A REVIEW OF THE RECENT 2,4-D EPIDEMIOLOGY STUDIES

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Several recent epidemiology studies have examined cancer risk among farmers and pesticide applicators utilizing phenoxy herbicides. These studies have become known for the place where they were conducted: the Kansas, Nebraska, Iowa & Minnesota, western Washington, Saskatchewan, Sweden and New Zealand studies. The herbicide 2,4-Dichlorophenoxyacetic acid, better known as 2,4-D, has been the focus of much attention. In particular, this occurred with a study that received a considerable amount of publicity in the media in the Fall of 1991. The study subjects were not farmers, herbicide applicators or 2,4-D production workers, but dogs.

The purpose of this paper is to review some of the strengths and limitations of these epidemiology studies. In order to do that, a brief epidemiology primer is in order. Epidemiology is the study of the distribution and cause of disease in populations. Physicians detect disease in individuals; epidemiologists detect cause and effect relationships in populations.

By necessity, epidemiology studies that evaluate the risk of disease are observational rather than experimental. Whereas toxicologists control their subjects' environment, epidemiologists usually only observe. This lack of control may produce different types of bias in the study which can produce misleading results. The results an epidemiologist obtains may be a result of a variety of factors, not necessarily related to the cause of the disease. In general, there are three explanations for the results. Either they were obtained by chance, by biased study methods, or they may be real.

Anytime a balanced coin is flipped, the chance of obtaining heads or tails is 50/50. Epidemiologists often discuss results that are "statistically significant." Simply stated, they are 95 percent sure the result they observed was not due to chance. This still does not mean the result was biologically significant. It is very important that statistical significance is not confused with biological significance. They are not identical.

Potential study biases have been divided into three principal types: selection bias, misclassification bias and confounding bias. Selection bias refers to how the subjects were selected for the study. Epidemiologists typically examine only a sample of people from the population who

could be studied. Hopefully, they have chosen this sample in an unbiased way. Misclassification refers to errors made in diagnosing disease or in deciding who was exposed and by how much. Questions have been raised about possible misclassification of exposures to 2,4-D in the studies published by the National Cancer Institute because those studies relied on interviews with the subjects, or often with their next of kin, to classify who did and did not use herbicides many years ago. Epidemiologists are concerned about confounding bias due to other factors that are also known to cause the disease, but have become mixed-up with the exposure of interest. The classic example is if a researcher was interested in the question whether exposure to a certain substance, let's say alcohol caused lung cancer, the investigator would have to be concerned about the confounder, cigarette smoking.

There are no 'black and white' results in epidemiology, only shades of gray. The intensity of the shade of gray may be a result of selection, misclassification or confounding biases. With such limitations of epidemiology studies, why does anyone put any faith in such an imprecise science? The answer is that epidemiology has provided the answer or at least important leads to such medical mysteries as super-absorbent tampons and toxic-shock syndrome, Reye's syndrome in children as the result of aspirin usage to treat an antecedent viral illness, and AIDS.

Epidemiologists also acknowledge that many of the associations they have observed do not represent causal phenomena. The question is, "what criteria have been developed to distinguish causal from noncausal associations?" Several criteria must be addressed to establish causal associations. The stronger the association, both in terms of the size of the risk estimate and its statistical significance, the less likely that it is due to bias or chance.

Epidemiologists understand that, except in very rare instances, no single epidemiologic study is capable of proving a cause and effect relationship. Instead, epidemiologists need to see the same consistent association in multiple studies of different design performed by different investigators. Epidemiologists prefer a high degree of specificity in the data. For example, known human carcinogens such as vinyl chloride cause a very specific type of cancer rather than a general increase in all cancers.

Temporality refers to the fact that exposure must precede the development of disease in order to be a cause. This seems straightforward but it is not when cancer is considered because of its 20 to 30 year latency period. This is the time from initial genetic damage at the cellular level until the clinical signs appear. Epidemiologists are not always certain that when they ask people about their potential exposures that the exposures preceded the initiation of cancer. Some exposures are not considered initiators of cancer but rather promoters. As is true in toxicology, a causal interpretation is more plausible if a dose-response relationship can be demonstrated.

