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February 7, 1982

ADVISORY COMMITTEE ON PESTICIDES: REPORT ON PHENOXY ACID HERBICIDES

In a Written Reply to a Question by Mr. Eric Cockeram, M.P., in the House of Commons today, asking the Minister whether he has received a report from the Advisory Committee on Pesticides on the safety of phenoxy acid herbicides, and if he will make a statement, the Rt. Hon. Peter Walker, M.P., Minister of Agriculture, Fisheries and Food, said:

"In May 1982, the Government invited the Advisory Committee to review the latest evidence on the safety of this group of herbicides, which includes 2,4,5-T among others. This followed publication in the Lancet of an article suggesting a possible association between exposure to phenoxy acid herbicides, chlorophenols or their contaminants and an increased risk of a rare type of cancer.

"The Committee's advice was received on December 14, 1982 and has now been the subject of full and careful consideration; copies are being placed in the Library of the House. In the light of the available medical and scientific evidence, the Committee has advised that formulations of phenoxy acid herbicides and related wood preservatives as presently cleared under the Pesticides Safety Precautions Scheme may continue to be used. The Government accepts this advice.

"The Committee has also made two recommendations for further research. The first is that some retrospective and prospective investigations should be made among groups exposed to phenoxy acids during their manufacture or use as herbicides, as a contribution to the work being done internationally in this area. My rt. hon. Friend the Secretary of State for Social Services is asking the Medical Research Council to follow up this recommendation. Secondly, the Committee has recommended, in the light of experience in the USA, that the possibility of risk arising from exposure to chlorophenols and related products in factory situations should be investigated.

"The Health and Safety Executive is already conducting studies on this matter, and my rt. hon. Friend the Secretary of State for Employment is asking the Health and Safety Commission to consider whether further studies are needed.

" I take this opportunity, on behalf of my rt. hon. Friends, to thank Professor Kilpatrick and his colleagues for the skilled and painstaking attention they have given to this sensitive subject, and to express the Government's confidence in them."

NOTE FOR EDITORS

Copies of the Advisory Committee's report can be obtained, free of charge, from the Ministry of Agriculture, Fisheries and Food, Room 678, Great Westminster House, Horseferry Road, London SW1P 2AE (telephone 01-216 6278 or 01-216 6801).

The Rt Hon Peter Walker, MBE, MP,
Minister of Agriculture, Fisheries and Food,
Whitehall Place,
London SW1A 2HH.

Dear Minister,

1. In your letter of 8 May 1982, you sought the Advisory Committee on Pesticides' observations on new evidence concerning the safety of 2,4,5-T herbicides, with particular reference to a review article published in the Lancet on that same date. We have now reached a point in our enquiries at which we think it would be helpful to report to you and the other Departmental Ministers with an interest in the safety of these herbicides.

Background to Study

2. The Committee decided that a panel of independent members should be set up under my chairmanship to consider the latest evidence, and the advice in this letter reflects their detailed examination of all the relevant studies known to us which are summarised in Appendix A to this letter. The panel included all areas of expertise needed for a study of a postulated association between use of a herbicide and a particular type of cancer, and consisted of:-

Professor C.L. Berry
Dr R.L. Carter
Dr R. Goulding
Professor J. Knowelden
Professor R.I. McCallum
Professor G.R. Sagar

3. Before giving you our conclusions, I think that a brief review of the evidence we have considered since publication of our December 1980 report might help you and your colleagues to assess our advice. You will recall that much of our 1980 enquiry was concerned with the question of whether the use of 2,4,5-T herbicides might be associated with miscarriages and birth deformities among humans and animals, and the evidence included a number of specific cases in which such an association was claimed. Each of these was investigated in detail by the appropriate Government Departments and the Health and Safety Executive in consultation with the general practitioners, hospital consultants and veterinary surgeons concerned, before the Committee reached its conclusion. Our examination revealed no evidence linking any of the cases with use of 2,4,5-T herbicides; and we could find no other evidence which established any association between use of these products and harmful effects on humans, other living creatures or the environment. We were thus able to conclude that: "2,4,5-T herbicides can safely be used in the UK in the recommended way and for the recommended purposes".

