Comment on Carran and Shaw’s “New Zealand Malayan war veterans’ exposure to dibutylphthalate” article

We read the paper by Carran and Shaw (27 July 2012)1 with some disquiet. We have a high degree of respect for veterans and consider that the flaws in the study are so serious that one must question why the paper has been published in its current form or indeed why the research went ahead at all.

This research was not hypothesis generating. It should therefore have been done properly using established epidemiological techniques. This is in fact neither a cohort nor a case-control study; it is a cross-sectional convenience sample and a cluster investigation without determination of the size of the cluster. If a power calculation had been carried out it would have shown that the study aims were not achievable. With an expected incidence of cryptorchidism of 1.09%, a follow up of approximately 4600 individuals would have been required to detect a relative risk of 2 at the 5% confidence level with a power of 80%. For hypospadias, at 0.33%, the numbers required are in excess of 15,000.

The epidemiological and statistical techniques were also inadequate. A well powered nested case-control study,2 with 78 cryptorchidism case and 56 hypospadias cases nested within a cohort of 8698 male births, did show an association between pesticide exposure and cryptorchidism. On the other hand hypospadias was not associated with pesticides but with paternal, and not maternal, smoking. Both abnormalities were associated with poorer maternal health, socioeconomic factors and pre-term delivery. A previous study also showed associations with maternal parity, low foetal growth and duration of gestation.3 The relationships are therefore complex, and require, at the very least, consideration that these factors should be included in a model that can adjust for them. This requires an appropriate regression model and calculation of either Standardised Incidence Ratios or Odds Ratios.

In addition there is a critical flaw in the response rate of the study at 33%. Response bias is quite likely to have occurred, with responders more likely to have been concerned about exposure and report one of the adverse events.

Additionally, the assumptions that the estimated doses of dermally administered doses of dibutyl phthalate increased the risk of multigenerational developmental effects are flawed. The doses absorbed by the soldiers were compared to a Lowest Adverse Effect Level of 50 mg/kg.4 The cited study investigated orally administered dibutyl phthalate to pregnant female rats which resulted in altered gene expression and testosterone synthesis in the fetal testes of the in utero males.

There can be no comparison between soldiers who were dermally exposed to dibutyl phthalate at least several years before they reproduced, and in utero male rats being exposed to dibutyl phthalate following maternal oral ingestion. Furthermore, estimated doses dermally absorbed by these soldiers were based on an investigation assessing percutaneous absorption of dibutyl phthalate in rats.5
The authors rejected the absorption rates across cadaver skin from the same study without giving evidential reasons why this approach was flawed; using human tissue is a well-established procedure and in vitro results are predictive of in vivo absorption. Rates of steady state absorption of dibutyl phthalate across rat skin can be up to 130 times greater than across human tissue. Any calculation estimating absorption across human skin based on animal models will therefore be substantially inflated.

Lastly there are the ethical issues of explaining the study results to what is, in effect, a vulnerable group. It includes the veterans, but also their offspring. There are already questions being raised about compensation. It is clear that New Zealand Veterans of Malaya, Vietnam and the Christmas Island Nuclear Tests were exposed to a toxic environment during their service. Decisions on compensation will however have to be made by the Government. Studies like this do not help in that process.

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References: