Review

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Cancer among pesticide manufacturers and applicators

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There are hundreds of studies of cancer and agriculture chemicals. However, few have focused on a single pesticide or class of pesticide. While cancer studies of nonspecific pesticide exposure among populations may provide hypotheses for additional testing, they contribute little to the understanding of the health risks of specific agricultural chemicals. This review concentrates on both the cancer findings and the exposure parameters in cohort studies of workers who manufacture or apply pesticides. Occupational studies of pesticide manufacturers and applicators provide important contributions to the causal assessment of the carcinogenicity of specific pesticides because the exposure is often longer, more intense, and better defined than for other study populations. Among the studies reviewed, there is little indication of increased cancer risk among pesticide manufacturers or sprayers. Limitations in sample size, exposure assessment, and the small number of studies make causal inference difficult. Additional methodological improvements with respect to exposure would contribute significantly to the understanding of the potential cancer risk from individual pesticides.

Key terms cohort; insecticide; phenoxy herbicide; review.

Modern pesticides are extensively tested with laboratory animals in vitro and in a variety of environmental settings. The experimental data, required in most developed countries, are designed to predict the hazard properties of each pesticide. However, the hazard data from animal studies are defined by high doses in exposure scenarios that may not be relevant to humans. The validation of these hazard estimates falls upon the discipline of epidemiology to examine the health risks among exposed human populations.

Indeed, epidemiologists have conducted and published a plethora of studies. For example, a Medline search with the terms "cancer", "pesticides", and "epidemiology" yielded 585 publications. A major limitation of this research is a lack of specificity with respect to the pesticides under study. Exposure is often assigned from an agricultural connection, such as vineyard workers (1), nationally registered farmers (2), golf course superintendents (3), residence on a farm (4), and residence in a rural area (5), or from agricultural occupations identified from death certificates (6) or a national census (7, 8). The pesticide literature is also replete with case–control studies, which are appropriate for studying rare cancers and controlling for potential confounders and multiple exposures. However, in the case of pesticide studies, population-based studies often include people with low and poorly defined exposures. At times, pesticides are not the primary focus of the study, with only a few questions addressing the household use of pesticides (9). In most case–control studies and some cohort studies (10), pesticide exposures are identified through the use questionnaires. While efforts are progressing to reduce recall bias (11, 12), recent studies suggest that self-reported exposure data may introduce significant exposure misclassification (13) and may not be adequate for determining use patterns of individual pesticides (14). In order to keep this review focused upon occupational exposure and its assessment, only case–control studies nested within a cohort of pesticide manufacturers and professional applicators were included.

Specific pesticide exposure assessment is required for causal assessment by such groups as the International Agency for Research on Cancer (IARC). Recent reviews of agricultural studies discuss the limitations of determining causality from studies when specific pesticide exposure is not evaluated (15–17). To facilitate causal assessment, studies of individual pesticides or classes of pesticides must be examined that attempt to assess exposure levels and dose rates.

Occupational studies of pesticide manufacturers or commercial applicators appear to offer several advantages over other study populations. First, on the average,

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the exposure intensity among these workers is higher and more frequent than that among farmers and groups nonoccupationally exposed through spray drift, traces on food, and environmental contamination (18–20). Second, occupational studies tend also to have objective documentation of exposure through exposure monitoring and job history. Workers with the highest exposures typically have the highest potential risk, and a dose–response is the hallmark of occupational carcinogens. The purpose of this review is to present the cancer findings of occupational cohort studies among pesticide applicators and manufacturers in the context of exposure assessments.

Methods

This review was limited to the published literature that assessed the risk of cancer among pesticide applicators or pesticide manufacturers. A search of Medline was conducted using the keywords "applicator", "manufacturing", and "pesticide". Bibliographies of review papers were scanned for studies of applicators or manufacturers. Where the follow-up period of a cohort was updated, only the most recent study is presented.

