REVIEW

Herbicides and Cancer

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Herbicides are a heterogeneous class of chemicals used in agriculture, forestry, and urban settings to kill weeds, shrubs, and broad-leaved trees. The role of herbicides in the etiology of cancer is controversial. Potential studies for review were identified through a MEDLINE[1] search and from a check of references in related review articles. This review of the literature shows reasonable evidence suggesting that occupational exposure to phenoxy herbicides results in increased risk of developing non-Hodgkin's lymphoma. Several studies have noted large increases in risk of soft-tissue sarcomas with phenoxy herbicide exposure. In contrast, others have failed to observe increased risks, and evidence of an exposure-risk relationship is lacking. Although there have been too few appropriate studies for adequate assessment of risk of cancer at other sites, some findings have linked herbicide exposure with cancers of the colon, lung, nose, prostate, and ovary as well as to leukemia and multiple myeloma. Future studies must better identify and quantify the nature of herbicide exposures. In the interim, it seems only prudent to monitor and promote safety practices among persons occupationally exposed to phenoxy herbicides, particularly farmers and professional sprayers. [J Natl Cancer Inst **84:1866–1874, 19921**

The role of herbicides in the etiology of cancer has been the subject of controversy for the last decade. The well-documented increased risk of certain types of cancer among farmers **(I),** coupled with the widespread use *of* herbicides, has raised concerns about the long-term safety of herbicide use. This interest has resulted in a number of recent review articles dealing with herbicides and long-term health effects *(2,3).*

Herbicides comprise heterogeneous classes of chemicals used in agriculture, forestry, and urban settings to control weeds, shrubs, and broad-leaved trees. In addition to phenoxy herbicides, they include triazines, amides, benzoics, carbamates, trifluralin, and uracils. Most research of the effects of herbicides on human health has focused on phenoxy herbicides, primarily 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and the chemically related chlorophenols. Some commercial preparations of both phenoxy herbicides and chlorophenols have been contaminated with dioxins and furans *(4).*

Although non-Hodgkin's lymphoma and soft-tissue sarcomas have been studied the most, possible links with herbicide exposure have been investigated for many other types of cancer, including Hodgkin's disease, multiple myeloma, leukemia, and cancers of the brain, lung, ovary, testis, and prostate.

Methods

Study Criteria

For this review, studies were identified through a MEDLINE[1] search and from a check of references in related review articles. Our inclusion criteria required that a study report individual herbicide exposures in relation to risk of any cancer. Case reports and studies in which individual herbicide exposures were not estimated were excluded.

For a number of reasons, studies of civilian and military populations who may have been exposed to herbicides during the Vietnam war were not examined. Most of these studies have not been based on individual exposure data because accurate estimation of doses to which military personnel were exposed has proven problematic *(5).* In addition, it is only now that the likely minimum latent period for cancer has elapsed. Also, the nature of herbicide exposure Vietnam veterans received was different from that of herbicide applicators and employees manufacturing

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'Ed. note: MEDLINE is the National Library of Medicine's bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, and the preclinical sciences.

herbicides (3). Vietnamese studies on this subject were excluded because they have not appeared in peer-reviewed Western journals and hence have been somewhat inaccessible (6).

Epidemiologic evidence of health effects of herbicide exposure is available from case-control studies or cohort studies of workers employed in either the manufacture or spraying of herbicides. The designs of the studies reviewed are summarized in Tables 1 and 2. Tables 3 and 4 show the estimates of risk of cancer, by cancer site; these estimates were obtained from the case–control and cohort studies, respectively. Table 5 summarizes the findings from these studies.

Epidemiologic Evidence

Gastrointestinal Cancer

Some reports have linked herbicide exposure with colon cancer. A case–control study by Hardell (*10*) noted an odds

Table 1. Design of case-control studies of herbicide exposure and selected cancers.

