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EPIDEMIOLOGY OF SOFT-TISSUE SARCOMA AND RELATED HUMAN RESEARCH

Initiation of Swedish Studies of Herbicides and Cancer

In 1972 Swedish newspapers published rumors that railroad workers were dying from lung cancer as a result of exposure to herbicides used in their work. The National Board of Occupational Safety, as a result, requested Professor Olav Axelson, a specialist in occupational medicine, to undertake an epidemiological investigation of the matter.

The results of this investigation have been reported in a series of four papers, 1-4. Another series, 5-7, was prompted by criticism of the epidemiological and statistical methods employed in this and related studies. Attention in the United States has focussed on the pre-publication manuscript of the 1980 paper by Axelson, Sundell, Andersson, Edling, Hogstedt, and Kling, 4.

This paper dealt with two aspects of the study of railroad workers. The initial phase was a cohort study of 348 men who had been exposed, individually rather than as a group, to herbicides for more than 45 days during 1957 to 1972 and who were followed through October 1978. Exposure information was incomplete but the workers were divided into subcohorts with exposure to phenoxy acids (which include the ingredients of Agent Orange), amitrol, or to both herbicides. The mortality rates for these exposed subcohorts were compared to the age-specific national death rates for Swedish men, the latter serving as the control cohort.

Overall 49 deaths were expected in the exposed cohort; 45 occurred, a result attributed to the "healthy worker effect." There were, however, 17 tumors found where 11.85 were expected. Among the deaths occurring at least ten years after the first exposure, 6 cancers were found although only 1.78 were expected. Dr. Axelson, 8, later increased this to 7 tumor cases. Each subcohort had an excessive number of tumor deaths, the greatest being in the group exposed to both phenoxy herbicides and amitrol.

Although initially, 2, amitrol was associated with an increased tumor mortality, somewhat different results were found in a second phase of the examination, described as a case-referent study (identical to a case-control study). The data indicated a "statistical association" of phenoxy herbicides and excess tumor mortality, 3. Suspicion was increased by finding that workers exposed to phenoxy acids

alone had a "statistically significant excess of stomach cancer", specifically 2 cases compared to 0.33 expected when this type of herbicide was used alone and 3 cases as compared to 5.1 expected (increased from 4.1, 8) for all workers exposed to phenoxy herbicides, alone or with amitrol.

The series of papers on railroad workers has been criticized on several methodological grounds, 9, and Axelson has replied to these criticisms, 6. Richard D. Remington, Dean of the School of Public Health, University of Michigan, reviewed this and other Swedish studies for the Office of Technology Assessment. His evaluation, 10, was that the Axelson investigations had been "carefully conducted" and "well reported." He pointed out the limitations of the statistical methods used and found that "the numbers available ... are inadequate to permit definite conclusions" although "the results ... are suggestive."

Of interest in connection with the question of soft-tissue sarcomas and phenoxy herbicides is the type of tumors found by Axelson's group, 4. One case of Hodgkin's lymphoma occurred among the eight tumors in men exposed to phenoxy herbicides alone and no soft-tissue sarcomas or non-Hodgkin's lymphomas was diagnosed among the eight tumors appearing in workers exposed to both amitrol and phenoxy herbicides. In other words, no sarcomas were reported for the total of 207 men exposed to phenoxy compounds, 2. A reticulum cell sarcoma and a Hodgkin's lymphoma were found among the 7 tumors of workers exposed to amitrol alone. Thus, there was one soft-tissue sarcoma reported for 152 men exposed to amitrol, 2. Another 28 persons described as exposed to "other herbicides and combinations" cannot be identified as to exposure to specific herbicides but apparently none developed a tumor.

Axelson's work is directly related to the later work on soft-tissue sarcomas and lymphomas by Lennart Hardell. Indeed, Axelson suggested to Hardell in 1976, that he conduct a case-control study of soft-tissue sarcomas and has actively assisted in Hardell's work since then.

Swedish Investigation of Soft-Tissue Sarcoma

That work began when Hardell admitted for treatment 3 patients in the autumn of 1976, each with a soft-tissue sarcoma, and a history of exposure to phenoxy herbicides. He then found a total of 7 patients with "malignant mesenchymal tumors" (soft-tissue sarcomas) who gave a history of having worked with phenoxy herbicides 10 to 20 years earlier. The cases were among 87 patients with soft-tissue sarcomas, 55 of

whom were men. Of these men, 9 were forestry workers, 6 worked in forestry and on farms, and 6 were employed in saw mills or pulp plants. Another two tumors appeared in men whose connection with forestry was less direct. The malignancies found were two leiomyosarcomas, two rhabdomyosarcomas, two neurofibrosarcomas, with one each of fibroid liposarcoma, myxofibrosarcoma, and polymorphocellular sarcoma, 12.

Following Axelson's advice, Hardell began a case-control study that was published in two journals, 13, 14, a common practice of reporting in Swedish with an almost identical paper in English. The second paper in English aroused much interest in the United States.

