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Occupational pesticide exposures and cancer risk. A review

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Abstract

A review of the epidemiological literature linking pesticides to cancers in occupational studies world-wide was conducted, with particular focus on those articles published after the release of IARC Monograph 53 (1991): Occupational exposures in insecticide applications and some pesticides. Important new data are now available. Chemicals in every major functional class of pesticides including insecticides, herbicide, fungicides, and fumigants have been observed to have significant associations with an array of cancer sites. Moreover, associations were observed with specific chemicals in many chemical classes of pesticides such as chlorinated, organophosphate, and carbamate insecticides and phenoxy acid and triazine herbicides. However, not every chemical in these classes was found to be carcinogenic in humans. Twentyone pesticides identified subsequent to the last IARC review showed significant exposure-response associations in studies of specific cancers, while controlling for major potential confounders. This list is not an exhaustive review and many of these observations need to be evaluated in other epidemiological studies and in conjunction with data from toxicology and cancer biology. Nonetheless, it is reasonable and timely for the scientific community to provide a multidisciplinary expert review and evaluation of these pesticides and their potential to produce cancer in occupational settings.

Introduction

Pesticides are a diverse group of chemicals used to control pests, including plants, molds, and insects. Pesticides are widely used in agricultural, and commercial and residential settings, making exposure to the general population ubiquitous. The National Health and Nutrition Survey found that the majority of the US population displayed detectable levels of various pesticide metabolites in their urine (Barr et al 2004; 2005; 2010) , adding evidence that the general population is readily exposed, primarily through ingestion of food treated with pesticides and other indirect exposure routes.

Pesticides are broadly known to exert adverse toxic effects to humans following high-dose acute exposure; however, knowledge about chronic low-dose adverse effects to specific

pesticides is more limited. Although the majority of pesticides currently registered for use in the United States, are neither overtly genotoxic nor carcinogenic in rodent studies, human cancer possibly resulting from exposures is an area of public concern and growing scientific interest.

In the past 10 years, an increasing number of case-control and cohort studies as well as meta-analyses (Akhtar . 2004; Alavanja 2003, 2004a; Andreotti et al. 2009; Band et al. 2010; Beane Freeman et al. 2005, Bonner et al. 2005; Chamie et al. 2008; Chiu et al. 2006; Chiu and Blair. 2009; Christensen et al. 2010; Dennis et al. 2010; Eriksson et al. 2008; Hou et al. 2006; Knopper and Lean 2004; Koutros et al. 2009; Lee et al. 2004a, 2004b, 2007; Mahajan et al. 2006a, 2006b, , Miligi et al. 2006; Multigner et al. 2010; Orsi et al. 2009; Purdue et al. 2007; Rusiecki et al. 2006, 2009; Samanic 2006; Schroeder et al. 2001; Spinelli et al. 2007; Van Bommel 2008; Van Maele-Fabry et al. 2006, 2008; Van Maele-Fabry and Willems 2003; 2004;) with exposure information on pesticides and other etiologically relevant factors have investigated hypotheses linking occupational pesticide exposures to a number of different cancers. Moreover, evidence is emerging that chronic low-dose exposure to various pesticides perturbs a number of biologic pathways, including oxidative stress (Abdollahi et al. 2004; Akhgari et al. 2003)and immunotoxicity (Galloway and Handy 2003), that have been linked with carcinogenesis.

Because a comprehensive review of all the extant literature on this topic is beyond the scope of this review, this review will only evaluate occupational exposures to pesticides because workers in certain occupational environments have higher cumulative exposures than do individuals in the general environment and it is sometimes possible to better document exposures to specific pesticides. Higher exposures in occupational studies may result in larger risks that are more readily detectable epidemiologically while permitting control of important confounders. Once an accurate identification of a human carcinogen is made in the occupational environment, the relevance to the general population may be largely the same other than the size of the cancer risk which is determined by the size of the exposure if a linear, no-threshold exposure-response pattern of cancer risk is assumed.

Methods

Relevant literature was identified by searching PUBMED using the search term 'Human Cancer Epidemiology AND Pesticides'. The result of this research produced 774 articles of which 602 were research articles and 172 were reviews and/or commentaries. The list was reduced to 721 articles when the search was restricted to articles published on or after 1990, which represents the bulk of the literature published subsequent to the publication of IARC monograph 53 (1991). The list was further restricted to cancer studies among adults in which there was some exposure-response information and narrowed the list to 103 studies. Based on these studies we compiled a list of selected pesticides (table 1) that have sufficient evidence to warrant a comprehensive and systematic review for human carcinogenicity. The pesticides listed in table 1 were selected based on the following guidelines: 1) pesticide-specific exposure data were reported by the study, 2) evidence of an exposure-response gradient across exposure levels, and 3) adjustment for potential confounders. We recognize that replication of epidemiologic results is important, but such data are not yet available for

many pesticides. We refrained from using strict criteria, such as Hill's criteria, because a comprehensive evaluation of the evidence necessary for making causal inference, which would include comprehensively assessing biological effects of exposure, is beyond the scope of this review. This review is focused on epidemiologic developments since the last comprehensive IARC evaluation of pesticides for human carcinogenicity.

While the predominant focus of this review is directed towards suggestive positive associations between occupational pesticide use and cancer incidence if the inclusion guidelines are met, it is important to note that most pesticides have not been found to be associated with cancer in epidemiologic studies. Further winnowing of the list will be made when the biological effects of exposure are evaluated. Further expansion of the list would be warranted as new epidemiological findings are published.

Epidemiologic Studies with External Comparisons Groups

Studying the health experience of farmers and pesticide applicators has provided the primary opportunity to evaluate the effect of pesticides directly in humans. In the United States and other developed countries farmers experience a lower mortality and cancer incidence rate compared to the general population (Alavanja et al. 2005; Blair et al. 1993; Dich and Wiklund . 1998; Koutros 2010a; Morrison et al. 1993; Saftlass et al. 1987; Wigle et al 1990). Lower risks: of lung and bladder cancer have been attributed to a relatively low tobacco use (Alavanja et al. 2004a; 2004b; 2005; Blair et al. 1985, 1993, 2009;) while lower colorectal cancer risk may be influenced by the higher prevalence of physical activity associated with agricultural work (Neugut et al. 1996; Thune and Furberg 2001). Excess risks for specific cancers were also noted in many (Acquavella et al.; 1998; Blair et al. 1992), studies of agricultural populations, including cancer of the lymphatic and hematopoietic system, connective tissue, skin, brain, prostate, stomach and lip. More recently a significantly elevated risk was also observed for ovarian cancer among female pesticide applicators (Koutros et al. 2010a).

Studies, using standardized incidence ratio (SIR) analysis, or standardized mortality ratio (SMR) analysis, all relied on external comparisons to estimate associations between farmers and a general population. Necessarily, these studies offer only limited information regarding the potential for causality because specific exposure data to individuals are not available. Nonetheless, these types of studies provide some insight into the nature of the relationship between pesticides and cancer risk.

Occupational Exposure to Pesticides and Select Cancer Sites

Prostate Cancer—Prostate cancer risk among farmers and other pesticide users has been evaluated in over 100 studies world-wide. Meta-analyses indicate that farming is more frequently associated with an increased risk of prostate cancer in North America than in Europe (Van Maele-Fabry and Wilems. 2004). A total of 8 of 15 studies in North America found a modestly increased risk among farmers compared to non-farmers, with effect estimates ranging from 1.1-4.3; whereas 7 studies reported no such association. Results from meta-analyses based on these studies are consistent with a weak, positive association that is

difficult to distinguish from the null (Van Maele-Fabry et al. 2006; Van Maele-Fabry and Wilhems et al. 2004).

In a population-based case-control study of prostate cancer in South Carolina, USA, farming related exposures were determined for 405 incident prostate cancer cases obtained from the South Carolina Central Cancer Registry and 392 controls matched for age, race, and region were obtained from the Health Care Financing Administration Medicare Beneficiary Files and occupational information was collected using computer-assisted telephone interviewing. Farming was associated with elevated risk of prostate cancer in Caucasians ($OR_{adjusted}=1.8[95\% \text{ CI: } 1.3-2.7]$) but not in African-Americans ($OR_{adjusted}= 1.0[95\% \text{ CI: } 0.6-1.6]$). Racial differences in the association between farming and prostate cancer may be explained by different farming activities or different gene-environment interactions by race (Meyers et al. 2007). These cancer incidence findings from South Carolina are not reflective of a 38% excess prostate cancer mortality rate among African-American men from three states from the southeastern United States (i.e., North Carolina, South Carolina and Georgia) engaged in farming, compared to the experience of African-American farmers in 21 states in other parts of the country (Dosemeci et al. 1994).

A significant association between prostate cancer risk and exposure to DDT ($OR=1.68$, 95% $CI:[1.04-2.70]$ for high exposure), simazine ($OR=1.89[95\% \text{ CI: } 1.08-3.33]$ for high exposure) and lindane ($OR=2.02$ 95% $CI: 1.15-3.55$ for high exposure) was observed among 1,516 prostate cancer cases and 4,994 age-matched controls consisting of all other cancer sites other than lung and cancers of unknown primary sites in a population-based case-control study in British Columbia, Canada. The study also reported more preliminary associations of prostate cancer risk for dichlone, dinoseb amine, malathion, endosulfan, 2,4-D, 2,4-DB, carbaryl, captan, dicamba, and diazinon (Band et al. 2010). Carbaryl (Mahajan et al. 2007), captan (Greenberg et al. 2007), diazinon (Beane Freeman et al. 2005), dicamba (Samanic et al., 2006) and malathion (Bonner et al. 2007) were not associated with prostate cancer risk in the U.S. Agricultural Health Study (AHS), a prospective cohort study of certified pesticide applicators and the spouse of farmer applicators in Iowa and North Carolina (Alavanja et al. 2003; 2005; Koutros et al. 2010a). Dichlone, dinoseb amine, endosulfan, 2,4-D, 2,4-DB were not evaluated in pesticide specific analyses in the AHS.

A significant excess risk of prostate cancer was observed in the U.S. Agricultural Health Study (AHS). This excess may be due in part to pesticide use. In the AHS, an age adjusted excess prostate cancer risk was observed with specific pesticide use (i.e., butylate, coumaphos, fonofos, phorate, permethrine for animal use) among those with a family history of prostate cancer and methyl bromide among those with and without a family history of prostate cancer (Alavanja et al. 2003). Similar findings were noted a few years later in the same cohort for butylate (Lynch et al. 2009), coumaphos (Christensen et al. 2010), fonofos (Mahajan et al. 2006a), phorate (Mahajan et al. 2006b) permethrin (Rusiecki et al. 2009) and terbufos (Bonner et al. 2010) with the accumulation of additional prostate cancer cases. These observed interactions were followed-up with a gene-by-environment association study of 776 cases and 1,444 controls from the AHS. In one of the analysis resulting from this project the 8q24 region of the genome which was previously associated with prostate cancer risk as a main effect (Yeager et al. 2009), showed significant interaction with fonofos (p-

interaction adjusted for multiple comparisons =0.02) and an exposure response pattern of enhanced risk with increased use ($OR_{\text{non-exposed}}=1.17$ [95% CI:0.93-1.48], $OR_{\text{low}}=1.3$ [95% CI: 0.75-2.27], $OR_{\text{high}}=4.46$ [95% CI:2.17-9.17]), other positive interactions were also observed for coumaphos, phorate, terbufos and permethrin (Koutros et al., 2010b) providing some biological context for the original link between these pesticides and prostate cancer (Alavanja et al. 2003).