Study	Ref. No.	Cancer	Location of study	Years	No. of cases	No. of controls	Source of controls	Herbicide exposure
Hardell and Sandstrom	(7)	STS	Sweden	1970-1977	52	205	NPR, DC	Phenoxys, chlorophenols
Eriksson et al.	(8)	STS	Sweden	1974-1978	110	220	NPR, DC	Phenoxys, chlorophenols
Hardell et al.	(9)	NHL. HD	Sweden	1974-1978	169	338	NPR, DC	2,4,5-T, 2.4-D, MCPA
Hardell	(10)	Colon	Sweden	1978-1979	154	541	NPR. DC	Phenoxys, chlorophenols
Hardell et al.	(11)	Liver	Sweden	1974-1981	98	200	NPR	Phenoxys
Donna et al.	(12)	Ovary	Italy	1974-1980	60	127	CR	Herbicides
Smith et al.	(13)	STS	New Zealand	1976-1980	82	92	CR	Primarily 2,4,5-T
Hoar et al.	(14)	Colon	Kansas	1976-1982	57	948	RDD. Medicare, DC	Phenoxys, uracils
Smith and Pearce	(15)	STS	New Zealand	1976-1980	51	315	CR	Primarily 2,4,5-T
Hoar et al.	(16)	STS, HD, NHL	Kansas	1976-1982	424	948	RDD, Medicare, DC	Primarily 2.4-D
Pearce et al.	(17)	NHL	New Zealand	1977-1981	83	396	CR, electoral rolls	Primarily 2,4,5-T
Pearce et al.	(18)	MM	New Zealand	1977-1981	76	315	CR	Primarily 2,4,5-T
Pearce et al.	(19)	NHL	New Zealand	1977-1981	183	338	CR	Primarily 2,4,5-T
Woods et al.	(20)	STS, NHL	Washington	1981-1984	704	694	RDD, Medicare, DC	Phenoxys, chlorophenols
Checkoway et al.	(21)	Prostate	North Carolina	1984-1985	40	64	Hospital	Herbicides
Vineis et al.	(22)	STS	Italy	1981-1983	68	168	Electoral rolls	Phenoxys
Hardell and Eriksson	(23)	STS	Sweden	1978-1983	54	321	CR, NPR	Phenoxys, chlorophenols
Musicco et al.	(24)	Brain	Italy	1983-1984	240	742	Hospital	Herbicides
Donna et al.	(25)	Ovary	Italy	1980-1985	65	137	Electoral rolls	Triazines
[illegible]son et al.	(26)	NHL, HD	Sweden	1964-1986	160	275	NPR	Phenoxys
[illegible]tuji-Garin et al.	(27)	Leukemia	France	1984-1988	185	513	Hospital	Herbicides
McDuffie et al.	(28)	Lung	Saskatchewan	1983-1986	273	187	Community health plan	Phenoxys
Zahm et al.	(29)	NHL	Nebraska	1983-1986	201	725	RDD, Medicare, DC	2,4-D
Hardell et al.	(30)	Nasal	Sweden	1970-1979	71	541	NPR, DC	Phenoxys, chlorophenols
Brown et al.	(31)	Leukemia	Iowa, Minnesota	1981-1984	578	1245	RDD. Medicare, DC	2,4-D, 2,4,5-T
Eriksson et al.	(32)	STS	Sweden	1978-1986	237	237	NPR	Phenoxys, chlorophenols
Cantor et al.	(33)	NHL	Iowa. Minnesota	1980-1983	622	1245	RDD, Medicare, DC	Phenoxys. triazines

*STS = soft-tissue sarcoma, NHL = non-Hodgkin's lymphoma, HD = Hodgkin's disease, MM = multiple myeloma, NPR = national population registry, DC = death certificates or death registry, CR = cancer registry, RDD = random digit dialing.

Table 2. Design of cohort studies of herbicide exposure and selected cancers

Study	Ref. No.	Location of study	Sex	Occupation	Years	No. of exposed workers	Exposure based on	Herbicide exposure
Axelson et al.	(34)	Sweden	Male	Railroad worker	1957-1978	348	Job title	Phenoxys. amitrol
Riihimäki et al.	(35)	Finland	Male	Applicator	1972-1980	1971	Job title	2.4-D, 2,4,5-T
Zack and Gaffey	(36)	West Virginia	Male	Manufacturing	1955-1977	884	Job title	2,4,5-T
Lynge	(37)	Denmark	Male	Manufacturing	1947-1982	3390	Job title	Primarily MCPA
Lynge	(37)	Denmark	Female	Manufacturing	1947-1982	1069	Job title	Primarily MCPA
Cook et al.	(38)	Michigan	Male	Manufacturing	1940-1979	2189	Job title	2,4,5-T
Coggon et al.	(39)	Britain	Male	Manufacturing	1947-1983	5784	Job title	Primarily MCPA
Ott et al.	(40)	Michigan	Male	Manufacturing	1940-1982	2187	Job title	2,4,5-T, chlorophenols
Bond et al.	(41)	Michigan	Male	Manufacturing	1945-1982	878	Job title	2,4-D
Wigle et al.	(42)	Canada	Male	Farmer	1971-1985	34637	Census records	Primarily phenoxys
Morrison et al.	(43)	Canada	Male	Farmer	1971-1987	76981	Census records	Primarily phenoxys
Green	(44)	Canada	Male	Forestry worker	1950-1982	1222	Job title	2,4-D, 2,4,5-T
Coggon et al.	(45)	Britain	Male	Manufacturing	1963-1987	2239	Job title	Phenoxys, chlorophenols
Morrison et al.	(46)	Canada	Male	Farmer	1971-1987	76981	Census records	Primarily phenoxys
[illegible]racci et al.*	(47)	10 nations	Male, Female	Manufacturing, sprayer	Various	18910	Various	Phenoxys, chlorophenols
[illegible]ngerhut et al.	(48)	USA	Male	Manufacturing	1942-1987	5172	Job title	2,4,5-T

*Includes results for some other listed cohorts (references 35,37,42,43), but for different follow-up periods.