Excluded were studies of occupational groups defined broadly as farmers, greenhouse workers, and the like. While these workers may engage in pesticide application, their specific exposures are uncertain. For example, in their study of farmers, Wiklund et al stated that "only a few in the cohort were full time pesticide applicators [p 811]" (21). Also excluded were several cohorts of commercial applicators that either did not report a specific pesticide or class of pesticide or the applicators used multiple classes of pesticides and therefore could not be stratified into a single class (22–26). Whereas these studies did provide information regarding the health risk of the *occupation* of commercial pesticide applicators, they contribute little information regarding the carcinogenic potential for humans with respect to a single pesticide or pesticide class.

This review also excludes cohort studies of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), (27) arsenicals (28, 29), and 1,2-dibromo-3-chloropropane (DBCP) (30) since they are no longer manufactured or marketed for crop protection globally. The studies of 2,4,5-T workers and dioxin contaminants have been extensively reviewed elsewhere, and the epidemiologic evidence of cancer risk is equivocal (31).

For each study, table 1 lists the number of study participants, exposures, and cancer relative risks for all malignant neoplasms, lung cancer, and non-Hodgkin's lymphoma (NHL). The results of other cancers are described in the text. The standardized mortality ratios (SMR) or standardized incidence ratios (SIR) are shown. When necessary, the SMR and 95% confidence intervals (95% CI) were calculated from the data provided using exact confidence intervals (32). The results presented for some studies are a subset of larger cohort studies.

Results

Phenoxy herbicides

The phenoxy herbicides in this review include 2,4-dichlorophenoxyacetic acid (2,4-D), 4-chloro-2-methylphenoxyacetic acid (MCPA), and other related compounds. A study of 2,4-D manufacturers (33), and another of MCPA manufacturers and applicators (34) showed no increased cancer risk (table 1). Two additional studies of phenoxy herbicide manufacturers (35, 36) also showed no increased cancer risk. Three of the phenoxy studies (34–36) were a part of the large IARC multisite cohort (37). Several other studies have shown an association between some of the lymphopoietic cancers and the use of phenoxy herbicides (38, 39). Some case–control studies (40, 41), but not others (42–44), have reported an association of phenoxy herbicides with NHL. In the five cohorts shown in table 1, there was no excess of NHL when compared with the levels of the national populations. When compared with the levels of the internal worker population at the same location, the three cases of NHL in the 2,4-D cohort of Burns et al (33) were higher than expected [relative risk (RR) 2.6, 95% CI 0.9–8.3].

There were only three deaths due to Hodgkin's disease with no increased risk (data not shown). The association with soft-tissue sarcoma was inconclusive with observations in only three of the five studies, two deaths observed by Kogevinas et al (SMR 1.4, 95% CI 0.2–4.9) (37), one death observed by Coggon et al (SMR 1.1, 95% CI 0–5.9) (34), and four incident cancers in the study by Lynge (SIR 1.6, 95% CI 0.4–4.1) (36).

Alachlor herbicide

There was a single manufacturing cohort of alachlor workers (45). As shown in table 1, the cancer mortality and cancer incidence rates were within the expected range for the 1000 plus workers (SMR 0.9, 95% CI 0.4–1.7). This study had only eight cancer deaths and thus could not credibly evaluate specific cancers. There were no deaths due to stomach, thyroid, or nasal cancer, which were the tumors observed in animal studies. A subset of 701 alachlor workers was classified as highly

Table 1. Cohort studies of exposures to pesticides and cancer risk. [DDT = dichloro-diphenyl-trichloroethane; MCPA = 4-chloro-2-methylphenoxyacetic acid; MCPP = methylphenoxy propanoic acid; NHL = non-Hodgkin's lymphoma; NR = not reported; SMR = standardized mortality ratio; TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin; 2,4-D = 2,4-dichlorophenoxyacetic acid; 2,4-DCP = 2,4-dichlorophenol; 2,4-DP = 2,4-dichlorophenoxy propanoic acid; 95% CI = 95% confidence interval]