There should be biological plausibility for the finding. Is the epidemiology finding supported by animal data, or mechanistic studies? In the instance of 2,4-D and non-Hodgkin's lymphoma, the answer is not very well. 2,4-D does not appear not to be mutagenic, immunotoxic or carcinogenic (Program on Risk Analysis and Environmental Health, 1989). There is no increased risk for lymphomas with 2,4-D exposure in the toxicology studies, whether in mice or rats (Hazelton Labs 1986).

Coherence of the evidence refers to how well does this finding fit in with other things known about the natural history of the disease. It turns out that non-Hodgkin's lymphoma, the cancer type which has been associated with 2,4-D in the epidemiologic studies, has been increasing in frequency throughout the Western world during the past two decades. It is also higher among rural residents, and farmers in particular. It is also a disease associated with AIDS due to the immunosuppressive actions of the HIV.

In order to complete this epidemiology primer, two types of epidemiology study designs must be discussed. The first type of study design is called the retrospective cohort design. In this study, the epidemiologist identifies a population of people who had exposure to a specific substance some time ago. The epidemiologist then examines for disease in this population from the time of exposure and follows the cohort of people forward until the present time. Most of the time, epidemiologists will examine the cause of death since death certificates are public information. The advantage of this study design is that exposure information can be relatively accurate. Often, this information can be

estimated based on historic records. A disadvantage is that most diseases, including deaths from cancer, are rare events and thus there may not be many cases of the disease of interest. Another disadvantage is that other information on potential confounders may not be available in the historic records.

The second type of study design is called a case-control study. In this study, epidemiologists select people who have already been diagnosed with a certain type of disease, such as non-Hodgkin's lymphoma. Researchers then ask the study subjects to recall their past history, to such things as herbicides. The case results are then compared to the frequency of herbicide usage of a group of controls. The advantage of case-control studies is that many cases of a single disease can be studied at once. The disadvantages have to do with potential selection bias of the cases and controls, misclassification bias (how well do people recall their past exposures) and confounding bias (could other factors distort the association under study).

As the epidemiology studies are reviewed, it is important to remember the potential for selection, misclassification and confounding biases and ask yourself whether they have been fully met to your satisfaction.

The epidemiology study that, until the dog study, received the greatest attention was done in Kansas by the National Cancer Institute (Hoar; et al, 1986a). It was reported in 1986 in the *Journal of the American Medical Association*. They did this study to explore some of the work done in Sweden by Hardell (1979) who in the late 1970's reported associations between a variety of rare cancers, principally soft-tissue sarcomas and malignant lymphomas, and short-term, low level exposure to the phenoxy herbicides and chlorophenols. Most epidemiologists agree that the methods used in the Kansas study were a significant improvement over Hardell's research.

The Kansas study was a population-based case-control study of 133 soft-tissue sarcomas cases, 121 Hodgkin's Disease cases, and 170 non-Hodgkin's lymphoma cases. Controls came from the general population. Kansas was targeted for the study because it is a major site of wheat production and herbicides are commonly used to control weeds in wheat. Ironically, they found no association between the three categories of cancer and the type of crop produced. They then went on and explored the additional data that had been gathered.

Hoar et al could not find any associations between herbicide use and either soft-tissue sarcoma or Hodgkin's disease. This is important because the work from Sweden that prompted the Kansas study had reported large risks for all three categories of cancer at comparable levels of exposure. In that sense the Kansas study conflicted with the Swedish work. The authors then focused their efforts on non-Hodgkin's lymphoma.

