
Item ID Number 01497

Author O'Keefe, Barry

Corporate Author

Report/Article Title Typescript: Chapter 7: Soft Tissue Sarcoma: Law, Science and Logic, An Australian Perspective

Journal/Book Title

Year 0000

Month/Day

Color

Number of images 84

Description Notes This manuscript is a draft version of a chapter or section from the following book: Agent Orange and its Associated Dioxin: Assessment of a Controversy. Young, A. L. and G. M. Reggiani, eds. New York: Elsevier, 1988. This book is available in the NAL collection, call no.: RA1242 T44 A3. "This chapter deals with the Final Report of the Royal Commission on the use and effects of chemical Agents on Australian Personnel in Vietnam, July 1985. It is based on the transcript of the examination and cross-examination of Professor Olav Axelson and Dr. Lennart Hardell as expert witnesses concerning chemically caused cancer, their published papers and the submissions made to the Royal Commission in relation to the subject as well as the Report itself."

CHAPTER 7

SOFT TISSUE SARCOMA

Law, Science and Logic (*)

An Australian Perspective

Barry O'Keefe Q.C. - Sydney - Australia

Introduction

The Royal Commission conducted by the Australian Federal Judge, the Hon. Mr. Justice Evatt D.S.C., presented an excellent opportunity for close examination of a number of studies relied upon by some statutory agencies and others in support of claims that 2,4-D, 2,4,5-T and the contaminant dioxin in Agent Orange are carcinogenic in man and induce male-mediated birth defects. The data and methodology involved as well as the conclusions reached in such studies were able to be examined in an objective, logical and disinterested manner by a Royal Commission well-equipped to make an accurate assesment of the reliability and scientific value of such studies.

(*) This chapter deals with the Final Report of the Royal Commission on the use and effects of chemical Agents on Australian Personnel in Vietnam, July 1985. It is based on the transcript of the examination and cross-examination of Professor Olav Axelson and Dr. Lennart Hardell as expert witnesses concerning chemically caused cancer, their published papers and the submissions made to the Royal Commission in relation to the subject as well as the Report itself.

A claim made repeatedly by those who represented the members of the Australian Vietnam Veterans Association or who purported to speak on behalf of the veterans was that Agent Orange had caused and was causing cancer in Vietnam Veterans. One type of cancer in particular (soft tissue sarcoma , a generic term for several types of rare cancer), was the focus concern because of surveys of Swedish agricultural, forestry and railway workers by the Swedish investigators Axelson and Hardell.

Both published several scientific papers, produced a number of documents for use in courtrooms, gave newspaper and radio-interviews and appeared on television. Both were identified in local and other media with the scientific work which was seeking to link specific cancer types with the use of phenoxy herbicides. This was more manifest in relation to Hardell.

Since these studies are the main epidemiological evidence relied upon to support an association between exposure to phenoxy herbicides and an increase of the relevant types of cancer, the Royal Commission examined these data very closely. This involved not only a close examination of the background of their research but also a careful analysis of their data case by case and of their methodology.

Epidemiological methodology - The case control study.

Epidemiology is said to be the science dealing with the environmental causes of diseases of humans as inferred from observations of human beings.

Whilst the discipline of epidemiology can be used to assess the risk of individuals in a human population developing a particular disorder or to demonstrate an apparent association or lack of association between an observed health phenomenon and a given substance or substances by the mathematical testing of a possible association between the observed health phenomenon and the postulate source of that phenomenon, such a demonstration cannot of itself be used as proof of causal relationship. It merely demonstrates statistical association. This may be a true association or only an indirect or artifactual association. In this regard the problems of confounding and of bias (whether of the selection or observational kind) are important because they can invalidate the conclusions.

Observational bias may take different forms. It may be bias of the subject arising, for example, out of memory problems or it may be bias in the investigator himself.

People who are suffering from a particular disease are more apt than healthy people to think about their condition and to try and find an explanation, for example, in exposure to various situations or agents which they believe may have caused their disease. This can affect the accuracy of the data obtained. Likewise the accuracy of data obtained may be affected by the subject having knowledge of the result which the investigator is seeking to achieve, just as it may be affected by the data collector being made aware of the object of the data collection.

Positive evidence (unless due to confounding) is important. Negative human evidence may not carry, unless it relates to prolonged and heavy exposure. If however it is related and is consistent in a variety of correlation studies over time (cohort studies of exposed individuals and/or case-control studies of affected patients) negative human evidence may justify the conclusion that for practical purposes the agent may be considered as not constituting a risk to human health.

In assessing the result of a particular epidemiological study the strength of the association demonstrated, the duration and degree of exposure, the presence of a dose/response relationship, confirmation or replication of the result by others and the specific

nature of the response are all relevant factors. So too is the knowledge that the data on which the result is based are accurate. If the data on which a study is based are subject to doubt, then the conclusions of the study must be treated as doubtful at best.

In proper epidemiological practice the events which generate an hypothesis should be kept separate from the events used to test that hypothesis.

The case control study is one of the methods which can be used for an epidemiological study to assess cancer association and is the one which has been used by Dr. Hardell.

A case control study is a retrospective study where one sample of a selected population is compared with another regarding one or more characteristics of interest.

The case-control study method has become widely used and refined during the last 50 years due to the increasing importance of chronic diseases where the low incidence and long interval between cause and effect are not well suited for other epidemiological approaches.

Given the extension of case control studies it is more than ever important to recognize the limitations of the method.

In the case of herbicides the case control study is an investigation of the exposure frequencies of two groups of subjects selected on the basis of their status with respect to exposure to the chemical or chemicals in question.

The method is valuable because it permits us to see back through time, commencing with the effect back to a postulated cause. It has advantages in relation to other methods: it is relatively inexpensive and requires little time; it is very well suited to the study of rare diseases; it allows the evaluation of several etiologic factors both as independent and interacting causes.

The method has also a number of important limitations; it is not suitable for the study of exposures which occur only rarely; it allows estimation of relative rates but not of absolute rates; and finally it is susceptible to bias.

Bias, especially selection and recall bias, is the most serious potential problem in case control studies. There are many kinds of selection bias: selective admission to the group; selective survival and death; selective detection; selective response

and participation.

There are other bias and confounding factors which can make the conclusions of a study untenable. There can also be demographic bias due to age and sex, which can be risk factors in cancer.

There can be clinical bias when a person is genetically predisposed to a specific disease. There is finally the anamnestic recall bias of the interviewed subject. In this case the disease itself acts as a stimulus which makes the subject concentrate his attention to the possibility or to the degree of an antecedent exposure.

There is also the problem of defining the exposure. Taking, for example, an industrial exposure which has occurred 20 years ago and which lasted only a few days, it is extremely difficult, perhaps verging on the impossible, to assess the validity of the information.

Efforts should be made to stimulate the memory of the control group of to check the statements made by both the cases and the controls.

A methodological standard which is used to lessen the possibility of bias is the interview with each single member of the group. However the interviewer should be "blinded". In many studies the interviewer who inquires about whether or not the patient was exposed to the causal agent is aware of the research hypothesis or of the subject's identity as a subject or as a control. This can lead to a preconception on the fact of the interview, which is another source of bias.

All these factors were thoroughly dealt with in the course of the testimony of Prof. Axelson and Dr. Hardell and considered in detail in the report of the Royal Commission.

Prof. Olav Axelson

In late 1971 and early 1972 Professor O. Axelson undertook a study (first analysis) of cancer mortality amongst railway workers because of rumors of excess lung cancer mortality amongst those exposed to 2,4-D and 2,4,5-T (1).

In an endeavour to determine if the rumors were justified he examined mortality amongst a cohort of 348 railway workers, inclusion in which cohort depended upon a workers having a given duration of exposure to herbicides during the period from 1951 to 1971. On analysis of the data Professor Axelson

found a total of 18 deaths from all causes compared with 20.54 expected and a total of 6 deaths from tumors compared with 4.88 expected when a zero latency period was allowed for. For tumors, therefore, the relative risk was close to unity (namely 1.2) and certainly not statistically significant. As far as deaths from lung cancer were concerned, 0.83 have been expected and 2 were found. Neither of these occurred in the sub-cohort said to be exposed to phenoxy acids and both of them (cases 256 and 257) occurred in people who have been smokers for a long time, perhaps decades.

From this analysis Professor Axelson concluded that: "There seems to be a possible association between excess tumor mortality and exposure to amitrol and its combinations, especially if a latent period is considered. On the contrary in the cohort exposed to phenoxy acids and combinations a fairly good agreement is found between the exposed and observed deaths independent of the latent period" (1).

Not only did his first analysis not demonstrate an association between phenoxy herbicides and an increase in cancer incidence but Professor Axelson expressed the view that his conclusion was: "as close as one can get to a negative epidemiologically".

After becoming aware of observations by Dr. Hardell i.e. "the first clinical report about soft tissue sarcoma and phenoxy herbicide exposure" Professor Axelson reanalysed his data (re-analysis). Two (2) cancer cases which in his first analysis had been classified as having been exposed to amitrol were now stated to be cases in which "it is possible that phenoxy acid exposure alone may have occurred" (2).

When these cases were reclassified in this way i.e. the possibility was converted to a fact and used as an assumption in the re-analysis, an excess of mortality from tumors was obtained amongst individuals with phenoxy acid exposure, as re-defined (3).

Thus to produce an excess of tumors in the relevant subcohort a change in classification had to be effected and the excess found in that cohort depended on only two (2) cases - the two who were re-classified.

It is no doubt because of considerations such as these that the Axelson re-analysis concedes that: 1) "the material is unsatisfactorily small"; 2) "the exposure pattern is complex" and 3) "it is not possible to clearly select any special herbicide as carcinogenic", and they explain why the conclusion in the

re-analysis are so nebulous in relation to the subcohort said to have been exposed to phenoxy acids: "certain indications suggest that an excess tumor mortality may also be referable to phenoxy acids", and "on the basis of these investigations it is not possible to select any special herbicide as carcinogenic but the suspicion against phenoxy acids as a group of preparations may have become somewhat increased".

Subsequently, using the same exposure data as before, Professor Axelson followed the cohort through to October 1978 and undertook yet another analysis (update). This time, however, he introduced a latency period of 10 years and reached a conclusion which was different from the conclusion in his first analysis. There are two (2) reports of his update (4). Whilst they are not identical both versions contain the following statement: "tumor incidence was also updated but provided little additional information. The incidence data have therefore been omitted from this presentation".

The omission of the incidence data is interesting since, in his first analysis, Professor Axelson had stated that: the "tumor incidence data, however, may be more relevant than the mortality data...."

It would seem reasonable to conclude that nothing abnormal was found in the update in relation to tumor incidence - an indicator which Professor Axelson had regarded as "more relevant" than mortality.

In his update Professor Axelson concluded that: 1) "no specific type of tumor is predominating; 2) "the aspects of causal relationship are rather unclear"; 3) "those exposed in 1962 or later did not show a clear excess mortality"; 4) "this finding might be interpreted in different ways, i.e. the variety of herbicides during the early period could be of importance and/or the work conditions may have been more primitive and the herbicide handling more careless resulting in a higher degree of exposure".