Reference	Cohort	Number of workers	Period of follow-up	Exposures	All cancer		Lung cancer		NHL	
					SMR or SIR	95% CI	SMR or SIR	95% CI	SMR or SIR	95% CI
Herbicide cohorts – phenoxy										
Bas Bueno de Mesquita et al, 1993 (35)	Manufacturers (plant B only)	414	1955–1986	MCPA, MCPP (also: 2,4-D, 2,4-DP, 2,4-DCP)	SMR 0.7	0.2–1.7	SMR 0	0–1.3	0 cases	·
Burns et al, 2001 (33)	Manufacturers	1517	1945–1994	2,4-D	SMR 1.0	0.8–1.2	SMR 1.0	0.6–1.3	SMR 1.0	0.2–2.9
Coggon et al, 1986 (34)	Manufacturers & applicators	5754	1947–1983	Mostly MCPA	SMR 1.0	0.8–1.1	SMR 0.9	0.8–1.1	SMR 0.4	0–1.3
Kogevinas, 1997 (37)	Manufacturers & applicators	7553	1939–1992	Chlorophenoxy herbicides and chlorophenols (no TCDD)	SMR 1.0	0.9–1.1	SMR 1.0	0.9–1.2	SMR 1.0	0.5–1.9
Lynge, 1998 (36)	Manufacturers	2119	1992–1993	MCPA, 2,4-D (also 2,4-DP, MCPP)	SIR 0.9	0.8–1.0	SIR 1.0	0.7–1.4	SIR 1.1	0.4–2.6
Herbicide cohorts – other										
Acquavella et al, 1996 (45)	Manufacturers	1199	1968–1993	Alachlor	SMR 0.9	0.4–1.7	SMR 0.4	0–2.4	NR	·
Acquavella et al, 1996 (45)	Manufacturers	1025	1968–1993	Alachlor	SIR 1.4	0.9–2.1	SIR 0.5	0–2.9 [a]	0 cases	·
Axelson et al, 1980 (47)	Applicators	152	1957–1978	Amitrol	SMR 1.5	0.5–3.5	SMR 3.2	0.4–11.6	0 cases	·
MacLennan et al, 2002 (49)	Manufacturers	2045	1985–1997	Triazine	SIR 1.1	0.8–1.5	SIR 1.0	0.4–2.3	SIR 1.4	0.3–4.0
Sathiakumar et al, 1996 (50)	Manufacturers	4917	1960–1987	Triazine	SMR 1.1	0.8–1.4	SMR 1.3	0.7–2.0	SMR 2.8	0.9–6.5
Morrison et al, 1994 (51)	Applicators	156 242	1971–1987	Herbicides (mostly 2,4-D)	NR	·	NR	·	SMR 0.9 [b]	0.6–1.4
Swaen et al, 1992 (52)	Applicators	1341	1980–1987	Herbicides	SMR 1.1	0.8–1.7	SMR 1.1	0.6–1.9	SMR 5.0	0.1–27.8
Zahm, 1997 (53)	Applicators, lawn workers	15 576	1969–1990	Mostly herbicides	SMR 0.6	0.3–1.1	SMR 0.7	0.1–2.4	SMR 1.6	0.3–4.8
Insecticide cohorts										
Shindell & Ulrich, 1986 (56)	Manufacturer, (update plant 1)	800	1946–1985	Chlordane	SMR 0.9	0.6–1.2	SMR 0.9 [c]	·	0 cases	·
MacMahon et al, 1988 (62)	Termite control applicators	6734	1976–1984	Chlordane, heptachlor	SMR 1.0	0.8–1.2	SMR 1.0	0.7–1.4	NR	·
Wang & MacMahon, 1979 (57)	Manufacturer (update plant 2)	835	1952–1976	Heptachlor, endrin	SMR 1.2	0.6–2.2	SMR 1.7	0.6–4.0	NR	·
Ditraglia et al, 1981 (55) [d]	Manufacturer (plant 4)	354	1947–1976	DDT	SMR 0.7	0.3–1.5	SMR 1.3	0.3–3.2	0 cases	·
Wong et al, 1984 (59)	Manufacturer (plant A only)	740	1935–1976	DDT	SMR 1.0	0.6–1.5	SMR 1.5	0.7–2.8	NR	·
Ott et al, 1980 (60)	Manufacturer	161	1925–1976	Ethylene dibromide	SMR 1.2	0.5–2.5	NR	·	NR	·
Figa-Talamanca et al, 1983 (61)	Applicators	168	1946–1987	Insecticides	SMR 1.2	0.7–2.0	SMR 1.2	0.4–2.9	NR	·
Amoateng-Adjepong et al, 1995 (58)	Manufacturer (update plant 3)	2384	1952–1990	Insecticides	SMR 1.1	0.9–1.3	SMR 0.9	0.6–1.3	NR	·
Zahm, 1997 (53)	Applicators (tree and shrub)	3010	1976–1990	Insecticides	SMR 1.0	0.2–2.8	SMR 2.9	0.04–16.1	0	0–12.2

