SOME COMMENTS ON THE KANSAS FARM WORKER EPIDEMIOLOGICAL STUDY[1]

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The Kansas Farm Worker Study by Hoar et al. is reviewed. The data came from telephone interviews. There are three main criticisms. First, the accuracy of quantitative exposure data based on memory is open to question particularly when it goes back many years. The accuracy of this exposure data is made even more open to question when obtained from next of kin as occurred in approximately 50% of the cases in this study. Second, no direct questions were asked regarding the use of 2,4-D. Therefore, the data apply only to herbicides in general not 2,4-D in particular or any other specific type of herbicide. Third, the conclusions are not consistent with results from several other epidemiological studies on this subject. Therefore, it is not valid to conclude from this data that there is an increased risk of getting NHL after exposure to 2,4-D.

A recent epidemiological study(6) investigated the possible association between pesticides and three general types of cancer, soft-tissue sarcoma (STS) Hodgkins disease (HD) and non-Hodgkins lymphoma (NHL), among adult males living in Kansas. The original hypotheses of these investigators were that the use of herbicides and insecticides might affect the risk of getting STS, HD, and NHL.

The abstract/summary of this paper reported positive findings linking the use of 2,4-D to the occurrence of NHL. These findings have been widely publicized and have caused considerable concern among both regulatory authorities and the public about the use of 2,4-D. Thus it was thought worthwhile to carefully examine the results of this Kansas Farm Worker Study (KFWS). Since the main thrust of this paper dealt with herbicides, these comments will deal mainly with the question of their findings about herbicides.

The Kansas Farm Worker Study made the following major points in the summary:

This was a case control study and concluded that farmers, men, exposed to herbicides more than 20 day per year had a six-fold increased risk of NHL over non-farmers.

This increased risk of NHL was associated with the use of phenoxy herbicides, specifically 2,4-D.

Neither STS nor HD was associated with pesticide exposure.

This confirms the Swedish studies reporting NHL is associated with herbicide use especially the phenoxyacetic acids by farmers.

It does not confirm the case-control studies or cohort studies linking herbicides to STS or NHL.

This paper is based upon telephone interviews and this method of gathering exposure data depends upon memory. The accuracy of a person's memory, particularly for quantitive data as long as 40 years ago, is open to serious question. For instance, if you were asked how many days you did X ten years ago how accurate would your answer be? Further, in this particular case 50% of the information came not even from the actual people with the disease but from the next of kin. Obviously, information from next of kin is even more open to question

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regarding its accuracy than when obtained directly from the individual with the disease.

To illustrate the inaccuracy of memory, since the growing of wheat is so common in Kansas, it is exceedingly difficult to believe that 71% of the Kansas farmers have never used herbicides as can be calculated from their data in Table 1.

Much has been made about the fact that the study has shown a relationship between NHL and 2,4-D. However, a look at the questionnaire used shows that the authors did not ask any specific questions about the use of 2,4-D or even specific questions about the general class of phenoxy herbicides. The actual herbicide questions asked were:

1. What are the names of the herbicides you used?
2. What herbicide or combination of herbicides did you use most often?
3. How many days were you exposed to herbicides?

It is unusual that if this paper was to test the hypothesis that NHL was associated with the use of 2,4-D that direct questions about the use of 2,4-D were not asked as well as other direct questions concerning frequency, duration, and dates of usage. Because direct questions were not asked about 2,4-D or phenoxy herbicides, their conclusions should have been confined to herbicides in general and not to any herbicide in particular.

The title in Table 3 had an error in the original article. The authors submitted a correction which was published later. The title should have been "Non-Hodgkin's Lymphoma in Relation to Duration, Frequency, and Latency of Herbicide Use Among 2,4-Dichlorophenoxyacetic Acid Users" which carries a different meaning from the original title in the printed article which was "Non-Hodgkin's Lymphoma in Relation to Duration, Frequency, and Latency of 2,4-Dichlorophenoxyacetic Acid Use." Thus the increased risks reported in Table 3 are associated with general users of herbicides who also used 2,4-D and not specifically with 2,4-D use as the erroneous title stated.

In measuring the strength of the association between exposure and disease in epidemiological papers the Odds Ratio is frequently used as was done in this KFWS. The Odds Ratio may be calculated as follows:

$$\text{Odds Ratio} = \frac{\dfrac{\text{Number of Cases with Exposure}}{\text{Number of Cases without Exposure}}}{\dfrac{\text{Number of Controls with Exposure}}{\text{Number of Controls without Exposure}}}$$

Note that when there is not an association between exposure and the disease the value of the Odds Ratio is one. Confidence limits are also determined and to be statistically significant these confidence limits (CLs) must exclude the value of one. Thus an Odds Ratio of 1.5 (95% CLs 0.8 - 2.5) is not statistically significant but an Odds Ratio of 1.5 (95% CLs 1.1 - 2.5 or even better CLs of 1.3 - 2.5) is significant. This review will usually refer only to statistically significant data as just discussed.