4. Our present enquiry arose out of a separate and specific question - that there might be an association between exposure to phenoxy acid herbicides, chlorophenols or the contaminants that may be present in these products and substances, and an increased incidence of a group of tumours classified as soft tissue sarcomas. The term soft tissue sarcomas includes some 50 varieties of tumour. As a group they are rare, in that they represent approximately one in every 1500 individuals who die each year, and three from every 1,000 people who die from cancer each year. Obviously such a low overall incidence makes assessment of changes related to possible causal agents a most difficult exercise in statistical significance.

5. The evidence we have reviewed is based on studies of two quite distinct types of populations. The first is of users of various herbicides and wood preservative products, and the second is of factory workers engaged in the production of chemicals. The ACP is concerned with advising on all risks that may arise from the use of pesticides, as distinct from any risks which may arise in the course of manufacture, and which are strictly speaking outside our remit. We, therefore, concentrated on the first type of population - pesticide users - and our advice is based on the weight of evidence emerging for this type. Nevertheless, we also examined factory studies to ensure that no evidence which might have a bearing on our task had been overlooked.

Discussion of Evidence - Herbicides and Wood Preservatives

6. Studies of pesticide user groups have been undertaken in various countries and consist both of case control and mortality investigations. The case control studies involved a comparison of individuals with soft tissue sarcomas whose exposure to herbicides and wood preservatives had been assessed mainly by memory recall, with control groups who either had no cancer or other types of cancer. In the mortality studies the incidence of death among groups of workers largely identified on the basis of occupational histories was compared with national or regional mortality statistics.

7. For users of herbicides and wood preservatives, a positive statistical association between reported exposure and soft tissue sarcomas had been suggested from two studies carried out in Sweden. Successive reports on a similar case control study have also become available from New Zealand. These showed no correlation between exposure to phenoxy acid herbicides and soft tissue sarcomas. It is our view that the procedures used for establishing the Swedish study groups, and some aspects of the collection of the exposure data, were not reliable. In that country, separate case control studies were undertaken in Northern and Southern Sweden following publication of a previous clinical report in which 7 individuals with soft tissue sarcomas recalled being exposed occupationally to phenoxy acid herbicides at some time during the 1950's and 1960's. I should explain that whenever clinical evidence of that kind becomes available in any area, it is normal epidemiological practice to follow up the findings by means of investigations among totally different groups, thus preventing the possibility of bias. In the follow up study in Northern Sweden, however, the 13 cases in which exposure to phenoxy acid herbicides was claimed (amongst a total of 52 cases of soft tissue sarcomas) included the 7 cases identified during the earlier clinical investigations. We consider this to be unorthodox epidemiological practice; if these 7 cases are omitted from the study, the relative risk is reduced to within error limits. This was not the only defect in the study. For example, patients and controls who reported exposure only to chlorophenols were excluded from the calculation of the relative risk factors associated with phenoxy acid herbicides while the control group excluded patients with any malignancies. The relative risk factor for chlorophenols was similarly artificially raised by excluding patients and controls who reported exposure only to phenoxy acid herbicides. Moreover, that study, and the further one in Southern Sweden, were conducted at least one year after a publication drawing attention to the possibility of the suggested association from clinical experience. Because public awareness of alleged risks from 2,4,5-T herbicides had been acute for some years, there is a probability that a bias from exposure recall occurred in both studies.

8. Although they may be valuable, case control studies are not a precise tool for establishing a causal relationship. They can be very unreliable and misleading unless supported by sound documented information on exposure. Such information was not available in either of the Swedish studies, where it was largely based on the memory recall of individual patients or their relatives. We have, therefore, looked for corroborative evidence from mortality studies of cohorts of herbicide users. We have found none. Two such cohorts have been studied in Sweden and one in Finland. A total of 2,461 individuals were included in them. There was no overall increase in deaths from all causes or from cancer. No case of soft tissue sarcomas was identified. Similarly, no correlation between soft tissue sarcomas and occupations involving the use of phenoxy acid herbicides emerged from a study of deaths in Washington State between 1950-1979. We comment further on this study in paragraph 13 below.