Hardell and Sandstrom found 21 living and 31 dead men who were diagnosed as having soft-tissue sarcomas in Hardell's oncology department in northern Sweden. They were matched for age and place of residence, as well as date of death for the deceased, with other men selected from the Swedish National Population Registry or from the National Registry for Causes of Death. Each living patient had 4 living controls; each dead man had 4 deceased controls. Exposure information was sought by the use of a mailed questionnaire that has never been published. It contained 130 questions, including 16 about the use of organic solvents, 4 about plastics, 3 about glues, 4 about drugs, "several" about smoking habits and an unstated number about exposure to phenoxy herbicides and chlorophenol as used in the lumber and paper mills. This questionnaire was mailed to the patient or to his next of kin if he were dead, 15.

When the answers to the questionnaire were less than clear, a supplementary interview was obtained, usually by telephone, with the interviewer unaware of the health status of the person in question. Employers, neighbors, and others were consulted "if necessary to verify and monitor the accuracy of the exposure information," 15.

Using the criteria for exposure established for the study, 36.5% of the 52 patients and 9.2% of the 208 controls had been exposed to phenoxy herbicides and/or chlorophenols. The "relative risk" of developing soft-tissue sarcomas was calculated as 5.7, i.e. men exposed to the chemicals had almost six times as great a change of developing a sarcoma as did those who were not exposed. The relative risk was 5.3 for the 46 men exposed to phenoxy herbicides alone, and 6.6 for the 40 men exposed only to chlorophenols. It was thought that confounding factors had an insignificant effect.

The authors concluded that "the investigation showed an increased risk for soft-tissue sarcomas" but "a specific evaluation of the effect of separate chemical substances was not possible," 14.

The study's methods have been criticized and doubts have been expressed about the 100% response rate to the questionnaire approach, 9. (Actually, 2 of 208 controls did not answer, 14.) The statistical approach was described as slightly misrepresented and a major criticism was leveled because of the possibility of "selective recall," the greater tendency for an ill person to remember a supposed "cause" for the illness than a well person would have to remember the same "causal" event.

The criticisms evoked several replies. Axelson defended the case-control design, the objectivity of obtaining exposure data retrospectively, and the statistical techniques, 6. He concluded that the use of interviews for determining exposure is justified, 7, and defended in principle the treatment of confounding factors, 16. Hardell recalculated the 1979 results and his subsequent papers to substantiate his earlier findings and performed a separate investigation in support of his confidence that "no substantial observational bias could exist in the studies," 15.

Remington, 10, expressed the view that "the findings of this particular investigation are suggestive" and that "a relative risk of 5.3 for exposure to phenoxyacetic acids must be taken seriously." However, "case-control studies are uniquely susceptible to hidden sources of bias" even when the investigators are "unusually careful" as they are in this "excellent investigation."

Hardell's group also undertook a second case-control study of identical design in southern Sweden which is more devoted to agriculture than to forestry, 17, 18. In this investigation each of 72 living and 38 dead patients was matched with two controls. Among the 110 cases, 22.7% reported exposure to phenoxy herbicides or chlorophenols and, among the 219 controls, 5.9% were so exposed. This gave a relative risk of 5.1 with matching and 4.7 when the matching was dissolved, i.e. when sorting by age was ignored during statistical calculations. The relative risk from exposure to phenoxy herbicides was calculated to be 6.8, and that from chlorophenols to be 3.3. Exposure to more than a dozen other noxious materials, e.g. asbestos, smoking, DDT, and lindane, were considered as possible confounding factors although none was found to be clearly associated with an increased risk by itself.

The reports list the diagnoses of all 110 cases of soft-tissue sarcoma as: leiomyosarcoma, 33; malignant fibrous histiocytoma, 19; liposarcoma, 15; neurogenic sarcoma, 11; angiosarcoma, 9; myxofibrosarcoma, 7; fibrosarcoma, 5; dermatofibrosarcoma, 3; atypical fibroxanthoma, synovial sarcoma, sarcoma NOS, 2 each; Ewings's sarcoma (extraskeletal) and rhabdomyosarcoma, 1 each. No statement is made as to which of these tumors was found in the 25 cases with identified exposures and no histological diagnoses are reported for the northern Swedish series, 13, 14.

The authors of the southern Swedish study conclude that "exposure to phenoxy acids and chlorophenols might constitute a risk factor in the development of soft tissue sarcomas," 18. The investigation has been the subject of the same criticisms and refutations as the earlier study.

Remington concludes that "the results are consistent with the hypothesis that phenoxy acid exposure increases the risk of tumors of this type" but adds that "case-control methodology is intrinsically susceptible to subtle and unmeasurable biases."

Swedish Investigation of Lymphoma

In May, 1978, Hardell was prompted to a new study by a patient with a malignant histiocytic lymphoma and a history of "massive exposure to phenoxyacetic acids." All men admitted to the oncology department with this type of tumor during the first nine months of 1978 were asked about their occupation and possible chemical exposure. Of 17 patients, 14 reported an occupation consistent with exposure and 11 of them had had contact with phenoxy herbicides or chlorophenols ten or more years earlier, 19.

