Author's response to reviews

Title: Analgesic and anti-inflammatory drug use and risk of bladder cancer: A population-based case control study.

Authors:
Joan Fortuny (jfortuny@imim.es)
Manolis Kogevinas (kogevinas@imim.es)
Michael S Zens (michael.s.zens@dartmouth.edu)
Alan Schned (alan.schned@dartmouth.edu)
Angeline S Andrew (angeline.s.andrew@dartmouth.edu)
John Heaney (john.heaney@dartmouth.edu)
Karl T Kelsey (kelsey@hsp.harvard.edu)
Margaret R Karagas (margaret.karagas@dartmouth.edu)

Version: 3 Date: 18 April 2007

Author's response to reviews: see over
Dear Editor,

We are pleased to submit the revised manuscript “Analgesic and anti-inflammatory drug use and risk of bladder cancer: A population based case control study”. We are grateful to the reviewers for their helpful comments that have been incorporated into the manuscript as follows:

Reviewer 1.

1.- **Recall bias issue:** We agree with the reviewer. We have expanded our discussion and provide further evidence on page 11 that our results on phenacetin are not likely due to recall bias. It is important to note that while phenacetin is a risk factor for urothelial cancers, the reason for its withdrawal from the market in the mid-eighties was its strong association with interstitial nephritis, and not the association with urothelial cancer. Also, our results support already published evidence on the effects of phenacetin on bladder cancer risk and have biological plausibility. Taken together, these factors argue against a strong recall bias affecting our findings. The fact that there has been a delay between the diagnosis/index date and the interview date may have caused a decrease in the recall of medications used, although there is no indication that this was differential between cases and controls as both interviews took place concurrently.

2.- **Exposure ascertainment issue:** Due to the nature of the study, we were unable to conduct validation studies on the use of medications. Unfortunately, this study is not well suited for validation studies using prescription databases or medical records because NSAIDs and analgesics are most often acquired without a prescription in the US.

3.- **Aspirin association: crude vs. adjusted:** We agree with the reviewer. The fact that aspirin is more prevalent among cases than controls is intriguing given the OR in the adjusted models. The reviewer is correct in attributing this paradox to the fact that users of aspirin tend also to be users of phenacetin. If models for aspirin are left unadjusted for phenacetin use, aspirin is no longer related to a decreased risk of bladder cancer (OR= 0.91, 95%CI= 0.7-1.3). The results of the aspirin exclusive users model strengthen these arguments. We have incorporated a brief paragraph on this issue on page 9.

Reviewer 2.

1.- **Background information issue:** We have eliminated a sentence referring to the relationship between aspirin use and a decreased risk of colorectal cancer, since this association is now widely known. We also added some details on the reported associations (pages 4 and 5). Table 1 shows a comprehensive review of the literature
including not only the risk estimates, but design issues and other study details. Thus, we also refer the reader to this Table.

2. **Limited information on confounding factors issue:** We agree it would have been interesting to be able to adjust for other potential confounders like the ones proposed by the reviewer as well as exposure to water chlorination by-products. We now have acknowledged this in the text and have argued against the likelihood of confounding by occupation or chlorination by-products. We are not aware of an association between medication use and job exposures or levels of chlorination by-products in drinking water, and in our case-control study from Spain, no appreciable change in the associations for analgesics and NSAIDs were seen after adjustment for these factors (page 12). We were able to adjust for educational level, but it had no appreciable effect on our estimates (page 12). This additional analysis has been included in the manuscript.

3. **Recall bias issue:** This point is addressed above.

4. **Historical drug information validity issue:** The reviewer notes that phenacetin has been off the market for the past 20 years. Thus, there may have been lower recall of phenacetin use compared to aspirin or other NSAIDs use. The latency period for phenacetin as a cause a renal pelvis cancer is thought to be 25 years (Steffens J, Nagel R, Br J Urol. 1988;61:277-83). Given this latency, it will be interesting to see whether, in future studies risks related to phenacetin use and decline; with the hypothesis that most cancers attributable to this risk factor would have already occurred.

5. **Stratification by cell type issue:** In the text we provide the actual numbers of tumors with a histology other than transitional cell carcinoma. The numbers are too small to allow for any meaningful comparisons. However, we conducted an analysis excluding all non-transitional cell carcinomas; results were largely unchanged from the analyses of all cases. To our knowledge this is the first study to provide data on the effect of past medication use in relation to bladder cancer invasiveness and TP53 alteration.

6. **Selection bias issue:** We agree that this point deserves mention and therefore added it to the discussion (page 12). Overall participants and non-participants were similar according to factors we were able to evaluate: age, sex and urban residence (data not shown). If non-participants were more or less likely to use analgesics or NSAIDs, the resultant bias would be predicted to occur in a similar direction for all drugs (as with recall bias) which did not appear to be the case in our data.

7. **Minor issues:** We have corrected the references and added brand names of phenacetin to the text (page 11).