[a] Reported only among employees with potential high alachlor exposure.
[b] ≥250 acres (≥100 hectares).
[c] Observed and expected not reported.
[d] Reported on plants 1–4. Plants 1–3 were subsequently updated in publications focusing on single pesticides.

exposed, and it exhibited similar cancer incidence rates (SIR 1.2, 95% CI 0.7–2.0).

Amitrol herbicide

An update of a study on Swedish railroad applicators classified workers by exposure to phenoxy herbicides, amitrol, and a combination of the two (46, 47). Because the phenoxy workers applied 2,4,5-T, their results are not presented. The 152 amitrol workers experienced a greater number of deaths than expected due to all cancers and lung cancer. Similar rates were observed with a 10-year latency period.

Triazine herbicides

The class of triazine herbicides includes atrazine, simazine, propazine, terbutylazine, and cyanzine. Atrazine is the most commonly used herbicide in the United States (48). Two cohort studies of triazine manufacturers have been published (49, 50). The mortality rates and incidence rates for cancer were close to the expected levels (table 1). Sathiakumar and her colleagues identified 2683 persons with definite or probable triazine-related work; among these workers there were 14 cancer deaths. Three deaths were due to NHL with an SMR of 3.9 (95% CI 0.8–11.2). Two of these three deaths

occurred among men employed for <1 year. No other elevated rates were observed. The incidence study by MacLennan and his co-workers found 11 prostate cancers compared with 6.3 expected (95% CI 0.9–3.1). The authors attributed this increased risk to early detection from prostate-specific antigen testing offered to active employees of the company. There were no deaths due to prostate cancer (with 1.1 expected) in the study by Sathiakumar et al (50).

Herbicide class

Three cohorts of applicators defined the group or subgroup as applicators of predominantly herbicides (51–53). As with the other herbicide cohorts, these were healthy workers with unremarkable overall cancer mortality. One death due to Hodgkin's disease and no deaths due to soft-tissue sarcoma were reported. No excess of NHL was reported by the Morrison et al for the cohort of Canadian farmer applicators (51). It was estimated that 2,4-D constituted 90% of all herbicides applied in the 1970s in the province of Saskatchewan (54). Results specific to Saskatchewan showed a higher risk of NHL for smaller farms [<1000 acres (404.64 ha)] that spray more than 249 acres (100.77 ha) (SMR 1.5, 95% CI 0.7–3) and no risk for all farms spraying more than 249 acres (100.77 ha) (SMR 1.0, 95% CI 0.5–1.7). Among the Dutch applicators, 921 workers were identified as having probable exposure to herbicides, for which the rates for multiple myeloma were significantly more than expected (3 observed, SMR 13.0, 95% CI 2.6–38.0) (52). No data exist on the particular herbicides used by this cohort. No deaths due to multiple myeloma were reported among the lawn care workers in the largest of the herbicide cohorts reviewed (53). Zahm (53) observed three deaths from NHL (SMR 1.6, 95% CI 0.3–4.8). An NHL SMR of >1 was observed for the 1409 workers employed ≥3 years (SMR 7.1, 95% CI 1.8–28.4). The three workers with NHL all applied 2,4-D, chlorpyrifos, dimethyl tetrachloroterephthalate (DCPA), dicamba, and mecoprop during their employment. The workers died within 6 years of their hire date.

