

## **Epidemiological study of workers at two California petroleum refineries 1950-95; a reply**

Parodi et al. raised several comments on our cohort mortality study of petroleum refinery workers in California.<sup>1</sup> Their comments are general in nature and apply to most, if not all, occupational cohort mortality investigations in general and refinery studies in particular, including such studies conducted in the US, the UK, Canada and Italy.<sup>2-7</sup> We have discussed the same issues in our original paper. Below we will reiterate and expand our discussion of these issues in the order raised by Parodi et al.

The first comment raised by Parodi et al. is the potential impact of the healthy worker effect (HWE) in our study. More specifically, Parodi et al. conjectured that the HWE might have masked an excess of leukemia, particularly in employees hired after 1949. The HWE is a potential problem common to all cohort studies that use general populations as the basis for comparison. All petroleum cohort studies conducted in the US, the UK, Canada and Italy are equally vulnerable. However, when raising the HWE as an issue, one must consider the following points. First, it is generally recognized that the disease most strongly affected by the HWE is cardiovascular disease and that the HWE has little impact on cancer. This view is supported by studies from the US, Canada and Europe.<sup>8-11</sup> Second, the HWE diminishes over time after hire. Monson<sup>8</sup> estimated that the HWE generally lasted about 15 years. In our study, there was no significant increase of leukemia among employees 20 or 30 years after hire, regardless of hire date (before or after 1949). Therefore, the lack of a leukemia excess in our study was not likely due to the HWE. Monson summarized most sensibly the impact of the HWE as follows: *“The healthy worker effect is relatively weak in comparison to causal excesses that can be detected in epidemiologic data.”*

The second comment raised by Parodi et al. concerns the lack of exposure information in our study that would have allowed us to classify workers by exposure and to conduct more detailed exposure-specific analyses. Again, the lack of detailed exposure information is a general problem for all retrospective cohort studies, and our study of California refinery workers is no exception. We acknowledged this limitation in our original paper. A similar comment regarding the lack of detailed classification of workers by exposure or job activity was raised previously concerning the finding of lung cancer in another study of US petroleum workers, but subsequent detailed analyses by job title revealed no increase of lung cancer for insulators, pipe fitters,

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electricians, boilermakers, or maintenance workers.<sup>12</sup> The most appropriate approach to deal with specific exposures is to conduct cohort-based or nested case-control studies. Such nested case-control studies have been conducted subsequently for a number of cohort studies of petroleum workers in the US, the UK and Canada.<sup>13-16</sup> Detailed exposure information (including quantitative estimates) was collected on individual cases and controls in these investigations. Furthermore, comparisons in these case-control studies are internal, thus avoiding the HWE. Based on nested case-control studies, Rosamilia et al.<sup>13</sup> did not find any relation between lung cancer and asbestos exposure at a US refinery; Wong et al.<sup>14</sup> did not find any increase of leukemia, kidney cancer or multiple myeloma in relation to gasoline (hence, benzene) exposure among US petroleum workers; Schnatter et al.<sup>15</sup> did not find any relation between lymphohematopoietic malignancies and benzene exposure in Canadian petroleum workers; and Rushton and Romaniuk<sup>16</sup> concluded that there was no evidence of an association between benzene exposure and lymphoid leukemia, either acute or chronic, among petroleum workers in the UK. Thus, none of the nested case-control studies contradicted the findings of the original cohort studies; nor is it axiomatic that the absence of analyses based on detailed exposure information automatically implies masked health effects.

Parodi et al. criticized the inclusion of employees hired after 1980 in our study, and argued that the latency of these workers (15 years maximum) might not have been sufficient, thus “diluting” the risk of prolonged exposures among those hired in or before 1980. We would like to point out that, first, our investigation is not merely an academic exercise but part of an ongoing corporate medical monitoring program that includes all employees. Second, an analysis stratified by latency was performed (Table 3 in our original paper). The groups with 20-29 and 30+ years of latency did not include any employees hired after 1980 and, therefore, could not have been “diluted” by workers hired after 1980. Third, with regard to prolonged exposures, an analysis stratified by duration of employment was also performed (Table 2 in our original paper), and the groups with 15-29 and 30+ years of employment would certainly have had prolonged exposures and the results would not have been “diluted” by employees hired after 1980.

With regard to statistical analysis, Parodi et al. questioned our analysis by period of hire before and after 1949, and suggested cut-points of 1969 and 1979. We do not understand the basis of their suggestion. We chose 1949 because of historical exposure patterns. In 1947, the recommended standard for benzene exposure in the US was reduced from 100 ppm to 50 ppm,

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which was further reduced to 35 ppm in 1948. Benzene exposure levels in the petroleum industry were significantly reduced after 1949, thus making 1949 a good surrogate measure for exposure.

Finally, Parodi et al. commented that mortality might not be a good indicator of cancer risk. This general comment, of course, applies to all studies based on mortality. In the US there is no national cancer registry, and it is simply not possible to ascertain cancer incidence in an historical cohort study of more than 18,000 workers that goes back to 1950. In their comments, Parodi et al. were concerned with exposures to asbestos and benzene. The cancers related to these exposures are lung cancer, malignant mesothelioma and acute myeloid leukemia. These particular cancers have relatively poor prognosis, particularly in the past, and mortality may not be an unreasonable outcome measure. Parodi et al. also commented on the diagnostic accuracy of death certificates. Again, this comment applies to all studies based on mortality. It should be noted that diagnostic accuracy varies by disease. For example, lung cancers are seldom misdiagnosed. Although some diagnoses on death certificates may not be as accurate as those based on detailed medical records, relying on death certificates in both the study and reference populations ensures comparability.

Furthermore, our interpretation of the results was based on not only what we observed, but also the findings of related studies. For example, for non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM), in addition to our results, we also relied on hospital-based case-controls studies which were included in previous reviews cited in our paper.<sup>17,18</sup> The diagnoses in these hospital-based case-control studies were based on detailed clinical, laboratory and pathological findings. The conclusion from these hospital-based case-control studies is that there is no relation between benzene exposure and NHL or MM. Therefore, our conclusion of MM and NHL based on our study is consistent with other studies in which diagnostic accuracy is not an issue.

In their conclusion, Parodi et al. cautioned that results should not be ignored simply on the basis of the lack of statistical significance and suggested nested case-control studies be conducted for further investigation. We concur on these two points. In discussing the results of our study, we did not ignore any findings simply because they were not statistically significant. We fully recognized that a result might not be statistically significant because the statistical power of an individual study might not be adequate and that the result must be interpreted in conjunction with other similar studies. As one of the objectives stated in our original paper, we assessed our findings (statistically significant or otherwise) in the context of results of other petroleum studies. To take all studies into consideration, we also relied on several reviews and meta-analyses of studies of

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petroleum workers around the world.<sup>12, 17-19</sup> For example, based on a combined database of more than 350,000 petroleum workers in the US, the UK, Canada, Australia, Finland Sweden and Italy, Wong and Raabe<sup>12</sup> reported that consistently not a single study demonstrated an increase of lung cancer and the summary lung cancer standardized mortality ratio was 0.81, with a 95% confidence interval of 0.79-0.83 (based on 5695 deaths). As to the suggestion of further investigations using nested case-control studies, such detailed case-control studies have been conducted among petroleum workers in the US, the UK and Canada.<sup>13-16</sup> As discussed above, none of these nested case-control studies contradicted the findings of the original cohort studies.

Therefore, while Parodi et al. have raised several limitations common to occupational retrospective cohort studies, we believe that we already have discussed these issues in our original paper and that we have not over-interpreted our data.

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