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Review of Hoar et al¹ and related literature

This review is prepared in response to EPA Purchase Order 6W-3948-NASA dated September 10, 1986. According to Jerome Blondell's letter accompanying the purchase order: "The key question is: What does the 'weight of evidence' say about the risk of lymphoma for agricultural workers exposed to 2,4-D? Is 2,4-D a likely cause of lymphoma?" This question was prompted by the referenced publication of Hoar et al in the September 5, 1986 issue of JAMA.

Hoar et al

This is a population-based case-control study of all male cases of soft-tissue sarcoma (STS), Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) identified in the State of Kansas over a 7-year period. 3 controls, matched for age and living-or-dead status, were selected - either by random digit telephone dialing (for living cases under 65 years of age), from Medicare files (for living cases 65 or older) or from Kansas state mortality files (for dead cases). Information on occupation and exposure to herbicides was obtained by telephone interview - with the case or control for half of the subjects with STS or NHL (and corresponding controls) and one-third of the HD cases and controls, and with the next of kin for the remaining, deceased subjects. This study shows every indication of having been carefully and competently carried out. I see no methodologic problems that are likely to have produced the reported positive association between use of herbicides (predominantly uracil and phenoxyacetic acids) and NHL. The strong and statistically

¹ Hoar SK, Blair A, Holmes FF et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 1986; 256:1141-7.

significant increasing risk of NHL with increasing frequency of herbicide use (days per year) supports the idea that the association is real, but the weak, and barely significant association with years of use argues somewhat against it. There are some points of detail which should be noted, although none jeopardize the principal findings, so far as I can judge:

- presumably to have series of the three tumors of approximately equal size (200, 173 and 200), the investigators selected a sample of 200 cases of NHL from the 293 available. The relevance of this sampling is that, if the investigators had had any inkling of what their results would be, they would probably not have discarded 93 cases of NHL, and it must be presumed that it was not an a priori hypothesis that an association would be found only for NHL.
- there is an unexplained, but statistically highly significant, difference between the three groups of cases in the proportion of identified cases which were interviewed. This is primarily due to the low proportion of NHL cases which were excluded, either because they were not confirmed histologically (i.e. were not eligible) or because, if eligible, they were not interviewed. The differential loss occurs at several levels. Thus, the percentages of SDS, HD and NHL cases not histologically confirmed were 19, 15 and 10 percent, respectively. Of the eligible cases, the percentages not interviewed were 4, 8 and 1, respectively. It is difficult to see any relevance of these differences to the study conclusions, but it is curious that determination of eligibility and success in interviewing were both more complete in the group of cases for which an association is found.
- for a high proportion of subjects (50% of cases of STS and NHL and

their controls), the exposure information was obtained from surrogates since the subjects themselves were dead. One would suspect that surrogate-supplied information on occupation would be reasonably accurate, but one must question surrogates' knowledge of what specific herbicides were used and on how many days of the year. Since any inaccuracy involved would presumably apply to both cases and controls this cannot be regarded as a possible explanation of the association noted. In fact, it would tend to reduce any true association that exists. One might even wonder, in fact, whether it could explain the lack of association found for STS and HD - tumors for which others have reported associations with phenoxyacetic acid exposures.

- although both years of herbicide use and days of use per year show statistically significant trends for NHL risk, it is useful to note the small numbers on which these trends rest. Only two individual categories show significant differences between NHL cases and controls - use for 16 years or more (based on 16 cases, RR 2.0 and of marginal statistical significance), and use for 21 or more days per year (based on 7 cases, RR 6.0 and more clearly significant). It is not stated to what extent these categories overlap - i.e. contain the same individuals - but it is noteworthy that, in the most persuasive category (use for 21 or more days per year), where there are 7 cases, the expected number based on the controls would be about 2.3. It would take only 2 or 3 cases misclassified to this category (or controls misclassified out of it) to render the difference not statistically (or biologically) significant.
- the authors' Table 1 shows that farmers for whom no use of herbicides were reported had RR higher than non-farmers (RR = 1.3) and while this

is not formally significant (at p less than 0.05) it is approaching significance (the lower 95% confidence limit is 0.8) and is not much different from that for all farmers (1.4). The latter similarity results, of course, from the small size of the group of herbicide users that does show substantially increased risk.

- the paper's Table 2 shows risk ratios associated with ever-use of specific herbicides. Among 8 groups of herbicides (including a category "nonspecified"), the RR associated with phenoxyacetic acid is lower than that for any other group except the uracils. The RRs range from 1.3 to 12.5, that for the phenoxyacetic acids being 2.2. Besides the phenoxyacetic acids, RRs significantly above 1.0 are seen for triazines (2.5), amides (2.9), trifluralin (12.5) and non-specified" (5.8). The focus on the phenoxyacetic acids seems to stem from their frequency of use (second only to the uracils), rather than from the level of risk associated with their use.