Thus the findings from the update do not single out phenoxy acids. Indeed the comment in (4) above together with the discussion concerning Table I in reference (1) (below) and the absence of any other data as to the herbicides used by the Swedish railways, support the inference that Professor Axelson's work in fact exculpates 2,4,5-T. As the Royal Commission found: "At the very least, there are serious problems in his work arising from confounding factors".

Because it has been suggested by some that Professor Axelson's first analysis, re-analysis and update in some way support Dr. Hardell's later findings, they should be examined.

In carrying out this examination it is desirable to look at:

- 1) methodological flaws;
- 2) the lack of expertise of those engaged in Axelson's study;
- 3) the inaccuracy of uncertainty of the data involving problems in the selection of the cohort, in the determination of exposure and arising from wrong diagnoses;
- 4) the weakness of the conclusions; and
- 5) the difference between the results obtained by Professor Axelson and those obtained by Dr. Hardell.

1) Methodological flaws

In proper epidemiological practice the events which generate an hypothesis should be kept separate from the events used to test that hypothesis. As Professor Axelson himself agreed: "To my understanding there is a tendency for some statisticians to take the view that one should not use individuals or such observations that have started - yes, started the study - I would not say generated the hypothesis because that is generated from the facts as well".

d

However, his study breached this basis principle, as is clear from the fact that what generated the study was an assertion of three lung cancer amongst the railway workers. One of those was subsequently excluded and leaving Professor Axelson with two cases and they were included as cases in his study.

2) Lack of expertise

A questionnaire was sent out as part of the data gathering process. At the time the questionnaire was designed and sent out and at the time the data were gathered, Professor Axelson had neither university qualifications nor professional training in either epidemiology or statistics. He was not a mathematician and his only training in epidemiology was self-training - by reading books. True it is that in 1972 he attended 14 days of lectures in Finland but that, as he conceded, "did not have any effect because it came later". (5)

Lack of training and experience may well explain the absence of a written protocol for the study as well as the absence of any formal development of a plan in which the design and purpose of the study and how it would be carried out were detailed (6).

3) Inaccuracy of the data

Inaccuracy of the data about exposure can affect the correctness of the conclusions in a study in which exposure to a given substance is the variable.

The collection of the data which were used for the first analysis was undertaken at a time there was a good deal of controversy in Sweden about the use of phenoxy herbicides, particularly 2,4,5-T, and a lot of adverse publicity both in the newspapers and on television (7). In addition, rumors were current about an association between cancer and use of such herbicides by railway workers (8). Thus the climate in the community generally and in the study population in particular raises a serious question of possible information bias. This possibility was conceded by Professor Axelson in his evidence to the Royal Commission.

The problem was heightened amongst railway workers by the distribution of questionnaires, in which the first question was : "Have you experienced any health problems which you relate to herbicides?" (9).

The questionnaires were sent first to the Chief Physician of the Swedish Railways. From him they went to the various districts in the railway network and then from each district to the men of that district (10). Professor Axelson did not know

who had actually filled out the questionnaires (10). However, it is clear that they went to the bulk of the workers who were included in the cohort as well as to others. All of those to whom the questionnaires went had asked for health check-ups, as appears from Professor Axelson's evidence both before the Royal Commission and the EPA (1980) deposition.

The questionnaires were distributed at the very time when lists of the workers said to have been exposed to herbicides in the period 1951 to 1972 were being compiled, or had been requested from, the Swedish railways. An examination of a copy of the questionnaire (9) reveals that no information was sought concerning the extent of exposure to any particular herbicide or chemical and that the instructions which formed part of the questionnaire did not differentiate between different herbicides, all of which were grouped together as "weed and brush killers". In view of the form of the instructions which appeared at the head of the questionnaire, and the first question in it, it is not surprising that Professor Axelson conceded that it was: "fairly clear what the investigation was all about" and that: "we did not camouflage that at all".

Despite the fact that the distribution of the questionnaires at such a sensitive time was likely to have exacerbated the problem of recall bias, the information obtained from them in relation to exposure was not used (10). The cohort was in fact compiled from exposure information derived from lists supplied by the Swedish railways. Thus the problem of information bias was made more severe by the adoption of a procedure which produced no countervailing positive or beneficial effect on the study.

It took a number of attempts to compile the study cohort. In the first attempts information as to exposure was sought from the Swedish railway authorities. They provided information in lists which were the result of a "joint assesement of exposure from the railway company and from the trade union representatives". That first or basic set of lists proved to be of little use "because we got in material which was fairly bad from some districts", and "therefore we repeated the whole procedure once more".

So instructions were given for the compilation of another set of lists: "At least in this respect, because we had a bad experience there from the first attempts,.. we had to be more detailed in the second one before we gave up".

There has been therefore a first set of lists from the Railways which were rejected because they were incomplete and inconsistent, due to differences in the various data provided from different districts.

A second set of lists was then compiled and in respect of that Professor Axelson made some mechanical exclusions i.e. everybody who had only exposure up to and including 45 days. The manuscript submitted by Professor Axelson to the Health Board of Occupational Safety and Health became the subject of media publicity. This led to a number of persons coming forward claiming that they should have been in the study. This new group of claimants who came forward to the Railways led to the compilation of a third set of lists.

In the compilation of the second set of lists there were instances in which the union insisted that the names of particular workers be added and, after discussion, addition were made for this reason. The lists were then signed as "mutually agreed" between the railways and the unions, although they probably included the names of workers who did not appear from the railways' records as persons who had been exposed for 45 days or more.

How many of the workers fell into this category was and remains unknown. The employees at the Swedish railways who gathered the material had not training in data collection. The potential for inaccuracy created by this circumstances was compounded by the fact that the exposure was determined by the people compiling the list looking at the salaries that were paid to the various workers, from those salaries deducing what work tasks were undertaken by the various workers and then implying what exposure they could have had. The process involved in the collection of exposure data was conceded by Professor Axelson to be "a sort of guessing". The extend to which any particular person may have been exposed was "guesstimated".

Professo Axelson agreed during the examination that in the railway records there was no indication in relation to any individual of any particular preparation or preparations of a chemical nature which were in fact involved in his job.

Thus the compilation of the lists relating to exposure was fraught with problems.

No checking of exposure was ever undertaken by Professor Axelson or his assistants. The data which were provided in the second and third sets of lists were accepted with "not even a spot check in relation to one or some random number", and "..except

for excluding persons who are (sic) exactly 45 days of alleged exposure and some accidental inclusions of those who were under 45 days (Professor Axelson) took no part in the selection of the cohort".

In these circumstances it is understandable that Professor Axelson did not attest the accuracy of the exposure data.

Professor Axelson's reservations about the accuracy of the data are highlighted by his decision to "modify the cohort selection basis after the data had been gathered" by increasing it from a minimum of 45 days exposure to a minimum of 46 days of exposure. This modification of the basis of selection of the cohort was regarded by the Royal Commission as being perhaps somewhat naive.

As indicated above the data relating to phenoxy herbicide exposure used in the first analysis, the re-analysis and the update were obtained from the lists supplied by the Swedish railways. These lists categorised potential exposure under three headings namely, Group A, Group O and Group F. Professor Axelson said that 'A' in the Group A heading stood for amitrol. However, an examination of his document (10) shows that a number of specific herbicides are referred to by name under and included within that heading.

The heading for Group O was "other herbicides". The heading for Group F was said by Professor Axelson to stand for "phenoxy acids". However it turned out that this was not so. It emerged that Group F was "all brush killers". Professor Axelson conceded that the word "brush killers" meant all chemicals of that the description. The description "brush killers" is not apt for 2,4-D and is certainly a category much wider than phenoxy herbicides. Therefore the fact that a person was included in the lists under the heading of Group F did not mean he had been exposed to phenoxy acids even if it be accepted (for the sake of argument) that it meant anything in relation to exposure to a herbicide. It could mean, for example, that the worker was exposed to a phenoxy acid in combination with another herbicide or other herbicides or that he had no exposure to phenoxy acids at all. This latter possibility was accepted by Professor Axelson as was the fact that : "The exposure data did not come from the men claiming to be exposed", "it came from railway officials which may or may not have had personal knowledge of exposure of any individual", "in conjunction with union people who may or may not have personal knowledge of any such exposure", "and it was derived substantially by way of inference from the category of employment revealed by the employment record".

It should be noted that the herbicides which fell within Group F included Primatol D43, Totalex extra, Uridal and MPCA (None of these contains 2,4-D, 2,4,5-T or TCDD.

In a Table included in his publication (1) on the exposure of the railway workers Professor Axelson reported the total quantity of specific herbicides "consumed" in 1957-1961 on the Swedish railways over the whole of Sweden. The records did not reveal any use of certain of these herbicides for some of the years 1957 to 1961 inclusive. Professor Axelson sought to avoid the consequences of the implication of this absence of evidence of use of phenoxy herbicides by saying that the word "consumed" really meant "purchased from suppliers" but not necessarily used in any given year. However the word "used" which appears in the footnote to the Table is clearly a synonym for "consumed" and not for "purchased".

It is difficult to understand Professor Axelson's reason for including the Table in his study unless he were of the belief that it showed the amount of herbicide actually "consumed" i.e. "used" throughout Sweden by the Swedish railways in the years against which entries are made. Either the Table (and the records on which it was based) indicated the amount of herbicides used in the years dealt with or it does not. If the records do so indicate, then they are destructive of the conclusions set out in the update. If they do not in fact so indicate then there are two further possibilities, namely Professor Axelson either believed

that they did so indicate of he did not so believe. It is unconceivable that he did not believe that Table (and the relevant records) showed what the heading said it showed.

If he did not so believe, the inclusion of the Table in his study would amount to a gross departure from the proper standards of scientific honesty. However, even accepting that he did believe the contents of the Table to be accurate (although his oral testimony indicates that they are not accurate) this very situation highlights the loose, untrained and unexperienced approach which was involved in the study and emphasizes the totally unsatisfactory nature of his exposure data.

The significance of Professor Axelson's change of stance in relation to this matter prompted the Royal Commissioner to ask: "THE COMMISSIONER: I mean, I am rather shattered to find that in that Table there that I have studied in some depth - to find that it has got nothing to do with the price of fish - if I may use a colloquialism of this country. I had assumed the men had been exposed, or there was potential exposure, to that amount of that chemical and I find I am wrong in making such an assumption?". "A-Yes".

Professor Axelson admitted in his answer that the Table does not tell explicitly the exposure of the men in question.

A little later, however, Professor Axelson said that the records "reflect indirectly at least how much of herbicide that was used"

The Table shows that no herbicides containing 2,4,5-T or any substance that could potentially contain 2,3,7,8-TCDD were used by the Swedish Railways prior to 1963.

When Professor Axelson undertook the updating of his data he ascertained that two cases (Nos. 268 and 334) which had previously been classified as having cancer (1) had not had their diagnoses of cancer confirmed by the National Central Bureau of Statistics (3). These cases were therefore excluded from the update (3) on the grounds of misdiagnosis.

The proposition that error in diagnosis can be quite important in a study in which the numbers involved are small is clearly applicable to the work of Professor Axelson.

The "other exposures" of the workers involved in the analysis, the reanalysis and the update were unknown (3). In this regard the update expressly stated that: "It should be made clear that the recognized exposure have been mixed with other unknown exposures; unfortunately there is no possibility of sub-dividing the material in this regard" (3).

