Reviewer's report

Title: Reanalysis of updated mortality among vinyl and polyvinyl chloride workers: confirmation of historical evidence and new findings

Version: 1 Date: 3 January 2007

Reviewer: Giuseppe Mastrangelo

Reviewer's report:

General
This is a mortality study in a cohort (1658 workers exposed to vinyl chloride of Porto Marghera) assembled by Comba P. and Pirastu R., using information provided by plant managers. The statistical analysis uses an internal reference instead of the general population in order to avoid the healthy worker effect, a selection bias.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Authors fail to evidence a significant increase of lung cancer in PVC baggers. However, it is known since 2003 [Mastrangelo G, Fedeli U, Fadda E, Milan G, et al. Lung cancer risk in workers exposed to poly(vinyl chloride) dust: a nested case-referent study. Occup Environ Med. 2003; 60:423-8], that the database from Comba and Pirastu was biased by misclassification of both disease (Table 5) and exposure (Table 6). Table 5 showed that on using the Dunn’s method, there was an agreement of 54% between the lung cancer diagnoses based on either death certificate (Comba P. and Pirastu R., personal communication on the extension of follow-up to July 1999) or histology (above study). Table 6 showed a poor agreement (Cohen’s Kappa = 0.348) in the definition of PVC bagger (known exposure only) between the study of Comba-Pirastu (personal communication) and the above study. The latter was a case-control study nested in the same cohort of Porto Marghera, which demonstrated that in PVC baggers lung cancer OR increases by 20% for each extra year of work (OR=1.2003; CI=1.0772–1.3469; p=0.0010), after controlling the influence of age and smoking habits.

2. Authors are not aware that the role of vinyl chloride monomer (VCM), alcohol intake, and viral hepatitis infection, and their interactions, in the etiology of hepatocellular carcinoma (HCC) and liver cirrhosis (LC) was appraised in another case-control study nested in the same cohort [Mastrangelo G, Fedeli U, Fadda E, Valentini F, et al. Increased risk of hepatocellular carcinoma and liver cirrhosis in vinyl chloride workers: synergistic effect of occupational exposure with alcohol intake. Environ Health Perspect. 2004; 112:1188-92]. By holding the confounding factors constant at logistic regression analysis, each extra increase of 1,000-years of VCM cumulative exposure was found to increase the risk of HCC by 71% (OR = 1.71; 95% CI, 1.28-2.44) and the risk of LC by 37% (OR = 1.37; 95% CI, 1.13-1.69). Authors report in autoclave workers an excess mortality risk of liver cancer, which could be due to both angiosarcoma and (HCC), and a non-significant increase in LA. Once again, the problem is misclassification of both exposure (use of occupation rather than cumulative VCM exposure) and disease (diagnoses based on death certificate rather than histology or clinical criteria).

Therefore, the main problem of this study is information bias, not the limited power of the cohort (Results, page 5, last paragraph), or selection bias (Discussion, page 9, second paragraph).

3. Authors stated, at statistical analysis, that in the model of Poisson regression, “exp(alpha) is the Standardized Mortality Ratio (SMR) with respect to Italy for person falling in the baseline category” (page 5, Statistical Analysis, second paragraph). It seems that the reference was the mortality experience of Italian population, not the internal reference (see on page 11, last paragraph). This procedure should examined by an expert statistician.

4. In Discussion (page 11, lines 16-17), authors wrote that length of employment was used as surrogate of cumulative exposure. However, the length of exposure was considered a confounding factor in Statistical analysis (page 5, first paragraph) and table 3 (footnote).

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The relevance of table 1 (a list of chemicals used in the production of PVC and VCM) is questionable, since the corresponding levels of exposure were unknown or not reported. I suggest deleting this table.

Discretionary Revisions (which the author can choose to ignore)

What next?: Reject because scientifically unsound

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing financial interests; I was the consultant of the Italian Government and Public Prosecutors in a lawsuit opposing several hundreds of claimants (workers, local municipalities, and the Italian national government) against the management of an Italian plant producing vinyl chloride monomer and polyvinyl-chloride.