The trend for frequency of herbicide use as measured by days per year was statistically significant (Table 1). This was based on an odds ratio that increased from a baseline of 1.00 among farmers reporting never having used herbicides to a value of 6.0 among farmers reporting 21 or more days of herbicide use per year. The odds ratio can be considered the "risk" of exposure among the cases compared to the controls. So, in the category of farmers reporting 21 or more days of herbicide use per year, the cases were 6 times more likely than the controls to be in this category. Statistical significance is considered when the null value of the odds ratio (O.R.=1.0) is not included within the confidence interval. In this example, the confidence interval ranges from 1.9 to 19.5. Thus, the null value of 1.0 (as seen with the reference comparison of non-farmers) is not included in the range and therefore the 6.0 can be considered statistically significant. However, note that of the 133 non-Hodgkin's cases who were farmers, only 7 were in the $\geq$ 21 time per year category. Based on the confidence interval, epidemiologists recognize this point estimate is highly unstable as the confidence interval is quite wide due to the few number of subjects in this category. Misclassification of exposure just among a couple of cases would have a dramatic impact on this result.

To summarize the consistent findings in this report, they were:

1) Increased trend with frequency of use.
2) Increased risk with time since first exposure.
3) Higher risk associated with mixing and application.
4) Higher risk associated with using backpack or handheld sprayers.
5) Protective equipment use eliminated excess risk.

However, not all of the findings supported a herbicide non-Hodgkin's lymphoma association. The inconsistencies included:

1) No association with the number of years worked on a farm.
2) No association with the number of acres farmed.
3) No association with the type of crop grown.
4) No association with duration of use.
5) No association with specific type or grade of non-Hodgkin's lymphoma.
6) Higher risk associated with pre-1946 use.

Please note that herbicides in general are discussed in the Kansas study rather than to 2,4-D specifically. The authors did not collect sufficient data to be able to evaluate frequency, duration, latency or other factors in relation to *specific* herbicides. Because 2,4-D was the herbicide most often reported, the authors assumed 2,4-D was synonymous with herbicide use. This is not necessarily correct. The authors, to their credit, published a correction (Hoar et al, 1986b) to their paper acknowledging that their table misled readers to believe their exposure information referred to 2,4-D usage, when in fact it referred to herbicide usage, of which 2,4-D was often used, but not the only usage. In fact, the authors found elevated risks associated with nearly every type of herbicide reported, including risk estimates for the triazines, amides and non-specific herbicides that were all statistically significant and greater than that for 2,4-D and the other phenoxys.

Herbicide and agricultural experts who have examined the data from the Kansas study have noted several peculiarities that suggest a cautious interpretation. For instance, more than 70% of the farmers who grew wheat, corn, sorghum or pasture reported never having used herbicides. Historical farm practices in Kansas would suggest that this figure is far too high and that perhaps there was a general underreporting of herbicide use by the controls in the study.

The highest odds ratio was found for farmers who reported 21 or more days of herbicide use per year. It would be very unusual for a farmer to spray herbicides on crops for this many days in a year; weather conditions, competing tasks, cost of herbicides, and the timing of application for maximum effectiveness do not allow for more frequent spraying.

About the same time that the NCI Kansas study was published, investigators in New Zealand published their results from a case-control study of non-Hodgkin's lymphoma (Pearce et al, 1986, 1989). Earlier case-control studies of soft-tissue sarcoma by this group failed to find an association with phenoxy herbicide use. Likewise, their study of non-Hodgkin's lymphoma found no association with the use of agricultural sprays containing 2,4-D or 2,4,5-T. No association was observed for frequency of herbicide use (Table 3).

Investigators conducted a case-control study of soft-tissue sarcoma and non-Hodgkin's lymphoma in western Washington state with special focus on phenoxy herbicides and chlorophenols (Woods et al., 1987). The findings by Woods et al provide weak evidence of an association between phenoxy herbicides and non-Hodgkin's lymphoma (Table 4). Several subgroups did display an increased risk for non-Hodgkin's lymphoma. For example, among persons who worked regularly in jobs involving the spraying of weeds in forests had an odds ratio of 4.8 (95% CI 1.2-19.4); however, their uses was of herbicides involved 2,4-D, 2,4,5-T and other chemicals, as well. Risks of similar magnitude were not observed for other herbicide spraying activities or in herbicide formulation.