The Royal Commission observed in relation to Professor Axelson's work that: "It was carried out by untrained and inexperienced people; there was no protocol; it was based on a cohort, the selection of which was completely outside the control and supervision of those conducting study; no responsibility for the accuracy of the exposure data was accepted; those conducting the work used data the accuracy of which they themselves doubted; the data on which the work was based were inaccurate"; and then concluded that: "(a) it was carried out by untrained and inexperienced people; (b) there was no proper protocol; (c) exposure data were obtained in a climate of considerable controversy about the very subject of the study; (d) the questionnaires distributed made apparent to the subjects the purpose of the information sought; (e) in a number of cases the data relating to exposure were little more than a guess; (f) persons who were counted as having been exposed to phenoxy acids may not have any such exposure; (g) the number and extent of confounding factors was unknown; (h) there was inaccuracy in diagnosis data."

4.- Weakness of the conclusions

The three conclusions reached by Professor Axelson in relation

to the effects of phenoxy herbicide exposure are different. The first is negative. The second raises a fairly nebulous possibility if a particular assumption as to exposure is adopted. The third is dependent on small numbers, involves a lack of specificity and the accuracy of the exposure data is questionable.

On their own these considerations would be adequate to justify the conclusion that Professor Axelson's work does not make any real contribution in relation to the problem of whether there is an association between exposure to phenoxy herbicides and the incidence of cancer.

But such considerations do not stand alone. There are other factors within Professor Axelson's material which support the conclusion just expressed.

In his first analysis Professor Axelson used a maximum latency period of 5 year. In his later analysis he changed the latency period to 10 years so as to bring it "more in line with standard epidemiological approaches". Such a period "seemed to be a reasonable latency or induction period" according to Professor Axelson.

After being questioned at length Professor Axelson agreed that if he had adopted the same latency period in his first analysis as he had in the update, the total number of tumors observed in the cohort said to have been exposed to

phenoxy acids and combinations would be reduced from five (5) to three (3) viz. Cases 173, 328 and 388 - the only cases who had both the potential for exposure to phenoxy acids and combinations as well as the necessary minimum latency period.

This reduced number of three (3) is to be compared with 2.83 expected: "And the relative risk then is 1.06 which is insignificant in any case."

This conclusion would flow through to the re-analysis (2).

When a minimum latency period of 10 years is adopted and the consumption data set out in Professor Axelson's publication are accepted as correct, the number of tumors observed in the so called "phenoxy acid" sub-cohort in the update is reduced to three (3) compared with 3.14 expected (1). The relative risk is then 0.95. Whilst the figure of 3.14 for the number of tumors expected would need some reduction, the extent of the reduction could not, according to Professor Axelson, be calculated from the data available. Although he was not able to agree that the adjustment would probably result in a figure of between 2.22 and 2.44 (Relative Risk of 1.35 and 1.22) such figures can fairly be derived from the data presented and are a reasonable indication of number of tumors to be expected.

As can be seen from Table I there is only one instance (Case 328 - cancer of the prostate) in which the first exposure occurred after 1963.

TABLE I (*)

Case No.	first year of exposure assigned by Axelson
127	1957
172	1958
173	1958
268	1960
317	1958
328	1967
388	1961
113	1960

In the original analysis, the re-analysis and the update the numbers from which the relative risks for the subcohort said to have been exposed to phenoxy acids and combinations were calculated are small and the existence of an excess depends

(*) From Reference No. 1

entirely on the classification as to exposure which is assigned to given cases. However, as the Royal Commission found, "the exposure data are inadequate, unreliable and non-specific". Its final word in relation to the value of his work is worthy of note. The Royal Commission concluded that: "because of number of faults, together with the extent of uncertainty or error in the data, Professor Axelson's doubtful positive conclusions should be given little or no weight".

Dr. Lennart Hardell

The relevant studies undertaken by Dr. Lennart Hardell in relation to the effects of herbicide exposure on various populations in Sweden are as follows:

- 1) the North Sweden Study concerning the incidence of soft tissue sarcoma (11, 12, 13, 14, 15).
- 2) the South Sweden Study also concerning the incidence of soft tissue sarcoma (11, 14, 15);
- 3) the Malignant Lymphoma Study (16, 17, 18);
- 4) the Nasopharyngeal Cancer Study (19);

5) the Colon Cancer Study (13) which had as its essential purpose the verification of the conclusions in the studies referred to in paragraph (1), (2) and (3) above (20).

Before undertaking his North Sweden study Dr. Hardell published the preliminary clinical observations which had caused him to undertake that study in North Sweden (21). These clinical observations had been made during the first three (3) months after he had gone to the Umea Regional Hospital in 1976. A like course was taken by him prior to undertaking his malignant lymphoma study (22).

Since Dr. Hardell's studies constitute the main body of epidemiological evidence which supports an association between exposure of humans to phenoxy acids and an increased incidence of soft tissue sarcoma and malignant lymphoma they will be examined in some detail. However, as Judge Weinstein noted in his judgment of 8 May, 1985 in the Agent Orange Product Liability Litigation, Hardell's studies "were widely recognised as flawed" (Gibbs et al. v Dow et al.; U.S. District Court, Eastern District of New York MDL 381 at page 48). This statement by Judge Weinstein adopts the conclusion of Mr. Justice Nunn in the Nova Scotian case of Palmer & Ors v Stora Kopparbergs Bergslags Aktiebolag trading as Nova Scotia Industries ([1983] 60 Nova Scotia Reports (2d) 271) in which His Honour referred

to the Hardell studies as "unacceptable as proof of the results claimed" and found "that they cannot be taken at face value" (supra at page 352).

1) The Nort Sweden Study

In August 1977 Dr. Hardell reported on clinical observations either made by him in his first three (3) months at the hospital or deduced from the earlier hospital records. These related to seven (7) initial and two (2) other instances of soft tissue sarcoma found amongst persons said to have been exposed to phenoxy herbicides during the 10 or 20 years preceding diagnosis and observed in the Oncological (Cancer) Centre at the Umea Regional Hospital between 1970 and 1976 (23). He treated the initial seven (7) of these cases as "a series."

In this first report (24) Dr. Hardell states that between 1970 and 1976 a total of 87 patients with malignant mesenchymal tumors (soft tissue sarcomas - STS) had attended the Umea Oncological Centre. Fifty five of these (68%) were men and of these 43 were still working. Nine (9) of the men who were still working were forestry workers, four (4) worked in agriculture and forestry and six (6) at saw mills or in the pulp industry - a total of 19 or 42.2%. Such a mix of occupations is not surprising in view of the geographic situation of Umea in Sweden's North and extent to which

forestry, activities associated with forestry and, to a lesser extent, agricultural pursuits are undertaken in the region .

In the report of his clinical observations concerning the seven (7) initial cases Dr. Hardell states that "the exposure was quite massive in all cases" (21) and that the exposure of five (5) of them was "direct" (21). In his North Sweden study these seven (7) initial cases are described as "a series of patients with soft tissue sarcomas and massive exposure to phenoxy acids" (24). Examination of the histories of these patients as ascertained by Dr. Hardell shows that these statements are far from accurate. His use of the word "massive" in fact reveals a good deal about his approach to exposure data as also, perhaps, does the form of his editing of the case histories of the seven (7) cases extracted from the hospital records.

Case I had sprayed with 2,4,5-T for barely one week in 1963 and 1964, two weeks in 1965, one month in 1966, one month in 1967 and 2 weeks in 1968. He was diagnosed as suffering from STS in 1976. Adopting, as both Professor Axelson and Dr. Hardell did, a minimum latency period of ten years the relevant exposure for Case I should be taken as that arising from something less than three weeks of herbicides spraying. The longer the latency

period adopted the less the relevant exposure, falling into nil if 15 years is adopted.

Case 2 sprayed for 3 weeks in each of three or four summers during the 1950's and 1960. He was diagnosed as suffering from STS in 1976. Thus his exposure was a maximum of twelve weeks spread over twenty years.

Case 3 was diagnosed as suffering from STS in 1976. His only association with herbicides was that "thousand of litres of phenoxy acid" were stored for about eleven months each year in the workshop in which he was employed. Some of these had been "stored partly in open containers" so that he could smell the material and it is stated that he "had also handled the preparation". In what circumstances or for what period the containers were left open (e.g. whether this was only when they were being handled), the extent and manner of handling of "the preparation" (singular) by the patient, what "the preparation" handled was or what the "phenoxy acids" (plural) were is not revealed. Similarly whether or not the man was wearing gloves or other protective clothing when he handled herbicide is not stated in the report and remains unknown. Such an absence of detail itself suggests that there was no great extent of exposure. Since Dr. Hardell saw his patient and appears to have taken a part in his extended treatment the data must have been known to

Dr. Hardell and, if substantial, surely would have been revealed by him either in one of his publications or in the course of his evidence to the various tribunals before which he has testified. This has never been done, indeed Dr. Hardell was unable to supply any further details about these relevant matters although he was expressly afforded such an opportunity.

However it is known, that case No. 3 never sprayed and that this case was classified as unexposed when Dr. Hardell undertook his North Sweden study (24).

Case 4 was exposed to unspecific phenoxy acids for about twenty days per annum in the years between 1961 and 1966. As the date of his diagnosis is not stated, the precise extent of his relevant exposure cannot be calculated. However, taking the date of Dr. Hardell's observations (i.e. 1976) as the latest date of diagnosis, the maximum relevant period would appear to be low.

If 15 years is adopted as the latency period the relevant exposure of this case falls to nil.

Case 5 was exposed to herbicides for a total of six weeks in 1945 and 1946. The nature of those herbicides is not revealed but having regard to the fact that 2,4-D and 2,4,5-T were introduced into Sweden after 1950 it is improbable that such early exposure would have involved phenoxy acids, Case 5 did spray phenoxy

acids for two weeks in each of the years 1960 to 1968. He was diagnosed as suffering from STS in 1974. Adopting a latency period of ten years, his relevant exposure is that arising from a maximum of eight weeks spraying spread over four years. His relevant exposure falls to nil if a latency period of 15 years (or more) is adopted.

Case 6 was diagnosed in 1972 as having STS. The only evidence that he had any exposure was that "over 4-5 summers in the fifties... he cut and removed grass along the verges sprayed by the Highway Department" and that "he had worked and lived in forests sprayed with phenoxy acids" (21).

In Dr. Hardell's report of this case neither the relationship between the time of cutting of the grass and the time of herbicide spraying nor the actual herbicide/s involved is revealed. However, it is unlikely that 2,4,5-T would have been used for grass killing since it is unsuitable for such a purpose. It is used for trees and for woody, tree-like growth. It is also inherently improbable that the grass would have been cut before such herbicide sprays as had been used would have had time to take effect. There is no point in spraying herbicide on grass and then immediately cutting the grass. This conclusion was accepted by Dr. Hardell.

Dr. Hardell also admitted that as far as the possibility of exposure of this man as a result of having lived and worked in the forest was concerned, he did not know the relationship between his place of residence and the location where spraying occurred, or the relationship between the time of spraying and when he worked in the forest. Nor did Dr. Hardell have any data as to whether the case was ever actually been in contact with the substances which had been sprayed or as to when and how often the spraying had occurred.

