

Author's response to reviews

Title: Neuropsychological effects of chronic low-dose exposure to polychlorinated biphenyls (PCBs)

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Author's response to reviews: see over

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28/09/2005

**Re: Ms Martin Peper, Martin Klett, and Rudolf Morgenstern:
Neuropsychological effects of chronic low-dose exposure to polychlorinated biphenyls
(PCB)**

Dear Dr. Grandjean,
dear Dr. Ozonoff,

in the second revision of our manuscript, we tried to clarify the open points. Attached below please find a point-by-point response to your comments. The accordance with instructions for authors was checked again with the pre-acceptance checklist.

If further changes are necessary, don't hesitate to contact me. We hope that this version will now meet with your and the reviewers' approval.

Yours sincerely,

Martin Peper, PhD MD
encl ms

Response to Comments

You did not use lipid adjustment of the serum concentrations. Was a lipid measurement not available, and if no, why not? We would prefer the results both as the volume-based and the lipid-based concentrations.

Lipid adjustment was not used because the German commission of human biomonitoring has decided not to refer to the lipid fraction. No particular advantages of this method were recognized as compared to blood volume relation and its accuracy.

Important arguments not to use lipid adjustment have been reported in a recent publication of Schisterman et al., 2005, who very clearly addressed the dangers of such adjustment:

„Additionally, factors that share a common cause will appear correlated in strata of that common cause. Given an alleged relation between PCB and serum lipids, their adjustment might generate spurious associations if an unmeasured factor is related to both serum lipid levels and the outcome.“

The Biological Monitoring Section was rewritten and the following statement was added:

“Although some authors recommended lipid standardization for the measurement of persistent lipophilic chemicals (e.g., Brown & Lawton, 1984), a recent simulation study showed that PCB lipid standardization or the division of serum concentrations by serum lipids is highly prone to bias (Schisterman et al., 2005). Since group differences of serum lipids were not evident and because lipid adjustment is likely to produce spurious associations and biased results (Schisterman et al., 2005), unadjusted values were used.”

Please define T on page 8, and likewise all abbreviations the first time they are used in the text (as well as in the list of abbreviations, which should be moved in front of the statement on competing interests).

T is a common scale of norm value that does not require further explanation (just like z-scores). We added “normative T-values”. The text was checked again for first appearance of abbreviations. However, standard abbreviations such as WHO, US, EU or IUPAC-Number, d, were not defined. The list of abbreviations was moved in front of the statement of competing interests.

You indicate that PCB 52 could not be measured – was it below the detection limit? Please state the reason.

PCB 52 could not be measured due to methodological/technical reasons: a blind-value test could not separate PCB 52 samples from unexposed samples. Statement was added.

In agreement with the reviewer comments, we agree that Bonferoni adjustment is controversial, and many statisticians prefer the Holm adjustment, if any. It would be better to present unadjusted data in the Results section, and to introduce the issue of multiple comparisons in the Discussion.

The Holm adjustment is applicable only for orthogonal comparisons. However, the present test battery approach yields correlated measures. Because the Bonferoni as well as Holm adjustment is still too conservative for correlated measures, at least two German statistics text books recommend an adjustment of the Bonferoni adjustment (Bortz, 2000; Bortz, Lienert &

Boehnke, 1990). Therefore, we do not agree with the suggestion that the Holm adjustment is a more appropriate technique.

However, to meet your recommendations, we present now unadjusted data in all tables and discuss this issue in the Discussion (The beginning of the section “Subjective and behavioral effects of chronic exposure to low chlorinated PCBs” was rewritten).

Since alpha inflation due to multiple testing is a fundamental problem to all test battery approaches, we believe that it is necessary to mention this already in the Methods section. Moreover, we renamed “original alpha” to “nominal alpha” which is used slightly more often in the literature.

Please check that tables are formatted in strict accordance with the journal rules. It is not necessary to indicate ‘legend’ below the tables.

‘Legend’ was omitted. Tables were reformatted and significance-* were omitted (only nominal alpha is given).

Please indicate in the footnote for Table 2 the criterion for listing correlation coefficients.

The footnote of Table 2 was improved by adding:

*: $p < .05$, **: $p < .01$, ***: $p < .001$ nominal α ; only correlations with at least small effect size are given; correlations with potential exposure sources such as indoor installations of chemically treated wood, frequent meat or milk consumption were trivial and are not presented; correlations with large effect sizes are printed in bold.

(This refers to the suggestion of Cohen that coefficients with a small effect size correspond to $d > 0.2$ and $r > 0.1$. Correlation coefficients with large effect sizes correspond to $d > 0.8$ and $r > 0.5$, respectively).

In Table 4, please explain what is meant by ‘potentially relevant effect’.

Improved explanation in Table 4 footnote: Δ : at least moderate attenuation of d_1 and d_2 suggesting potential reproducibility.

Substitute inhalation for inhalative in the abstract throughout the text. Please say reproducibility instead of replicability (p. 8 and later on). Please correct spelling of ‘nicotine’ on p. 8 and ‘venous’ on p. 9.

Changed.

Because you seem to have chosen US English, please spell ‘plasticizers’ accordingly on p. 9, ‘partialing’ on p. 16, and ‘dichotomized’ on p. 18.

Done.

Test battery is two words on p. 10, and ‘headache’ is one word on p. 18.

Changed.

On p. 20, you mention a ‘world list learning’ – do you mean a ‘word list’?

This is the AVLT word list learning task (see Table 4). “AVLT” was added on page 20.

In the legend for the two figures, leave out ‘are given’.

Done.

In Figure 2, please indicate that the black columns show the values for the ‘PCB-exposed’ subjects.

The Figure legend (box within Figure 2) was changed and the legend was slightly modified.