In a case-control study of prostate cancer conducted on 709 consecutive cases of histologically confirmed prostate cancer identified between June 2004 to December 2007 in Guadeloupe, a French archipelago in the Caribbean, prostate cancer risk rose with increasing plasma chlordecone concentration (i.e., Kepone) (Multigner et al. 2010). Chlordecone is an estrongenec insecticide that was used extensively in the French West Indies for more than 30 years. An odds ratios of 1.77; [95% CI: 1.21- 2.58] was observed in the highest tertile of values above the limit of detection, P trend=0.002. Stronger associations were observed among those with a positive family history of prostate cancer. Among subjects with plasma chlordecone concentrations above the limit of detection and two single-nucleotide polymorphisms (rs3829125 and rs171345920) the risk of prostate cancer was elevated ($OR=5.23$ [95% CI: 0.82-33.32]). These polymorphism control chlordecone reductase in the liver and may lead to lower levels of biliary excretion of chlordecone clearance from circulation (Multigner et al. 2010) Chlordecone also binds the estrogen receptor alpha (ER alpha) and beta (ER beta), ER alpha mediates the adverse effects of estrogen on the prostate , such as aberrant proliferation, inflammation, and malignancy (Multigner et al. 2010). This study provides some additional support for the hypothesis that estrogens increase the risk of prostate cancer.

In a second analysis from the AHS project, pesticides and single nucleotide polymorphisms (SNP) in genes in xenobiotic metabolizing enzymes (XME) which have been independently associated with prostate cancer were evaluated currently for statistical interaction. A significant interaction was observed between petroleum oil herbicides and rs 1883633, in the glutamate-cysteine, ligase catalytic subunit (*GCLC*) ($p\text{-interaction}=1.0 \times 10^{-4}$ after controlling for multiple comparisons). Among men carrying at least one variant allele, the risk of prostate cancer associated with high petroleum oil herbicide was 3.7 fold higher than those with no use ($OR=3.7$, 95% CI: 1.9-7.3) (Koutros et al. In Press). To rule out the possibility that these results are due to chance, replication in other studies is necessary. To our knowledge attempts to duplicate the link between specific pesticide exposures, genetic polymorphisms and prostate cancer risk in other studies has not yet been made.

In summary, the epidemiologic evidence from a number of different studies now more convincingly shows that prostate cancer is related to pesticide use. The cancer risk observed after exposure to certain pesticides revealed disparities among races and between those with and those without a family history of prostate cancer. These differences may be explained by chance or by 1) differences in pesticide use patterns, or 2) differences in genetic susceptibility. Evaluating these disparities more intensively may provide important biological insights concerning mechanisms of action that will help more clearly identify links between specific pesticides and prostate cancer. The exposure-response evidence from British Columbia linking simazine, DDT and lindane to prostate cancer is important

etiological information that needs to be replicated. While, the prostate cancer effect-modification observed among those with selected polymorphisms and chloredone exposure in Guadeloupe and the effect- modification among those with selected polymorphisms and exposures to fonofos and butylate exposures among applicators in Iowa and North Carolina is important mechanistic data that needs to be replicated and extended. The evidence for other pesticides with interesting preliminary gene-environment analyses is now being completed. Ongoing evaluations of telomere shortening and epigenetic aberrations are additional biomarkers that may be useful for etiologial studies of pesticides and prostate cancer risk.

Lung cancer—Over 85 % of all lung cancer in Western countries results from cigarette smoking (IARC 2004). Farmers, as a group, smoke less than the general population and usually experience significantly less lung cancer and other chronic disease compared with the general population (Alavanja et al. 2004a; Blair et al. 1985;). In the AHS, for example, the respiratory cancer incidence among private applicators (mostly farmers) was only 47% (SIR=0.47[95% CI: 0.41-0.52]) of the general population of Iowa and North Carolina. Among the farmer's spouses only 41% (SIR=0.41[95% CI: 0.32-0.51]) and among commercial pesticide applicators only 61% (SIR=0.61[95% CI: 0.33-1.02])(Alavanja et al. 2005). The strong influence of smoking on lung cancer rates can mask the effect of pesticides on lung cancer rates in Western agricultural populations, if smoking is not adequately controlled in the analysis. An excess risk of lung cancer was found among vineyard workers exposed to arsenic-based pesticides ((Luchtrath 1983) and (Mabuchi et al.; 1979; 1980). Among licensed pesticide applicators in Florida, the risk of lung cancer rose with the number of years licensed and a standardized mortality ratio greater than 2 was observed among applicators licensed for 20 or more years (Pestori et al. 1994), this excess was attributed to exposure to organophosphate and carbamate insecticides and phenoxyacetic acid herbicides. Phenoxy herbicides or contaminants of phenoxy herbicides (dioxin and furans) and excess lung cancer mortality was also observed in a cohort of workers from 4 manufacturing plants in Germany (Becher et al. 1996). Similar results were observed in a pooled analyses of 36 cohorts from 12 countries (Kogevinas et al. 1997). These positive findings were not observed in a number of earlier studies of pesticide applicators (Mac Mahon et al. 1988; Wang and Mac Mahon 1979) and pesticide manufacturers (Ott et al.1987; Coggon et al.1986).

In the AHS, two widely used herbicides, metolachlor (OR=1, 1.6, 1.2, 5; $P_{trend}=0.0002$) pendimethalin (1.0, 1.6, 2.1, 4.4; $P_{trend}=0.003$ respectively) and two widely used insecticides, chlorpyrifos (OR=1, 1.1, 1.7, 1.9; $P_{trend}=0.03$) and diazinon (OR=1, 1.6,2.7, 3.7; $P_{trend}=0.04$ respectively) showed some evidence of exposure response for lung cancer (Alavanja et al. 2004a) in a nested case-control study which controlled for tobacco use and age. These associations were later replicated in the same study using a cohort analysis for diazinon (Beane Freeman et al. 2005), chlorpyrifos (Lee et al. 2004a), pendimethlin (Hou et al. 2006), and metolachlor (Rusiecki et al. 2006). An association was also observed for dicamba and lung cancer risk in the highest tertile of life-time exposure days (RR=2.16[95% CI:0.97-4.82, $p_{trend}=0.02$] (Samanic et al. 2006)); and for dieldrin and lung cancer risk (RR=2.8 95% CI: 1.1-7.2. $p_{rend}=0.02$, (Purdue et al. 2007)) and for carbofuran and lung

cancer risk (RR=3.05 95% CI: 0.94-9.87) among those in the highest tertile of exposure (Bonner et al. 2005).