9. One feature of our 1980 enquiry again became evident during the current one and has already been referred to above. This is that much of the evidence depends on personal recollection of what took place well before the association was claimed, and that recollection may have been influenced by later publicity. In our 1980 report we argued, in relation to miscarriages and birth deformities, that it can be relatively easy to select some products, or other factor, and without enquiring very closely, to assume some connection with family misfortunes of that kind. This tendency has again been illustrated by a recent publication in this country ("Portrait of a Poison: The 2,4,5-T Story") in which two deaths were attributed to soft tissue sarcomas developing after alleged exposure to 2,4,5-T herbicides. We have enquired carefully into these cases, which have been given some publicity. In addition to the lack of reliable exposure data, we have established beyond doubt that in neither case was the tumour involved a soft tissue sarcoma.

Conclusions - Herbicides and Wood Preservatives

10. In summary, a number of factors have emerged from our analysis of studies of user groups that are relevant to the assessment of the safety of 2,4,5-T herbicides in this country. Firstly, none of the reports we have examined is concerned only with use of formulated 2,4,5-T herbicides, or indeed, only with production of 2,4,5-T. These studies relate to the phenoxy acid group of herbicides as a whole, as well as to wood preservatives. In this country, use of 2,4,5-T herbicides constitutes only a small fraction of the total use of all these products. Secondly, deficiencies in those studies that gave positive results are such as artificially to raise the calculated relative risk factor. And thirdly, we are not aware of any instance in this country where an individual has used 2,4,5-T herbicides and developed a soft tissue sarcoma. We conclude that there continue to be no grounds for changing our previous advice that formulations of 2,4,5-T herbicides as presently cleared, or, for that matter, other phenoxy acid herbicides and related wood preservatives, do not pose a safety hazard, whether used in agriculture, forestry, the home and garden, or elsewhere.

11. However, it has always been our normal practice to keep the safety of any pesticide under continuous review, and to take account of any additional relevant evidence that may become available. In the present case, we believe it would be practicable and desirable to pursue some further enquiries, based on available UK cancer mortality data, in order to establish whether there has been any change in the incidence of soft tissue sarcomas over the past 20 years, and whether there has been any correlation between such sarcomas and particular occupations. This will take a little more time, but without such an analysis the examination we have made of all known relevant studies would not be complete. We will, therefore, be reporting further.

12. Separately from this we suggest that the Government should consider arranging for systematic and complementary retrospective and prospective case control investigations to be undertaken as a contribution to the work being done internationally in this area. To this end we set out, in Appendix B, details of the kind of enquiries which would be appropriate and comment on the problems involved in setting them up, and on their potential value.

Discussion of Evidence - Production of Chemicals

13. The second type of evidence we have reviewed (paragraph 5 above) comes from mortality and disease data of cohorts of chemical workers in the USA, West Germany, Czechoslovakia and the UK. Whereas in the last three of these countries the findings were negative, positive evidence has emerged only from the USA, where 7 individual cases of soft tissue sarcomas have been identified in various studies. Three of these cases were the subject of individual clinical reports where neither the size of the exposed population nor the nature and extent of exposure, if any, of the patients was established. Another case occurred among an undefined group of chemical production workers. The remaining three cases, each of which had a prior history of chloracne testifying to the fact and intensity of toxicologically significant exposure to dioxins, were drawn from two cohorts comprising a total of 182 chemical production workers. Exposure to chlorophenols was common to the latter 4 cases. Other cohort studies in the USA and elsewhere among workers similarly exposed to chlorophenols have revealed no cases of soft tissue sarcomas among a total of 460 workers. Two further American studies, involving the retrospective analysis of mortality data, did not establish any association between the incidence of soft tissue sarcomas and likely occupational exposure to either phenoxy acid herbicides or chlorophenols.

14. We do not consider these studies to be relevant to any assessment of the safety in use of the phenoxy acid group of herbicides, because the circumstances, nature and extent of possible exposure differ greatly between the factory and the field, the forest or the garden. The studies of cohorts of chemical production workers which we have examined, and which identified the occurrence of chloracne among some of the individual cases, indicated that exposure was to both a wider range of substances and to higher levels than was the case with users of formulated products, and that it included exposure to contaminants which have now been virtually eliminated from formulated products. There was no such evidence among the populations who had merely used the formulated products.