In addition there was nothing to indicate that the man in question had carried out spraying himself, indeed it was not suggested that he had ever done so.

Case 7 was diagnosed as having STS in 1970. However symptoms had been manifest in mid-1969. His only association with phenoxy acids was that he "had worked in forests up to 1970" (21) where "he carried out thinning in the phenoxy acids sprayed areas from 1956 to the beginning of the 1960's (21). Whilst it is hardly likely that he would have been carrying out thinning immediately after spraying had taken place, the report is silent about any such temporal association and Dr. Hardell was unable to provide any further information on this subject in the course of his evidence before the Royal Commission. The only other possible source of exposure for this patient was that he had worked "in conjunction with spraying a few years later" (21). What this involved remains

obscure as does the description of the spray or sprays used. There may in fact have been no exposure whatsoever. However, deficient as it is, the information set out above in relation to this man was agreed by Dr. Hardell to be "... a fair summary of the total information you were able to get about exposure of this man".

Once again, if a 15 years latency period is adopted, this man would have no relevant exposure.

From the foregoing it can be seen that it is doubtful whether there was any exposure of Cases 3,6 and 7 and that, insofar as there may have been any exposure at all, it was minimal at **most**. If a latency period of 15 years is adopted then Cases 1, 4 and 5 would also be excluded because of absence of relevant exposure.

Dr. Hardell's description of the extent of exposure of the cases include in the series as "massive" and "quite massive" was found by the Royal Commission to be both "inaccurate" and "highly emotive". It is the language of the advocate rather than the language of the detached scientist.

In his role as advocate Dr. Hardell manifested a readiness to adapt his evidence in the light of cross-examination. His description of the exposure of the initial seven (7) cases referred to in his clinical observations (21), the special meaning

he ascribed to the word "massive" in his Agent Orange deposition, his realization in the course of giving evidence that this created problems for him and his change in position when it was clearly demonstrated that he had been inaccurate in his description of the extent of exposure, all demonstrate his approach.

A ban on the use of 2,4,5-T was imposed in Sweden (25) in or about April 1977. This was done for reasons which were political rather than scientific. At that time phenoxy herbicides were the subject of intense debate and there was grave concern amounting to alarm about 2,4,5-T (25), indeed so great was the intensity of the controversy in the North of Sweden that it led to accusations that an academic from the Umea area, Professor Rappe, was a liar because he defended the use of Hormoslyr, one of the constituents of which was 2,4,5-T (25).

It was against such a background that Dr. Hardell's clinical observations were published. With the active co-operation of Dr. Hardell they received widespread publicity (26). He gave a number of newspaper and radio interviews and also appeared on television (27). He was increasingly identified in local and other media as involved in the scientific work which was seeking to link specific cancer types with the use of phenoxy herbicides (28).

He became a prominent figure of the then current controversy. (25,26,27,28,29,30).

The publicity which he and his clinical observations received and the extent to which he was identified with the controversy concerning phenoxy herbicides are relevant in relation to the problem of information bias in his studies. Because of the extent and heat of the controversy which surrounded the use of phenoxy herbicides in Sweden, information bias was always likely to be a problem, however, this problem was accentuated by Dr. Hardell's involvement and prominence in ~~the~~ controversy.

Thus a climate which was already unsuitable for epidemiological research in relation to the possible association between phenoxy herbicides and cancer was made even worse by Dr. Hardell's actions. Indeed, it was admitted by him that at the material time there were "very few topics in the environmental debate... discussed as much as phenoxy acids. The debate was concerned with both the possible carcinogenic properties and the teratogenic properties" (24).

Dr Hardell recognized that in a climate which was already conducive to information bias "it would be most undesirable for a researcher who was going to undertake a study to do anything that would exacerbate or make worse the situation which existed at that time". However that is precisely what he did. Not only did he give newspaper interviews, appear on radio and television and pose for photographs, he also took part in public meetings and generally ensured that his work was put before the Swedish public.

A number of criticisms of Dr. Hardell's studies have been advanced. These include: 1) the inclusion within the studies of the data which generated the hypothesis which the studies were intended to test; 2) information bias as a result of:

- a) selective recall by the cases because of the prevailing publicity and other factors including a preliminary phone call from Dr. Hardell;
 - b) a difference in the completeness of the histories of exposure of cases when compared with those of controls;
 - c) interviewer bias arising out of the fact that the interviewers knew the purpose of the various studies;
- 3) inadequate and unsatisfactory exposure data; 4) methodological problems arising from:

- a) the inadequacy of the instructions for the telephone interviewer;
- b) the form of the questionnaires which required only "Yes" or "No" answers and gave no opportunity for a "Don't know" reply or for explanations (25, 30, 31).
- c) the use of the Oncological Centre's letterhead and the requirement that the questionnaire be returned to the Centre at Umea:
- 5) the linking by the results of 12 different histological types of sarcoma with exposure -- a unique and improbable situation, the previous highest link being three (3) sites in human (See Palmer & Ors v Stora Kopparbergs Bergslags Aktiebolag at page 307) ;
- 6) the presence of confounding factors for which no adjustment was, or could on the available data be made.

After a lengthy and careful examination of the evidence the Royal Commission concluded that "each of these criticisms is validly applied to Dr. Hardell's North Sweden Study and most of them also apply to his later studies".

Dr. Hardell's North Sweden Study was a case control study of 52 male patients aged from 26 to 80 years. Each had been diagnosed as suffering from soft tissue sarcoma and all had been treated at the Umea Oncological Centre between 1970 and 1977.

Each case was matched for sex, age and town of residence with four (4) controls. Dr. Hardell then contacted all subjects by

telephone. This was followed by a letter and a printed questionnaire (32,33). The letter was signed by Dr. Hardell and was on the letter-head of the Umea Oncological Center (24). The questionnaire was headed "Umea Regional Hospital Oncological Centre" (33).

North Sweden is a fairly sparsely populated area and although Umea is a relatively small place (80-90,000 people) it is a centre for the north. Its hospital is a specialist hospital dealing with cancer and is the only such hospital in the north of Sweden. All soft tissue sarcomas would be referred to it and so its cancer section would be well known to the people of the region.

Although a proper application of the principles of epidemiology requires that hypothesis generating data and hypothesis testing data be kept separate, Dr. Hardell included the hypothesis generating cases in his North Sweden Study.

There were 13 patients with soft tissue sarcoma included in the Study as exposed cases. At least six (6) of these were drawn from the seven (7) initial cases in the hypothesis generating material referred to in Dr. Hardell's clinical observations (21). The number drawn from the hypothesis generating data and included amongst the exposed cases in the study may well have been as high as eight (8) from the nine (9) cases referred to in his published clinical observations (21).

Of the initial seven (7) cases who were clearly included in the Study only one (1), namely Case 3, was treated as unexposed. Thus six (6) out of 13 of the exposed cases, and possibly as many as eight (8) of such cases, were derived from the hypothesis generating data.

In view of this the Royal Commission found that: "The first criticism of Dr. Hardell's studies is clearly justified in relation to the North Sweden Study".

In addition to the publicity which preceded Dr. Hardell's North Sweden Study and his prominence in the debate which was then raging about phenoxy herbicides, every case "had already been treated in the Department of Oncology at the University of Umea," so the fact that the letter accompanying the questionnaire as well as the questionnaire itself were linked with the Oncological Centre at Umea is highly material.

The questionnaire:

- a) specifically referred to Hormoslyr in question 10, 14 and 28;
- b) included seven (7) questions out of a total of 31 which were either concerned with the spraying of herbicide nominated a herbicide;

- c) contained 20 questions which expressly referred to exposure to some form of chemical or chemicals;
- d) included as its remaining questions, eight (8) which were concerned only with occupation or place of work, **one** (1) which dealt with medical details, one (1) which asked about cigarettes and one (1) at the end of the questionnaire, namely question V, which gave the subject an opportunity to add any "additional information".

An examination of the questionnaire clearly shows that its major concern was with exposure to chemicals, the emphasis being on herbicides, particularly Hormosylr (2,4,5-T). In the context of the then current controversy about 2,4,5-T the subject matter of the inquiry by Dr. Hardell would have been patent to anyone who received the letter and questionnaire and even more obvious to those who had been treated at the Oncological Centre at Umea.

Having regard to all these considerations it is perhaps not surprising that Dr. Hardell finally agreed that: "there could be a recall bias which probably is in our study"

and that the Royal Commission decided that : "clearly information bias taints the study..."

The question of exposure to phenoxy herbicides had been expressly raised with each of the patients referred to in the clinical observations (21) and the diagnosis of cancer and its associations with the patient's history of exposure discussed in detail with the patient. In taking the history the connection between the patient's cancer and its exposure to phenoxy herbicides was said to have been "probed". At least one of those initial cases "spontaneously told me (i.e. Dr. Hardell) about his work as a forestry man and that he constantly talked about spraying within the occupation". No such probing or volunteering of association can be found in relation to the controls.

Each questionnaire revealed the name of the relevant patient when it went out. Numbers were assigned to the cases only after interviews had taken place. The telephone interviewer (Miss Damber) had no written instructions in respect of the interview and Dr. Hardell had no direct knowledge of her mode of questioning. It appears that she was not experienced in such studies.

The exposure data relating to the cases included in the study were described by the Royal Commission as "both unsatisfactory and inadequate". In the first instance the statement about exposure contained in the study says that: "Exposure to phenoxy

acids of chlorophenol was admitted by 36.5% of the patient group..." (24). However, the words "phenoxy herbicides do not appear in the questionnaire.

For the purposes of the Study exposure was defined by Dr. Hardell as including "working in a freshly sprayed moist area". However, whether a person had worked in such an area or had "wet contact" was not asked in the questionnaire (24).

The only question which touched upon this subject was question 14 that asked whether a person had "worked in treated area". However Dr. Hardell ~~conceded~~ that the answer to this question did not inform as to whether the area had been sprayed five minutes, five days or five months before the exposure had occurred.

It is clear from the use of the seven (7) original cases referred to in the clinical observations (21) that no uniform approach to exposure was maintained (e.g. see above regarding Cases 6 and 7 in the clinical observations).

In addition Dr. Hardell said that questionnaires were sent to the employers of all those cases and controls who had been working in forestry i.e. 50 persons in total (16) and "we could only get answers from twenty persons since the employers did not keep the records". As a result the information was regarded by Dr. Hardell as "weak data and nothing I can set up on a scientific basis and argue about".

Some of the data on which the North Swedish Study is based are included in a paper which was published in 1979 (16). This paper is very revealing since the additional data relating to exposure and the substances involved can be analysed to some extent. It is not possible, however, to relate the numbers assigned to the cases in that publication with those assigned in Dr. Hardell's clinical observations (21). Dr. Hardell was unable to do this when he gave evidence and, although the material was going to be forwarded by him to the Royal Commission, it was not forthcoming. What is known is that at least six (6) of the original seven (7) cases and possibly as many as eight (8) of the initial nine (9) cases observed by Dr. Hardell were included as exposed cases in the North Sweden Study.

The North Sweden Study contains details relating to the 13 soft tissue sarcoma cases who are said to have been exposed to phenoxyacetic acids. It is worthwhile looking in more detail at six of these cases, namely Cases 160, 180, 390, 490, 510 and 520.