In summary, a large number of studies published subsequent to the IARC monograph 53 (1991) noted associations between several widely-used classes of insecticides, herbicides and herbicide contaminants and lung cancer. Significant exposure-response gradients were also observed between specific pesticides and lung cancer in studies that carefully controlled for smoking, age and some other lung cancer determinants. Arsenical insecticides are a recognized cause of human cancer (IARC; volume 53). While epidemiologic data linking chlorpyrifos, diazinon and dieldrin to lung cancer are relatively new, they are of particular interest because they are unlikely to be attributed to uncontrolled confounding or differential exposure misclassification. Observed associations for carbofuran, dicamba, metolachlor and pendimethalin and lung cancer are of interest but the associations were not quite as strong as the other pesticides identified. The link between specific phenoxy acid herbicides and lung cancer is not chemical specific and the link needs to be examined in other studies where associations with specific pesticides and the mechanisms through which these pesticides may increase cancer risk can be studied.

Colorectal cancer—Colorectal cancer is the third most common incident cancer in the United States, and colorectal cancer is not commonly associated with an occupational etiology. As with lung cancer, colorectal cancer incidence rates are generally found to be lower among farmers as compared with the general population. While the reason for this lower rate is not known, it is suspected that lower smoking rates and higher levels of occupational physical activity may be involved (Garabrant DH et al. 1984). A few epidemiological studies found a link between pesticides and increased risk of colorectal cancer. The risk of rectal cancer mortality was elevated among farmers in Italy (Forastiere et al. 1993) and Iceland (Zhong and Rafnsson 1996). In the Netherlands, the risk of rectal cancer among pesticide manufacturing workers was approximately 3-fold higher among those with exposure to two chlorinated pesticides dieldrin and aldrin but the highest risk was not associated with the highest exposure (Swaen et al. 2002; Van Amelsvoort et al. 2009). Although quantitatively elevated colorectal cancer risks were observed in American cohorts of manufacturing workers exposed to the herbicide alachlor (Acquavella et al. 2004), no discernable exposure-response relationship was observed for any cancer.

Aldicarb is an oxime carbamate insecticide that was associated with a significantly increased risk of colon cancer ($p_{\text{trend}}=0.001$) with the high exposure category resulting in a 4.1-fold increased risk in the highest exposure group [95% CI:1.3-12.8 with a $p_{\text{trend}}=0.001$] (Lee et al. 2007)

Dicamba is a benzoic acid herbicide that was used by 22,036 (52.5%) AHS cohort applicators. Exposure was not associated with overall cancer incidence, however, a significant trend of increasing risk for colon cancer with total lifetime days of exposure was observed. (RR=1.76 [95% CI:1.00-3.07 $P_{\text{trend}}=0.002$]). (Samanic et al. 2006). These results were largely due to elevated risk at the highest exposure level

EPTC (s-ethyl-N-,N- diprolythiocarbamate), is a thiocarbamate herbicide used in every region of the United States. It was used by 9,878 pesticide applicators in the Agricultural Health Study and these applicators were observed to have an excess risk of colon cancer at the highest cumulative number of days of use (RR=2.05[95%CI: 1.34-3.14, p trend <0.01]) (Van Bommel et al. 2008). No excess risk was noted for rectal cancer.

Imazethapyr, a heterocyclic aromatic amine, is a widely used crop herbicide first registered for use in the United States in 1989. Among, 20,646 applicators who reported use of imazethapyr, a significant trend in excess risk for colon cancer was observed but limited to proximal colon cancers, (RR = 2.73[95% CI: 1.42, 5.25, p for trend 0.001]) (Koutros et al. 2009).

Trifluralin is a 2,6-dinitro herbicide used by 25,712 pesticide applicators in the AHS. Trifluralin exposure was not associated with cancer incidence overall, however, there was an excess of colon cancer in the highest exposure category (rate ratios (RR) of 1.76 [95% CI: 1.05-2.95, p for trend=0.036] compared to the non-exposed as a referent (Kang et al. 2008).

Chlordane is an organochlorine insecticide that was widely used for termite control. It was introduced in 1948 and was phased out in the 1970s. A statistically significant increase in rectal cancer risk among AHS pesticide user of 2.7 [95% CI: 1.1-6.8] was observed with a significant trend of increasing use and increasing exposure ($P_{\text{trend}}=0.02$). (Purdue et al, 2007).

Chlorpyrifos use showed significant exposure response trend ($p_{\text{trend}}=0.008$) for rectal cancer with a relative risk of 2.7, [95% CI: 1.2-6.4] in the highest exposure category (Lee et al. 2007).

Pendimethalin, a widely used dinitroaniline herbicide, has been classified as a possible human carcinogen (Group C) by the USEPA. The compound was used by 9,089 pesticide applicators in the Agricultural Health Study and these applicators were observed to be at a significant excess risk of rectal cancer compared to non-users in the AHS (RR=4.3[95% CI: 1.5-12.7]) for the highest exposed subjects; P for trend=0.007(Hou et al. 2006).

In summary, colon cancer and rectal cancer had not been widely thought to be associated with farming or pesticide exposures at the time of IARC monograph 53. Subsequent studies among farmers in Italy (Forastiere et al. 1993) and Iceland (Zhong and Rafnsson 1996) observed significant excesses in rectal cancer mortality. In the AHS, chlordane, chlorpyrifos and pendimethalin were linked to rectal cancer and aldicarb, dicamba, EPTC, imazethapyr and trifluralin were linked to colon cancer after adjustment for age, smoking and total days of pesticide exposure. Based on AHS data it seems that the pesticides associated with colon cancer are distinct from those associated with rectal cancer, but excesses in colon cancer and rectal cancer are associated with herbicides and insecticides.