Conclusion - Production of Chemicals

15. In this country, chlorophenols are produced and used in many situations outside agriculture and wood preservation. A few have limited use in their own right, but the majority are used, or have been used, in the production of a wide range of products such as adhesives, dyes, paints, inks, disinfectants, wax emulsions, cutting oils, fire extinguishers, ropes, tents, pharmaceuticals, toothpastes and cosmetics, as well as in the leather, textile and paper and board industries. The evidence we have examined concerning chemical production workers leads us to the conclusion that it would be prudent for the Government to undertake further relevant investigations in factory situations in this country. Neither the factory processing of chlorophenols nor the safety of the products and practices described above is within the remit of the Advisory Committee on Pesticides; but we would wish to be involved in any such wider investigations in so far as these might relate to the specific area of the production of herbicides and wood preservatives.

Yours sincerely,

Robert Kilpatrick
Chairman

Advisory Committee on Pesticides

**SUMMARY OF EPIDEMIOLOGICAL AND CLINICAL STUDIES CONTRIBUTING ORIGINAL
OBSERVATIONS CONCERNING A POSSIBLE ASSOCIATION BETWEEN CHEMICAL
EXPOSURE AND SOFT TISSUE SARCOMAS**

<u>Ref</u>	<u>Country of Origin</u>	<u>Study Population</u>	<u>Summary of findings</u>
CASE CONTROL STUDIES			
1	Sweden	52 cases of soft tissue sarcoma and 208 matched controls from Northern Sweden	Exposure to phenoxy acids reported by 25% of cases and 7% of controls. Exposure to chlorophenols reported by 13% of cases and 3% of controls. Relative risk* of developing a soft tissue sarcoma associated with exposure to phenoxy acids = 5.3. (Relative risk associated with exposure to chlorophenols = 6.6). Chlorinated dibenzodioxins and dibenzofurans possibly involved.
2	Sweden	110 cases of soft tissue sarcoma and 219 matched controls from Southern Sweden.	Exposure to phenoxy acids reported by 13% of cases and 3.2% of controls. Exposure to chlorophenols reported by 10% of cases and 3.7% of controls. Relative risk of developing a soft tissue sarcoma associated with exposure to phenoxy acids = 6.8. (Relative risk associated with exposure to chlorophenols = 3.3).
3	Sweden	169 cases of malignant lymphoma (60 Hodgkin's disease and 109 non-Hodgkin's lymphoma) and 338 matched controls.	Exposure to phenoxy acids reported by 24% of cases and 7% of controls. Exposure to chlorophenols reported by 30% of cases and 10% of controls. Relative risk of developing a lymphoma associated with exposure to phenoxy acids = 4.8. (Relative risk associated with exposure to chlorophenols = 4.3).
4	Sweden	154 cases of colon cancer and 541 unmatched controls. (Supplementary study to 1, 2 and 3 above).	A re-examination of the data presented in 1, 2 and 3 above confirms relative risk factors of 4.2, 5.6 and 4.1 respectively for an association between the development of soft tissue sarcoma and malignant lymphoma and exposure to phenoxy acids following a 5 year latency period. No association was established between exposure to such chemicals and the development of colon cancer, relative risk = 1.3.

*Relative risk is the statistically derived expression of the ratio between the incidence of exposure reported by cancer patients and that reported by the control group.