In cross-examination it emerged that Case 390 had only two (2) days of exposure at some time between nine (9) and 19 years prior to diagnosis. This occurred while he was mist blowing with a chemical the nature of which was undefined but was perhaps 2,4-D.

2,4-D does not contain 2,3,7,8-TCDD.

Case 160 was stated in the Study to have seven (7) days exposure 19 years prior to diagnosis. However, it emerged that the only information available about the exposure of this case was that he had worked as a supervisor and whilst so working he had either sprayed the material himself or had got it on himself or on his clothes.

It should be noted that if only two (2) cases had been wrongly included in this sample the findings would not be statistically significant, i.e. the result depends on a claimed excess of only two (2) soft tissue sarcomas. Cases 390 and 160 could properly be treated as unexposed.

In addition it is worthwhile looking at some of the cases who were included in the Study and to examine their latency periods:

- 1.- Case 180 was said to have had seven (7) days of exposure to MCPA alone at some time between 13 and 15 years before the study. MCPA does not contain 2,3,7,8-TCDD.
- 2.- Case 490 had a latency of between five (5) and 10 years.
- 3.- Case 510 had an exposure of five (5) months "somewhere between 3 and 9 years before the date of diagnosis".

The maximum latency period for this case was thus nine (9) years, a period said to be "improbably short".

4.- Case 520 had a latency period which was between eight (8) and
- 12 years.

Thus in relation to the 13 "exposed" cases included in the
Study the Royal Commission pointed out that:

- a) "at least six (6) and perhaps as many as eight (8) formed
part of the hypothesis generating data;
- b) three (3) had either doubtful or minimal exposure;
- c) one (1) had a clearly inadequate latency and another one (1)
of even two (2) had a latency period which was barely adequate."

Dr. Hardell did not dispute that of the 13 cases included as many
as eight of them could be cases he had referred to in his clinical
observation and that in two (2) cases (Case 490 and 510) had a
latency period significantly less than that usually attributed to
soft tissue sarcoma and the same is probably true for Case 520.

Thus even adopting a 10 years latency period, 10 or even 11 of
the 13 cases could properly be excluded on grounds of wrong
classification or as irrelevant to the question of causation.

Looking at a best case (from Dr. Hardell's point of view)
exclusions would not be fewer than:

- six (6) because they formed part of the hypothesis generating
data;

- one (1) because of no real evidence of exposure to phenoxy herbicides;
- one (1) with a latency period which was clearly inadequate.

There are then only five (5) cases remaining if a 10 years latency period is adopted and fewer if a 15 year period is adopted. Five (5) cases would not give rise to a result which was statistically significant.

If the proper principles of epidemiology were applied and the initial 7 (7) cases referred to in the clinical observations (21) were excluded from the Study it was admitted by Dr. Hardell that the relative risk would fall "to something just below 3". Dr. Hardell did not have material from which the precise figure could be calculated. However he offered to forward copies of relevant data to the Royal Commission. This was not done so his claim has not been able to be verified.

The above reduction in the relative risk is achieved by eliminating only one (1) of the sources of error in the Study, namely the inclusion in the study of the hypothesis generating data. However, even the reduced figure is still influenced by the effects of subject recall bias, interviewer bias and the presence of confounding factors for which no adjustment has been made in the Study.

Another matter which is worthy of note is that exposure to phenoxyacetic acids alone cannot be determined although Dr. Hardell asserted in the report of his study that he had analysed "exposure to phenoxy acids alone" (24), and obtained a relative risk of 5.3 in relation to such exposure. It is apparent both from the Study itself and from Dr. Hardell's oral testimony that no such analysis was done.

The study states that: "It is impossible... to assess the effects of the individual chemical substances separately since practically all patients may have been exposed to chlorinated dioxins as well, including tetrachlorodibenzodioxin (TCDD)... and also to other compounds" (24).

In that part of Dr. Hardell's publication in which the results of the so-called analysis of "exposure to phenoxy acids alone" are set out (24) persons who had also been exposed to chlorophenols are included. In this context it should be remembered that Dr. Hardell claims that exposure to chlorophenols is associated with a relative risk for soft tissue sarcoma of 6.6, so such exposure constitutes a confounding factor of importance.

Yet another consideration which is relevant to the accuracy or adequacy of the exposure data on which the study is based is the unsuccessful attempt to verify exposure to particular substances with employers, the results of which were: "uncertain

and difficult to evaluate. Records of individual working manuals had not been kept, and the answers were mainly based upon reminiscence. Replies from the employers were obtained for 20/50 persons involved" (14).

Thus the exposure data for the 13 cases said to have been exposed to phenoxyacetic acids alone depend very much on the outcome of the interviews for which there were no written instructions and which were carried out by a lady who had had no a prior experience whatsoever in conducting interviews for epidemiological studies.

An examination of the effect of interview on rejection of study subjects and on relative risk assessment (see Tables II and III below) reveals that the relative risk of the cases when compared with controls more than doubled after interview. There is also a marked disparity in the effect of interview on the percentage of controls rejected when compared with cases - nearly 4:1. Thus not only is there justification for the criticisms which assert that the circumstances gave rise to the possibility of interviewer bias, but Dr. Hardell's own later analyses provide material which, the Royal Commission found "suggests that this, in fact occurred".

All cases were given the suffix 0. Controls were given suffixes of 1, 2, 3 or 4. The consequence was that those classifying the subjects in the study "knew just by looking whether a person was a case or a control" - yet another avenue for information bias.

A preliminary classification of the subjects was carried out by Dr. Hardell and his assistant and then discussed with others. These included Professor Axelson. The classifying process was carried out with knowledge of the numbers which had been assigned to the subjects who were to be classified, so "there was no question as to classification being blind"

For some deceased subjects that fact that their next of kin who washed their clothing said that the clothes of the deceased smelt was sufficient to result in them being classified as exposed.

The Study itself admits the presence of a number of confounding factors such as: diesel oil - about which there was insufficient information for a proper evaluation, and other pesticides - about which no information was available (16).

It is relevant to the problem of confounding to note that Dr. Hardell conceded that none of the 13 exposed cases of soft tissue sarcoma in the study were exposed to phenoxyacetic acids alone. One of the 13 had high grade of exposure to chlorophenols and Dr. Hardell was unable to say how many had been exposed to organic solvents, but he conceded that a number had been and that no calculation whatsoever could be made about the effect of organic

solvents because no data were available on them.

It is interesting to note the limited conclusion to which Dr. Hardell came as a result of his North Sweden Study. These are set out in the Royal Commission Report. The Royal Commission noted these, commented upon the fact that Dr. Hardell was influenced by an anxiety to prove the integrity of his study and concluded that: "The North Sweden Study is open to criticism and... that is is rightly regarded as flawed and unacceptable as proof of the result claimed".

2.- The South Sweden Study

Following the completion of his North Sweden Study, Dr. Hardell undertook an investigation into "the potential effects of MCPA, 2,4-D and the analogous phenoxy propionic acids" all of which were widely used in agriculture in the southern areas of Sweden (16). The study was commenced in February 1979 and, as in the case of the North Sweden Study, the data gathering took place in the spring, with the telephone interviews for this particular study being conducted in May/June 1978. The study involved 110 patients diagnosed between 1974 and 1978 as suffering from 12 different types of soft tissue sarcoma (16). These were matched with 219 controls.

The gathering of exposure data involved advance contact with people by telephone, then sending them a nine page questionnaire and later supplementing the information derived from the responses by means of selective telephone interviews of these respondents who had worked in agriculture, forestry or horticulture during the relevant period. In some instances (unspecified) the interviewer also contacted employers, neighbours and others "to elucidate possible exposure" (16).

Exposure to phenoxy acids of less than one day was not considered nor was exposure within five (5) years before the year of diagnosis i.e. a latency period of only five (5) years was adopted.

As an aside it is worth referring to the Swedish railway workers dealt with in this Study - in relation to whom it is stated that: "the embankments of the Swedish State Railways have been sprayed mainly with amitrol, but pesticides including phenoxy acids have also been used. It is not possible to determine completely all the substances to which individuals had been exposed, despite contact with the people themselves, their workmates, or their employers. Therefore, railway workers who reported exposure to pesticides were regarded as unexposed to phenoxy acids". (16).

This is to be contrasted with the approach adopted by Professor Axelson in his Study (1).

Eighty five (85) of the 100 cases (i.e. 77,3%) were not exposed to any phenoxy acids or chlorophenols. Of the remaining 25, seven (7) are said to have been exposed to phenoxy acids other than 2,4,5-T and 11 to chlorophenols alone. This left only seven (7) cases who were exposed to 2,4,5-T as well as to other phenoxy acids and other known and unknown chemical substances, included amongst which were organic solvents.

Based upon these seven (7) cases and one control Dr. Hardell calculated the point estimate of the relative risk of exposure to 2,4,5-T and other phenoxy acids as 17.0 (16). The Royal Commission regarded this as "an extraordinary figure" and "so far out of step as to lack credibility".

Relative risks in the South Sweden Study (16) were stated to be as follows:

- exposure to phenoxy acids or chlorophenols: 5.3;
- exposure to all phenoxy acetic acids: 6.8;
- exposure to all phenoxy acetic acids excluding 2,4,5-T: 4.2;
- exposure to chlorophenols alone: 3.3.

An examination of a different print of South Sweden Study (15) is revealing. It includes material which does not appear in versions of the same study published elsewhere (11 - 16).

In the publication under examination (15) Dr. Hardell concedes that "when exposure data are collected via questionnaires and interviews a certain possibility exists that the cases will have a greater interest in the questions than the healthy controls do". This concession is not included in later published versions of the Study. Also, for a reason which is unexplained, the results reported in the two versions differ. Thus in Table 6 to reference 15 the relative risk amongst agriculture/forestry workers exposed to phenoxy acids is calculated at 6.4 based upon 13 cases and five (5) controls. On the same data i.e. 13 cases and five (5) controls, a relative risk of 5.7 is reported in Table 7 of reference 16.

The very conclusion of the study would seem to reflect a concern, even a reservation, on the part of Dr. Hardell about the accuracy of the results because, despite the high relative risk reported, the conclusion is expressed in very guarded terms: "this investigation has indicated that exposure to phenoxy acids and chlorophenols might constitute a risk factor in the development of soft tissue sarcomas" (13).

Except for the fact that no hypothesis generating data were included in the South Sweden Study, the problems with and criticisms which can be levelled at it are similar to those dealt with in relation to the North Sweden Study. In addition,

the media publicity which the North Sweden Study attracted in Sweden is likely to have accentuated the problem of information bias.

Having examined the South Sweden Study and the author's testimony about it, the Royal Commission was of the view that the study "has properly been widely regarded as flawed, unacceptable as proof of the results claimed and such that it cannot be taken at face value"

3.- The Malignant Lymphoma Study

In January 1979 Dr. Hardell published his preliminary clinical findings relating to 17 male patients who were suffering from malignant lymphoma (22). As a result of the findings he undertook his third study, the Malignant Lymphoma Study. In it Dr. Hardell deals with 169 patients aged between 25 and 85 who were diagnosed in the period from 1974 to 1978 as suffering from either Hodgkin's Disease or non-Hodgkin's lymphoma. The cases included the 17 patients referred to in the preliminary findings who formed the group from which the hypothesis to be tested was generated (22). Cases were matched for sex, age, place of residence and year of death with a total of 338 controls.