It seems reasonable to assume that since exposure is so important that the results of increased exposure should be the same, not only as the number of days exposure to herbicidal use increased but also as the number of years exposure increased. This did not occur and the dramatic increase in Odds Ratio risk occurred only after 20 or more days annual exposure to herbicide use. Furthermore, the number of cases which gave the dramatic six fold increase of NHL after exposure of more than 20 days per year was only seven. If the individual's memory in two or three of these cases with the disease or even one-half a dozen of the controls has been faulty, resulting in a misclassification, the statistical significance of the major point in the KFWS summary would disappear.

Table 2 of the Kansas Farm Worker Study gives data of NHL in relation to herbicide use, but the data are given only for phenoxyacetic acids and there is no data given specifically for 2,4-D. It is not clear why 2,4-D has been singled out from these data for particular concern since results were also given for the triazines, amides, and trifluralin and the data for all these compounds were statistically significant in relation to NHL besides the data for phenoxy acetic acids. Clearly the validity of the classification of these other herbicides is also subject to the same criticisms that have been discussed for 2,4-D.

There is another criticism of Table 3, namely it reports the use of 2,4-D prior to 1946 and 2,4-D was not generally available to farmers until 1947 or later. Further, it is stated that 2,4-D was first available in 1942 which is incorrect as it was not even reported to be a herbicide until 1944.

There are several other inconsistencies in the data reported in this paper. For instance the data did not show an increased risk of NHL correlated with an increase in the number of acres treated with herbicides. Another inconsistency is there was no association with the type of crop grown. That is, the risk of getting HHL was the same regardless of whether 2,4-D would or would not be used to treat the crop. The various types of NHL were grouped together and to assume that one compound has the

same effect on the various subtypes of NHL is not in accord with medical experience.

This article reports that the data confirm Hardell's case-control study[5] finding an association between phenoxy herbicide use and NHL which is correct. However, Hardell and other Swedish scientists[3,4,5] also claimed that phenoxy herbicide use was associated with STS and HD. The KFWS specifically says neither STS or HD were associated with pesticide exposure. Therefore, the implication that this study is in conformity with the Swedish studies is misleading although they do agree on one point. It is also worth noting that the principal phenoxy herbicides used in Sweden mentioned in the Hardell study[5] were 2,4,5-T and MCPA although 2,4-D was also used.

The Kansas study has a lengthy discussion about the possibility of dioxin contamination of 2,4-D being responsible for the association between NHL and 2,4-D and that the increased risk of getting NHL prior to 1946 might be due to a more impure product. As has been pointed out, 2,4-D was not in general use in 1946 and, as the article itself points out, it is generally accepted that 2,3,7,8-TCDD is not a contaminant of 2,4-D. So such speculations are unwarranted.

It is worth mentioning that EPA had this paper reviewed by four independent experts outside the agency[3]. Three of the four reviewers agreed that the data in the Kansas Farm Worker Study did not support the view that NHL is associated with or caused by 2,4-D. The fourth reviewer tended to support the conclusions in the KFWS although the supportive conclusion used words such as "suggest" and the evidence is "beginning" to "lean toward possible causation" between herbicide exposure and particularly 2,4-D and the development of NHL.

It is always easy to be critical about a report and epidemiological studies are unusually difficult to perform. Therefore, although this paper points out some criticisms of the Kansas Farm Workers Study it should be noted that epidemiologists are in general agreement that the study profited from the earlier Hardell work and was better designed and carried out.

In this connection the data in the KFWS indicated the use of protective clothing reduced the risk of NHL to the same as for non-herbicide users.

[3]Copies of these reviews may be obtained from EPA and an abridgment of them is printed in "2,4-Dispatch" Issue 1, Spring 1987 published by Industry Task Force on 2,4-D Research Data, McKenna, Connor, Cuneo, 1575 Eye St., N.W. Washington, DC 20005.

My concluding comments are:

1. The data upon which the Kansas Farm Worker Study is based do not seem to represent an accurate picture on the use of herbicides in Kansas. Further none of the data in this article relating to duration or frequency of herbicide use are specifically on 2,4-D. Their data relate only to herbicides in general that includes several other classes of herbicides besides the phenoxy acids.
2. The accuracy of the exposure data is quite questionable. The small numbers involved in the different subgroups would take only a few errors in memory recall to change their statistically significant findings to non statistical significant results.
3. The latest information on the case-control studies and the cohort studies does not link the use of 2,4-D with NHL as may be seen in the Woods[9] and Cantor[2] papers.
4. It is axiomatic among epidemiologists that no one study proves a cause and effect association and it should be in accord with other similar studies. Therefore it should be noted this Kansas Farm Worker Study is not confirmed by several other epidemiological papers[2,7,8,9] on the same subject which present a contrary view. In this connection the reader is referred to an excellent review of epidemiological papers on 2,4-D by Bond[1] et al.
5. Thus in my opinion, to assume as some have done that the data from the Kansas Farm Worker Study show that there is an increased risk of getting NHL after exposure to 2,4-D is not a valid conclusion.

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