The Iowa-Minnesota study examined leukemia and non-Hodgkin's lymphoma in relation to a number of agricultural practices, including herbicide use (Blair et al, 1989; Brown et al, 1990).

Although 2,4-D was the most common reported herbicide used, no significant associations were reported for leukemia and non-Hodgkin's lymphoma. To be specific, an odds ratio of 1.2 was reported which was not statistically significant. Unfortunately the investigators did not collect data relating to the frequency of herbicide use. This, of course, was the variable that showed the strongest association with non-Hodgkin's lymphoma in the Kansas study. The authors have re-interviewed a sample of subjects from the Iowa portion of the study in an effort to obtain this information. The results have been recently submitted for publication and should be made available to the public later this year.

The Nebraska study (Zahm et al., 1990) was a case-control study of non-Hodgkin's lymphoma conducted in 66 counties of eastern Nebraska. It was conducted by the same NCI principal investigator as the Kansas study. A total of 201 cases were interviewed and compared to 725 controls from the same geographic area. Information was obtained by telephone interview, using a 33 page questionnaire. For deceased cases, the questionnaire was administered to a next of kin.

There was an association between the number of days per year spent using or mixing 2,4-D (Table 5). The three-fold risk of non-Hodgkin's lymphoma among men who used 2,4-D for 21 or more days per year is based on just 3 cases and 4 controls providing, again, a very unstable risk estimate as evidence by the very wide 95% confidence interval.

However, there was no association with years of 2,4-D use (Table 6). Also, there was no association with year of first use of 2,4-D. Men, who wore for more than one day the clothes worn while using 2,4-D, had a significantly elevated risk as seen with an odds ratio of 4.7 (95% CI 1.1-21.5). When the investigators adjusted for the use of organophosphates, the risks for 2,4-D and non-Hodgkin's lymphoma were greatly reduced and the trend with days of use per year was not significant. After such an adjustment, the odds ratio associated with 21 or more days per year use was 1.8 compared to 3.3 without adjustment.

Another disturbing finding regarding this paper was the information provided that risks varied depending on who was interviewed. Among the proxy interviews, that is next of kin who were interviewed about the subjects past usage of herbicides, the risks were the same for all categories of days per year usage, whereas for the self-respondents, the risk are much less (Table 7). This raises the question of differential recall bias by subject type. In other words, there could be substantial misclassification bias with regards to 2,4-D usage which could distort any risk estimate. If this bias was different between cases and controls, the risk estimates could be artificially inflated. If the bias is comparable between cases and controls (and their surrogates), the bias could be artificially decreased. Fortunately, an on-going study from the University of Minnesota is examining these methodology issues concerning herbicide usage.

A cohort of 20,245 Swedish pesticide applicators were studied to assess whether soft-tissue sarcomas, Hodgkin's Disease or non-Hodgkin's lymphoma were associated with exposure to phenoxy acid herbicides (Wiklund, 1987). In Sweden, MCPA was used much more frequently during this period than either 2,4-D or 2,4,5-T. No increased risk was observed for these three diseases (Table 8). The major limitation of this study was the short follow-up period and inadequate exposure data.

A cohort mortality study of 70,000 Canadian male farm operators in Saskatchewan who were initially identified on a 1971 census of agriculture (Wigle, 1990). Their mortality experience was followed from 1971-1985. Overall there were 103 deaths from non-Hodgkin's lymphoma versus 112.1 expected.

The investigators observed an increased risk of non-Hodgkin's lymphoma and acres sprayed in 1970 with herbicides, as well as with dollars spent on fuel and oil for farm purposes in 1970 (Table 9). Interestingly, the risk seen for farmers who sprayed 250 or more acres was an odds ratio of 2.14 (95% CI 1.05-4.24) for farms less than 1000 acres in size but for farmers farms greater than 1000 acres a negative risk was observed as the odds ratio was 0.60 (95% CI 0.22-1.68). The investigators suggested that the larger the farm, the more likely the herbicide spraying was done on a contract basis.