These observations led to a case-control study, the report of which in 1981, 21, differs considerably from that in 1980, 20. The earlier report was commented upon in manuscript form by various experts but the later version will be used here.

The investigation, in collaboration with Axelson, 20, included both Hodgkin's disease and non-Hodgkin lymphomas. The 169 cases consisted of 60 Hodgkin's disease patients (lymphocyte predominance, 20; nodular sclerosis, 3; mixed cellularity, 27; lymphocyte depletion, 10), 105 men with non-Hodgkin's lymphomas (follicular center cell (FCC) type, 53; non-FCC type, 52), and 4 individuals with unclassifiable lymphomas. Each case had two matched controls, 338 in all. Of the cases, 62 had died as had 124 of the controls.

Questionnaires and interviews were used to determine exposure to phenoxy herbicides, chlorophenols, organic solvents, or medicines and to characterize jobs, hobbies, and smoking as they were determined in the soft-tissue sarcoma investigations, 20. All cases and controls were from northern Sweden.

Cases in which exposure was reported to chlorophenol, or to "mutagenic" solvents (benzene, trichloroethylene, perchloroethylene and styrene) were divided into high-grade and low-grade exposure groups. Continuous exposure for a week or less or repeated exposures totaling less than a month were considered low-grade. Analyses also divided cases into two groups depending on whether 5 years had elapsed as a latency period between the first exposure to the chemical and the tumor diagnosis.

Of the cases, 36.1% had been exposed to phenoxy herbicides or chlorophenols; 9.6% of the controls had been so exposed. The relative risk for these exposures was 6.0 with matching and 5.3 without it. Phenoxy herbicides gave a relative risk of 4.8 although it was greater if exposure was for 90 days or more. Chlorophenols gave relative risks of 8.4 for high-grade exposure, 2.9 for low-grade. High- and low-grade exposure to organic solvents gave relative risks of 2.8 and 1.2 respectively. On the other hand the few cases with both phenoxy herbicide and high-grade organic solvent exposure was calculated to have a relative risk of 11.2 and some other combinations also gave large relative risks. The length of the latency period, however, seemed to have no effect.

The authors conclude that "this investigation suggests that exposure to organic solvents, chlorophenols, and/or phenoxy acids constitutes a risk factor for malignant lymphoma," 21. Dr. Remington commented that "a substantial and statistically significant relative risk is found for this group of tumors. And again, pnenoxy acid exposure is specifically incriminated." He continues, however, that the limitations of case-control methods have to be considered as well.

Swedish Investigation of Carcinoma of the Colon

Hardell undertook to answer doubts that his questionnaire and interview methods allowed observational bias in assessing exposure by conducting a case-control study of "colon cancer." The condition is not suspected of having any association with phenoxy herbicides or chlorophenols. In consequence, if the previously used exposure determination

resulted in a relative risk of 1.0 or near it, there had been no observational bias in the questionnaire-interview procedure used in the earlier studies of soft-tissue sarcomas and lymphomas.

Of the 157 men with colon cancer all but 3 answered the questionnaire. The controls consisted of the control groups from the soft-tissue sarcoma study (206 men) and the malignant lymphoma study (335 men). In all, 41% of the cases and 45% of the controls were dead. Of the cases and controls, 11.0 and 10.4% respectively had been exposed to phenoxy herbicides or chlorophenols. For phenoxy herbicides, the relative risk was calculated to be 1.3 and for chlorophenol it was 1.8. Neither was significantly above 1.0. The conclusion was that "the previously reported associations between exposure to phenoxy acids or chlorophenols and soft-tissue sarcoma and malignant lymphoma cannot to any essential degree be explained by observational bias," 15.

Later Criticism of Swedish Studies

There remain, however, doubts about the practical significance of the Swedish epidemiological studies stemming from several of their characteristics. The main criticism is the reliance on recall of the men or their relatives, employers and associates for undramatic events years earlier as well as the possibility of unconscious bias on the part of the interviewer, the "observational bias" discussed above. Coggan and Acheson point out that the positive association between exposure to phenoxy herbicides and the development of several or many soft-tissue sarcomas, Hodgkin's disease and non-Hodgkin's lymphoma may indicate "a serious undetected bias" even though the explanation has been offered that all these tumors are embryologically related, 22. These authors conclude that "it is as yet impossible to estimate with any precision the risk of soft-tissue sarcoma due to phenoxy herbicides" but add that "there is suggestive evidence of a biological association between phenoxy herbicides (or their contaminants) and soft-tissue sarcomas." They feel that there is weaker evidence for an association between herbicides and lymphomas.

Hardell and Axelson reject the idea of observational bias, citing the colon cancer study as evidence, 23. They also defend the aggregation of tumors because of the "so-called addition theorum for chi-square and Poisson distributions" as well as the embryological relationship of the neoplastic tissues.