<u>Ref</u>	<u>Country of Origin</u>	<u>Study Population</u>	<u>Summary of findings</u>
5	New Zealand	102 cases of soft tissue sarcoma first diagnosed between 1976 and 1980 and 306 other cancer patients as matched controls.	Preliminary report. On the basis of Cancer Registry Records there is no evidence of an excess of soft tissue sarcomas among the occupational group involving agriculture and forestry.
6	New Zealand	80 cases of soft tissue sarcoma and 92 other cancer patients as controls. (Further data from the study reported at 5 above).	Further preliminary report. Exposure to phenoxy acids reported by 26% of soft tissue sarcoma cases and 21% of controls. Estimates for the relative risk of developing a soft tissue sarcoma following exposure to phenoxy acids varied from 1.3 for potential exposure of more than 1 day at least 5 years before cancer registration to 1.6 for probable exposure. No soft tissue sarcoma patient had worked full time on phenoxy acid herbicide spraying.
COHORT STUDIES			
7	West Germany	75 chemical workers involved in a trichlorophenol plant accident in 1953	42 cases of severe chloracne associated with exposure during the accident or subsequent cleaning work. By 1978 17 deaths had occurred (11 to 25 expected), 6 due to cancer (4 expected). The incidence of stomach cancer (3 cases) was higher than expected. There were no cases of soft tissue sarcoma.
8	Finland	1971 herbicide sprayers (Railway, forestry, highway and electric company workers)	Retrospective study 1955-1971, 49 deaths occurred (87.8 expected), 13 due to cancer (16.4 expected). Prospective follow-up, 1972-1976, 62 deaths occurred (92.9 expected) 9 due to cancer (18.1 expected). Prospective follow-up, 1977-1980, 82 deaths occurred, (91.1 expected), 17 due to cancer, 18.4 expected. No cases of chloracne. No cases of soft tissue sarcoma.
9	USA	61 chemical workers involved in trichlorophenol production and exposed to 2,3,7,8-TCDD in 1964	49 cases of chloracne were reported ranging from mild to severe. By 1978 4 deaths had occurred (7.8 expected), 3 due to cancer (1.6 expected). One case was a soft tissue sarcoma (fibrosarcoma).

<u>Ref</u>	<u>Country of Origin</u>	<u>Study Population</u>	<u>Summary of findings</u>
10	USA	204 chemical workers involved in 2,4,5-T production between 1950 and 1971	No case of chloracne. By 1976 11 deaths had occurred (20.3 expected), only 1 due to cancer (3.6 expected). This was not a case of soft tissue sarcoma.
11	USA	121 chemical workers involved in a trichlorophenol plant accident in 1949	All members of the selected cohort exhibited chloracne attributable to exposure during the accident. By 1978 32 deaths had occurred (46.6 expected), 9 due to cancer (9 expected). One case was a soft tissue sarcoma (malignant fibrous histiocytoma).
12	Sweden	142 forestry workers exposed to phenoxyacetic acid herbicides between 1954 and 1978 and 244 forestry workers not so exposed	The pattern of deaths among both exposed and unexposed cohorts is in accord with Swedish national mortality statistics. However among foremen, the most extensively exposed workers, there is an excess of mortality (8 observed/4.1 expected) due to an excess of both cancer (3 observed/1.0 expected) and cardiovascular disease (4 observed/1.9 expected). There were no soft tissue sarcomas.
13	Sweden	348 railway workers (herbicide sprayers between 1957 and 1972)	No cases of chloracne. By 1978 45 deaths had occurred (49 expected), 17 due to cancer (11.9 expected). No specific type of tumour predominates and no soft tissue sarcoma was reported.
14	Czecho-slovakia	55 chemical workers exposed to 2,3,7,8-TCDD over a 10 year period during the production of 2,4,5-T from trichlorophenol	52 cases of chloracne. By 1980 6 deaths had occurred, 2 due to cancer. There were no cases of soft tissue sarcoma.
15	USA	Review of 9, 10 and 11 above plus additional data on chemical workers involved in the production of 2,4,5-T from trichlorophenol	An additional case of soft tissue sarcoma (generalised liposarcoma) is reported in a worker involved in the production of 2,4,5-T from trichlorophenol. There was no prior history of chloracne.
16	USA	Supplementary data concerning the cohort studied at 9 above	An additional case of soft tissue sarcoma (malignant fibrous histiocytoma) in a trichlorophenol production worker is reported. There was a previous history of chloracne.