While the biological explanations for these epidemiological relationships are lacking, exposure-response patterns for these chemicals tend to strengthen the epidemiologic evidence relating pesticide exposure and colon and rectal cancer. Further evaluation of these

findings in independent samples and other studies are important next steps in assessing the potential carcinogenicity of these chemicals.

Pancreatic cancer—Pancreatic cancer is the fourth leading cause of cancer death in the United States (American Cancer Society 2008) and the sixth leading cause of cancer death in Europe (Bray et al. 2002). Smoking is the only firmly established modifiable risk factor, but unlike lung cancer, smoking only accounts for approximately 25% of pancreatic cancer cases in Western countries (Silverman et al. 1994; International Agency for Research on Cancer 2004)). Occupationally, exposure to chlorinated hydrocarbon solvents (CHS) seems the most consistent occupational association with pancreatic cancer (Ojajarvi et al. 2001), while chlorinated pesticides and pancreatic cancer yielded mixed results. Garabrant et al. (1992) found statistically significant pancreatic cancer excess among chemical manufacturing workers (28 exposed cases) exposed to DDT (OR=4.8,[95% CI:1.3-17.6]), DDD (OR=4.3[95% CI:1.5-12.4]) and ethylan (OR=5.0, [95% CI: 1.4-18.2]). In a population-based case-control study Fryzek et al. (1997) observed significant excesses of pancreatic cancer among workers exposed to ethylan, DDT and overall organochlorine pesticides among 66 exposed cases. An excess risk of pancreatic cancer was associated with high serum levels of DDE but the risk was diminished after adjustment for polychlorinated biphenyls (PCB) (Hoppin et al. 2000) . In another study which used a job-exposure-matrix to estimate the level of occupational exposure to pesticides among 484 cases and 2,095 controls (Ji et al., 2001). Information on potential confounders was obtained by questionnaire. Excess risks were found for occupational exposure to fungicides (OR=1.5[95% CI: 0.3-7.6]) and herbicides (OR=1.6[95% CI: 0.7-3.4]) in the moderate/high level after adjustment for potential confounding factors but specific chemicals were not identified. An increased risk for insecticides exposure disappeared after adjustment for fungicides and herbicide exposures.

In the AHS, 93 incident pancreatic cancer cases were diagnosed subsequent to completing a detailed questionnaire. Risk estimates were calculated controlling for age, smoking and diabetes. Two herbicides (EPTC and pendimethalin) of the 13 pesticides examined for intensity-weighted lifetime exposure use showed a statistically significant exposure response association with pancreatic cancer. Applicators in the top half of lifetime pendimethalin use had a 3-fold higher [95% CI : 1.3-7.2, p trend= 0.01] risk compared with never users, and those in the top half of lifetime EPTC use had a 2.56-fold [95% CI: 1.1-5.4, p-trend=0.01]) risk compared with never users (Andreotti et al. 2009) after adjustment for age, smoking and a history of diabetes. Since pendimethalin and EPTC are able to form N-nitroso-compounds, these findings are consistent with evidence suggesting a carcinogenic effect of nitosoamines on the pancreas (Andreotti et al. 2009). Because this was the first study to observe an association between these two herbicides and pancreatic cancer the possibility exists that this was a chance finding. Organochlorine pesticides were not associated with an excess risk of pancreatic cancer in the study, but a real association may have been missed in this cohort since DDT and many other chlorinated pesticides were banned in the 1970s and exposures were greatly diminished after that time(Purdue et al. 2007).

Melanoma—The incidence of cutaneous melanoma has steadily increased over recent decades and there is striking risk variation by geographic location (Mackie et al. 2009). Ultraviolet radiation (UVR) exposure and individual phenotype (common nevi, atypical nevi, familial melanoma, fair eye and skin color, inability to tan, high-density freckles, premalignant and skin cancer lesions) are well-known major etiologic risk factors for cutaneous melanoma, but data have suggested that the combination of these factors is not sufficient to explain the melanoma risk (Mackie et al. 2009; Fortes et al. 2007; Fortes and de Vries 2008).

An Italian case-control study observed that melanoma patients had a higher use of pesticides in a residential setting compared with controls (Fortes et al. 2007). A study of white, Ranch Hand Vietnam veterans found an increased risk of melanoma related to dioxin exposure and herbicide exposure (Akhtar et al. 2004). An additional report of an elevated SIR for melanoma among Pan Britannica industry's pesticide workers suggests that pesticides are related to the development of melanoma (Wilkinson et al. 1997).

In the AHS, specific pesticide exposures ascertained by questionnaire prior to the onset of disease were found to be significantly associated with cutaneous melanoma. No significant associations were seen with overall herbicide, insecticide, fungicide, or fumigant use, or with chemical classes of pesticides including phenoxy herbicides, triazine herbicides, organochlorine insecticides, or organophosphate insecticides. However melanoma was significantly associated with the fungicide maneb/mancozeb (OR=2.4[95% CI: 1.2-4.9 for those with over 63 days of exposure, trend p=0.006]), the insecticides parathion (OR=2.4[95% CI: 1.3-4.4 for over 56 days of exposure, trend p=0.003]), and carbaryl (OR=1.7[95% CI: 1.1-2.5 for over 56 exposure days, trend P=0.013]) (Dennis et al. 2010; Mahajan et al. 2007) after adjustment for age and measures of skin pigmentation. While the evidence linking specific pesticides to melanoma is growing, specific links have yet to be replicated.

Multiple Myeloma—Multiple myeloma (MM) is a malignancy arising from mature plasma B-cells in the bone marrow producing a serum immunoprotein. Among hematopoietic malignancies MM has the poorest prognosis and lowest survival rates (i.e., 5-year 15-30%) (Grogan et al. 2001). According to the American Cancer Society, approximately 20,000 new cases and 11,000 multiple myeloma deaths are expected in the United States in 2010 (American Cancer Society 2008).