Table 4. Cancer relative risk estimates from cohort studies of herbicide exposure by cancer type (No. of cases)[a]

Cancer	Axelson et al.[b,c] (*34*)	Riihimäki et al.[b,c] (*35*)	Zack and Gaffey[b] (*36*)	Lynge[b] (*37*)	Lynge[d] (*37*)	Cook et al.[b] (*38*)	Coggon et al.[b,e] (*39*)	Ott et al.[b] (*40*)	Bond et al.[b] (*41*)	Wigle et al.[b] (*42*)	Morrison et al.[b] (*43,46*)	Green[b] (*44*)	Coggon et al.[b] (*45*)	Saracci et al.[f] (*47*)	Fingerhut et al.[b,g] (*48*)
Stomach	6.1[i] (2)	1.08[h] (4)	0.61 (1)	1.36 (2)	0.00 (0)	1.56 (5)	0.91 (26)	1.58 (6)	0.0 (0)	NA	NA	1.9 (2)	NA	0.89 (40)	1.38 (4)
Colon	0.0 (0)	0.0 (0)	NA	NA	N/A	NA	1.02 (19)	1.41 (10)	2.12 (4)	NA	NA	NA (2)	NA	1.13 (41)	1.78 (13)
Rectum	0.0 (0)	0.0 (0)	NA	2.68 (4)	0.00 (0)	NA	0.59 (8)	0.43 (1)	1.67 (1)	NA	NA	0.0 (0)	NA	1.10 (24)	1.15 (2)
Liver	0.0 (0)	0.0 (0)	0.0 (0)	NA	N/A	NA (1)	NA	0.53 (1)	0.0 (0)	NA	NA	0.0 (0)	NA	0.44 (4)	0.59 (1)
Nasal	0.0 (0)	0.0 (0)	0.0 (0)	NA	N/A	NA	4.93[i] (3)	NA	0.0 (0)	NA	NA	0.0 (0)	NA	2.91 (3)	0.0 (0)
Lung	0.0 (0)	1.08 (12)	1.41 (14)	2.06[i] (11)	1.28 (1)	0.82 (18)	1.15 (117)	0.82 (23)	1.04 (8)	NA	NA	1.09 (5)	1.34 (19)	1.02 (173)	1.39 (40)
Connective	0.0 (0)	0.0 (0)	NA	3.33[j] (1)	0.00 (0)	NA (1)	0.96 (1)	0.0 (0)	0.0 (0)	NA	NA	0.0 (0)	0.0 (0)	2.01 (4)	9.22[i] (3)
Breast[d]	—	—	—	—	0.53 (2)	—	—	—	—	—	—	—	—	0.30 (1)	—
Cervix	—	—	—	—	2.75 (5)	—	—	—	—	—	—	—	—	—	—
Ovary	—	—	—	—	1.02 (1)	—	—	—	—	—	—	—	—	—	—
Prostate	NA (1)	1.82 (2)	NA	0.55 (1)	—	1.88 (6)	1.32 (18)	1.90 (8)	1.04 (1)	NA	1.19[k] (127)	NA (1)	NA	1.11 (30)	1.52 (9)
Testis	0.0 (0)	0.0 (0)	NA	NA	—	0.0 (0)	2.23 (4)	0.0 (0)	4.62 (1)	NA	NA	0.0 (0)	NA	2.25 (7)	0.0 (0)
Bladder	0.0 (0)	0.0 (0)	9.89[i] (9)	NA	NA	NA	0.85 (8)	NA	0.0 (0)	NA	NA	0.0 (0)	NA	0.80 (13)	1.86 (4)
Brain	NA (1)	0.0 (0)	NA	NA	NA	NA	1.24 (11)	0.36 (1)	0.0 (0)	NA	0.80[k] (24)	0.0 (0)	NA	0.38[i] (6)	1.06 (2)
NHL	0.0 (0)	0.0 (0)	NA	NA	NA	2.38 (5)	0.37 (2)	1.92 (5)	3.91 (2)	2.1[i,l] (10)	NA	0.0 (0)	2.72 (2)	0.95 (11)	0.93 (2)
HD	NA (1)	0.0 (0)	NA	NA	NA	NA (1)	0.29 (1)	0.9 (1)	2.65 (1)	NA	NA	0.0 (0)	0.0 (0)	0.39 (2)	2.76 (1)
MM	0.0 (0)	5.0 (1)	NA	NA	NA	NA	1.62 (5)	2.0 (2)	0.0 (0)	NA	NA	0.0 (0)	NA	0.69 (4)	2.62 (3)
Leukemia	0.0 (0)	0.0 (0)	NA	1.35 (1)	44.00 (1)	NA	1.77 (14)	1.21 (4)	2.20 (2)	NA	NA	0.0 (0)	NA	1.17 (18)	0.77 (2)
All	1.9 (6)	0.82 (20)	1.13 (35)	1.05 (28)	0.87 (13)	0.96[m] (61)	1.07[m] (297)	1.02 (81)	1.15 (26)	0.81[i] (3198)	0.79[i] (8411)	1.09[m] (18)	1.01 (37)	1.01 (499)	1.46[i] (114)

[a] NA = not available; — = not applicable; NHL = non-Hodgkin's lymphoma; HD = Hodgkin's disease; MM = multiple myeloma.