Information about exposure to various chemicals including organic solvents, chlorophenols and phenoxy acetic acids was obtained by questionnaire. However, there were severe problems about identifying the substances to which any individual had been exposed. Indeed Dr. Hardell conceded in cross-examination that he could not present any separation of figures which showed the number of cases exposed to phenoxy acid alone.

On Dr. Hardell's analysis of the data the relative risk for exposure to phenoxy acetic acids or chlorophenols was 6.0; to phenoxy acetic acids 4.8 and to chlorophenols 4.6 (18). However, in view of the concession above it is difficult to understand how the relative risk of 4.8 was calculated, or to know what it really means.

A fivefold increased risk of malignant lymphoma was found for those exposed to phenoxy herbicides and chlorophenols. The increased risk for those with high grade exposure to chlorophenols was eightfold and threefold for those with low grade of exposure . An increased risk was also found for those exposed to organic solvents.

The study did not reveal any difference between the risk of Hodgkin's Disease and non-Hodgkin's lymphoma despite the fact

that Hodgkin's Disease seems to occur in two peaks, one affecting the young and one affecting the old and there is thought to be some viral association in the etiology of Hodgkin's Disease, at least as far as the younger group is concerned. Whilst the etiologies of Hodgkin's Disease and non-Hodgkin's lymphoma appear to be different, Dr. Hardell (18) does not differentiate between the two. He groups them together and, in addition, includes lymphomas which are unclassifiable.

At page 10 of reference 18 it is stated that "exposure to phenoxy acid was analysed separately excluding all persons who had high grade exposure to chlorophenols". However, this is just not correct, because Dr. Hardell agreed in cross-examination that a number of them may have been exposed to low grade chlorophenol and five (5) of them had been exposed to high grade chlorophenol.

Table 3 to reference 18 had a heading which was held by the Royal Commission to be "inaccurate and misleading".

It reported on cases and controls exposed to phenoxy acids after those exposed to chlorophenols were excluded. However a number of the persons included in the Table had low grade exposure to chlorophenols and five (5) had high grade exposure.

Thus the relevant data is not looking at those cases which were exposed only to chlorophenols. It includes cases who were exposed to phenoxy acids, fourteen (14) who were exposed to a low level of chlorophenols and five (5) instances of exposure to a high level of chlorophenols.

Dr. Hardell was also asked about the subdivision of cases as reported in Table 5 to reference 18. That table is headed "Exposure to organic solvents in cases and controls after matching was dissolved and those exposed to phenoxy acids (F) or with high grade exposure to chlorophenols (K) were excluded, assuming there was no joint exposure".

Exposure to organic solvents was characterized as low grade (1) and high grade (2). In Table 5 there are 23 cases who had both phenoxy acid exposure and high grade chlorophenol exposure. Dr. Hardell could not say how many cases were exposed just to phenoxy acids and nothing else.

This was despite the fact that Dr. Hardell "set out in this paper to examine the relationship between phenoxy acid exposure and lymphoma". In addition, he did not publish a figure in respect of phenoxy acid exposure alone. He said in his testimony that he had carried out such an analysis but that he had not submitted it for publication. The result was not produced to the Royal Commission although Dr. Hardell was afforded an opportunity to do so. His published conclusion

namely: "The present investigation... suggests... that exposure to organic solvents, chlorophenols and/or phenoxy acids constitutes a risk factor for the incidence of malignant lymphoma", certainly gives no scientific support for the proposition that phenoxy acetic acids cause malignant lymphoma.

It can thus be seen that not only is the Study misleading in the form in which some of its data are presented but there are also very serious, multiple confounding factors which have not (and cannot) be adjusted for. The Study is also subject to the same criticisms as the North Sweden Study, including the fact that hypothesis generating data were used in it.

No one has been able to replicate the findings in Dr. Hardell's studies relating to soft tissue sarcoma and malignant lymphoma and the results of his three studies are contrary to the findings obtained by others.

This absence of replication, the absence of specific outcome (i.e. 12 types of soft tissue sarcoma, non Hodgkin's malignant lymphoma and Hodgkin's Disease), admitted information bias, the presence of significant confounding factors which are not adjusted for, the unreliability of the exposure data and the other factors detailed above led the Royal Commission to conclude that "the statistical associations asserted by Dr. Hardell are suspect" and that it could not "accept them as

supporting an inference of causal connection between soft tissue sarcoma, malignant lymphoma and exposure to phenoxy herbicides".

4.- The Nasopharyngeal Cancer Study

In 1981-82 in conjunction, inter alia with Professor Axelson, Dr. Hardell undertook a case-control study of nasal and nasopharyngeal cancer and their relation to phenoxy acid or chlorophenol exposure. The Study (19) dealt with 71 patients (being 44 cases of nasal cancer and 27 of nasopharyngeal cancer) who were aged between 25 and 85 years, who had been reported to the Swedish Cancer Registry in the years 1970-1979 and who were resident in the three most northern counties of Sweden at the time of diagnosis. These cases were matched with 541 controls. A questionnaire which was identical with that used in previous studies was sent to the cases, or the next-of-kin of deceased cases. It is claimed by Dr. Hardell that the Study in question "follows the methodological design" of the previous studies undertaken by him. The controls had been used in earlier studies in North Sweden, but no further contact was made with them for the purposes of this Study. On analysis of the data "no significant association was found" between the cancers of interest and phenoxy herbicides (19).

Dr. Hardell claimed that this Study could be used as a verification of previous studies. However, despite the assertion that this and previous studies used the same procedures, there are a number of differences between the procedures for the Nasopharyngeal Cancer Study and those used in Dr. Hardell's earlier studies. In the Nasopharyngeal Cancer Study:

- a) no contact was made by telephone with the cases before they received the questionnaire;
- b) there was no publicity linking phenoxy herbicides and nasal cancer at the time the study was undertaken and the debate about phenoxy herbicides had no doubt abated with the banning of 2,4,5-T in 1977;
- c) no hypothesis generating cases were included amongst the cases examined in the Study;
- d) the interviewer who made telephone contact with the cases was "blind", since the questionnaires for this study were mixed with identical questionnaires from the Colon Cancer Study (19).

The existence of differences in the procedures adopted for this Study means that it cannot be used as a verification of the earlier studies. The fact that a negative result was obtained in relation to exposure to phenoxy herbicides may even be

regarded as further evidence supporting the criticisms advanced in respect of Dr. Hardell's first three (3) studies.

It is also of interest to note that, contrary to what had been done by Professor Axelson in his study of Swedish Railway workers, employees of the Swedish Railways who were reported as exposed to pesticides: "were considered unexposed to phenoxy acids, since the type of preparation could not be established with certainty". (19).

In summary therefore it can be said that the Nasopharyngeal Cancer Study not only produces a negative result in relation to phenoxy herbicide exposure but it may even reinforce the criticisms of Dr. Hardell's earlier studies.

5.- The Colon Cancer Study

The Colon Cancer Study (13) Involved 157 male colon cancer patients who had been extracted from the Swedish Cancer Registry and were resident in northern Sweden.

Each was sent a questionnaire and interviewed. The group which had been used as a control group for the studies previously carried out by Dr. Hardell in relation to soft tissue sarcoma and malignant lymphoma was used as the control group for this

study, but not further contact was made with the controls. The results show no difference in the incidence of colon cancer amongst those exposed to phenoxy acids and it is argued by Dr. Hardell that this verifies that there was no information bias in his earlier studies. There are, however, differences in the methodology for the Colon Cancer Study when compared with the earlier studies. For example the cases were not telephoned by Dr. Hardell before they receive a questionnaire, the interviewer did not have knowledge either of the object of the Study or of the classification of patients (as the interviewer in the previous studies had) and there had been no publicity linking colon cancer with phenoxy herbicides.

In the course of his testimony, Dr. Hardell was shown a document which had been produced by him in Washington in the 1980 EPA proceedings as a true analysis of his previous studies.

This document shows that before interviews were conducted:

- in the North Sweden Study, 28.8% of the 52 cases of soft tissue sarcoma (i.e. 15 cases) had originally been classified as exposed and 13.6% of the 206 controls (i.e. 28 controls) had been so classified;
- in the South Sweden Study, 16.4% of the 110 cases of soft tissue sarcoma (i.e. 18 cases) had been classified as exposed and 4.6% of the 209 controls (i.e. 10 controls) had been so classified;

- in the Malignant Lymphoma Study, 24,9% of the 169 cases of soft tissue sarcoma (i.e. 42 cases) had been classified as exposed and 11% of the 335 controls (i.e. 37 controls) had been so classified.

After interview 13 cases and 14 controls classified as exposed remained in the North Sweden Study. In the South Sweden Study 14 cases and a mere five (5) controls remained after interview. In the Malignant Lymphoma Study 41 cases remained after interview but only 24 controls.

These results are set out in Tabel II below.

TABLE II

<u>EFFECT OF INTERVIEW</u>			
<u>ON REJECTION OF STUDY SUBJECTS</u>			
	<u>North Sweden</u>	<u>South Sweden</u>	<u>Malignant</u>
	<u>STS Study</u>	<u>STS Study</u>	<u>Lymphoma Study</u>
Controls - Before Interview	28	10	37
Controls - After Interview	14	5	24
<u>Reduction</u>	50%	50%	35%
Cases - Before Interview	15	18	42
Cases - After Interview	13	14	41
<u>Reduction</u>	13%	22%	2.1%
Comparative) Effect of) interview) Controls) <u>v.</u>) Cases)	3.8:1	2.27:1	16.66:1

The differential effect of the interview on cases and controls is both obvious and telling. At the very lowest, it "is at least suggestive of interviewer bias" as the Royal Commission put it.

A comparison of documents tendered to the Royal Commission shows that the percentage of exposed cases in the Malignant Lymphoma Study in the former version is 24.9. However, in a later one it is shown as 27.2% (13).

When this difference was pointed out to Dr. Hardell he said that this change had taken place after he had been cross-examined in the EPA proceedings and that the change was effected because he "must have overlooked some exposure (sic) ones which he had not noticed before".

Dr Hardell then conceded that by changing that figure he had built up the relative risk from 2.7 to 3.

That such a mistake should have had escaped not only him but also the four people who had gone through the data concerning the Malignant Lymphoma Study is curious to say the least. Dr. Hardell explained the difference by saying that "different criteria for exposure were discussed. The first part says all phenoxy acid exposure and that means exposure that has been notified somehow in the questionnaire or by interviews, but during the evolution of the exposure it has turned out that these people are not exposed".

However, when pressed on his answer he admitted that this explanation was wrong since the document in question was dealing with information derived from questionnaires alone, unadjusted by any value judgements made in the assesement process and unaffected by the results of the interview i.e. not taking into account the effect of interview.

When data derived from the questionnaires alone are used, a point estimate for the relative risk revealed by the study is 2.6 compared with 5.3 when the effects of ther interviews are taken into account.