Farming has been consistently associated with an increased risk of MM since the 1970s when Milham (1971) reported a higher than expected number of MM deaths among American farmers. Khuder and Mutgi (1997) published a meta-analysis of farm employment and MM and assessed 32 case-control and cohort studies done between 1981 and 1996.. The pooled analysis of the OR from individual papers showed a relative risk of 1.23 with 95% CI: 1.14 to 1.32 for the association between MM and farming. Most recently, a systematic review of case-control studies of multiple myeloma of occupational exposure to pesticides showed a pooled odds ratio (OR) for working farmers of 1.39[95% CI: 1.18-1.65] for pesticide exposure 1.47 [95%CI: 1.11-1.94]. For working on a farm for more than 10 years OR was 1.87[95% CI: 1.15-3.16] (Merhi et al. 2007) .

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma-cell proliferative disorder associated with a life-long risk of progression to multiple myeloma. In a prospective study, Landgren et al.(2009a) found that virtually all MM cases are preceded by MGUS 2 or more years prior to MM diagnosis, establishing a key role for MGUS in the pathway to MM.

In the AHS, a 1.34-fold [95% CI: 0.97-1.81] risk of multiple myeloma was observed (Alavanja et al. 2005). Compared with men from Olmsted County, Minnesota, the age-adjusted prevalence of MGUS was 1.9-fold [95% CI, 1.3-2.7-fold] higher among male pesticide applicators in the AHS (Landgren et al. 2009b). Among applicators, a 5.6-fold [95%CI: 1.9 to 16.6-fold], 3.9-fold [95% CI: 1.5- to 10.0- fold], and 2.4-fold [95% CI: 1.1- to 5.3-fold] increased risk of MGUS prevalence was observed among users of the chlorinated insecticide dieldrin, the fumigant mixture carbon-tetrachloride/carbon disulfide, and the fungicide chlorthalonil, respectively. A previous AHS examination determined that a relationship between exposure and disease is not likely confounded by farming or non-farming activities (Coble et al. 2002) , increasing the likelihood that pesticides and not confounding factors are responsible for these associations.

In the same study a statistically significant risks for multiple myeloma were associated with lifetime exposure-days (RR=5.72 [95% CI: 2.76-11.87; $P_{trend}=0.01$]), compared with applicators reporting that they never used permethrin (Rusiecki et al. 2009) in analysis adjustment for age, gender, family history of cancer, cigarette smoking, state of residence and enrollment year. The elevated risk was limited to the highest exposure category which had 10 cases of MM. These findings were similar across a variety of alternative exposure metrics, exposure categories and reference groups.

In summary, although the evidence linking pesticide exposure to multiple myeloma has increased in recent years, additional epidemiological evidence is needed to test the hypothesis that specific pesticides are positively associated with multiple myeloma. The significant association between MM and permethrin exposure needs to be carefully evaluated in other studies. The use of preclinical biomarkers of multiple myeloma (i.e., MGUS) may be a powerful approach to test etiological hypotheses concerning MM, since pesticide exposure seems to give rise to more cases of MGUS than MM.

Leukemia—Leukemia is a heterogeneous category of hematopoietic malignancies, including chronic and acute subtypes that have complicated the identification of etiologic factors. Moreover, pesticides include large number of diverse chemicals and formulations that also exacerbates the difficulty in identifying associations between specific pesticides active ingredients and specific subtypes of leukemia. Notwithstanding, causal associations with leukemia were demonstrated for 2 agents: benzene and ionizing radiation. Other suspected occupational causes include pesticides, infectious agents, electromagnetic fields, and solvents and aromatic hydrocarbons (Descatha et al. 2005; Rukkala et al., 2002).

Since the various subtypes of leukemia are relatively infrequent and since they are likely to have different etiologies (Greaves 1997; Keller-Byrne et al. 1995), identifying a clear link to specific pesticides has been challenging. A recent meta-analysis of 14 cohort studies of

workers in plants manufacturing pesticides and leukemia was published (Van Maele-Fabry et al. 2008) and a meta-rate ratio was estimated at 1.43 [95% CI:1.05-1.94]. A recent meta-analysis of 13 case-control examining the association between occupational exposures and hematopoietic cancers, observed a OR of 1.35[95% CI: 0.9-2.0] (Merhi et al. 2007). Epidemiological evidence was insufficient to permit identification of a specific pesticide or chemical class that would be responsible for the increased risk in either cohort or case-control studies. With limited exposure data, it is impossible to assess the contribution of the active ingredient or other ingredients and to distinguish the diversity of leukemia.

Organophosphates have been associated with leukemia and other immunologically related cancers in the epidemiological literature (Brown et al. 1990; Cantor et al. 1992; Clavel et al. 1996; De Roos et al. 2003; Waddel et al. 2001). The leukemogenic effects of organophosphates may be related to immune function perturbation. In the AHS, leukemia risk was elevated for the high category of intensity-weight exposure-days for fonofos, an organophosphate insecticide applied to corn, sugar cane, tobacco and several other crops (RR=2.67[95% CI:1.06-6.70, $p_{\text{trend}}=0.04$]) (Mahajan et al. 2006a). Diazinon, another common organophosphate insecticide, is registered for a variety of uses on plants and animals. In the AHS, diazinon was associated with leukemia (RR=3.36[95% CI: 1.08-10.49 $p_{\text{trend}}=0.026$]) (Beane Freeman et al. 2005). A positive association was also observed between the use of alachlor in the AHS cohort and an elevated risk of leukemia (Lee et al. 2004b) and EPTC and leukemia (Van Bemmelen et al. 2008), although the risk associated with both pesticides was limited to the highest exposure group and further follow-up will be necessary. All leukemia risk estimates in AHS cohort analyses are adjusted for age, other pesticides that are potentially confounders.

Organochlorine (OC) insecticides are a class of insecticides characterized by their cyclic structure, number of chlorine atoms and low volatility. Chlordane and heptachlor are structurally related organochlorine insecticides and the technical grade of each compound contains approximately 10-20% of the other compound (IARC). IARC has judged that the weight of evidence suggests that chlordane and heptachlor as well as DDT and toxaphene are possible human carcinogens (IARC-2B) with excesses observed for lung cancer, leukemia, non-Hodgkins lymphoma and soft tissue sarcoma but aldrin, dieldrin and lindane are not classifiable as to their carcinogenicity (IARC and Cancer 2001). In the AHS chemical-specific associations with leukemia were observed for chlordane/ heptachlor 2.1 (95% CI: 1.1-3.9) and lindane 2 (95% CI:1.1-3.5) (Purdue et al. 2007), although the evidence for lindane was considered equivocal by the authors.

