in quantitative risk assessment in current conditions is to apply this evidence to the estimation of the risks associated with exposure levels 100–1000 times lower. The standard assumption is that, other things being equal, the risk will be proportional to dose: but this is more a cautious default assumption than anything more soundly based. To quote from the HEI review: "The assumption of dose-linearity for low-dose assessment purposes is thus a widely accepted and scientifically reasonable compromise rather than an established scientific principle of carcinogenesis".

However, if the true relationship between exposure and response was not linear, the impact on low dose extrapolations could be dramatic. There is some indication in the present data suggesting a non-linear exposure response, particularly for peritoneal mesothelioma, and the next sections examine this question.

*Relationship of pleural and peritoneal mesothelioma*

Figure 4 plots the percentage excess mortality from peritoneal mesothelioma against that from pleural mesothelioma. Cohorts with no mesothelioma cases of either kind are excluded. Cohorts with no peritoneal mesotheliomas are plotted on the peritoneal scale on or close to the 0.01 ordinate. The positioning of the cohort points strongly suggests a pattern of two alignments, one defined by the pure crocidolite cohorts, the other by the two pure amosite cohorts. Four mixed exposure cohorts lie very close to the amosite line: the US/Canada Insulators, New Orleans plant 1, the Johns Manville retirees and the Albin cohorts. All but the last of these clearly had amosite as the main amphibole fibre. The point representing the Ontario cohort lies very close to the crocidolite line, suggesting perhaps that the anomalous results from this cohort may be explained by underestimated exposure to crocidolite.

The position of the (male) Carolina cohort seems somewhat anomalous. The single peritoneal mesothelioma in this group is the only one in a cohort without material amphibole exposure, and the equality between pleural and peritoneal numbers (one of each) is only otherwise seen in cohorts with much higher levels of mesothelioma (and substantial amphibole exposure). The possibility of unrecognised amphibole exposure again suggests itself, but too much should not be read into this single peritoneal case. It is clear that the three fibre types produce different mesothelioma responses overall. The question of differential responses by mesothelioma site can really only be addressed for the amphibole fibres.

This relationship does not depend on quantified exposure data, and if it is real it should be reproduced in other cohorts with predominant amphibole exposure. The most informative cohorts will be those with crocidolite or amosite exposure, but not both. A Medline search identified eight such cohorts. The relevant data are summarised in Table 3, and a plot of the percent excess mortalities from these cohorts (and the pure fibre quantified cohorts) is shown in Fig. 5.

There is still an apparent separation between crocidolite and amosite cohorts, though the segregation is now less clear cut (as might be expected given the small numbers often involved). There is, of course considerable statistical uncertainty in both of these variables, and a simple regression (in which uncertainty about 'x' values is ignored) would be misleading. Table 4 summarises the results of regressions in which the fit is optimised in both variables simultaneously (fit being measured by deviance, assuming Poisson variation for the numbers of mesotheliomas at each site).

Fitting a single line through all the data produces a line with a slope (on the log–log scale) of 1.2, but the overall fit is unsatisfactory ($P<0.001$). Allowing the two fibres to have separate fits makes a very significant improvement to the fit ($P<0.001$), and both fits have steeper slopes (2.3 for crocidolite and 3.1 for amosite — not shown in table). These slopes are not very precisely determined, and constraining them to be equal does not materially degrade the fit ($P=0.75$). The central estimate for this common slope is 2.4.

This model provides a very close statistical fit to all but two of the cohorts. The two exceptions are the gas mask cohorts in Canada (McDonald and McDonald, 1978) and in Leyland (Acheson *et al.*, 1982), which contribute 6.1 and 4.5 respectively to the total deviance. Possible reasons for these cohorts to be untypical can be identified. The Leyland cohort was not ascertained from employment records, but from occupational details recorded on the wartime population register compiled in September 1939. If the numbers directly involved with gas mask assembly have been over estimated the percentage excess mortalities will be proportionately under estimated. If, for example, only 2/3rds of the identified women were in fact exposed, the expected mortality denominator would fall to around 120, and the residual falls from 6.1 to 4.3—still an outlier, but materially less extreme ($P=0.038$ instead of 0.014). The overall excess mortality from mesothelioma recorded in the Leyland cohort is much lower than in the Nottingham cohort engaged on the same process: 2.7% at Leyland and 16.5% at Nottingham, again suggesting the possibility of underestimation (eg by dilution of the exposed population), perhaps substantial.

The assessment of mesothelioma in the Canadian gas mask cohort was particularly exhaustive, involving review of pathological data for all cancer cases. Three of the six peritoneal cases were only identified after this review. If the number of peritoneal mesotheliomas is reduced by three, the residual for this cohort falls from 4.5 ($P=0.034$) to 2.0 ($P=0.16$).

However these are post-hoc rationalisations, and it is not clear whether it is better to remove these cohorts from the model or not. Despite the large