A cohort study published in 1991 examined the mortality experience of 18,910 workers whose exposures were either related to the production or spraying of chlorophenoxy herbicides, as well as chlorophenol exposure (Saracci et al., 1991). Exposure to specific chlorophenoxy herbicides could not

be determined. A nonsignificant 2 fold increase in soft-tissue sarcoma was observed but this was based on just 4 cases. Of course, no risk for soft-tissue sarcoma and herbicides was observed in the Kansas study. In this cohort study, there was no evidence for an increased risk of non-Hodgkin's lymphoma. Eleven deaths were observed versus 11.64 expected. For those whose exposure was only with the phenoxy herbicides, there were 7 deaths versus 8.96 expected. No dose response was observed for duration of exposure (Table 10). Again, it bears repeating that these results were not specific to 2,4-D but to chlorophenoxy herbicides and chlorophenol exposure, in general.

The study that has received the most attention lately is the NCI canine malignant lymphoma case-control study (Hayes et al., 1991). It received an inordinate amount of publicity.

This was a case-control study conducted at three veterinary colleges (University of Minnesota located in Minneapolis, Purdue University located in West Lafayette, Indiana; and Colorado State University located at Fort Collins). The lead investigator, Dr. Howard Hayes, was from the National Cancer Institute. Cases were 491 dogs with pathologically-confirmed malignant lymphomas. This histology can be considered comparable to non-Hodgkin's lymphoma in humans. There were two sets of controls: 479 control dogs were dogs seen at these veterinary clinics and diagnosed with other tumors; the other set of controls were 466 dogs hospitalized at the veterinary hospitals for non-cancer reasons. The owners of these dogs were contacted anywhere from several months to more than 4 years after the dog was seen. The owners were asked to either complete a selfadministered postal questionnaire or a telephone interview which examined a variety of issues including fertilizer, insecticide and herbicide potential exposure, the environment of the dog (e.g., indoor, outdoor), dog food consumed, potential exposure to a variety of substances found in the home (e.g., woodworking materials, pottery, house paints) and human illness in the home.

There was good reason to use two sets of controls in this study because there was a chance for differential recall bias. It is not uncommon for people diagnosed with cancer to recall during the course of their disease, their life history including potential exposures to a variety of substances. Thus, these people are inadvertently 'primed' to recall aspects of their life, whereas controls who do not have cancer are not. In this study, owners of dogs with cancer may be more likely to recall the history of the dog compared to owners of dogs without cancer. Therefore, two sets of controls were chosen. Risk estimates could then be calculated for each control group separately. If the risks are comparable between the two control groups, then both sets of controls can be combined to form one control group since there is no evidence of a greater recall bias in one group or the other.

However, the investigators chose not to report the data separately. The investigators explanation was that they found the two control groups comparable demographically and so they chose not to analyze them separately. Unfortunately, this explanation has nothing to do with recall bias which is the reason why they had the two control groups to start. This has raised a great deal of suspicion among the epidemiology community regarding the findings from this NCI study.

Nevertheless, the following data are from the published paper with both control groups combined. When all dogs who did not have access to their owner's yard were classified as unexposed, the odds ratio for owner application of 2,4-D and/or the employment of commercial lawn care service was 1.3 (95% CI 1.04-1.67). The authors overstated their data by saying that the 1.3 combined risk estimate was a 'modest association.' Most epidemiologists would regard any risk estimate under 1.5 as a weak association, at best.

An increasing trend of lymphoma risk was reported with the annual number of owner applications of 2,4-D (Table 11). However, there was no increasing trend reported with commercial application (Table 12). There was also no increased risk of lymphoma with the number of years the owner applied 2,4-D. Certain breeds of dog are at greater risk for malignant lymphoma. However, the largest risk for 2,4-D and malignant lymphoma came from those breeds at lowest risk.

Although the study investigators wrote that testing for a 2,4-D association was a major hypothesis going into the study, the study questionnaire was not specific for any given herbicide or insecticide. However, it was specific for dog foods consumed!

