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**Mis-specified and Non-Robust Mortality Risk Models for Nasopharyngeal
Cancers**

Background

An IARC (International Agency for Research on Cancer)¹ working group categorized formaldehyde as a human carcinogen (Group 1). This decision was mainly driven by the analysis published by Hauptmann et al. (2004)² of the NCI (National Cancer Institute, USA) cohort comprising sub-cohorts from 10 plants. Altogether, 8 formaldehyde-exposed nasopharyngeal cancer (NPC) cases and two unexposed NPC cases were documented during follow-up. The authors emphasized the relationship found between highest formaldehyde peak exposure and death from NPC, and argued that adjusting for plant did not substantially change the results (Hauptmann et al. 2004)².

However, Marsh and Youk (2005)³ carried out an analysis of the same data emphasizing that there is a cluster of 6 formaldehyde-exposed NPC cases in one specific plant (plant 1). They argued that the increased NPC mortality was restricted to that plant.

However, both groups of scientists used different statistical approaches and model assumptions.

Objectives and Methods

One target of this study re-analyzing the data of the NCI cohort was to examine whether it would be necessary to consider an additional variable for an interaction between working at a plant/plant group (1 vs. 2-10) and peak exposure. A rigorous statistical evaluation was performed to determine whether this interaction term could be dropped from the model or not. This extended modeling combined in one analysis both analytical approaches of Hauptmann et al. (2004)² and Marsh and Youk (2005)³. If the interaction term could be dropped without reducing the goodness of fit relevantly the Hauptmann et al. (2004)² approach was appropriate, otherwise the arguments of Marsh and Youk (2005)³ could not be neglected. This interaction analysis was no post-hoc approach because a heterogeneous distribution of cancer cases across plants was already mentioned in Blair et al. (1990)⁴ and described in detail by Marsh et al. (2002)⁵.

The second aim of this re-analysis was to consider the impact of the small number of NPC cases on the robustness of the statistical analyses presented in Hauptmann et al. 2004². Given the rarity of NPC cancers, the robustness of the results (coefficients, p-values) was explored by adding only one more pseudo-case of NPC to the data repeatedly. These pseudo-cases were identified by stratified random sampling from all survivors up to the end of follow-up (12/31/1994). Stratification was done by the

four exposure categories of highest peak exposure and the ten risk sets. This generated 40 scenarios with one imputed pseudo-case each. We replicated the imputation procedure three times (if possible) to take within-strata variation into account. Again, this sensitivity analysis was no post-hoc approach because it was known from the beginning that the NCI study would suffer from a small number of NPC deaths (Blair et al. 1986)⁶.

Results

According to this re-evaluation, Hauptmann et al. (2004)² missed an important interaction between the plant group (1 vs. 2-10) and the exposure variable, which prohibits a generalization of the plant 1 findings to the other plants investigated. It would be even less appropriate to generalize plant 1 findings beyond the NCI study. In addition, the sensitivity analysis demonstrated considerable uncertainties in the risk estimates particularly related to plant 1. This instability of the NPC risk estimates was not reflected in the confidence intervals and p-values published in Hauptmann et al. (2004)².

Conclusions

Clearly, the results of this reanalysis of the NCI study did not support the suggestion of a causal association with formaldehyde exposure and NPC. The decision of the working group at IARC to classify formaldehyde as a Group 1 substance should therefore be reconsidered. Both statistical approaches (interaction analysis, sensitivity analysis) should also be carried out in the upcoming NCI analysis of the extended follow-up. The results of this study were published in Marsh et al. 2007⁷.

References

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