American Support for Swedish Conclusions

Support for the connection between soft-tissue sarcomas and exposure to phenoxy compounds has been reported in several papers from outside Sweden. The data most often cited as favoring the relationship are derived from observations in the American chemical industry.* The first was a note by Honchar and Halperin in which they pointed out that of 105 deaths in four exposed industrial "cohorts" 3 (2.9%) were due to soft-tissue sarcoma, whereas only 0.07% of deaths among adult American men are so caused. The three cases were malignant fibrous histiocytoma, fibrosarcoma, and liposarcoma. The authors felt that these "suggest a common pattern," 24. Cook added a fourth case, another malignant fibrous histiocytoma and noted that all four were smokers and two had chloracne, 25.

Moses and Selikoff reported a fifth case, a non-smoker, with neurogenic sarcoma (malignant schwannoma). They give the total annual incidence of soft-tissue sarcomas as 4500 (less than 1% of newly diagnosed cancers) in the U.S. and quote 4.9% of soft-tissue sarcomas as malignant schwannoma, 26.

Johnson and his co-workers briefly described a young man who died of fibrosarcomatous mesothelioma some four years after first being exposed to phenol. His father had a liposarcoma after "prolonged exposure" in a plant manufacturing chlorinated phenols among other chemicals, 27.

Hardell and Ericksson accepted the two additional cases to total 7 deaths from soft-tissue sarcoma among 105 deaths among American industrial workers, the expected number being 0.07%. This would "fit in with" the Swedish investigations, they believe, 28.

To date no critical review has been made of the cases and the industrial population in which they were detected. The reports have been brief "Letters to the Editor" and each discusses one to three cases. The total of 105 deaths used as the number of dead workers has not been kept current as new soft-tissue sarcoma cases were added and the total number

*Data given by Honchar and Halperin, Cook, Moses and Selikoff, and Johnson et al pertain to workers at Monsanto Company and Dow Chmical Company. For details of studies of these workers see 24a and 25a.

of exposed workers has not been given. No use has been made of controls, even in the form of a retrospective cohort comparison.

A case report without statistical data briefly described three soft-tissue sarcomas among Vietnam veterans who reported exposure to phenoxy herbicides in that country. One man had an inflammatory histiocytoma, another suffered from a fibrosarcoma, and the third had a leiomyosarcoma, 29.

European Support for Swedish Conclusions

Barthel determined the frequency of malignant neoplasms among 1791 pesticide sprayers and agricultural technicians in East Germany during 1976 to 1979. He states the retrospective cohort study used police as controls but gives no data for them. After eliminating "on statistical grounds" 133 cases who died before 1970, he compared the mortality rate and cancer incidence with corresponding figures from the death statistics and the cancer registry of the Health and Social Welfare. The "case" group had multiple exposures over the years to fungicides, insecticides, and herbicides including phenocyacetic acids. Among 169 malignant neoplasms in 1658 exposed men were 1 lymphosarcoma, 3 plasmacytomas, 1 described as a malignancy of lymphoid tissue, and 1 of soft-tissue, not otherwise characterized. Bronchogenic carcinoma was the most common malignancy with 59 cases, double the expected occurrence, although the cases had smoking habits like those of the general population, 30. A brief report describes a case of non-Hodgkin's lymphoma and a second of malignant lymphoma among 158 workers with pentachlorophenol. This type of neoplasm would have an expected occurance of 0.28, 31.

Studies Not Supporting Swedish Conclusions

In contrast to the reports of an association between phenoxy herbicides or related compounds and soft-tissue sarcomas and malignant lymphomas, some investigators have found no association. Some of these investigated a possible relation, others were "follow-up" studies of industrial workers in whom no sarcomas or lymphomas were found.

Dr. Riikimaki and his collaborators have completed nine years of mortality study following 1,926 persons who worked with phenoxy herbicides in Finland during the 1955-1971 period. All had at least two weeks of exposure and a quarter of the men totalled eight weeks or more as of 1971. The mortality rates among the workers were compared with the national death rates. As of 1980, there had been 82 deaths

of exposed men as compared to 91 expected and, of these, 17 were cancer deaths with 18.4 expected. There were no cases of soft-tissue sarcoma nor of lymphomas although 0.1 and 0.8 would have been expected. The authors believe that "the ... investigation cannot be regarded as a conclusive negative study" but point out that the "results do not confirm the ... association between mixed herbicide exposures" and cancer risk, 32.

Hogstedt and Westerlund compared the mortality rate of Swedish supervisors and workers in forestry. The supervisors were fewer in number (142) than the workers (244) but the former were judged to have been more heavily exposed. The relative risk of death was about the expected but, after a 10-year latent period, the relative risk for cancer was about 4 for the supervisors and only about 0.4 for the workers. The fatal tumors were of various types but there was no soft-tissue sarcoma or lymphoma, 33.