If for each of Dr. Hardell's first three (3) studies a comparison is made between the point estimates obtained using data from the questionnaire alone and the point estimates obtained when the effects of the interviews on the data are taken into account, the relative risks are: 2.6 for the North Sweden Study - compared with 5.3 as published; 4.1 for the South Sweden Study - compared with 6.8 as published; 2.7 for the Malignant Lymphoma Study - compared with 4.8 as published. If the data are changed in the way which a comparison of tendered documents reveals, the figures becomes 3 compared with 4.1 for the Malignant Lymphoma Study.

TABLE III
RELATIVE RISKS - EFFECT OF INTERVIEW

	<u>North Sweden</u> <u>STS Study</u>	<u>South Sweden</u> <u>STS Study</u>	<u>Malignant</u> <u>Lymphoma Study</u>
RR* - Before Interview	2.6	4.1	2.7
RR - After Interview	5.3	6.8	4.8
Increase in RR following Interview	103.8%	65.8%	77.8%

*Relative Risk (References 21, 34, 18, 20)

When Dr. Hardell was cross examined on Table I of the Colon Cancer Study, the heading to which is "Exposure Frequencies to Phenoxy Acids", he conceded that these cases were not exposed only to phenoxy acids but some cases also had exposure to chlorophenols and organic solvents.

At this point it is relevant to return to the 13 exposed cases of soft tissue sarcoma included in the North ~~Sweden~~ Study. Dr. Hardell agreed that none of the cases were exposed to phenoxy acids only. One of them in fact had high grade chlorophenol exposure and there was an unknown number who had low grade chlorophenol exposure and whilst Dr. Hardell was unable

to say how many were exposed to organic solvents, he agreed that some of them were.

Although Dr. Hardell claimed that organic solvents had been excluded from the analysis of the North Sweden Study (11) when he was asked to clarify this he referred to a passage at page 715 of reference 12 . However, this passage makes no reference to organic solvents . When this was pointed out to Dr. Hardell he said they were included "with the emulsifiers which contain organic solvents " In the end, however, he conceded that organic solvents had not been dealt with in the paper .

It is also clear from Dr. Hardell's cross-examination that the heading to Table IV in the North Sweden Study (11) is not accurate when it refers to exposure to "phenoxy acetic acids only" since the persons included under that heading were exposed to chlorophenols and to organic solvents as well.

It is not possible to make any calculation about or allowance for the confounding effect of exposure to organic solvents.

Dr. Hardell was then asked about information bias as a result of which response from the subject may be inaccurate and differ between case to control and he said that the existence

Of a controversy and of publicity may have influence on the interviewer with consequent difference in classification of the cases. This interview could influence the result and lead to a distortion in the risk ratio.

5) Inconsistencies between Axelson and Hardell

a) Hardell claims that there is an increased risk of soft tissue sarcoma and malignant lymphoma both of the Hodgkins and non-Hodgkins types from exposure to pehnoxy herbicides. In Axelson's work there were no cases of soft tissue sarcoma or of non-Hodgkin's lymphoma found and only one case of Hodgkin's Disease.

b) It is claimed that Hardell's work indicates specificity in the type of tumor produced by phenoxy herbicide exposure namely, soft tissue sarcoma and malignant lymphoma. However, in his update Axelson concludes that: "no specific type of tumor can be considered as predominating". (3)

c) Hardell asserts relative risks in excess of 4 for the association of cancer and phenoxy herbicide exposure. In Axelson's first analysis his finding in relation to the "phenoxy acids and combination" subcohort was close to a negative as one can get. In his re-analysis, even when

the exposure classification was changed for two (2) cases so as to produce an excess of tumors observed over those expected in the subcohort exposed to phenoxy acids and combinations, the relative risk was still only 1.6 and not statistically significant. In his update the relative risk when properly determined (i.e. with exclusion of wrong diagnoses, adoption of a ten years latency period and using the data detailed in Table I to reference 3) lies close to unit and is certainly not statistically significant.

Thus far from supporting Dr. Hardell, Professor Axelson's work and his conclusions are different from and, destructive of Dr. Hardell's conclusions.

The Axelson Technique

Both Dr. Hardell and Professor Axelson sought to rely upon a mathematical calculation undertaken by Professor Axelson in an endeavour to demonstrate that the procedures adopted by Dr. Hardell in his early studies did not give rise to information bias (35, 36).

Dr. Hardell was asked about the Axelson Technique and from his cross examination on this topic

it emerged that the Axelson technique depends upon a number of assumptions:

- 1) both cases and controls will have like recall on the subject of exposure and such recall will be accurate;
- 2) the classification of workers into categories of agriculture and forestry (AF) on the one hand and other occupations (O) on the other hand is accurate;
- 3) there will be an equality of incidence in the soft tissue sarcoma amongst the unexposed members of the AF group and the O unexposed members of the group;
- 4) there is no other factor which operates in one group and does not operate in the other.

It would seem that the technique assumes the result sought to be proved. Certainly, as Professor Allan Smith pointed out (37) "there seems to be little basis for the assumption that there would be differential recall as between cases and controls".

In addition Professor Smith stated that it is possible on a theoretical, i.e. mathematical basis "that diminution due to recall bias in the proper number of unexposed cases employed in agriculture or forestry could be compensated for and masked by an increased incidence of the disease amongst the workers in agriculture or forestry not exposed to phenoxy herbicides but exposed to other

environmental factors prevalent in their industry".

Professor Smith also expressed the view that there was "little value to be found in the application of the Axelson technique especially in relation to the South Sweden Study" and that such technique was "not a reliable indicator of the absence of recall bias in that Study". This view was accepted by the Royal Commission.

CONCLUSION

The conclusion of the Royal Commission in relation to the Hardell studies is worth setting out verbatim since it is in marked contrast to the way in which one statutory agency in the United States has recently dealt with in the same studies:

"...absence of replication, the absence of specific outcome (i.e. 12 types of soft tissue sarcoma, non-Hodgkin's malignant lymphoma and Hodgkin's Disease), admitted information bias, the presence of significant confounding factors, the unreliability of the exposure data and the other factors detailed above all indicate that the statistical association asserted by Dr. Hardell are suspect. The Commission cannot, on the balance of probability, accept them as supporting an inference of causal connection between soft tissue sarcoma, malignant lymphoma and exposure to phenoxy herbicides."

" . . . the Commission does not accept the Hardell studies as proving, on the balance of probabilities, any causal association between Soft Tissue Sarcoma and Lymphoma and exposure to 2,4-D, 2,4,5-T, and TCDD."

The conclusion of the Australian Royal Commission in relation to the Hardell studies is congruent with the judicial conclusions reached in relation to those same studies in the United States in the Agent Orange Product Liability Litigation (Gibbs et al. versus Dow et al.: U.S. District Court, Eastern District of New York MDL 381/14; 1985, Weinstein C.J.) and in Canada in the forest spraying litigation (Palmer & Ors versus Stora Kopparbergs Bergslags Aktiebolag trading as Nova Scotia Industries, 1983, 60 Nova Scotia Reports, 2d, 271; Nunn J.).

It is also significant that others have not confirmed Dr. Hardell's findings. The epidemiologic studies on soft tissue sarcoma and cancer risk among agricultural and forestry workers as well as factory workers with exposure to the relevant herbicides or their manufacturing processes which have been carried out in Sweden (42,43,44), in Finland (45, 46), in New Zealand (47,48,49,50,51), in the United States of America (52,53,54,55,56,57,58,59,60,61,62,63,64) and in the United Kingdom (65,66,67,68,69) have not confirmed Hardell's results.

The Hardell Studies should now be laid to rest. Perhaps an appropriate epitaph is that written by the eminent epidemiologist Sir Richard Doll, of Green College, Oxford. In a letter (70) written to Hon. Mr. Justice Philip Evatt, the Australian Royal Commissioner, on December 4, 1985, he gave his view on Hardell's studies as follows:

"your review of Hardell's work with the additional evidence obtained directly from him at interview shows that many of his published statements were exaggerated or not supportable and that there were many opportunities for bias to have

been introduced in the collection of his data. His conclusions cannot be sustained, and, in my opinion, his work should no longer be cited as scientific evidence."

LIST OF REFERENCES

- 1 AXELSON, O. and Sundell, L. Herbicide Exposure. Mortality and Tumor Incidence. An Epidemiological Investigation On Swedish Railroad Workers. Work. Environ. Health. Vol. 11 (1). 1974; pp 21-8.
- 2 AXELSON, O. and Sundell, L. Phenoxy Acids and Cancer. Translated for EPA and revised in accordance with comments by Dr. Axelson. Lakartidningen. Vol 74. 1977. pp 2887-8.
- 3 AXELSON, O. et al. Herbicide Exposure and Tumor Mortality: An Updated Epidemiological Investigation on Swedish Railroad Workers. Scand. Jnl. Work Environ. Health. Vol. 6 (1). Mar. 1980: pp 73-79.
- 4 AXELSON, O. Sweden. Document. Document Digest 1974. Railroad Workers Study 1974. 23 pages.
- 5 Axelson, Olav. Curriculum Vitae & List of Publications. 13.8.84, 9 pages.
- 6 AXELSON, O. EPA Transcript. In the Matter of the Hearing of 2,4,5-T and Silvex. The Dow Chemical Company, et al. 7.7.80. Washington pp 8821-9100 and Appendices. Evidence of Prof. Olav Axelson.
- 7 R.C. Transcript 3375 and see for example FOLKBLAD. Copy of Swedish Newspaper No. 190. Torsdag 18 August 1977 and English translation labelled Clipping 9. Umea doctor with the cancer report. 2 pages.
- 8 See reference 1 at p. 21 and see for example FOLKBLADET. Copy of Swedish Newspaper. Torsdag 18 August 1977 and English translation labelled Clipping 10. The doctor who investigates the cancer cases. 4 pages.
- 9 AXELSON, O. Sweden. Questionnaire in Swedish to all railroad workers in the cohort under study headed "Document Digest" 4 pages.

- 10 AXELSON, O. Sweden. Document Digest 1974. Railroad Workers Study, 1974. 23 pages.
- 11 ERIKSSON, M. et al. Soft-tissue Sarcomas and Exposure to Chemical Substances: a Case Referent Study. British Journal of Industrial Medicine, Vol. 38, 1981: pp 27-33.
- 12 HARDELL, L. & Sandstrom, A. Case-Control Study: Soft Tissue Sarcomas and Exposure to Phenoxyacetic Acids or Chlorophenols. British Jnl of Cancer 1979. Vol. 39 pp 711-717.
- 13 HARDELL, L. Relation of Soft Tissue Sarcoma, Malignant Lymphoma and Colon Cancer to Phenoxy Acids, Chlorophenols and other Agents. Scandinavian Jnl. of Work, Environment & Health. Vol 7, 1981 pp 119-130.
- 14 ERIKSSON, M. et al. Soft-Tissue Sarcomas and Exposure to Chemical Substances: A Case Reference Study. British Jnl. of Industrial Medicine, Vol. 13, 1981. pp 27-33.
- 15 ERIKSSON, M. Hardell, L. Berg, N.O. Moller, T. Axelson, O. Case Control Study on Malignant Mesenchymal Tumors of Soft Tissue and Exposure to Chemical Substances translated for EPA. Originally in Lakartidningen Vol. 76, 1979. pp 3872-75.
- 16 HARDELL, L. et al. Malignant Lymphoma and Exposure to Chemicals, especially Organic Solvents, Chlorophenols and Phenoxy Acids: A Case-Control Study. British Jnl. of Cancer 1981. Vol 43. pp 169-176.
- 17 HARDELL, L. et al. Malignant Lymphoma and Exposure to chemicals especially Organic Solvents, Chlorophenols and Phenoxy Acids. Case Control Study in Br. Jnl. of Cancer Vol. 43, 1981, pp 169
- 18 HARDELL, L. et al. Malignant Lymphoma and Exposure to Chemical Substances especially Organic Solvents, Chlorophenols and Phenoxy Acids in Lakartidningen Vol. 77 (4), 1980. pp 208-210.
- 19 HARDELL, L. et al. Epidemiological Study of Nasal and Nasopharyngeal Cancer and their Relation to Phenoxy Acid or Chlorophenol Exposure. American Jnl of Industrial Medicine 3, 1982. pp 247-257.