Insecticide cohorts

Nine cohorts of insecticide applicators and manufacturers met the criteria for review. A study of four organochlorine pesticide-manufacturing facilities was reported by Ditraglia et al in 1981 (55). The vital status and mortality experience of three of these facilities was updated and reported individually for plant 1 (chlordane) (56), plant 2 (heptachlor, endrin) (57), and plant 3 (aldrin, dieldrin, endrin, and other insecticides) (58) (table 1). In addition to the DDT (dichloro-diphenyl-trichloroethane) plant (plant 4), Wong et al reported on 740 DDT manufacturing workers (59). Ott et al studied ethylene dibromide workers (60). The applicator studies included those of nonspecified insecticide applicators (61), termite control applicators (62), and the tree and shrub workers from the lawn care company (53).

Although diverse in location, size, and specific exposure, the overall cancer mortality of these cohorts was not elevated. Given the small sample sizes, lung cancer was the only cancer reported in all the studies (table 1). The rates were higher than expected in five of the eight studies, but the confidence intervals were very wide. No cases of NHL were reported. A nested case–control study of pest control workers reported higher lung cancer risk among applicators of propoxur (OR 12.4, 95% CI 1.5–100.3) when compared with deceased controls and applicators of phenoxyacetic acids (OR 22.4, 95% CI 1.8–276.2) when compared with living controls (63). This study of 65 cases also suffered from a small sample size with respect to investigating individual pesticide uses.

Liver cancer has been associated with chlordane exposure in mice (64); however no liver cancers were reported in the chlordane cohort reported by Shindell & Ulrich (56). One death due to liver cancer was identified by Wang & MacMahon (57). A liver cancer death was also reported by MacMahon et al (62); however, they did not report whether the death occurred in a termite control applicator or in the other applicators under study (ie, with no presumed exposure to insecticides). Although the data are sparse, these studies do not support a liver cancer association for chlordane workers.

Both investigations of DDT manufacturers consisted of relatively few workers and thereby had poor precision to detect differences. It is noteworthy that, in a nested case–control study of pancreatic cancer among 5886 employees of another DDT manufacturing facility, the authors concluded that DDT and two derivatives, ethylan and dichlordiphenylethylene (DDE), were significantly associated with pancreatic cancer after control for smoking (65). Among the cohort studies in table 1, Ditraglia et al identified one death due to pancreatic cancer (with <1 expected) (55), and Wong et al reported no deaths due to pancreatic cancer (59).

Exposure characterization

The studies are summarized in table 2 according to the range of cohort definition and exposure assessment. The manufacturing plants of 2,4-D, alachlor, triazine, and DDT (33, 45, 49, 50, 59) provided adequate job and department records to identify workers with specific exposure. These studies provide the greatest confidence that appropriate workers were included. Other manufacturing workers were defined only by employment in the plant. Consequently, the larger the operations and number of chemicals produced or formulated, the greater the

Table 2. Assessment of exposure in cohorts of pesticide manufacturers and applicators. (EDB = ethylene dibromide; MCPA = 4-chloro-2-methylphenoxyacetic acid; MCPP = methylphenoxy propanoic acid; NR = not reported; TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin; 2,4-DCP = 2,4-dichlorophenol; 2,4-D = 2,4-dichlorophenoxyacetic acid; 2,4-DP = 2,4-dichlorophenoxy propanoid acid)