Two case-control studies in New Zealand have been initiated by Smith et al to examine the association suggested by Swedish studies of phenoxy herbicides with soft-tissue sarcomas and malignant lymphomas. In the first investigation, 102 cases of soft-tissue sarcoma have been identified in men from the New Zealand Cancer Registry between 1976 and 1980. An equal number of matched controls with other forms of cancer were selected for comparison. The sarcomas are fibrosarcomas, 25; liposarcomas, 20; rhabdomyosarcomas, 9; leiomyosarcomas, 7; malignant histiocytomas, 6; other types, 22; and unspecified, 13. The preliminary report compares cases and controls as to the occupation shown on the Registry enrollment. There was no significant difference betwen the groups as to the number of men working in agriculture, forestry, and fishing, the occupations with the greatest likelihood of exposure to phenoxy herbicides and chlorophenols. The only occupations associated with soft-tissue sarcomas exclusively are blacksmiths, machine tool operators, electrical fitters, and electrical workers. The investigators are now obtaining work histories for cases and controls by telephone interviews and warn that later results may change their conclusions. The data at present "do not give evidence for a relationship (of soft-tissue sarcoma) with occupational exposure to phenoxy herbicides and chlorophenols" but "should not be taken as substantive evidence against the hypothesis", 34.

A second report by Smith et al includes the results of the telephone interviews regarding 80 cases and 92 controls already completed. Probable or definite exposure to phenoxy herbicides for more than one day earlier than five years before cancer registration was found in 17 cases and 13 con-

trols, giving an odds ratio of 1.6. This would be expected to increase when the exposure criteria were more stringent, but, when exposure was at least five days and more than ten years before registration, there were 13 cases and 12 controls included reducing odds ratio of 1.3. Neither ratio is statistically significant and there have been no soft-tissue sarcomas reported among the most highly exposed group of 2000 aerial and ground sprayers. The results, the authors believe, "do not generally support the hypothesis that exposure to phenoxy acid herbicides cause soft-tissue sarcoma," 35.

A brief initial report by Edling and Granstam compared the causes of death for 375 Swedish forestry workers, aged 25 to 69 years, who died during 1968 to 1977, with the mortality figures from the Swedish national statistics. There were 75 deaths from all malignant tumors, as compared to 86 expected. Renal tumors killed 8 with 3.84 expected and "tumors of lymphatic and hematopoetic systems" were responsible for 14 deaths with 7.5 expected. No deaths were attributed to soft-tissue sarcoma, 36.

In addition to these studies, several small industrial groups have been followed well into the latent period for solid tumors. None has been reported to include cases of soft-tissue sarcoma or malignant lymphoma. May examined 41 of 79 workers who developed chloracne following accidental exposure to trichlorophenol in 1968 at the Coalite Company in Great Britain. Another 54 employees were possibly exposed. None of the workers had significant changes ten years after the accident and neither death from nor evidence of neoplasm was found, 37. Jirasek's group has closely followed 55 men who were intensely exposed during the manufacture of 2,4,5-trichlorophenoxyacetate from 1965 to 1968 in Spolana, Czechoslovakia, and who developed evidence of acute intoxication. Two workers died of bronchogenic carcinoma 5 to 5.5 years after the first exposure. There was no other evidence of malignant neoplasms during a ten-year follow-up, 38.

In 1963 an explosion at Philips-Duphar, Amsterdam, exposed 106 workers involved in manufacturing 2,4,5-tetrachlorophenyoxy acewtate. Among the 93 workers followed to 1977, only one death 14 months after the accident was due to cancer and the pancreatic carcinoma involved was apparently symtomatic before the explosion. No case of soft-tissue sarcoma or malignant lymphoma was reported, 39.

One study is often cited with the Swedish studies although it did not deal with soft-tissue sarcomas and malignant lymphomas, 40. A more recent review by Thiess et al reports that all 74 exposed persons are still being followed

after 26 years. There have been 21 deaths, about equal to the 18 to 20 deaths expected from major comparative populations and 18 and 19 deaths expected among matched unexposed controls. Cancer was responsible for 7 deaths as compared to 4.1 expected from the comparative populations and 5 in each internal control group. Gastric carcinoma in 3 exposed persons exceeds the expected 0.61 to 0.70 expected cases. There were, however, no soft-tissue sarcomas or malignant lymphomas among these chemical workers at BASF, 41.

A number of other industrial exposures to phenoxy herbicides, their precursors or contaminants were reported before 1973, 42. The populations were small but generally heavily exposed. Unfortunately it has not been possible to locate late reports on the exposed populations although ten years or more have elapsed since exposure.

The accident at the ICMESA factory in Seveso, Italy, in July 1976 exposed many people to trichlorphenol; more than 5400 adults and children of both sexes are known to have been in contact with the chemicals for several days, 43. Although only about six years have elapsed since the exposure, the population has been under surveillance and the rate and causes of death are being followed. To date no soft-tissue sarcomas or malignant lymphomas have been reported.

Another less systematic observation bears on the situation. The phenoxy herbicides have been used frequently and extensively in agriculture and forestry in the United States since the late 1940's. They were used on lawns in cities, as well, for most of that period. If the relative risk of developing so distinctive a group of tumors as the soft-tissue sarcomas and the malignant lymphomas had increased by 5 of 6 fold over that before 1945 as the Swedish studies would predict, it almost certainly would have been evident to clinicians and pathologists, especially in the rural areas, even without systematic studies. No such increase was noted.

