

the 1960s. Access was given to the employees' roll although employment details during the war were virtually non-existent. We think that the information gathering process when taken together with the records of the coroner and the histopathology review was as detailed as any other similar study in existence.

As the "non-exposed" group was classified as such by history it is obvious to most readers that we are unable to state how they acquired excessive amounts of amphibole fibres within their lung tissues. If these eight cases with high amphibole concentrations are deducted the rate of mesothelioma becomes 1.6 million a year which is similar to the generally estimated background rate.

Greenberg seems to be unaware that high aspect ratio amphibole fibres have been found in the pleura.<sup>1</sup> By contrast with animal studies, which rely on the administration of enormous doses and overload of the respiratory defences, human studies have been remarkably consistent in showing a strong association between amphibole exposure and mesothelioma whereas for chrysotile it has been weak or non-existent.<sup>2</sup> Even in chrysotile miners and millers, in whom there have been few mesotheliomas, the evidence indicates that they were related to tremolite rather than chrysotile exposure.<sup>3,4</sup> To the best of our knowledge the forthcoming review of chrysotile by the *International Programme on Chemical Safety* will not present any new evidence although it might give a different opinion. Other reviews conclude that amphiboles have a much greater potency than chrysotile for producing mesothelioma.<sup>5,6</sup>

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#### Biomarkers of exposure to low concentrations of benzene: a field assessment

Editor—Ong *et al*<sup>1</sup> present data on the relation between concentration of benzene in ambient air and urinary muconic acid concentration. With the formula they provided in figure 3, the urinary concentration of muconic acid equivalent to exposure to 1 part per million (ppm) is 144.4 or 128.6

ng/mg creatinine, depending on whether log to the base 10 or natural log is used, respectively. This number seems to be very low compared with that given in many studies which are usually in the range of > 1000 ng/mg creatinine.<sup>2,3</sup> It will be helpful if Ong *et al* could provide some explanation for this apparent discrepancy.

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- 1 Ong CN, Kok PW, Ong HY, Shi CY, Lee BL, Phoon WH, Tan KT. Biomarkers of exposure to low concentrations of benzene: a field assessment. *Occup Environ Med* 1996;53: 328-33.
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*Author's reply*—The overall objective of our article<sup>1</sup> was to evaluate the usefulness of five commonly used biomarkers in low level (< 0.25 ppm) exposure to benzene and as stipulated in the conclusion all the biomarkers were unable to provide sufficient specificity for biomonitoring at the low concentration range. All data (figs 1-3) suggested that they are not to be used for estimation of exposure to low level environmental exposure to benzene, particularly < 0.25 ppm. Our earlier data<sup>2-4</sup> showed that trans,trans-muconic acid could be useful for environmental exposure to benzene > 0.5 ppm; with a calculated exposure to 1 ppm benzene, about 0.9-1.7 mg/g creatinine would be expected at the end of eight hours of exposure.

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#### Offspring sex ratios and reproductive hazards

Editor—Weijin and Olsen<sup>1</sup> write: "A conception closely associated with ovulation has been suggested to result in more boys". There seems to be an error here because to substantiate this statement, these authors cite France *et al*<sup>2</sup> who write: "The birth sex ratio favored males when intercourse preceded ovulation/fertilization by two days or longer". Indeed the data of France *et al*<sup>2</sup> give some corroboration to the conclusion of Gray<sup>3</sup> who, after a meta-analysis of human data, suggested that the regression of offspring sex ratio (proportion male) on time of insemination within the cycle is U shaped.

I have cited<sup>4</sup> evidence that:

(1) There is a positive relation between offspring sex ratio and parental coital rate in several mammalian species (including humans).

(2) Under some models, coital rate would determine the time of fertilisation within the cycle.

(3) Distributions of the sexes within litters of several mammalian species suggest that  $P_{\text{male}}$  (the probability that a zygote is male) varies from one zygote to another within litters.

Interpretation of the data is not established, but it seems likely that the variation of  $P_{\text{male}}$  with time across the female cycle is partially controlled by the varying female hormone concentrations across that time. In particular such an interpretation can be construed to explain Weijin and Olsen's<sup>1</sup> report of a significant decline of offspring sex ratio with waiting time to pregnancy. This confirms the data of Renkonen<sup>5</sup> and may be caused by the different mean times of fertilisation within the cycle associated with different coital rates (which decline very rapidly during the first year of marriage<sup>6,7</sup>).

If I am right, the sexes of mammalian (including human) offspring are partially controlled by the hormone concentrations of both parents around the time of fertilisation.<sup>8</sup> So deleterious environmental agents which are endocrine disruptors may show themselves in biased offspring sex ratios. Thus it may be expected that offspring sex ratios will be increasingly used as indicators of adverse occupational exposures to men and women.

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