Metrobuzin is a selective triazinone herbicide that is used to control broadleaf weeds and grasses in vegetable and field crops. The results from this study suggest a potential association between metribuzin use as measured by intensity-weighted lifetime exposure days and certain lymphohematopoietic malignancies. The highest exposure tertile for lymphohematopoietic malignancies were 2.09 [95% CI: 0.99-4.29], $p_{\text{trend}}=0.02$ and for leukemia 2.42 [95% CI: 0.82-7.19; $p_{\text{trend}}=0.08$]; however, having not been observed previously, caution needs to be used to interpret the data (Delancey et al. 2009)

In a prospective study, peripheral blood obtained up to 77 months before a diagnosis of chronic lymphocytic leukemia (CLL) diagnosis, prediagnostic B-cell clones were present in 44 of 45 patients with CLL (Landgren et al. 2009c). Use of B-cell clones as prediagnostic markers of CLL may be a valuable tool in the evaluating the link between specific pesticides and CLL.

In summary, leukemia is not one disease but many related diseases with varying etiologies. While the evidence linking pesticide exposure in general to leukemia is abundant, the evidence linking specific pesticides to leukemia is limited and the evidence linking a specific pesticide to a specific leukemia subtype is largely nonexistent. Recent epidemiological evidence linking specific pesticides to leukemia has established hypotheses that need to be evaluated in other studies, the associations between leukemia overall and diazinon (an organophosphate insecticide) and chlordane (an OC insecticide) are statistically significant and are of particular interest. The use of preclinical biomarkers MBL to study the etiology of chronic lymphocytic leukemia may be a powerful approach for this leukemia subtype (Landgren et al. 2009a).

Non-Hodgkin lymphoma (NHL)—Non-Hodgkin lymphoma is a diverse group of over 20 different malignancies affecting the immune system/ lymphatic system (Jaffe et al. 2001). The classification system of specific subtypes is now based on immunohistochemistry, cytogenetics and evolving knowledge in clinical presentation (Jaffe et al. 2001). Interest in the etiology of NHL has increased since there has been a substantial rise in the incidence of the disease from the 1960's through the 1980's with a leveling off in the 1990's. The established risk factors for NHL include different immunosuppressive state including human immunodeficiency virus (HIV), autoimmune diseases as Sjogren's syndrome, systemic lupus erythematosus rheumatoid arthritis, and psoriasis and celiac disease (Grulich and Vajdic . 2005). These conditions cannot account for the increases observed (Grulich and Vajdic 2005). A meta-analysis of case-control studies focusing on 13 case-control studies published between 1993-2005 observed an overall significant meta-odds ratio between occupational exposure to pesticides and NHL (OR=1.35[95% CI: 1.2-1.5]). When observations were limited to those that had more than 10 years of exposure the risk elevation (OR=1.65[95% CI: 1.08-1.95]) (Merhi et al. 2007). While the meta-analysis supports the hypothesis that pesticides are associated with NHL, they collectively lack sufficient detail about pesticide exposure and other information on risk factors for hematopoietic cancers to identify specific causes (Merhi et al. 2007).

Since the publication of the meta-analysis by Merhi et al. (2007), several new studies add weight to the evidence linking pesticides to NHL. A new population-based case-control study in Sweden with 910 cases and 1016 controls observed a significant excess risk of NHL associated with the phenoxyherbicide MCPA (OR=2.81 [95% CI: 1.27-6.22]) and glyphosate (OR=2.02 [95% CI:1.16-3.71]). Glyphosate was observed to have an exposure-response association with NHL when comparing NHL risk for those with no exposure, 10 days of exposure and >10 days of exposure (OR=1.0 ref, OR=1.69 (95% CI:0.70-4.07), OR=2.36 (95% CI:=1.04-5.37 respectively) but MCPA users did not show a mono-tonic exposure-response pattern. Glyphosate users had over a 5-fold excess risk of unspecified non-Hodgkin lymphoma (OR=5.63 [95% . CI:1.44-22.0]), and MCPA had over a 9-fold

excess risk with unspecified non-Hodgkin's lymphoma (OR=9.31 (95% CI: 2.11-41.2) Insecticides overall gave OR of 1.28 (95%CI: 0.96-1.72) and impregnating agents OR of 1.57 [95% CI:1.07-2.30] 2,4-D and 2,4,5,T (2,4,5-trichlorophenoxyacetic acid) have been banned from Sweden and could not be evaluated (Eriksson et al. 2008). No excess risk of NHL was observed among glyphosate users in any exposure category in the AHS, even among those with 57 or more days of occupational exposure, although a non-significant 2-fold excess of myeloma was observed (De Roos et al. 2005).

A new hospital-based case-control study conducted in 6 centers in France examined the association between pesticides and 244 cases of NHL and other lymphoid neoplasms (Hodgkin's lymphoma, lympho-proliferative syndromes (LPS) and multiple myeloma). While increased odds ratios for NHL was observed for users of organochlorine and organophosphate insecticides, carbamate fungicides, and triazine herbicides, the study was too small to evaluate the association with specific pesticides (Orsi et al. 2009).

Collins et al. (2009) noted there were 8 deaths from non-Hodgkin's lymphoma (standardized mortality ratios = 2.4, 95% CI : 1.0 to 4.8) among workers exposed to dioxins in pentachlorophenol (PCP) manufacturing. No trend of increasing risk for any cause of death with rising dioxin exposure was observed. However, the highest rates of non-Hodgkin's lymphoma were found in the highest exposure group (standardized mortality ratios = 4.5, 95% CI : 1.2 to 11.5).

