COLUMBIA CENTER FOR CHILDREN'S ENVIRONMENTAL HEALTH

MAILMAN SCHOOL OF PUBLIC HEALTH
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Memo to: Carrol Christensen, Ph.D
From: Robin M. Whyatt, DrPH
Date: April 9, 2015

Re: July 2011 letter to Deborah Smegal, M.P.H.

In reading through the 2014 chlorpyrifos risk assessment document, we were pleased to see that it contained almost all of our correspondence answering questions from both the SAP and EPA on our various chlopyrifos articles. However, the letter we prepared answering a series of questions from Deborah Smegal, MPH, on our 2011 manuscript[1] was not included in document and, we believe, should also be part of the docket. As you will see, the letter first lists each question from Ms. Smegal followed by our answers to that question. Please let us know if you have any questions.

[1]Rauh V, Arunajadai S, Horton M, Perera F, Hoepner L, Barr DB, Whyatt R. Seven-year neurodevelpmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide, Environ Health Perspect. 119(8): 1196-201, 2011. PMCID: PMC3237355

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Dear Debbie,

The questions are quite straight-forward, so hopefully this will clarify your reading of the results. The important point is that we have modest yet meaningful findings that are consistent across several different analytic approaches. We note that you have suggested other statistical approaches, such as generalized Linear Model, which is typically employed in situations where departures from normality are more extreme than the present case. It is always a judgment call to select the single 'best' approach. Thank you for pointing out the one digit error in the online version of the paper (Table 2), and this has been corrected in the final version. Otherwise, please let us know if you have additional questions.

1. The paper reports the decline of IQ, and Working memory in terms of 1 standard deviation increase of CPF. However it is recognized that usually chloropyriphos exposure follows log- normal distribution. Infect the authors made the same distributional assumption of CPF while imputing the non-detects. It would be more helpful for interpretation purposes to express the decline of IQ and Working memory in terms of geometric standard deviation of CPF instead of arithmetic standard deviation. In table 9.2 of page 262 of Environmental Statistics and Data Analysis by Wayne R. Ott, relationship between arithmetic parameters (mean and standard deviation) and geometric parameters (mean and standard deviation) were provided. Using these transformation CEB found that 1 geometric standard deviation increase of CPF prenatal exposure will decrease the full scale IQ by 0.87 % and working memory by 1.73%.

We are not sure how exactly the calculations above were done. We computed the Geometric Mean (GM) and Geometric Standard Deviation (GSD) of the Chlorpyrifos exposure from the data and were found to be 0.65 and 6.22 respectively. Thus for one GSD increase in CPF, the Full Scale IQ on average decreases by 1.85% and Working Memory by 3.66%.

2. In Figure 1 page 29, the upper bound of the x axis(Chlorpyrifos) is shown to be 25 pg/gm. However in the second paragraph of page 11 it was reported that the maximum CPF exposure is 63 pg/g. It was not clear to us why in figure 1 the range of CPF was truncated.

The maximum CPF exposure in the sample was indeed 63 pg/g. The number of children with CPF levels above 25 pg/g were 4. The x-axis was truncated at 25 pg/gm for the following reasons

1) One of the subjects did not have the outcomes measured

2) The subject with 63 pg/g was a highly influential observation (outlier) and drastically impacts inference. This was confirmed based on residual analysis in most analyses. Where appropriate this observation was removed from the analysis. This influence was observed in the spline plots as well and this lone outlier at the extreme end of the exposure made the plot unstable and uninformative

3) With just two observation left in this range, the data were too sparse and the splines too unstable in this region.

Moreover, being exploratory in nature, the spline plots were constructed to assess the adequacy of a linear relationship between log-transformed CPF and WISC scores. We therefore restricted the splines to the range of CPF values were the data were not sparse and the curves were stable.

3. In table-2 for the fully adjusted model of Full scale IQ the 95% confidence interval for the coefficient of CPF includes 0. Therefore the CPF is not statistically associated with Full scale IQ based on C.I. However the p value for the same coefficient is shown to be less than 0.05. It is statistically impossible to have p value less than 0.05 and 95% confidence interval includes 0 at the same time. The author should explain this inconsistency between the p value and the C.I -- perhaps this inconsistency is simply due to rounding?

The Fully adjusted coefficients in Table 2 should have values consistent with the values in the supplementary material Table 1. Thus for Full scale IQ , rounded to three significant digits, the 95% CIs were -0.006 to 0.000, and the p-value rounded to 2 decimal places is equal to 0.05 (0.048). The values in table 2 in the main paper should have read -0.006, 0.000 as opposed to -0.006, 0.001. Thanks so much for picking up this incorrect digit.

4. Using Lasso model, it was shown in Table 2 that prenatal exposure and Full scale IQ is not statistically associated at alpha=0.05 level. However in the result section of the abstract it was stated that for each standard deviation increase in exposure of CPF full scale IQ declined by 1.4. The paper should include a discussion about non significance of prenatal exposure of CPF for the Full scale IQ when interpreting the association between IQ and CPF exposure.

We direct the reader to the comparability of the LASSO and the fully adjusted models in terms of effect size (coefficient). The fully adjusted model is the more familiar approach to regression analysis, and includes all of the covariates. We were interested in using LASSO to demonstrate that the effect sizes do not vary in a meaningful way, using a procedure that may be less vulnerable to over-fitting. In interpreting the results, the effect size may be more important than statistical significance alone, as the significance can be affected by sample size and power. Specifically, when sample size and power are modest, the results of significance tests can be misleading because of being subject to Type II errors (incorrectly failing to reject the null hypothesis). In these situations, it can be more informative to use the effect sizes (how much of an effect), especially with the confidence intervals.

5. The authors stated in the data analysis section of page 9 that WISC-IV composite index scores have been log transformed to stabilize the variance and to improve the linear model fit. Another alternate approach may be to use the generalized linear model which may be better able to deal with the issues of concern.

The intention here is to investigate the shape and the strength of the possible dose-effect relationship. While a Generalized Linear Model might also be used, log transformation usually provides consistent results when we have normal residuals (as we do here). Generalized Linear Models are a kind of extension of the linear modeling process that allows models to be fit to data that follow probability distributions other than the Normal distribution, such as the Poisson, Binomial, Multinomial, and etc. Generalized Linear Models also relax the requirement of equality or constancy of variances that is required for hypothesis tests in traditional linear models. While it is certainly possible to use Generalized Linear Models (and there are many different ways to test our hypotheses), there is no indication that this procedure would result in a better fit or a more precise estimate.