<u>Ref</u>	<u>Country of Origin</u>	<u>Study Population</u>	<u>Summary of findings</u>
17	United Kingdom	126 chemical workers involved in a trichlorophenol plant accident in 1968	79 cases of chloracne were reported after the accident. By 1981 no deaths had occurred nor had any case of cancer been identified. No abnormal biochemical or clinical effects attributable to exposure.
18	USA	Retrospective analysis of mortality data - Washington State (1950-1979)	In occupations with exposure to phenoxy acid herbicides or chlorophenols 49 soft tissue sarcomas were observed (41 expected). In those occupations with the greatest excess of deaths from soft tissue sarcoma there was no obvious association with exposure to phenoxy acid herbicides or chlorophenols.
19	USA	Retrospective analysis of mortality data - butchers and slaughterhouse workers (1965-1980)	An analysis of cancer mortality among butchers and slaughterhouse workers revealed an increased risk relative for soft tissue sarcoma of 5.6 (1 observed case/0.18 expected).

CLINICAL REPORTS

20	Sweden	7 cases of soft tissue sarcoma (included in the case control study reported at 1 above)	Exposure to phenoxy acids is reported in all 7 cases. In 5 cases the exposure was direct and heavy.
21	Sweden	17 cases of malignant lymphoma (included in the case control study reported at 3 above)	Exposure to phenoxy acids, is reported in 8 cases.
22	USA	1 case of soft tissue sarcoma in a chemical worker	A case of retroperitoneal neurogenic sarcoma is reported in a truck driver and maintenance worker in a chemical plant producing trichlorophenol or 2,4,5-T. No history of prior chloracne.
23	USA	2 cases of soft tissue sarcoma in chemical workers (father and son)	Two cases of soft tissue sarcoma are reported (a fibro-sarcomatous mesothelioma and a liposarcoma). Both individuals had been employed at a chemical plant producing chlorophenols. No history of prior chloracne.

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PROPOSALS FOR EPIDEMIOLOGICAL INVESTIGATIONS OF
MORBIDITY ASSOCIATED WITH HERBICIDES

- 1 The assessment of the available data concerning a possible biological association between exposure to phenoxy acid herbicides and soft tissue sarcoma has led to the conclusion that there is a need for further research to permit the confirmation or refutation of this suggestion. It has also been noted that a number of studies are already in progress or are about to be initiated in several countries around the world using data which are available on both a national and international basis. These include systematic epidemiological studies of both a retrospective and a prospective nature which constitute the only appropriate methods available for this purpose. In view of the known temporal and geographical variations in the incidence of a number of malignant conditions and of the importance of the phenoxy acid herbicides to agriculture and forestry in this country it is considered advisable to investigate the situation as it exists in the United Kingdom. Appropriate information is available to enable epidemiological studies of both a retrospective and a prospective nature to be carried out. In addition to being the only way of obtaining information of direct relevance to the UK workforce it should be possible, from the data available, to obtain evidence which is less open to the criticisms that have been levelled against some of the reports that have been published so far. There would also be an opportunity to extend the scope of the investigations to include aspects other than the occurrence of soft tissue sarcoma and the possible involvement of other chemicals such as the chlorophenols.

Retrospective Study

- 2 This would examine whether patients suffering from soft tissue sarcomas (or other specified malignant conditions) had an unusual history of exposure to phenoxy acids during their manufacture or use as herbicides. The first step would be to establish a group of sarcoma patients and an appropriate control group. Since comprehensive cancer registration data are available covering the whole country, basic information eg age, sex, type of malignancy, when and where registered, for all identified cases in specified categories of soft tissue sarcoma is readily accessible. However, these are relatively rare tumours, and a decision would have to be taken whether to study all of them in relevant age groups, or only those in parts of the country where herbicide use is likely to be more common. The control group, which would have to be matched at least by age and sex, could be cancer registrations for body sites where there are no reasons to believe that tumour occurrence could be associated with herbicides.
- 3 The major problem with retrospective studies is in obtaining the history of herbicide exposure. For most patients the occupational exposure will not have been documented precisely, if at all. Memories are notoriously fallible, even in the short term and recall concerning events many years

previously will probably be uncertain. For patients who have died recourse might be had to their families to obtain the history, as in some of the published reports, but this would be even more unreliable. Furthermore, whether obtained from the patient or a relative, there is the possibility of a bias in the histories of herbicide use from cases compared with controls because of the publicity on possible hazards.