[b] Males only.

[c] Adjusted for 10-year latency.

[d] Females only.

[e] Expected numbers of deaths reflect a rural correction factor.

[f] Includes results from other listed cohorts (*37,42,43*), but for different follow-up periods. Includes workers exposed to chlorophenols.

[g] ≥20-year latency; ≥1-year exposure.

[h] Stomach + esophagus.

[i] $P<.05$.

[j] Includes all sarcomas in organs.

[k] ≥250 acres sprayed with herbicides.

[l] Farmers of farms <1000 acres, ≥250 acres sprayed with [illegible]

[m] All neoplasms.

Table 5. Summary of epidemiologic studies of herbicide exposure and relative risk of cancer by cancer type

Cancer site/type	No. of study group	Range of relative risk	No. with risk >1.0	No. with statistically significant. Elevated risk	No. with statistically significant. Decreased risk	Ref. Nos.
Stomach	12	0.0-3.1	7	1	0	(34-41,44,47,48)
Colon	9	0.0-2.1	7	0	0	(10,14,34,35,39-41,47,48)
Liver	9	0.0-1.7	1	0	0	(11,34-36,40,41,44,47,48)
Nasal	9	0.0-4.9	3	1	0	(30,34-36,39,41,44,47,48)
Lung	14	0.0-2.1	10	1	0	(28,34-41,44,45,47,48)
Prostate	10	0.6-1.9	9	0	0	(21,35,37-41,43,47,48)
Testis	9	0.0-4.6	3	0	0	(34,35,38-41,44,47,48)
Ovary	3	1.0-4.4	3	2	0	(12,25,37)
Brain	9	0.0-1.6	3	0	1	(24,35,39-41,44,46-48)
Soft-tissue sarcoma	21	0.0-9.2	9	5	0	(7,8,13,15,16,20,22,23,32,34,35,37,39-41,44,45,47,48)
Non-Hodgkin's lymphoma	19	0.0-6.0	12	4	0	(9,16,17,19,20,26,29,33-35,38-42,44,45,47,48)
Hodgkin's disease	10	0.0-3.8	3	0	0	(16,26,35,39-41,44,45,47,48)
Multiple myeloma	9	0.0-5.0	5	0	0	(18,34,35,39-41,44,47,48)
Leukemia	12	0.0-4.0	8	1	0	(27,31,34,35,37,39-41,44,47,48)

*$P<.05$.

On the other hand, several cohort studies of herbicide workers (37,48) have noted an increased risk of lung cancer, but these risk estimates were not adjusted for smoking. In a case–control study in Saskatchewan in which smoking was controlled for (28), there was a decreased risk of lung cancer among those reporting herbicide use. In a cohort study of Saskatchewan farmers (42), no increase in lung cancer risk with increasing number of acres sprayed with herbicides was noted.

Soft-Tissue Sarcoma

The role of herbicides in the etiology of soft-tissue sarcomas is unclear. A number of Swedish case–control studies (7,8,23) have found a statistically significant increase in risk of soft-tissue sarcoma after exposure to phenoxy herbicides, as has a Danish study (37). An increased risk of soft-tissue sarcoma was observed among female, but not male, rice weeders exposed to phenoxy herbicides (22). A review by Honchar and Halperin (50) of four U.S. cohort studies of workers employed in the manufacture of phenoxy herbicides noted that three (2.9%) of the 105 deaths observed were from soft-tissue sarcomas; only 0.07% of deaths among U.S. males aged 20-84 years were from soft-tissue sarcomas. Fingerhut et al. (48) observed a large increase in risk of soft-tissue sarcomas among workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (SMR = 9.22; 95% CI = 1.9-26.95).

Case-control studies in North America (16,20) and New Zealand (13,15) and recently in Sweden (32) have shown either very small increased risks or no increased risk of soft-tissue sarcoma among persons exposed to herbicides.

Prostate Cancer

Farmers have been observed to be at increased risk of developing prostate cancer (1). Limited evidence suggests that herbicide exposure may increase risk of prostate cancer. A cohort study of western Canadian farmers (43) noted a significant dose–response relationship between risk of dying of prostate cancer and the number of acres sprayed with herbicides. Nine of the 10 studies reviewed (Table 5) noted an increased risk of prostate cancer with herbicide exposure; however, only the Canadian study observed a statistically significant trend in risk.