Critical Evaluations

The Swedish investigators have been cautious in interpreting their results. In his medical dissertation based on his epidemiological studies, Hardell judges that the similar results in the two case-control investigations (12, 13, 14, 16) "seem to increase the confidence that the observed association of exposure to phenoxy acids and soft-tissue sarcoma was not spurious" and did not believe that confounding factors "could account for the observed relation." In summary, he concluded that "it is suggested that exposure to phenoxy

acids should be looked upon as an occupational cancer hazard," 44.

Other reviewers have been more skeptical as to the significance of the work. Remington's overall opinion was that "in toto, the Swedish work is credible if not fully conclusive. Certainly this work would seem to justify further investigation," 10. Coggan and Acheson, after reviewing other work as well as the Swedish studies, state that "on the present evidence it seems possible that soft-tissue sarcomas have arisen in association with exposure to phenoxy herbicides" but continue that "it is as yet impossible to estimate with any precision the risk of soft-tissue sarcoma due to phenoxy herbicides." They conclude that "there is suggestive evidence of a biological association between phenoxy herbicides (or their contaminants) and soft-tissue sarcoma. The evidence relating these products to the occurance of lymphoma is weaker," 22. An unsigned editorial in Lancet commenting on the opinions of Coggan and Acheson seems to agree with their conclusions with regard to soft-tissue sarcomas, 45.

Hardell and Axelson disagreed with both the Coggan and Acheson's opinions and the Lancet editorial, 23. They have been at some pains to counter charges of "observational bias," 15, but have not convinced everyone that faulty memories do not result in significant errors in evaluating exposure, 45.

The causal connection between phenoxy herbicides and soft-tissue sarcomas would be much more likely if there were a unique preponderance of one type or even of a few types in the exposed men. The Swedish reports never compare the morphological types or location of the malignant tumors in cases with those in controls, 45. Their only justification for aggregating the types, and presumably for omitting the data from their reports is "the uncertainty of relations between the various histological groups in terms of causal mechanisms" and "the so-called addition theorem for chi-square and Poisson distribution," 23. The uncertainty of causal relations is precisely the reason for reporting the groups and the addition theorem cannot justify the aggregation of unlike

*2,3,7,8-tetrachlorodibenzo-p-dioxin has been suggested as the principal carcinogen in the phenoxy herbicide 2,4,5-T and trichlorophenols but this has been disputed. See 22, 23, 45, 46. The controversy is not considered in this discussion.

entities unless significant common factors have been demonstrated.

Scientific results are strengthened greatly when independent investigators substantiate them. The Swedish studies have been said to be independent and confirmatory. The two soft-tissue sarcoma investigations do support one another (12, 13, 14, 16) but they are the work of the same group of investigators. The investigation of malignant histiocytic lymphoma was also conducted by the same group but was a case-control study of a separate entity, (19-21). Axelson's work on herbicide exposure and cancer (1-4) was not truly independent from Hardell's efforts since Hardell has recognized his indebtedness to Axelson for his assistance in the first case-control study, (13, 14). More important Axelson did not associate phenoxy herbicides or chlorophenolic compounds with soft-tissue sarcomas nor with malignant lymphomas among railroad workers, 1-4.

The reports of soft-tissue sarcomas among chlorphenol workers in the United States (24-27) have been cited as supporting Hardell's conclusions, 24, 28, 44, 46. The data have been reported piecemeal without a clearly enumerated total population from which they were drawn. The comparison was made to mortality data for the general population of the appropriate age and sex. The type of soft-tissue sarcoma is known for each case; among the 7 men were 2 malignant fibrous histiocytomas, 2 liposarcomas, as well as one each of fibrosarcoma, malignant schwannoma, and fibrosarcomatous mesothelioma. As before, the tumors are not of a uniform type.

Coggan and Acheson comment that the Swedish studies and the American reports taken separately do not "provide convincing evidence that the incidence of soft-tissue sarcomas is increased after exposure to phenoxy acids and chlorophenols, -- Considered together the whole becomes more persuasive." They add that "it is surprising that the association should apply to tumors of such a variety of tissues," 22. The Lancet editorial finds only that "the number of deaths due to soft-tissue sarcomas [in the American data] is disturbing," 45.

In addition to the American experience, the British (37), European (30, 32, 33, 36, 38-41) and New Zealand (34, 35) medical and scientific writers have studied populations five years or longer after exposure to phenoxy herbicides and/or chlorophenols in a variety of situations, some intense and acute, others prolonged. Only one observer (30) reported a case described as a soft-tissue malignant neoplasm without

further characterization. The same report included a lymphosarcoma, a malignant neoplasm of lymphoid tissue and 3 plasmocytomas. No other study found a soft-tissue tumor.