- 20 HARDELL, L. On the Relation of Soft Tissue Sarcoma, Malignant Lymphoma and Colon Cancer to Phenoxy Acids, Chlorophenols and other Agents. Scand. J. Work Environ. Health 7; 119-130; 1981.
- 21 HARDELL, L. Clinical Observations regarding Malignant Mesenchymal Tumors, in Lakartidningen (the Doctor's Journal) No. 33 of 1977 pp 2753-2754 (Study 1 in Green Book).
- 22 HARDELL, L. Malignant Lymphoma of Histiocytic Type and Exposure to Phenoxyacetic Acids of Chlorophenols. Lancet, Vol. 1 (8106) January 1979: pp. 55-56
- 23 HARDELL, L. Epidemiological Studies on Soft-Tissue Sarcoma and Malignant Lymphoma and Their Relation to Phenoxy Acid of Chlorophenol Exposure. Umea, Univ. Press, 1981. 139 pages.
- 24 HARDELL, L. & Sandstrom A. Malignant Tumors and Exposure to Phenoxy Acids of Chlorophenols (Case Control Study). Br. J. Cancer: 39; 711-17; 1979.
- 25 SWEDEN. Newspaper clippings in Swedish relating to Hormosly 1977, 6 clippings.
- 26 SWEDEN. Swedish Telex of 16.8.77 - Stockholm
- 27 SWEDEN. Newspaper. Vasterbottens-Kuriren, 18.8.77. Undersokningen Pekar pa Samband Men ar Inget Bevis.
- 28 FOLKBLAD. Copy of Swedish Newspaper No. 190. Torsdag 18 August 1977 and English translation labelled Clipping 9. Umea doctor with the cancer report. 2 pages.
- 29 FOLKBLADET. Copy of Swedish Newspaper. Torsdag 18 August 1977 and English translation labelled Clipping 10. The doctor who investigates the cancer cases. 4 pages.

- 30 HARDELL, L. Accompanying letter in Swedish to Swedish Questionnaire. Northern Sweden Soft Tissue Sarcoma study on letterhead of "Regional Hospital", Umea. Undated, 1 page.
- 31 AXELSON, O. Umea Regional Hospital, Northern Sweden. Questionnaire B. Undated 12 pages.
- 32 AXELSON, O. Umea Regional Hospital, Northern Sweden. Questionnaire A. Undated 11 pages.
- 33 SWEDEN. Oncology Centre. Questionnaire in Swedish from Regionsjukhuset I Umea (Northern Sweden). Undated. 8 pages.
- 34 ERIKSSON, M. Hardell, L. Berg, N.O. Moller, T. Axelson, O. Case Control Study on Malignant Mesenchymal Tumors of Soft Tissue and Exposure to Chemical Substances translated for EPA. Originally in Lakartidningen Vol. 76, 1979. pp 3872-75.
- 35 AXELSON, O. Some comments on the Swedish Experiences from Studies of Cancer and Exposure to Phenoxy Acid Herbicides and Chlorophenols - largely an extension and updating of a presentation by O. Axelson, Hardell at a conference on Health Hazards of Chlorophenols in Vancouver, May 16-17, 1984. 25 pages.
- 36 AXELSON, O. A note on observational bias in case-referent studies in occupational health epidemiology. Scandinavian Jnl. of Work & Environmental Health 6, 1980, pp 80-82.
- 37 Smith A.H.: Outline of additional testimony of 25.9.1984. 6 pages.

- 38.- Cole, P. Direct testimony of Dr. Philip Cole Before the Environmental Protection Agency of the United States of America. In Re: The Dow Chemical Company, et al. FIFRA Docket Nos. 415, et al. (Exhibit 860) Appearance Date: November 6, 1980.
- 39.- Anonymous. Further review of the safety for use in the U.K. of the herbicide 2,4,5-T, Advisory Committee on Pesticides, Ministry of Agriculture, Fisheries and Food (December 1980).
- 40.- Rt. Hon. Peter Walkers, M.P., Minister of Agriculture, Fisheries and Food, In: Advisory Committee on Pesticides: Report on Phenoxy Acid Herbicides. London: Ministry of Agriculture, Fisheries and Food, February 7, 1983.
- 41.- Cook, R.R. Soft Tissue Sarcomas: Clues and Caution. Tucker, R.E., Young, A.L. and Gray, A.P., Eds. Human and Environmental Risks of Chlorinated Dioxins and Related Compounds. New York: Plenum, 1983. pp. 613-618.
- 42.- Eklund G.: Does occupational exposure to chemical pesticides increase the risk of cancer. Weed and plant protection conferences. Uppsala, Sweden, 1983. pp 6-12.
- 43.- Wiklund K, and Holm L.E.: Soft Tissue Sarcoma risk in Swedish agricultural and forestry workers. Journal of National Cancer Institute. In press.
- 44.- Stenbeck G., and Wiklund K.: Multiple myeloma in Swedish agricultural workers. Int. Journal of Epidemiology. In press.
- 45.- Riihimaki, V., Asp, S, and Hernberg, S. Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland. Scandinavian Journal of Work Environment and Health 8:37-42, 1982
- 46.- Riihimaki, V., Asp, S., Pukkala, E. and Hernberg, S. Mortality and cancer morbidity among chlorinated phenoxyacid applicators in Finland. Chemosphere, Vol. 12. No. 4/5. pp. 779-784, 1983.
- 47.- 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. Presented at 3rd International Symposium on Chlorinated Dioxins and Related Compounds, October 12-14, 1982, Salzburg, Austria.

- 48.- Smith A.H., Fisher D.O., Pearce N.E. and Teague C.A.:
Do Agricultural Chemicals Cause Soft Tissue Sarcoma?
Initial Findings of a Case-Control Study in New Zealand.
Community Health Studies 6: 114-119, 1982.
- 49.- Smith A.H., Pearce N.E., Fisher D.O., Giles H.J., Teague
C.A.: Soft Tissue Sarcoma and exposure to phenoxy her-
bicides and chlorophenols in New Zealand. I.N.C.I. 73;
1111-17, 1984.
- 50.- Smith A.H., Pearce N.E.: Update on Soft Tissue Sarcoma
and Phenoxy herbicides in New Zealand.
5th International Symposium on chlorinated dioxins and
related compounds. September 16-19, Bayreuth, F.R.G., 1985.
- 51.- Pearce N.E., Smith A.H., Howard J.K., Giles H.J.: Case
Control Study of non Hodgkin's Lymphoma and exposure to
phenoxy herbicides, chlorophenol, fencing work and meat
employment.
British Journal of Industrial Medicine. In press.
- 52.- Zack J.A. and Suskind R.S.: The Mortality Experience
of Workers Exposed to Tetrachlorodibenzodioxin in a
Trichlorophenol Process. Journal of Occupational Medicine
1980: 22:11-14.
- 53.- 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. Journal of Occupational
Medicine 1980; 22:47-50.
- 54.- Cook R.R., Townsend J.C. and Ott M.G.: Mortality Experience
of Employees Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin
(TCDD). Journal of Occupational Medicine 1980; 22:530-532.
- 55.- Zack J.A. and Gaffey W.R.: A Mortality Study of Workers
Employed at the Monsanto Company Plant in Nitro, West
Virginia. Environmental Science Research 1983; 26:575-591.
- 56.- Suskind R.R.: Long Term Health Effects of Exposure to
2,4,5-T and/or its Contaminants. Chemosphere, Vol. 12
No. 4/5, p 769, 1983).
- 57.- Cook R.R. and Cartnill J.B.: Soft Tissue Sarcoma and Dioxins.
Putting the data onto perspective.
Symposium on public health risk of dioxin.
October 19-20, 1983, New York, N.Y.
- 58.- Fingerhut M.A., Halterin W.E., Honchar P.A., Russel W.O.:
Review of exposure and pathology data for seven cases
reported as soft tissue sarcoma among persons occupationally
exposed to dioxin-contaminated herbicides.
Symposium on public health risks of the dioxins.
October 19-20, New York, N.Y.

- 59.- Fingerhut M.A., Halperin W.E., Honchar P.A., Smith A.B., Groth D.H., Russel W.O.: An evaluation of reports of dioxin exposure and soft tissue sarcoma pathology among chemical workers in the United States. Scand. J. Work Environ Health 1984; 10(5): 229-303.
- 60.- Milham S.J.: Herbicides, Occupation and Cancer. Lancet 1; 1464-65, 1982.
- 61.- Zack J.A. and Suskind R.R.: The Mortality Experience of Workers Exposed to Tetrachlorodibenzodioxin in a Trichlorophenol Process Accident. Journal of Occupational Medicine 22: 11-14, 1980.
- 62.- Cook R.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). Journal of Occupational Medicine 22: 530-532, 1980.
- 63.- Cook R.R.: Dioxin, Chloracne and Soft Tissue Sarcoma. Lancet 1: 618-619, 1981.
- 64.- Zack J.A. and Gaffey W.A.: A Mortality Study of Workers Employed at the Monsanto Company Plant in Nitro, West Virginia. Tucker R.E., Young L.A. and Gray A.P., Eds. Human and Environmental Risks of Chlorinated Dioxins and Related Compounds. New York: Plenum, 1983. pp. 575-591.
- 65.- Balarajan R., Acheson E.D.: Soft tissue sarcomas in agriculture and forestry workers. Journal of Epidemiology and Community Health 1984; 38:113-116.
- 66.- May G.: TCDD: A Study of Subjects 10 and 14 years After Exposure. Chemosphere, Vol. 12, No. 4/5, pp 771-778, 1983.
67. Coggon D. Acheson E.D.: Do phenoxy herbicides cause cancer in man? Lancet: 1; 1057-1059; 1982.
68. Gallagher R.P. Threlfall N. J.: Cancer and occupational exposure to chlorophenols. Lancet 11; 48; 1984.
69. Olsen J.H. Möller Jensen O.: Nasal cancer and chlorophenols. Lancet 11; 47-48; 1984.
70. Doll Richard: Director, Imperial Cancer Research Fund, Cancer Epidemiology and Clinical Trials Unit, Green College, Oxford, U.K.; Letter to Hon. M. Justice Philipp Evatt, Australian Royal Commission on the use and effects of chemical agent on Australian personnel in Vietnam. Page... of this volume.