Testicular Cancer

Both Bond et al. (41) and Coggon et al. (39) noted an increased risk of testicular cancer among employees manufacturing phenoxy herbicides. However, Bond et al. observed only one case, and Coggon et al. observed only four.

Ovarian Cancer

Two Italian case–control studies have linked an increased risk of ovarian cancer with exposure to herbicides. One study by Donna et al. (12) revealed a significantly increased risk of mesothelial ovarian tumors (OR = 4.38; 95% CI = 1.90-16.07) corresponding to reported herbicide exposure. In a similar study by the same investigators (25), a significantly increased risk of epithelial ovarian tumors was associated with triazine herbicides (OR = 2.7; 95% CI = 1.0-6.9). However, a study in Denmark by Lynge (37) showed no significant excess risk associated with exposure to phenoxy herbicides (SMR = 1.02).

Brain Cancer

The available evidence does not substantiate any association between herbicide exposure and brain cancer. Only two of eight occupational cohorts reported an excess of brain cancer, and the excess was not statistically significant in either of the two cohorts. An Italian case-control study (24) reported an increased risk of brain gliomas associated with use of agricultural chemicals. An OR of 1.6 (95% CI = 0.6-4.4), which was not statistically significant, was

Table 3. Odds ratios from case-control studies of herbicide exposure **by** cancer type

Study	Ref. No.	Odds ratio for cancer type: Colon	Liver	Nasal	Lung	Soft-tissue sarcoma	Prostate	Ovary	Brain	Non-Hodgkin's lymphoma	Hodgkin's disease	Multiple myeloma	Leukemia
Hardell and Sandstrom	(7)					5.3[a,b]							
Eriksson et al.	(8)					6.8[a,b]							
Hardell et al.	(9)									4.8[a,b,c]			
Hardell	(10)	1.3[b]											
Hardell et al.	(11)		1.7[b]										
Donna et ai.	(12)							4.4[a,d]					
Smith et al.	(13)					1.3[d]							
Hoar et al.	(14)	1.9[b]											
Smith and Pearce	(15)					0.7[b]							
Hoar et al.	(16)					0.8[e,f]				6.0[a,e,f]	1.0[e,f]		
Pearce et al.	(17)									1.3[b]			
Pearce et ai.	(18)											1.3[b]	
Pearce et al.	(19)									1.0[b]			
Woods et al.	(20)					0.8[b]				1.1[b]			
Checkoway et al.	(21)						1.7[d]						
Vineis et al.	(22)					0.9[b,g]							
Vineis et al.	(22)					2.7[a,b,h]							
Hardell and Eriksson	(23)					3.3[a,b]							
Musicco et al.	(24)								1.6[b]				
Donna et al.	(25)							2.7[a,i]					
Persson et al.	(26)									4.9[b,j]	3.8[b]		
Bastuji-Garin et al.	(27)												3.6[a,b]
McDuffie et al.	(28)				0.6[b]								
Hoar Zahm et al.	(29)									3.1[e,f]			
Hardell et al.	(30)			2.1[b]									
Brown et al.	(31)												1.2[l]
Eriksson et al.	(32)					1.3[b]							
Cantor et al.	(33)									1.2[b]			

[a] $P<.05$.
[b] Phenoxy herbicides.
[c] Hodgkin's disease + non-Hodgkin's lymphoma.
[d] Herbicides, not specified.
[e] Based on highest exposure category.
[f] 2,4-D.
[g] Males only.
[h] Among living females only.
[i] Triazines.
[j] $P<.10$.

ratio (OR) of 1.3 (95% confidence interval [CI] = 0.6-2.8) for exposure to phenoxy herbicides. Although a study by Hoar et al. *(14)* observed an increased risk of colon cancer associated with phenoxy herbicide use (OR = 1.9), there was no dose-response relationship, and the authors concluded that their data did not support an association. Seven of the nine studies of colon cancer we reviewed (Table *5)* reported a risk greater than one.

Several occupational cohort studies have noted excess risk of stomach cancer. In an investigation of Swedish railway workers, a significant excess of stomach cancer among workers exposed to phenoxy acids was observed, after an adjustment for a 10-year induction-latency period (34). However, in a recent study of Saskatchewan farmers (*42*), no relationship emerged between risk of stomach cancer mortality and acreage sprayed with herbicides. Only seven of the 12 study groups of patients with stomach cancer reviewed showed an excess risk, and only the Swedish study results were statistically significant (Table *5).*

Nasal Cancer

A Swedish study by Hardell et al. (30) revealed a twofold increase in risk of nasal cancer for persons exposed to phenoxy herbicides. A cohort of workers exposed to 2,4-D experienced a significant excess of deaths from nasal cancer (standardized mortality ratio [SMR] = 4.93; 95% CI = 1.0-14.4) (39).