Other very disturbing methodologic aspects to this study included the fact that about half the answers came from a self-reported written response to a postal questionnaire and the other half came from telephone interviews. These are two different mechanisms for obtaining data. Again, no risk

estimates were provided, by data collection method. There is also the disturbing aspect that the increased risk estimate occurred only among owners who applied 2,4-D herbicides to their lawns 4 or more times per year. It is doubtful that this frequency occurs in these northern climates.

As mentioned previously, biological plausibility is an important tenet for determining causation. A major weakness of the study was the lack of estimating exposure data. A number of studies of persons exposed to 2,4-D such as aerial applicators, forestry workers, lawn care specialists and casual observers have shown the greatest human exposure is well below the "no observed effect level" in laboratory animals (Frank et al., 1985; Yeary 1986; Grover et al., 1986). The most important route of exposure is through the skin. However, studies indicate that only six percent of the 2,4-D that contacts skin is absorbed into the body. The investigators argued that exposure may occur by the fastidious grooming habits of dogs through the licking of the paws, thereby ingesting any substances it has walked in while on the lawn. However, dogs do not routinely lick their paws like cats. Most dogs who lick or chew their paws do so because of allergy-related problems. Observe your own dog, should you have one. Where dogs routinely clean themselves is in their groin area, an area that would be highly unlikely to have contact with the lawn.

The authors wrote that there were no other significant risks to the variety of questions asked concerning insecticides, dog food, or other indoor exposures to chemicals. However, there were no questions about the dog's own medical history and, in particular, about viral-related diseases. This is curious since malignant lymphoma in cattle, cats, monkeys and mice has been shown to be caused by viruses.

None of the negative data were supplied in the published paper. That is, there is no detailed information about what was not associated with canine malignant lymphoma. This lack of reporting negative data is often referred to as "publication bias." Only positive findings get reported. Negative results often go unpublished because of either lack of interest by the study investigators or by the editor of the journal for which the investigators submitted their manuscript for publication.

Finally, just a comment about the publicity this report received. Despite the reports methodologic weaknesses, it grabbed the public's attention. The principal investigator was quoted recently as saying (Late Breaking News, 1991), "I was just on the phone trying to convince a woman with a 15-year old dog that developed lymphoma that the fact her landlord used pesticides did not necessarily make an accomplice in her dog's death."

Given the epidemiology and toxicology data that exists today, is there any scientific consensus? A group of prestigious scientists from academic, government and industry met in the Fall of 1989 at the request of the Harvard School of Public Health's Program on Risk Analysis and Environmental Health (1989). This workshop was sponsored by the National Association of Wheat Growers Foundation through a grant by the Industry Task Force on 2,4-D research data. The panel of scientists was called to consider the weight of the evidence on a possible link between the use of 2,4-D and cancer. Studies that were not examined at that time (because they were published after 1989) include the Saskatchewan study, the IARC study and the NCI dog study. However, it is doubtful that the results of these studies would change the panel's consensus.

As for the toxicology data concerning 2,4-D, the panel concluded, "Considered collectively, the toxicological data on 2,4-D do not provide a strong basis for predicting that 2,4-D is carcinogenic to humans." To quote this panel's final report, "In assessing all of the evidence on 2,4-D workshop participants were not convinced that a cause-effect relationship between exposure to 2,4-D and human cancer exists."

About the same time period, similar opinions were stated by Agriculture Canada (Ag. Canada, 1989). "Based on recent studies and findings in this report, Agriculture Canada believes that the safety associated with 2,4-D remains acceptable. Because it is not possible to provide infallible assurances of infinite safety, Agriculture Canada's position is one of continued but cautious use."