In summary, the Swedish studies of soft-tissue sarcomas cannot be considered to have proved that exposure to phenoxy herbicides is the cause of one or more types of this varied group of malignant tumors. There are no fully reported systematic studies to confirm what the Swedish investigators describe as an association. There are an epidemiological study (32) and observations of exposed populations that do not support the finding as opposed to uncorrelated American observations and an East German study (30) that do strengthen the case for such an association.

At best, the Scottish verdict of "Not proven" seems most realistic at this time. The Advisory Panel on Toxic Substances of the American Medical Association says that "while 2,4,5-T and 2,4-D pesticides (phenoxy herbicides in Agent Orange) have been used in agriculture, forest management and residential landscaping for over 30 years, there is still no conclusive evidence that they and/or TCDD (a contaminant of Agent Orange) are mutagenic, carcinogenic, or teratogenic in man, nor that they have caused reproductive difficulties in the human," 47.

BIBLIOGRAPHY

1. Sundell, L., Rehn, M., and Axelson, O. Exposure to herbicides - mortality and tumor incidence. An epidemiological investigation in Swedish railway workers. Lakartidningen 71:2466-2470. 1974

2. Axelson, O. and Sundell, L. Herbicide exposure, mortality, and tumor incidence. An epidemiological investigation on Swedish railroad workers. Work Environ. Health 11:21-28. 1974

3. Axelson, O. and Sundell, L. Phenoxy acids and cancer. Lakartidningen 74:2887-88. 1977

4. Axelson, O., Sundell, L., Andersson, K., Edling, C., Hogstedt, C., and Kling, H. Herbicide exposure and tumor mortality. An updated epidemiological investigation on Swedish railroad workers. Scand. G. Work Envirn. & Health 6:73-79. 1980

5. Axelson, O. Aspects on confounding in occupational health epidemiology (Letter.) Scand. J. Work Environ. & Health 4:85-89. 1978

6. Axelson, O. Views on criticism of pesticide studies (Reply to note by Jannerfeldt, E.). Lakartidningen 77(12):1096-1099. 1980

7. Axelson, O. A note on observational bias in case-referent studies in occupational health epidemiology. Scand. J. Work Environ. & Health 6:80-82. 1980

8. Axelson, O. Testimony before EPA Hearing, EPA Exhibit No. 587. 1980

9. Jannerfeldt, E. Epidemiologic methodology and pesticide studies. Lakartidningen 77(12): 1096. 1980

10. Remington, R. D. Specific summary critique of five investigations related to concerns about Agent Orange. Congressional Record, pp. S 10911, S 10912, August 6, 1980.

11. Hardell, L. Verbal testimony at EPA Hearing. September 29, 1980.

12. Hardell, L. Malignant mesenchymal tumors and exposure to phenoxy acids - A clinical observation. Lakartidningen 74(33):2753-2754. 1977

13. Hardell, L. and Sandstrom, A. Malignant mesenchymal soft tissue tumors and exposure to phenoxy acids or chloramphenacol. Lakartidningen 75:3535-3536. 1978

14. Hardell, L. and Sandstrom, A. Case-control study: Soft tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Brit. G. Cancer 39:711. 1979

15. Hardell, L. Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents. Scand. G. Work Environ. & Health 7(119-130). 1981

16. Axelson, O. Aspects of confounding and effect modification in the assessment of occupational cancer risk. J. Toxicol. & Environ. Health 6(5-6):1127-1131. 1980

17. Eriksson, M., Hardell, L., Berg, N. O., Moller, T. and Alexson, O. Case-control study of malignant mesenchymal tumors of the soft tissue and exposure to chemical substances. Lakartidningen 76:3872-3875. 1979

18. Eriksson, M., Hardell, L., Berg, N. O., Moller, T., and Axelson, O. Soft-tissue sarcomas and exposure to chemical substances: a case-referant study. Brit. J. Industr. Med. 38:27-33. 1981

19. Hardell, L. Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. Lancet 1(8106):55-56. 1979

20. Hardell, L., Erikson, M., Lenner, P. Malignant lymphoma and exposure to chemical substances, especially organic solvents, chlorophenols and phenoxy acids. Lakaridningen 77(4):208-210. 1980

21. Hardell, L., Erikson, M., Lenner P., and Lundgren, E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Brit. J. Cancer 43:169. 1981

22. Coggon, D. and Acheson, E. D. Do phenoxy herbicides cause cancer in man? Lancet 1(8278)1057-1059. 1982

23. Hardell, L. and Axelson, O. Soft-tissue sarcoma, malignant lymphoma, and exposure to phenoxy acids on chlorophenols. Lancet 1(8286):1408-1409. 1982

24. Honchar, P. A. and Halperin, W. E. 2,4,5-T, trichlorophenol, and soft-tissue sarcoma. Lancet 1(8214):268-269. 1981

24a. Ott, M. G., Holder, B. B., and Olson, R. D. A mortality analysis of employees engaged in the manufacture of 2,4,5-trichlorophenoxyacetic acid. J. Occup. Med. 22:47-50. 1980

24b. Cook, kR. R., Townsend, J. C., Ott, M. G., and Silverstein, L. G. Mortality experience of employees exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). J. Occup. Med. 22:530-532. 1980

25. Cook, R. R. Dioxin, chloracne, and soft-tissue sarcoma. Lancet 1(8220)618-619. 1981

25a. Zack, J. A. and Suskind, R. R. The mortality experience of workers exposed to tetrachlorodibenzo-dioxin in a trichlorophenol process accident. J. Occup. Med. 22:11-44. 1980

25b. Zack, J. A. A mortality study of workers employed at the Monsant Plant in Nitro, W.Va. Unpublished.