Lung Cancer

Many studies have reported significantly lower lung cancer mortality risks among farmers (I). However, the prevalence of cigarette smoking among farmers is typically lower than that among the general population (*1,49*); this situation makes it difficult to assess any association of herbicides with development of lung cancer for farmers compared with occurrence of lung cancer in the general population.

associated with herbicide use. However, the risk among farmers who reported exposure to herbicides and/or fertilizers in the absence of insecticides was not elevated (OR = 0.9). In addition, a study of brain cancer among Canadian prairie farmers *(46)* suggested an excess risk associated with insecticide use, but not herbicide use.

Non-Hodgkin's Lymphoma

The most convincing evidence suggesting that herbicides may be human carcinogens arises from studies of non-Hodgkin's lymphoma. An increased risk of non-Hodgkin's lymphoma among farmers has been reported from the United States, Australia, and New Zealand *(2)*. Although several studies have noted an increased risk associated with farm exposure to phenoxy herbicides (*16,29,42*), studies by Pearce et al. (*19,51*) have not.

A case-control study conducted in Kansas by Hoar et al. *(16)* reported a statistically significant dose–response relationship between the annual number of days on which a farmer applied herbicides and risk of non-Hodgkin's lymphoma. Farmers exposed on 20 or more days per year had a sixfold increase in risk of this disease relative to nonfarmers. A case-control study of non-Hodgkin's lymphoma in eastern Nebraska (29) noted an increased risk (OR = 1.5) for men who reported mixing or applying 2,4-D; this risk increased to 3.1 for those who reported exposure for 20 or more days per year.

A Swedish case-control study (26) showed an OR of 4.9 associated with occupational exposure to phenoxy acids for at least 1 year. An analysis of data from Saskatchewan farmers *(42)* showed a dose–response relationship between the number of acres sprayed with herbicides and risk of non-Hodgkin's lymphoma. In a case-control study of non-Hodgkin's lymphoma in Washington state (*20*), risk of developing the disease was elevated among males potentially exposed in any occupation to phenoxy herbicides for 15 or more years (OR = 1.71; 95% CI = 1.04-2.8).

Of the 11 occupational cohort studies reporting information on non-Hodgkin's lymphoma, five noted an increased risk, although none of the values were statistically significant. However, most of the studies (*38,40-42,45*) were small, with limited statistical power.

A small case-control study in New Zealand by Pearce et al. *(17)* observed a weak positive but not statistically significant excess in risk of non-Hodgkin's lymphoma with exposure to phenoxy herbicides. After the study was enlarged, no association was observed *(19)*. Finally, little evidence of an association of non-Hodgkin's lymphoma with either duration or frequency of use of phenoxy herbicides was observed in a subsequent analysis of the data *(51)*.

Exposure to triazine herbicides has also been associated with an increased risk of non-Hodgkin's lymphoma. Analysis of data from Kansas farmers exposed to triazine herbicides showed an increased OR of 2.2 (95% CI = 0.7-7.1) for non-Hodgkin's lymphoma, independent of exposure to phenoxy herbicides *(16)*. A lower risk was associated with triazine exposure in an Iowa/Minnesota case-control study *(33)* (OR = 1.1; 95% CI = 0.8-1.6). A significantly increased risk of non-Hodgkin's lymphoma was also observed in the Kansas study *(26)* of farmers exposed to trifluralin (OR = 12.5; 95% CI = 1.6-116.1) or amides, such as alachlor and propachlor (OR = 2.9; 95% CI = 1.1-7.6).

Hodgkin's Disease

An elevated risk of Hodgkin's disease among farmers has been reported by many studies (1), but there is only limited evidence linking Hodgkin's disease with exposure to herbicides. In a Swedish study (*26*), increased risk of Hodgkin's disease was associated with phenoxy herbicides and chlorophenols. However, a case-control study conducted in Kansas by Hoar et al. *(16)* failed to support this finding. Only three of 10 studies reviewed (Table 5) reported risks greater than one, and these lacked statistical significance.

Multiple Myeloma

Although several studies have related multiple myeloma tb exposure to pesticides, there is only limited evidence linking this cancer with herbicide exposure. Five (*18,35,39,40,48*) of the nine studies (Table 5) of herbicides and multiple myeloma were positive; however, most of the studies had low power, and none attained statistical significance.

Leukemia

Evidence supporting a possible association between herbicides and leukemia is weak and is limited by the availability of only one study with reasonable power. This case-control study (27) linked exposure to herbicides with acute leukemia. Some cohorts of workers employed in the manufacture of phenoxy herbicides have been reported to be at an elevated risk of leukemia. Eight of the 12 study groups reviewed (Table *5)* showed an excess leukemia risk among individuals exposed to herbicides; only one *(27)* (the only case-control study) attained statistical significance. However, the cohort studies reviewed had very low power.

Methodologic Issues

Studies of the relationship between herbicides and cancer among farmers often fail to give information about other exposures that may confound the herbicide–cancer association. Most farmers apply a wide variety of farm chemicals, such as insecticides, fumigants, and fungicides, and are exposed to others, such as solvents and paints. Farmers may also be exposed to fuels and exhausts in the process of applying herbicides. In addition, most studies in this review did not differentiate between specific types of herbicides.