What about any future research regarding 2,4-D? The Iowa reanalysis of the data as it relates to non-Hodgkin's lymphoma is completed but not yet published. Therefore, this information remains with NCI. NCI is also conducting two large cohort studies: one with employees of the Kansas Noxious Weed Department and the other with ChemLawn employees. Case-control studies are in the planning stage in Saskatchewan and Ontario. Finally, the 2,4-D Task Force has sponsored a methodologic

research study with investigators at the University of Minnesota to examine the validity and reliability of pesticide recall among farmers and their 'next of kin.' This methodologic study will be completed by late summer. A somewhat similar methodologic study was published by NCI last year (Brown et al., 1991) and they showed minimum differences between next of kin and subject recall. However, the study was quite small in numbers. The University of Minnesota study will be several times larger and also investigates validity as well as reliability issues.

The question that must be addressed at this time is, "What should I do at the present time, while waiting for any additional research to be reported, if indeed the weight of the evidence suggesting an association between 2,4-D and non-Hodgkin's lymphoma is not strong, but nevertheless cannot be dismissed out-of-hand?" The answer is to strictly follow the label directions.

1) Avoid breathing vapors or mists;
2) Avoid contact with skin, eyes or clothing;
3) Wash thoroughly after handling and before eating or smoking;
4) Remove contaminated clothing and wash before re-use;
5) Do not apply product in such a manner that direct or via drift exposure might occur;
6) Wash surfaces of equipment following use to avoid secondary contamination; and
7) Vacate treated areas of unprotected persons and pets.

Table 1

Non-Hodgkin's Lymphoma in Relation to Occupation and Frequency of Herbicide Use

	Cases	Controls	Odds Ratio	95% CI
Non-farmers	37	286	1.0	
Farmers	133	662	1.4	0.9-2.1
Frequency of Herbicide Use days/year				
0	94	497	1.3	0.8-2.0
1-5	9	102	1.4	0.7-2.6
6-10	6	29	1.6	0.5-4.3
11-20	5	13	2.6	0.8-8.8
≥21	7	12	6.0	1.9-19.5

Adapted from Table 1 of Hoar et al (1986)

Table 2

Non-Hodgkin's Lymphoma in Relation to Potential Exposure Group

Herbicide group	Odds Ratio	95% CI
Never farmed	1.0	-----
Ever used		
Phenoxyacetic acids	2.2	1.2-4.1
Triazines	2.5	1.2-5.4
Amides	2.9	1.1-7.6
Benzoics	4.0	0.1-62.6
Carbamates	5.6	0.6-45.9
Trifluralin	12.5	1.6-116.1
Uracils	1.3	0.7-2.5
Nonspecific	5.6	1.9-17.2

Adapted from table 2, Hoar et al (*JAMA*, 1986)

Table 3

New Zealand Non-Hodgkin's Lymphoma Case-Control Study: Findings by Frequency of Phenoxy Herbicide Use

Frequency of Herbicide Use days/year	Cases	Controls	Odds Ratio	95% CI
0	139	266	1.0	
1-4	20	40	0.9	0.5-1.6
5-9	8	11	1.2	0.4-3.3
40-19	4	3	2.2	0.4-12.6
>20	5	7	1.1	0.3-4.1

Adapted from Pearce (1989)

Table 4

Risk of developing non-Hodgkins lymphoma in relation to phenoxyherbicide exposure in western Washington State.

Exposure category	STS		NHL	
	Odds ratio	95% CI	Odds ratio	95% CI
None	1.0		1.0	
Low	0.56	0.3-1.1	0.90	0.6-1.3
Medium	0.99	0.6-1.7	0.95	0.7-1.3
High	0.89	0.4-1.9	1.24	0.8-1.9

Adapted from Woods et al (1987)

Table 5

Number of White Men with Non-Hodgkin's Lymphoma, Number of Controls, and Odds Ratios by Characteristics of Exposure to 2,4-Dichlorophenoxyacetic Acid (2,4-D)

Use of 2,4-D	Cases	Controls	Odds Ratio	95%CI
Never lived or worked on farm	54	184	1.0	
Days/year mixing or applying 2,4-D:				
1-5	16	44	1.2	0.6-2.4
6-20	12	25	1.6	0.7-3.6
21+	3	4	3.3	0.5-22.1
Unknown days/year	12	25	--	

Test for trend, p = 0.051 Adapted from Zahn et al. (1990)

