

STUDY PROTOCOL: POOLED ANALYSIS OF PETROLEUM WORKER CASE-CONTROL STUDIES (DATED 6TH AUGUST, 2010)

Comments from Prof Tom Sorahan, responses by Pooled Anal co-PI's

27th September, 2010

1. Abstract, page 5. The reviewers summarise the findings of the various nested case-control studies in the petroleum industry in the following terms: "the Australian study reported a leukaemogenic effect at low benzene exposures, while results were less clear in the other studies". The 2005 review into data quality and comparability of these studies carried out by Dr Brian Miller and colleagues from the Institute of Occupational Medicine (IOM) summarised the same findings in the following terms; "The results from these studies were broadly similar in showing little evidence of an effect of low benzene exposure, except for the Australian study, which reported a leukaemogenic effect at much lower levels than the other studies" (Miller et al, 2005). The IOM summary appears to me to be a more reasonable summary.

.I don't see much difference here and prefer our wording.

We could not see any real difference.

2. Existing Studies, page 7. The protocol states that three nested case-control studies have been carried out. I understand there to be four such studies, but that only three are available for the current protocol. This should be made clear.

OK but we also need to state that the 4th study from API didn't have benzene exposure data only THC. (There are only three studies that investigated bz per se, so no change is needed).

3. Exposure estimation, page 9. The researchers state that "All exposure estimates were carried out blind as to case/control status". This is true if we only mean the work carried out by the researchers. But it is not true, at least for the Australian study, if we

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include the key data used in the exposure estimation, i.e. information on work histories and tasks carried out supplied by workers (cases, controls and colleagues). In other words the studies are not all 'double-blind'. In the 2002 workshop on leukaemia risks in relation to benzene exposure, Dr Glass noted that for the Australian study "it is possible that recall bias might have occurred in the collection of job histories from the cases" and that "thirteen of the 33 cases supplied partial job histories after diagnosis of leukaemia" (Glass, 2003). Furthermore "it is also possible that there was recall bias from the colleague who provided task specific information about a worker's job history" (Glass, 2003), and "some of the site interviewees might have been able to identify the subjects" (Glass et al, 2003).

Analyses need to be carried out with and without all information that has the potential for being biased; such potential needs to be assessed in all three studies. The issue of bias in the work histories was not considered in the IOM audit which "explicitly excluded the detailed checking of ... extraction of data from source" (Miller et al, 2005).

This is selective reading. The last para of the section explains that the recall bias would be low or we would expect to see the same effect for MM and NHL. Doll didn't think that this was likely see below.

4. The protocol should include a commitment to relating and reconciling the new findings with the overall findings from the parent cohort studies. Professor Sir Richard Doll noted in connection with the Australian study that the "interpretation of the case-control study has to be consistent with the findings of the cohort study". (Doll, 2003)

Also selective reading, the whole para is: "Finally how are we to regard the Health Watch findings as fitting in with the many other reports? Personally, I do not see much difficulty as, in my opinion the interpretation of the case-control study has to be consistent with the findings of the cohort study: in other words the very high relative risks reported cannot be regarded as reflecting causality. To my mind they are much more readily explained as chance findings associated with random variation in the

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small number of cases (three) in the lowest exposure group of cases and in the highest exposure group of controls (again 3). I see no justification for questioning the findings or interpreting them as due to recall bias, the potential effect of which has been thoroughly investigated; but the results have to be compatible with those of the cohort study and the apparent difference is, I suggest, most readily explained by the combination of selective cut points and chance. The potential effects of the latter would be easier to see if the results were presented with floating absolute risks rather than with invariable points for minimal exposure as the focus for comparisons.”

When we combined the 2 lower exposed groups to a more stable reference category there was still an effect. We will use spline analyses- a similar concept as suggested by Doll (e.g. floating absolute risks).

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References

Doll R. Closing Remarks: leukaemia risks in relation to benzene exposure. In “Leukaemia risks in relation to benzene exposure”. Report of a meeting held on 22nd October, 2002. London, Institute of Petroleum, 2003, pp 63-64.

Glass DC, Gray CN, Jolley DJ, Gibbons C, Sim MR, et al. Leukaemia risk associated with low level benzene exposure. *Epidemiology* 2003;14:569-577.

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