Studies of cancer usually require some proxy interviews to ascertain exposure information, and it is often assumed that information supplied by proxies is less reliable than that supplied by the subjects themselves. In a study by Hoar et al. *(16)* of lymphoma and soft-tissue sarcoma and herbicide exposure in Kansas, fully one half of the case patients had died prior to interview. However, results for proxies were similar to those for living subjects. Other evidence that the

accuracy of data obtained from farmers themselves and their surrogate respondents on use of pesticides is comparable was reported by Brown et al. *(52)*. If recall of exposure was less accurate among proxy respondents than among exposed subjects, the nondifferential misclassification that would result from the use of proxy interviews should bias any estimates toward the null and therefore would not account for positive results.

Case-control studies may be limited, however, by the ability of both case patients and control subjects to recall specific agents used many years previously. In the Kansas study (*16*), information was obtained from pesticide suppliers to corroborate farmers' reported use. ORs using these data were similar to those derived from farmers' self-reported exposure.

A more worrisome concern with a case-control design is that the large amount of recent publicity about herbicides and cancer may increase the possibility of recall bias, i.e., a greater likelihood among case patients than control subjects for reporting of exposure. In this regard, the finding by Hoar et al. ***(16)*** of a phenoxy herbicide effect for non-Hodgkin's lymphoma, but not for soft-tissue sarcomas or Hodgkin's disease, is reassuring.

Retrospective cohort studies are characterized by the necessity of using pre-existing and limited exposure information. For example, in the study of Saskatchewan farmers (*42*), which noted a significant dose–response relationship between herbicides and non-Hodgkin's lymphoma, exposure was defined as the number of acres sprayed with herbicides on each farm, as reported on census forms. No information was available about herbicide application actually carried out by individual operators, much less the use of protective equipment. However, because the normal effect of nondifferential misclassification is to bias any risk estimates toward the null, the true risk of herbicide exposure in the Canadian farm operator study is probably greater than that observed.

Because of the many chemicals to which farmers are occupationally exposed, there are theoretical advantages to studying workers employed in the manufacture of herbicides rather than studying farmers. However, most manufacturing workers appear to have been exposed to a variety of phenoxy herbicides or herbicide precursors over the course of their working lives. Workers in herbicide plants are exposed on more days per year to herbicides than farmers. Higher doses may make it easier to detect an effect. However, it is far from clear that exposures among manufacturing workers equal or exceed those among farmers. The main limitations to studying workers employed in manufacturing herbicides are the lack of quantitative exposure information and the small size of study populations, with few cases of cancer available for study. The latter fact has severely limited the usefulness of these studies.

A further difficulty is that several of the occupational cohort studies were of workers exposed to 2,4,5-trichlorophenol, a precursor to 2,4,5-T, and not to 2,4-D itself **(53).** Various cohort and case-control studies have reported on exposures to many different phenoxy herbicides. It is difficult to know 1) if the results of such studies should be combined, to gain greater statistical power, or 2) whether the specific potential carcinogenic effects of 2,4-D, 2,4,5-T, 2-methyl-4-chiorophenoxyacetic acid (MCPA), or other phenoxy herbicides are likely to be so different as to make combining the results of such studies inappropriate. This situation may be further complicated by the potential role of dioxins as the agents responsible for the putative carcinogenic effect of phenoxy herbicides. One study (48) defined exposure on the basis of the dioxin 2,3,7,8-TCDD, a trace contaminant of certain phenoxy herbicides, instead of on the basis of direct exposure to the herbicides.

A limitation of occupational cohort studies has been the use of fatal rather than incident cases of cancer. This is particularly problematic for soft-tissue sarcomas, because cancer deaths are coded to anatomic site, not histologic type. Cohort studies that rely on death certificates to determine cancer status will miss many sarcomas, such as those of the gastrointestinal tract.

There are no clear reasons why the results of the New Zealand non-Hodgkin's lymphoma studies and the Scandinavian soft-tissue sarcoma studies are at variance with most of the studies from North America. No major methodologic flaws limit the New Zealand and Scandinavian studies, and the level of risk they report is such that chance is not a likely explanation.

One possible explanation is the difference in relative exposures to specific phenoxy herbicides or their contaminants. The predominant phenoxy herbicide used in Scandinavia was **MCPA,** whereas 2,4-D was used primarily in North America, and 2,4,5-T was used principally in New Zealand. Scandinavian use of phenoxy herbicides is principally in forestry, while use in North America is primarily in agriculture. Application techniques and exposures in agriculture and forestry are likely to differ. ***Also,*** the lifestyle of forestry workers in Scandinavia is likely to differ from that of North American farmers (2).