Reference	Exposures	Exposure definition	Employment duration (years)	Level of exposure
Herbicide cohorts – phenoxy				
Bas Bueno de Mesquita, (35)	MCPA, MCPP (also: 2,4-D, 2,4-DP, 2,4-DCP)	Employment by department or exposed in an accident or entered department weekly	0–9, 10–19, ≥20	NR
Burns (33)	2,4-D	Employment specific to 2,4-D	Cumulative exposure by years employed	Negligible, low, medium, high based on industrial hygiene monitoring and job titles
Coggon (34)	Mostly MCPA	Employment at plant	<1 month, 1–6 months, ≥6 months	Background, low, high based on job titles
Kogevinas (37)	Chlorophenoxy herbicides and chlorophenols (no TCDD)	Employment	<1, 1–4, 5–9, 10–19, ≥20	5 job categories, year of 1st exposure
Lynge (36)	MCPA, 2,4-D (also 2,4-DP, MCPP)	Employment	NR	5 job categories, 2 plants
Herbicide cohorts – other				
Acquavella (45)	Alachlor	Employment specific to alachlor	<5, ≥5	Negligible, low, medium, high based on job titles and dates employed
Axelson et al, 1980 (47)	Amitrol	Sprayed herbicides ≥45 days	0, ≥10	Exposed 1957–1961, ≥1961
MacLennan et al, 2002 (49) (incidence)	Triazine	Employment specific to triazine	<5, ≥5	Employee type, 2 job categories
Sathiakumar et al, 1996 (50)	Triazine	Employment specific to triazine	<1, ≥1	Possible, probable, definite; regular versus intermittent
Morrison et al, 1994 (51)	Herbicides (mostly 2,4-D)	Self-reported in national agricultural census	NR	Acres sprayed (4 levels), amount spent on fuel (4 levels)
Swaen et al, 1992 (52)	Herbicides	Employment (herbicides described by percentage of total use)	NR	NR
Zahm, 1997 (53)	Mostly herbicides	Work history matched to application programs	<1, 1–2.9, ≥3	NR
Insecticide cohorts				
Shindell & Ulrich, 1986 (56)	Chlordane	Employment at plant	0–4, 5–9,…up to ≥35	Blood pesticide levels by job classification, 2 job categories
MacMahon et al, 1988 (62)	Chlordane, heptachlor	Employment as termite control operator	0–4, 5–9, ≥10	Minimal, intermediate, highest based on job titles
Wang & MacMahon, 1979 (57)	Heptachlor, endrin	Employment as termite control operator	<10, 10–19, ≥20	NR
Ditraglia et al, 1981 (55)	DDT	Employment at plant	NR	NR
Wong et al, 1984 (59)	DDT	Employment specific to DDT	NR	NR
Ott et al, 1980 (60)	Ethylene dibromide	Employment specific to EDB	< 15, 15–24, ≥25	Jobs with highest exposure, 2 units
Figa-Talamanca et al, 1983 (61)	Insecticides	Employment	1–5, up to 26–35	NR
Amoateng-Adjepong et al, 1995 (58)	Insecticides	Employment	<1, 1–4, 5–9, ≥10	8 job categories, pay type, period of hire
Zahm, 1997 (53)	Insecticides	Work history matched to application programs	<1, 1–2.9, ≥3	NR

potential for the misclassification of exposure for any specific pesticide. The studies by Zahm (53) and MacMahon et al (62) used job titles to stratify the workers by potential for exposure (ie, termite control operators versus all other applicators).

Duration of employment can be obtained from the company records of hire date and termination date. These analyses assume that exposure is uniform and continuous over the employment period. Many circumstances challenge this assumption. Career advancement and plant improvements may reduce exposure in later years. A false negative dose response may result in this and other scenarios in which co-existing exposures dilute a true effect from a single exposure under study. Conversely, accidents or careless work habits may lead to varying exposure over time, potentially resulting in a false positive association due to high exposure occurring later in one's career. Nonetheless, duration of employment is often used as a surrogate of an increasing cumulative exposure potential and is often used in dose–response analyses.

Most of the studies reviewed categorized duration into 5- and 10-year intervals, the highest interval per study ranging from 5, to 10, to 20, and to 35 years. The shortest interval was used by the MCPA study, in which the highest category was 6 months (34). There was no consistency between the applicator studies and the manufacturing study in how duration was defined.

The exposure level was also estimated in many studies. Several used job titles to categorize workers from background to the highest exposed levels. This is an important characterization. The authors concluded that many subjects, for example, those with administrative positions, had no appreciable exposure. Other employees were engaged in tasks with greater potential for exposure and assigned to a higher exposure category. Often this assignment was based on both job title and the time period, such that workers in the 1950s and 1960s were considered to have higher exposure than recent employees with the same job. Other studies used categories relating to activity, such as maintenance, production, and nonproduction to predict groups with different exposure opportunities. A single study used industrial hygiene monitoring data and job exposure matrices to create a cumulative dose estimate (33). In addition, uniquely, the study of chlordane workers was the only study to have blood-testing data available to support the job categorization (56).