In summary there are some questions and uncertainty in the data from this study - as there are in all epidemiologic studies - but, if there were no other evidence available, this study would stand as a good basis for the hypothesis that the risk of non-Hodgkin's lymphoma is increased by agricultural exposure to the phenoxyacetic acids - principally 2,4-D - and perhaps other herbicides. I would not accept this study as grounds for concluding that such associations do exist - only as a basis for hypotheses which must be tested in other data.

Other studies

Paradoxically, it is unfortunate that this study is not the only one to provide evidence on this topic. In fact this study was prompted by previous studies suggesting that STS, HD and NHL were all increased in persons exposed to phenoxyacetic acid and other herbicides. It is when one tries to fit the results of the Kansas study into the context of previous work that matters become difficult.

I do not believe that the authors' conclusion that "the study confirms the reports from Sweden and several US states that NHL is associated with farm pesticide use, especially phenoxyacetic acids" is justified. The Swedish studies of Hardell et al² showed elevated risks of 5- 6-fold for all three cancers investigated by Hoar et al. Exposure in the Swedish study was defined as "ever exposed" - principally on the basis of occupational history - and it is not possible to compare levels of exposure in the two studies to determine whether lower exposures could account for the lower RRs found in the US study (among all exposed). However, the important discrepancy is that the Swedish study found significant associations for all three tumors and the US study only for one. Before concluding that the US study is confirmatory of the Swedish one with respect to NHL one must understand the reason for the discrepancy with respect to STS and HD. The reasons for these discrepancies - whether in the exposures studied, the method of study, or simply chance - are as cogent as is the agreement with respect to NHL. Until there is an adequate explanation for the discrepancies one can have little confidence that the agreement represents reality.

² Hardell L, Eriksson M, Lenner P, et al. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br J Cancer 1981; 43:169-76.

It is beyond the scope of this contract to review all the published relevant literature but perusal of the articles accompanying the review request does not lead to any clear impression of support for or evidence against the conclusion of Hoar et al. Pearce et al³ report a case-control study of 83 cases of NHL and conclude that there was no significant difference between cases and controls with regard to potential exposure to phenoxy herbicides. However, in this relatively small study, the results (RR 1.4, 90% CL 0.7-2.5) are not statistically incompatible with the RR (2.2) reported by Hoar et al for ever-use of phenoxyacetic acids.

Lynge⁴ reports a cohort study of persons exposed in the manufacture of various pesticides. The numbers are very small but are more suggestive of an association for STS (obs. 5, exp. 1.84) than for lymphoma (HN and NHL not distinguished) (obs. 7, exp. 5.37) among all employees, and there was no case of NHL among the 41 cancer deaths among persons employed in the manufacture and packing of phenoxy herbicides specifically. The total number of cancer deaths expected in this group was 41.46. Lung cancer showed a significant excess (obs. 12, exp. 6.11).

Other studies, because of small numbers, lack of specificity of exposure and/or other reasons, carry little evidential weight.

The key question

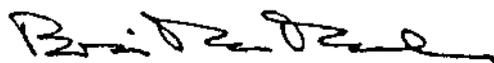
The key question in Mr. Blondell's letter quoted earlier is in fact two questions - what does the 'weight of evidence' say about the risk of lymphoma

³ Pearce NH, Smith AH, Howard JK, Sheppard, RA, Giles HJ, Teague CA. Non-Non-Hodgkin's lymphoma and exposure to phenoxyherbicides, chlorophenols, fencing work, and meat works employment: a case-control study. Br J Ind Med 1986; 43:75-83.

⁴ Lynge E. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. Br J Cancer 1985; 52:259-70.

for agricultural workers exposed to 2,4-D; and is 2,4-D a likely cause of lymphoma? The second question cannot be answered (except perhaps by animal experiment) until the first is answered, since without an association there is no causation.

In my opinion the weight of evidence does not support the conclusion that there is an association between exposure to 2,4-D and NHL. It is axiomatic that, except when relative risks are very high - and sometimes even then - no single study will establish an association between an exposure and an outcome. The acceptance of an association depends on a number of studies showing consistent results across populations and across different epidemiologic methods. The study of Hoar et al is a strong study - strong enough on its own to establish a hypothesis of relationship of exposure to 2,4-D with some small proportion of cases of NHL - a hypothesis that clearly deserves attempts at refutation or support in other populations. When one attempts to place the results of this study among the results of those published previously, the picture becomes very confusing - much more so than if Hoar et al had been the only study published. Taken as a whole, I believe that the weight of evidence indicates that an association between 2,4-D and NHL remains a hypothesis that is still to be tested. I am unwilling to speculate as to whether 2,4-D causes NHL (or some cases of NHL) until the evidence is clear that there is an association between them.


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September 29, 1986