Response to "μg/kg-day or μg/day? A commentary on Georgopoulos et al., *JESEE* 2008"

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We thank Dr. David T. Mage for his comments on our paper (Georgopoulos et al., 2008, JESEE, 26 March 2008; doi:10.1038/jes.2008.9), which include many insightful observations. In particular, his letter presents a valid argument for the type of dose metrics relevant to characterizing exposures to pesticides. This is important in a broader context, although it is not central to the issues of exposure reconstruction addressed in the paper.

The focus of our paper was primarily on the formulation and evaluation of approaches for mathematical reconstruction of human exposures from available biomarker data (analysis of an "inverse" problem), and on identifying challenges and gaps associated with such data. Specific case studies for demonstrating "inverse solution" algorithms included the reconstruction of chlorpyrifos (CPF) intakes for adults using the National Human Exposure Assessment Survey (NHEXAS) (Whitmore et al., 1999; USEPA, 2008) data set. A CPF intake metric in units of μg/day was used in the demonstration, primarily because the actual amount of food consumed by each individual was not readily available. Only total intake estimates were available in the form of a population distribution function from Pang et al. (2002) (i.e., "matching" intake and biomarker data were not available at the "individual level" for the above demonstration).

We certainly agree with Dr. Mage's comment that "one cannot tell from the authors' results expressed as μg intake/day, which simulated subject in their cohort is at the greatest risk of a CPF health effect…" However, that was not the aim of the analysis presented in the paper. It should be noted, nevertheless, that it is a straightforward task to estimate the distribution of intakes (in units of μg/kg-day) using data on body weights of each subject and the distributions of intakes — for example, through randomly sampling from the intake distribution (in units of μg/day) and allocating the samples to different individuals. However, the incorporation of such an additional calculation would not alter the analysis or conclusions of the paper and, furthermore, it would not increase the actual information content of the analysis. One should keep in mind that the case studies focused on the assessment of the significance of data gaps and employed various assumptions to fill some of these gaps (i.e., to "synthetically augment" the data) for evaluation purposes; therefore, identifying subjects that are at the highest risk would be influenced by these assumptions and it was not the objective of the paper.

In general, exposure and dose reconstruction involves estimation of multiple entities such as concentrations in various media, frequencies and time lengths of contact with these media, intake rates through different exposure routes, total uptakes (scaled by body weight or unscaled), and so on. Depending on the specific objective of an analysis, the corresponding calculations for the most relevant metrics would be performed. So, when, for example, the objective of an assessment is to compare risks or RfDs, we fully agree with Dr. Mage's comment that computing the CPF intake in units of μg/kg-day would result in more direct comparisons. When, however, the objective is the reconstruction of concentrations in relevant ambient or microenvironmental media (e.g., concentrations of pesticides in foods), or the estimation of route-specific contributions to total exposure, scaling by body weight is not as critical. Actually, unscaled estimates of intakes are directly "translatable," through exposure route-specific "intake rates" (e.g., ingested mass or inhaled volume per day), to contaminant concentrations in the different exposure media — and these concentrations are in fact the regulated metrics corresponding to the common forms of environmental standards. Hence, these were the metrics used in the case studies presented in the paper.

In conclusion, we again thank Dr. Mage for his comments on our paper, and we agree that a dose metric in units of μg CPF intake/kg-day would be useful for direct comparison with metrics such as chronic RfD. However, as explained above, the focus of the paper was on evaluating inversion approaches and data gaps associated with exposure reconstruction, and on interpreting reconstruction results in ways that would allow to "link" them with contaminant concentrations in specific exposure media. After considering the limitations in available data for the case studies, and taking into account the need to "translate" route-specific intake rates to concentrations in

exposure media, we selected an intake metric in units of μg/day for the simulated population.

References

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Letter to the Editor

Magnetic fields and miscarriage: A commentary on Mezei et al., *JESEE* 2006

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In a recent publication of your journal, Mezei et al. (2006) stated in their abstract and discussion that "These findings are consistent with the hypothesis suggesting that the association between maximum magnetic fields (MFs) and miscarriage are possibly the result of behavioral differences between women with healthy pregnancies and women who experience miscarriages". Their conclusion was not supported by their evidence because it did not compare behaviors or MF exposures of women whose pregnancies ended normally or ended with miscarriages. It simply showed once again what common sense would suggest and what a study by Lee et al. (2002) had already clearly documented that there will be a very poor correlation between the size of a maximum field from 1 month to the next and brief high fields are more likely to occur in some environments than in others. Their results showed only one of the several conditions that are required to support the above statement. They still have long way to go.

In 2002, Li et al. (2002) and Lee et al. (2002) simultaneously published two studies, one a prospective cohort study and the other a population-based nested case–control study, which demonstrated a twofold increased risk of miscarriage associated with the maximum (peak) level of MF exposure during a 24-h personal measurement period.

The Mezei et al. (2006) study and a 2006 study by Savitz (2006) were funded by the Electric Power Research Institute (EPRI) to explore the hypothesis that this association was not a causal association but rather a reflection of increased activity and resulting peak MF exposures among women whose conceptus had died and was about to be expelled. If this explanation were true, the death of the conceptus would somehow cause increased activity thus leading indirectly to the high MF exposure instead of high MFs causing the death.

Common sense and some pilot study results suggest that most of such brief high exposures come from getting near to certain appliances and underground electrical conduits. Thus, if brief high EMF exposures cause miscarriage it would have important policy implications for the design of appliances and the utility grid.

One of us (RRN) initially had doubts about the Lee and Li findings based on the following factual assumption and the following general inferential rule:

Assumption: Any EMF/miscarriage effect from ambient peak fields must be small or modest because it has not been obvious to us before this.

General rule: Using highly unstable exposure metrics to detect small or modest effects will almost always produce null results due to random misclassification of exposure. Thus, if an association is seen there must be some noncausal explanation for seeing it.

Although the general inferential rule may be valid, the factual assumption may well be premature. Miscarriages are private events that are not well documented, and a substantial effect might indeed be missed. The fact is that two well-designed studies that were subjected to two rounds of peer review did show such associations. There are four possible explanations for Li et al.'s findings (for a cohort study similar to his, selection bias is not a candidate):

(a) The effect is real and is so large that it was still detectable despite the random misclassification that resulted from