Discussion

Soft-tissue sarcoma and the lymphopoietic cancers have been frequently associated with exposures to the phenoxy class of herbicides (66). However, among the studies presented, soft-tissue sarcoma and Hodgkin's disease were rarely observed. The rates for NHL were not elevated among the workers who manufactured phenoxies. Elevated rates for NHL were observed in the triazine studies and other herbicide studies. A small number of observed cancers (1 versus 0.2 expected in the study by Swaen et al) (52) and a short latency period (53) weaken any causal inferences.

Like the herbicide cohorts, those of insecticide workers were limited by very small sample sizes. Meta-analyses may be considered to appraise these studies more analytically. It was not done for this review because there were so few studies of workers with similar exposures. In the example of NHL, meta-analyses of studies of farmers did identify an elevated risk but could draw no conclusions regarding exposures (67, 68). Continued follow-up of the current cohorts and identification of additional exposed groups would begin to address this limitation. For example, the 2,4-D worker cohort has been updated twice (33, 69), resulting in an additional 639 workers and 219 deaths (70).

Whereas the cohorts reviewed are composed of occupationally exposed workers, the studies remain somewhat heterogeneous with respect to study design and resulting exposure criteria. For example, the entry criteria for the studies reviewed ranged from 1 to 365 days. Some authors performed analyses on groups by duration of exposure, which varied from 30 days to 35 years. For the most part, these criteria were based on stratification of the cohorts into quartiles or equal groups and were not based on a hypothesis of threshold or no-observed-effect level, as determined from animal studies. Consideration of the range of human exposure in the context of toxicology results has been recommended (71). Nonetheless, these exposure duration criteria are in stark contrast to those of some studies in the literature, which consider one or two uses to be significant for carcinogenesis (72, 73).

In their review of more than 400 papers, Maroni & Fait (74) concluded that one of the main limitations preventing causal inference from many epidemiologic studies is poor assessment of exposure. Later reviews similarly recommended improved exposure details (75, 76). Unfortunately, exposure is not easily characterized. Occupational data are not readily available for each person (57, 59), or they are only available for a small percentage of the workers (58). When chemical-specific data are available, a substantial effort may be required to create exposure categories from the thousands of job entries (53). In one study, serum levels of the compound of interest were available, but they did not correlate with the classification of presumed exposure from the job category. This finding raises serious concerns about exposure misclassification. (57)

The exposure classifications in the studies in this review were based on employment categories, which provide an accurate assessment of duration of exposure but are not useful by themselves for assessing exposure levels. Given the absences of personal or biological monitoring in many of these studies, exposure misclassification should be a concern. A further limitation of these studies relative to case–control studies is a lack of data about personal risk factors for cancer, such as lifestyle, family history, and other occupational exposures. As such, unmeasured confounders limit the conclusions of these studies.

On the other hand, these publications have many strengths over the many other studies of pesticides in the literature. Compared with the general population, these occupational study participants have significantly higher exposure—in both duration and intensity. Employment records confirm that each person was employed at each company or facility. Some studies have personal exposure monitoring data that further confirm the exposure and duration categories. These studies are more useful for the causal assessment of pesticide risks than are those that equate exposure with nonspecific or infrequent pesticide use.

In conclusion, the studies of manufacturers and applicators provide the best epidemiologic evidence to date regarding the putative cancer risk from specific pesticides. Among the studies reviewed, little indication

was found of increased cancer risk among these groups of pesticide manufacturers and applicators. Nonetheless, further improvements in study design and increased sample size would contribute significantly to the understanding of risk. The ability to assess potential risk from any individual pesticide on the basis of available data varies and should be assessed on a case-by-case basis. The inferences made from epidemiologic studies would benefit from improved methods. Use of more extensive personal monitoring for exposure estimation would reduce exposure misclassification. Validation of these exposures with biomonitoring could also improve causal determinants. Incorporation of experimental data into designing epidemioloic studies could also determine potential effects on humans at occupational exposure levels and could provide insight into the importance of dose rate for carcinogenesis by specific pesticides. Epidemiologists have both a challenge and a responsibility to understand the exposures studied in the context of a rich experimental background. With these improvements, epidemiology can provide the human data required to validate the hazards predicted from experimental studies.

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