not negligible [6,7].

- Study population: Line 41 3th year should be replaced by 3rd year.

Error has been corrected accordingly.

- Estimation of IQ loss, line 42, check the use of duplication, I would suggest a doubling

Sentence has been corrected to: A doubling in BLL was associated with a decrease in IQ of 1.88 points (95% CI: 1.16-2.59).

- Page 11: For each period the IQ loss and and economic loss (...) were calculated instead of was

Error has been corrected accordingly.
Comments to Author:

This is a generally clear and thoughtful presentation of analyses that estimate the IQ gain and cost savings associated with the decrease in the blood lead levels of Flemish adolescents over a 15 year period. The authors identify the key assumptions made and justify them. The calculations themselves are straightforward. The results are specific to the situation in Flanders, but the principles can easily be applied to other regions. The approach can be used to estimate the impacts of many other environmental policies, so the specific value of the paper is the generalizability of the methods to other issues.

Two issues that the authors mention warrant more attention. First, the assumption is made that there is no IQ loss associated with a blood lead concentration below 2 micrograms per deciliter. Although the dose-effect relationship on which the calculations are based, the pooled analyses of Lanphear et al. (2005), did not estimate IQ loss in that range, other literature supports the hypothesis that there is no safe (“threshold”) blood lead concentration for adverse cognitive effects. Assuming a linear relationship between IQ loss and blood lead concentration below 2 would produce a much greater estimate of total IQ loss in the population due to the large proportion of children in the cohort studied for whom concentration fell in that range.

We agree to the reviewer that there is no safe threshold for BLL. As such, we introduced the following sections to the methods and results sections respectively:

Although reliable dose response functions are lacking below 2 µg/dL, it has been argued that there is no safe threshold for BLL. Hence, we calculated the additional IQ loss below 2 µg/dL, extrapolating the linear dose response function reported by Gould et al [22] for the range between 2 µg/dL and 10 µg/dL.

Extrapolating the linear dose response function below 2 µg/dL, an additional amount of respectively 29,917; 54,597; and 52,219 IQ points would be lost per 100,000 individuals over the 1st, 2nd, and 3rd cycle.

The second issue is that in most settings, especially higher-income countries, blood lead concentrations are considerably higher in young children than in adolescents. Therefore, calculating IQ loss based on adolescent concentrations will seriously underestimate the total health losses. The authors’ contention that it is blood lead concentrations in middle childhood that are most predictive of IQ loss does not rest on very compelling evidence (even in the pooled analyses). This limitation should be given greater prominence in the Discussion.

We introduced an additional sentence on the higher absorbance in children in the discussion: “Absorption of ingested lead can be up to five times greater in children than in adults and even greater when intakes of dietary minerals are deficient.”

In response to the reviewers comment, we agree that our original statement “This justifies using BLL distribution in adolescents in our study to assess impact on IQ.” (that was based on the observation little difference has been reported in BLL between adults and children) might have been too strong.

We introduced the paragraph below with BLL data from Canadian Health Measures Survey (CHMS) and NHANES stratified for age group, to give the reader better understanding how
different the distribution between children and adolescents may be. We removed our former statement “This justifies using BLL distribution in adolescents in our study to assess impact on IQ.”; and replaced it by “These findings indicate that our results based on BLL in adolescents of 14-15 years old likely underestimate the actual impact of lead on IQ in the population."

In 2013, Health Canada published detailed BLL statistics over different age groups for Canada (2007-2009, Canadian Health Measures Survey (CHMS)) and the US (2007 – 2009, NHANES) [29]. For Canada, the geometric mean BLL was 11% lower in teenagers (12 – 19 years) as compared to children (6 – 11 years), i.e. 0.90 µg/dL in children and 0.80 µg/dL in teenagers. The 95th percentile was 1.95 µg/dL in children and 1.64 µg/dL in teenagers. For the US, the difference in the geometric mean and 95th percentile between children and teenagers was slightly higher, i.e. 19% (0.988 in children compared to 0.800 µg/dL in teenagers) and 24% (2.5 µg/dL in children compared to 1.9 µg/dL in teenagers) respectively. These findings indicate that our results based on BLL in adolescents of 14-15 years old likely underestimate the actual impact of lead on IQ in the population.