CORRESPONDENCE

Offspring sex ratio as an indicator of reproductive hazards associated with pesticides

Editor—De Cock et al note that waiting times to conception are significantly longer in the wives of men exposed to pesticides. They cite the evidence that the nematocide dibromochloropane (DBCP) is associated with diminished sperm counts. It is worth noting that there is other evidence of hazard in these effects. DBCP reportedly have significantly high gonadotrophin concentrations although their testosterone concentrations remain normal.1 I have hypothesised that the sexes of human offspring are associated with the hormone concentrations of their parents at the time of conception, high testosterone producing boys, and high gonadotrophins, girls. In conformity with this hypothesis, there is a highly significant excess of daughters among the offspring of male DBCP applicators.2

So it would be interesting to know whether there was an excess of daughters among the 91 children sired by the pesticide workers studied by de Cock et al.3 More generally, workers in industrial medicine might consider offspring sex ratios as a criterion of reproductive hazard: they are cheaply and painlessly ascertained, and are not subject to the measurement errors and biases that characterise assessments of sperm quality and hormone concentrations. It should be noted that although a bias towards daughters may be indicative of hazard in male workers, there are no grounds for supposing this in female workers. At any rate, in any such analysis, the sex of offspring should be categorised by sex of parent.

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Author’s reply

Editor—We would like to thank James for his letter on offspring sex ratio among children of fruit growers in our study on time to pregnancy.1 In his letter James refers to a highly significant and large excess of daughters among the offspring of male 1,2-dibromochloropropane (DBCP) applicators2 and wonders if information on sex ratio is also available for the fruit growers in our study. In our initial survey, we did not gather these data. As data on sex ratio are easy to obtain, we gathered this information recently by telephone. We asked wives of fruit growers the outcomes of their pregnancies. Except for one pregnancy, we were able to gather all the information on 140 pregnancies. The total number of pregnancies was 127 (excluding 12 miscarriages for which the sex ratio was unknown and one pregnancy before the period of study). The overall sex ratio was 51:51 with a 95% confidence interval (95% CI) of 0-43–0-59 (based on a binomial distribution with expected population value for sex ratio (proportion of males) was 0.514). For the 91 pregnancies in our time to pregnancy study, the overall sex ratio was also 51:51.

In a more detailed analysis we first related the sex ratio to the exposure variables that were also studied in the time to pregnancy study. A decrease in sex ratio was found when recent years of birth were compared with earlier pregnancies. Also, time to pregnancy increased with more recent years of birth (table 1).

The most recent period (1987–90) showed a lower sex ratio of borderline significance (0-33) compared with the previous periods (0-56) (Fisher’s exact test, two sided, P = 0-08). A similar trend in sex ratio was found for the total group of 127 pregnancies. We also found a change in sex ratio dependent on gravidity. For the first, second, third, and subsequent children, sex ratios of 0-60, 0-57, 0-42, and 0-31 were found respectively. The first two pregnancies of a couple in comparison with next pregnancies showed a sex ratio of 0-58 and 0-38 respectively (Fisher’s exact test, two sided, P = 0-08).

This raises the question whether gravidity acts as a confounder in this analysis, as does time to pregnancy. Because of small numbers, stratification of sex ratio according to gravidity and year of birth was not possible. Surprisingly, a difference in time to pregnancy according to year of birth was found for boys but not for girls. The figure is a Kaplan-Meier curve (PROC LIFETEST) by year of birth for boys. The curves, did not differ significantly. A univariate survival analysis with the PHREG SAS procedure as described in our study on time to pregnancy,1 for the period of birth comparing pregnancies occurring in 1983 or before (1) with more recent pregnancies (0) as the independent variable, showed a fecundability ratio of 1:61 (95% CI 0-83–3-13) for boys and 1:13 (95% CI 0-59–2-15) for girls. No differences in age at the time of conception of men or women, or the age difference between both parents were found in our study. Therefore, a role of age dependent hormone concentrations of the parents on offspring sex ratio at the time of conception is not a very likely explanation for these findings.

In our study on time to pregnancy, we focused on seasonal effects of exposure of men. No significant differences according to season were detected in the sex ratios. Observed sex ratios for the quarter of a year in which conception took place were: 0-64 (January-March), 0-44 (April-June), 0-48 (July-September), and 0-52 (October-December).