Table 6

Number of White Men with Non-Hodgkin's Lymphoma, Number of Controls, and Odds Ratios by Characteristics of Exposure to 2,4-Dichlorophenoxyacetic Acid (2,4-D)

Use of 2,4-D	Cases	Controls	Odds Ratio	95%CI
Years 2,4-D used on farm:				
1-5	3	12	0.9	0.2-3.6
6-15	11	15	2.8	1.1-7.1
16-20	3	18	0.6	0.1-2.1
21+	13	33	1.3	0.6-2.7
Unknown years	15	29	--	

Test for trend, p= 0.274 Adapted from Zahn et al. (1990)

Table 7

Number of White Men with Non-Hodgkin's Lymphoma, Number of Controls, and Odds Ratios and 95% Confidence Intervals by 2,4-D Exposure Characteristics and Respondent Type

	Self-Respondents				Proxy Respondents			
	Case	Control	O.R.	95% CI	Case	Control	O.R.	95% CI
Never Farmed	38	88	1.0	—	16	96	1.0	—
Farmers: Days per year mixed or handled 2,4-D								
1-5	13	33	1.0	0.4-2.3	3	112.2		0.4-11.7
6-20	9	16	1.6	0.6-4.4	3	9	2.2	0.3-13.0
21+	2	3	1.4	0.2-13.7	1	1	2.4	0.2-103.2

Adapted from Zahn et al (1990)

Table 8

Observed and Expected Cancers Among Swedish Licensed Pesticide Applicators

Cancer Type	Observed	Expected	Rate Ratio	95% CI
Soft-Tissue Sarcoma	7	7.7	0.9	0.4-1.9
Hodgkin's Disease	11	9.2	1.2	0.6-2.2
Non-Hodgkin's Lymphoma	21	21.8	1.0	0.6-1.5

Adapted form Wiklund et al (1988)

Table 9

Dose-Response Analysis of 1970-1971 Farming Practices and Non-Hodgkin's Lymphomas, for Saskatchewan Farmers aged 35 or More, 1971-1985

Farming practice	Observed deaths	RR*	95% CI Lower limit	95% CI Upper limit
Acres sprayed with herbicides,1970				
0	46	1.0		
1-99	14	1.11	0.62	2.00
100-249	28	1.47	0.94	2.41
250+	15	1.34	0.74	2.38
Dollars spent on fuel and oil for farm purposes 1970				
<360	22	1.0		
360-599	23	1.18	0.66	2.13
600-899	27	1.45	0.81	2.55
900+	31	1.83	1.03	3.25

Adapted from Wigle et al (1990)

Table 10

Mortality for Non-Hodgkin's Lymphoma, Both Sexes, IARC Study

	Non-Hodgkin's Lymphoma			
	Obs	Exp	SMR	95% CI
Duration of exposure (yr)				
<1	6	3.35	1.79	0.66-3.90
1-9	3	5.36	0.56	0.12-1.64
10-19	1	1.81	0.55	0.01-3.08
20+	1	1.02	0.98	0.03-5.46

Adapted from Saracci et al (1991)

Table 11

Odds Ratios of Canine Malignant Lymphoma by Exposure

Characteristic	No. of cases	No. of controls	Odds ratio	95% CI
0 or dog never allowed in yard	300	641	1.0	
1	2034		1.3	0.72-2.50
2	2847		2.3	0.74-2.13
3	1117		1.3	0.57-3.13
≥4	1717		2.0	0.92-4.15

Test for trend p <.02

Adapted from Hayes et al (1991)

Table 12

Odds Ratios of Canine Malignant Lymphoma by Exposure

Characteristic	No. of cases	No. of controls	Odds ratio	95% CI
No. of commercial lawn chemical treatments/y				
0	300	641	1.0	
1	16	25	1.40	0.70-2.84
2	20	25	1.50	0.75-2.86
3	19	33	1.10	0.60-2.14
≥4	76	122	1.30	0.95-1.87

Test for trend: not significant

Adapted from Hayes et al (1991)

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