- 4 A retrospective study would have to be conducted in the expectation that only in a small proportion of cases and controls could the histories of herbicide use be validated. In such an investigation particular attention would have to be paid to ethical considerations. Information in cancer registries is confidential, and a proper procedure would have to be established before any approach could be made to consultants, general practitioners, to the patients and their families, or to any other source of data.
- 5 Despite these drawbacks a retrospective study has certain advantages. It can be mounted fairly quickly and is relatively cheap. It does not take long, the duration being governed largely by the time required to obtain occupational histories.

Prospective Study

- 6 In this study a cohort with known exposure to herbicides would be identified and monitored to determine whether they subsequently suffered any excess of soft tissue sarcomas or morbidity of other kinds. There would be a need for a control cohort comprised of individuals not exposed to herbicides. The subsequent morbidity of this group would be recorded in exactly the same way as for the herbicide user cohort.
- 7 Since reliable information concerning exposure is of paramount importance in such a study an essential pre-requisite is that there should be good documentation available concerning herbicide use. Organisations such as the Forestry Commission or commercial sprayers who keep routine records should therefore be selected in preference to farmers whose occasional use of herbicides may go unrecorded. The documentation system would have to be reviewed to assess the need for possible changes to ensure that complete, uniform and appropriate data are obtained.
- 8 The essence of the prospective study would be the collection of morbidity information in cohorts defined as either using or not using herbicides. Leaving aside the choice of the control cohort, the non-users, there are different problems depending on what aspect of morbidity is selected for study. The extreme event, death, could be readily ascertained, even if members of the cohort moved or changed their occupation, by tagging their entries in the NHS Central Register. Cancer registrations, as well as deaths from any cause, are reported to this Register so that the cancer morbidity as well as mortality can be obtained for the defined cohort.
- 9 Other expressions of morbidity, leading to consultation with a general practitioner, out-patient referral or admission to hospital, are not obtainable from a central register. If there was a case for seeking evidence on anything besides general mortality and cancer morbidity,

eg on liver disease, this would need a separate organisation such as a questionnaire to the patient or his doctor to determine whether there was any episode of illness worth further enquiry. It would add considerably to the cost and complexity of the study to extend the range of outcomes in this way, and there would need to be a strong case for such addition.

- 10 It could be difficult in a prospective study to establish a satisfactory control cohort. Ideally it should comprise individuals of similar age, sex, and social class distribution, and probably from the same areas. In occupational studies of this kind it is sometimes possible to find groups within the same organisations, such as administrative and clerical staff, who are not in contact with the process, but their numbers may well be too small in this instance. It is always possible to use national or Regional data on mortality and cancer registration as a standard of comparison for the cohort of users, and this compromise may be a reasonable one to adopt.
- 11 The main disadvantage of a prospective study is the length of time before sufficient events have occurred to warrant comparisons between users and non-users particularly where rare events such as the occurrence of soft tissue sarcomas is concerned. Furthermore, the cohorts defined initially will not remain 'pure' in the sense that additional exposures to similar or different agents may occur. Nevertheless this type of study is more likely to lead eventually to a valid measure of the risk, if any, of exposure to specific herbicides and should, therefore, be given serious consideration, although the difficulties which have been outlined above should not be underestimated.
- 12 A cohort, prospective, study set up now could provide evidence only on phenoxy acid herbicides currently produced. However, there may be scope for conducting a cohort study retrospectively. If in selected organisations, such as the Forestry Commission, it was possible to prepare nominal lists of all employees in some period in the past, say the decades 1945-54, 1955-64, and to categorise them by pesticide use, their subsequent experience up to the present day of mortality and cancer registration might be retrievable. The mortality picture could be virtually complete, but cancer registration was not fully established in the earlier years and would be reliable only for the last 10-15 years. The study would not be easy, but might be valuable because it would provide information on exposure to herbicides with a relatively high dioxin contamination. Unlike a new cohort study established now, some measure of the outcome 20-30 years after exposure could be obtained relatively quickly.