As no relation between sex ratio and any of the exposure variables used in our study on time to pregnancy was found, other available information on exposure was considered as well. Because offspring sex ratio is a dichotomous variable, we studied outcome in a case-control like design with maximum likelihood logistic regression models by computing odds ratios (ORs) with SAS PROC LOGISTIC. As the odds

Table 1 Offspring sex ratio and time to pregnancy according to year of birth (n = 85)*

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Pregnancies</th>
<th>Sex ratio</th>
<th>Time to pregnancy (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978-80</td>
<td>18</td>
<td>0.56</td>
<td>2.9</td>
</tr>
<tr>
<td>1981-83</td>
<td>22</td>
<td>0.55</td>
<td>3.5</td>
</tr>
<tr>
<td>1984-86</td>
<td>24</td>
<td>0.58</td>
<td>4.2</td>
</tr>
<tr>
<td>1987-90</td>
<td>21</td>
<td>0.53</td>
<td>4.1</td>
</tr>
</tbody>
</table>

* n = 91 pregnancies from the time to pregnancy study, excluding six miscarriages of unknown sex.
Table 2  Odds ratios of 16 cases (more daughters than sons within a family) compared with 27 controls (43 sons) for exposure variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spraying days 1990</td>
<td>18.4 (1.72–196)</td>
</tr>
<tr>
<td>(30 days)</td>
<td></td>
</tr>
<tr>
<td>Cross current sprayer</td>
<td>1.7 (1.05–2.59)</td>
</tr>
<tr>
<td>(10 days)</td>
<td></td>
</tr>
<tr>
<td>Herbicide sprayer (5 days)</td>
<td>3.6 (1.11–11.6)</td>
</tr>
<tr>
<td>(Manual) knapsack sprayer</td>
<td>2.2 (1.06–4.66)</td>
</tr>
<tr>
<td>(5 days)</td>
<td></td>
</tr>
<tr>
<td>Metiram (days)</td>
<td>1.3 (1.05–1.61)</td>
</tr>
<tr>
<td>(Spraying)</td>
<td></td>
</tr>
<tr>
<td>Azinphos-methyl (0/1)</td>
<td>4.4 (1.11–17.3)</td>
</tr>
<tr>
<td>Parquat (0/1)</td>
<td>&gt;5.6 (&gt;5.6 &lt; 13.4)</td>
</tr>
</tbody>
</table>

*Parquat was used by all families with more daughters compared with 74% in the control group.

Discussion

Overall sex ratio was different from the expected ratio of 0.51. James hypothesised that high concentrations of testosterone at the time of conception produce boys, and high concentrations of gonadotrophin produce girls. Among the offspring of DBCP applicators a highly significant excess of daughters was found. As exposure to pesticides in fruit growing typically includes more than one of these pesticides, it is not possible to predict the direction of a shift in sex ratio induced by exposure to pesticides among the families. As the number of subgroups is small it is impossible to draw firm conclusions, but some of the results are of interest. From our results there are some indications that exposure to pesticides in agricultural work has an effect on offspring sex ratio. The shift towards daughters in the most recent period (sex ratio of 0.33) was remarkable. Also the finding that spraying frequency, frequency of use of specific equipment, and use of some specific pesticides are related to a shift towards more daughters within a family may point to an exposure effect. One should be careful in interpreting these results. The fact that use of some pesticides is related to sex ratio does not necessarily imply that individual pesticides are causally related to sex ratio. Fruit growers use a complex mixture of agents and the use of one agent is often correlated with the use of another. It is unlikely that the shift in sex ratio is caused by the introduction of particular pesticides as all pesticides have been applied to some extent during the study period. Because application was found to be consistent over time, the introduction of certain techniques seems a more plausible explanation for this finding. It is possible that other underlying mechanisms, effects may not be caused by exposure of the male worker only, as most women live near the orchard and they often participate during particular activities like pruning, thinning, and harvesting. No seasonal trends were found in this analysis as was found for time to pregnancy. Our finding that there might be a difference in time to pregnancy for boys and girls as well, may indicate that both sex ratio and time to pregnancy are interlinked. Why exposure variables associated with time to pregnancy are not related to sex ratio.

In conclusion, we think that the suggestion by James to analyse sex ratio is a useful one and should be explored further. To consider both sex ratio and time to pregnancy simultaneously may have advantages in elucidating occupational hazards of pesticide exposure. Our results do show that other variables in the families with predominately daughters or sons, which are indicative of a shift in sex ratio, might be more powerful because they use another sampling unit (family instead of a crude stratification by exposure). Especially in this study among agricultural workers an analysis on a family level might be relevant because the exposure might be aggregated at the family level as well. In general, it seems useful to explore, after time to pregnancy and sex ratio, the presence of families with a predominance of one of the sexes as little is known about the underlying biological mechanisms as well as the statistical properties of these indices.

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