A possible explanation for the failure of the New Zealand studies to observe a positive relationship between non-Hodgkin's lymphoma and phenoxy herbicides may relate to how herbicide exposure was measured. The Kansas study by Hoar et al. ***(16)*** observed that average annual number of days of exposure was the critical variable in risk determination. It may be that studies not using this variable cannot be expected to observe risks as large as those observed in the Kansas study.

Uncontrolled confounding is not a likely explanation. Many studies were able to control for known risk factors, and no known common sources of exposure are strong risk factors for these cancers.

Animal Studies

Some animal studies suggest that phenoxy herbicides may be carcinogenic. A New Zealand study ***(54)*** noted a statistically significant relationship between adenocarcinoma of the small intestine in slaughtered sheep and exposure to phenoxy herbicides. Dogs exposed in residential settings to 2,4-D appear to be at an increased risk of developing malignant lymphomas ***(55).*** A statistically significant in-

crease in astrocytomas was observed in rats fed high doses of 2,4-D *(41).* However, several 2-year animal bioassay studies have failed to note any carcinogenic effects *(56).*

Evidence of a genotoxic effect is equivocal *(57).* Both 2,4-D and 2,4,5-T are able to inhibit intercellular communication. There is evidence that 2,4-D increases the rate of sister chromatid exchanges *(58).* In addition, 2,4-D has been reported to induce mitotic and meiotic chromosomal aberrations in barley *(59).* Exposure to commercial 2,4-D resulted in a statistically significant increase in the number of chromosomal aberrations in cultured human peripheral lymphocytes (60).

The International Agency for Research on Cancer (IARC) has concluded that there is limited evidence that phenoxy herbicides are carcinogenic in humans and that there is inadequate evidence of carcinogenicity in animals *(57).* Wild oat herbicides, such as diallate and triallate, have been shown to possess mutagenic potential in in vitro tests (61), but the IARC considers that there is limited evidence that diallate is a carcinogen in animals (62).

Herbicides used for corn production, including alachlor and atrazine, have tested positive in Ames tests (63). The IARC has concluded that there is limited evidence that atrazine is carcinogenic in animals and that atrazine is a possible human carcinogen (64). The known effects of atrazine on the hypothalamic–pituitary–gonadal axis are consistent with the types of tumors observed in both animals and humans *(64).*

Conclusions and Recommendations

There is reasonable evidence to suggest that phenoxy herbicide exposure results in an increased risk of developing non-Hodgkin's lymphoma. Most studies have revealed an elevated risk, and those that have examined dose–response relationships have usually noted statistically significant trends.

Evidence regarding soft-tissue sarcomas is equivocal. Although a number of studies have noted large increases in risk with phenoxy herbicide exposure, evidence of a dose–response relationship is lacking. There have been too few studies appropriately designed to properly assess other sites, but some data suggest a link between herbicide exposure and cancers of the colon, lung, nose, prostate, and ovary as well as leukemia and multiple myeloma.

Studies of the effects of herbicide exposure have typically suffered from two major limitations: inadequate sample size and poor determination of specific herbicide exposures. In an attempt to overcome the problem of lack of statistical power, the IARC has established a register of over 18000 workers exposed to either phenoxy herbicides or chlorophenols *(4).* The first report of the mortality in these cohorts has been recently published *(47).*

Future studies must better identify and quantify the nature of herbicide exposures. Most case-control studies have had to rely on proxy interviews. Those that do should analyze and present data obtained from interviews with living patients and proxies for deceased patients separately to determine if results from the two groups differ.

Some of the conflicting findings in the literature may reflect the effect of exposure to different herbicides, only some of which may increase the risk of cancer. In addition, issues of latency must be better addressed. Risks should be examined with regard to various windows of exposure. Almost all previous studies have examined only males exposed to herbicides. Future studies should also examine exposed female populations.

One useful approach would be to study farmers or other exposed populations prospectively. The U.S. National Cancer Institute, in conjunction with the U.S. Environmental Protection Agency, is presently assembling a large prospective cohort of pesticide-exposed farmers *(65).* This cohort study should alleviate concerns of recall bias that may affect case-control studies and will provide much more accurate and detailed exposure information than is available from retrospective cohort studies.

In the interim, it seems only prudent to monitor and promote safety practices of persons occupationally exposed to phenoxy herbicides, particularly farmers and professional sprayers. Public education with respect to safety practices is also required, given the general population's increasing use of lawn-care chemicals.

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gienists were based on their general knowledge of the coded industries and occupations rather than interview or monitoring data. This method of evaluation had a number of limitations: (i) exposure misclassification may have occurred if occupation and industry codes could not be linked specifically to exposures; (ii) the specific chemicals used by certain industria may not have been evident from the industry codes; and (iii) changes in exposures over time could not be addressed.

Despite these potential limitations, the Danish Linkage computerized system was an excellent resource for identifying female myeloma cases and controls and for investigating employment history a d workplace exposures as potential risk factors. Our findings of an increased myeloma risk among Danish women employed in agricultural and textile industries are consistent with previously suggested associations and deserve further investigation,

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