26. Moses, M. and Selikoff, I. J. Soft-tissue sarcomas, phenoxy herbicides, and chlorinated phenols. Lancet 1(8234):1370. 1981

27. Johnson, F. E., Kugler, M. A., and Brown, S. M. Soft tissue sarcomas and chlorinated phenols. Lancet 2(8236):40. 1981

28. Hardell, L. and Erikson, M. Soft-tissue sarcomas, phenoxy herbicides and chlorinated phenols. Lancet 2(8240):250. 1981

29. Sarma, P. R. and Jacobs, G. Thoracic soft-tissue sarcoma in Vietnam veterans exposed to Agent Orange. New Engl. J. Med. 306(18):1109. 1981

30. Barthel, E. Cancer risk in agricultural workers exposed to pesticides. Arch. Geschwulstforsch. 51(7):579-585. 1981

31. Bishop, C. M. and Jones, A. H. Non-Hodgkin's lymphoma of the scalp in workers exposed to dioxin. Lancet 2(8242):369. 1981

32. Riikimaki, V., Asp, S., and Hernberg, S. Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland. Scand. J. Work Environ. & Health 8:37-42. 1982

33. Hogstedt, C. and Westerlund, B. Cohort study of mortality rates of forestry workers with and without exposure to phenoxy compounds. (No translation available) Lakartidningen 77(19):1828-1830. 1980

34. Smith, A. H., Fisher, D. O., Pearce, N. and Teague, C. A. Do agricultural chemicals cause soft-tissue sarcoma? Initial findings of a case-control study in New Zealand. Unpublished report at ANZSEARCH Annual Conference, May, 1982

35. Smith, A. H., Fisher, D. O., Giles, H. J., and Pearce, N. The New Zealand soft-tissue sarcoma case-control study: interview findings concerning phenoxyacetic acid exposure. Unpublished report at Third International Symposium on Chlorinated Dioxins and Related Compounds. October 1982

36. Edling, C. and Granstam, S. Pattern of causes of death among forestry workers, a pilot study. Hygiea 88(3):74. 1979

37. May, G. Tetrachlorodibenzodioxin: a survey of subjects ten years after exposure. Brit. J. Industr. Med. 39:128-135. 1982

38. Pazderova-Vejlupkova, J., Nemcova, N., Pickova, J., Lukas, E., and Jirasek, L. The development and prognosis of chronic intoxication by tetrachlorodibenzo-dioxin in man. Arch. Environ. Health 36(1):5-11. 1981

39. Cited in Huff, J. E., Moore, J. A., Saracci, R. and Tomatis, L. Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans. Environ. Health Prespectives 36:221-240. 1980; and Hay, A. Accidents in trichlorophenol plants: a need for realistic surveys to ascertain risks to health. Ann. N.Y. Acad. Sci. 320:324. 1979

40. Thiess, A. M. and Frentzel-Beyme, R. Mortality study of persons exposed to dioxin following an accident which occurred in the BASF on November 13, 1953. Presented at the Fifth International Conference on Medichem. September 1977

41. Thiess, A. M., Frentzel-Beyme, R., and Link, R. Mortality study of persons exposed to dioxins in a trichlorophenol process accident that occurred in the BASF AG on November 17, 1953. Am. J. Industr. Med. 3:179-189. 1982

42. Young, A. L., Calcagni, J. A., Thalken, C. E., and Tremblay, J. W. The toxicology, environmental fate, and human risk of Herbicide Orange and its associated dioxin. USAF OEHL Technical Report (Report OEHL TR 78-92) pp. V-7, V-8

43. Caramaschi, F., del Corna, G., Favaretti, C., Giambelluca, S. E., Montesarchio, E., and Fara, G. M. Chloracne following environmental contamination by TCDD in Seveso, Italy. Intern. J. Epidemiol. 10(2):135-143. 1981

44. Hardell, L. Epidemiological studies on soft-tissue sarcoma and malignant lymphoma and their relation to phenoxy acid or chlorophenol exposure. Umea University Medical Dissertations, New Series No. 65. 1981

45. Anonymous. Phenoxy herbicides, trichlorophenols, and soft-tissue sarcomas (Editorial). Lancet 1(8278):1051-1052. 1982

46. Hardell, L. and Axelson, O. Phenoxy acids, chlorophenols, and cancer. Lakartidningen 78(34):2862-2863. 1981

47. Council on Scientific Affairs' Advisory Panel on Toxic Substances (American Medical Association). The health effects of "Agent Orange" and polychlorinated dioxin contaminants. October 1, 1981