In a population-based NHL case-control study in British Columbia significant exposure response trends were observed for 6 pesticides including *p,p'*-DDE, hexachlorobenzene (HCB), beta-hexachlorocyclohexane (beta-HCCH), mirex, oxychlordan, cis-nonachlor and trans—non-achlor. The strongest association was found for oxychlordan which is a metabolite of chlordane. The OR for quartiles of exposure of oxychlordan in blood was 1. (ref), 1.36 [95 % CI:0.88-2.08], 1.39 [95% CI:0.88-2.19], 2.68 [95% CI: 1.69-4.24] *p-trend*,=0.001 (Spinelli et al. 2007).

In a population-based case-control study conducted in 6 Canadian provinces including Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia with cases diagnosed between September 1, 1991 and December 31, 1994 a positive family history of cancer both with (OR=1.72 [95% CI 1.21-2.45]) and without pesticide exposure (1.43 [95% CI:1.12-1.83]) increased risk to NHL (McDuffie et al. 2009).

Two epidemiological studies reported that the association of NHL with pesticides was largely limited to NHL cases with chromosomal translocations t(14;18) (Schroeder JC et al. 2001; Chiu BCH et al. 2006). In the Schroeder et al. (2001) study conducted in Iowa and Minnesota NHL with t (14:18) translocation were significantly elevated for dieldrin (OR=3.7[95% CI: 1.9-7.0]), lindane (OR=2.3 [95% CI: 1.3-3.9]), toxaphene (OR=3.0 [95% CI: 1.5-6.1]), and atrazine (OR=1.7 [95% CI: 1.0-2.8]). In the Chiu et al. (2006) study conducted in Nebraska the NHL with t (14:18) translocations were significant elevated for dieldrin (OR=2.4 [95% CI: 0.8-7.9]), toxaphene (OR=3.2 [95% CI:0.8-12.5]), and lindane (OR=3.5; [95% CI:1.4-8.4]) compared with nonfarmers. Atrazine was not reported in this study, but triazine herbicide users were at a significantly elevated risk for t (14:18) positive

NHL. A direct connection between agricultural pesticide use, t(14,18) in blood, and malignant progression to follicular lymphoma (FL) was found in a prospective cohort study of farmers (Agopian et al. 2009). This study provides a molecular connection between agricultural pesticides, t (14:18) frequency in blood, and clonal progression but links to specific pesticides was not possible.

In summary, non-Hodgkin lymphoma (NHL) is not one disease but many related diseases with seemingly varying etiologies. New evidence linking pesticide exposures (i.e., dieldrin, lindane, toxaphene, and atrazine) to NHL subtypes with t (14:18) translocations suggests an etiological link. These studies are important in further refining understanding of the link between pesticides and NHL but they were too small to assess exposure response relationships. A large case-control study in Sweden linked use of glyphosate and MCPA to NHL. While glyphosate was observed to have an exposure-response association, MCPA did not. No excess risk of NHL was observed among glyphosate users in the AHS with even a greater number of exposure days. With two relatively strong studies giving inconsistent results, glyphosate is included on table 1 pending evaluation of the biological effects of exposure and additional epidemiological data.

Another large case-control study in British Columbia provided further evidence that organochlorine pesticides contributed to NHL risk. The risk was particular strong for oxychlordane, a metabolite of chlordane.

Soft Tissue Sarcoma—Soft tissue sarcoma (STS) is a rare malignant neoplasm affecting supporting tissue other than bone and cartilage. An association between STS and dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin or TCDD) was examined in a number of studies with somewhat inconsistent results. A positive association was observed between soft tissue sarcoma and TCDD among 5,172 men at 12 different chemical plants (Fingerhut et al. 1991). Among workers with one or more years of exposure and 20 years of latency 3 STS cases were observed and only 0.3 were expected (SMR=922 [95% CI: 190-2695]).

In an international cohort study, 21,863 male and female workers exposed to phenoxy herbicides and dioxin, had an excess risk of STS with an SMR equal to 2.03 [95% CI: 0.75-4.43] (Kogevinas et al. 1997). In contrast, Fleming et al. (1999) found no cases of STS in a cohort of 33,658 pesticide applicators in Florida who were followed from January 1, 1975 through December 31, 1993, and Becher et al. (1996) found no cases of STS in a cohort of 2,479 German workers exposed to phenoxy herbicides and dioxin with 54,063 person-years of observation. In Seveso, Italy the health consequences of an industrial accident resulting in dioxin exposure to the surrounding community was studied by Bertazzi et al. (2001). No STS cases were found in the two areas nearest the accident but in an area further from the highest contamination a non-significant excess of STS RR=2.1 [95% CI: 0.6-5.4] was observed. IARC classified 2,3,7,8-tetrachlorodibenzo-p-dioxin a human carcinogen in 1997 based on exposure-response with cancers overall, but not based on an exposure-response association with a specific cancer. This decision met with some criticism in the literature (Cole et al. 2003). Since IARC designated dioxin a human carcinogen, a review of the literature (Steenland et al. 2004) provided additional support for the IARC's classification. More recently, a study following the morality experience of 1,615 workers

from 1942-2003 who had occupational exposure to dioxin in a plant in Midland, Michigan observed 4 deaths from STS (SMR=4.1 [95% CI: 1.1-10.5]), but no excess deaths from other cancers (Collins et al. 2009).

Other Organs—Ovarian cancer is the fifth most common type of cancer among North American women and it is a leading cause of gynecological cancer death. Since hormones and reproductive factors are so influential in the etiology of ovarian cancer, several investigators (Garry et al. 2002; Salehi et al., 2010) suggested that certain pesticides with estrogenic and anti-estrogenic activity may also play a role in the etiology. Two case-control studies from Italy suggested a possible role for the triazine herbicides atrazine, simazine and cyanazine in the etiology of ovarian cancer. The initial observation was made in a hospital-based study with a relative risk of 4.4 for ovarian cancer among women with definite or probable exposure to triazine herbicides (Donna et al. 1984). A follow-up population-based study observed a significant relative risk of 2.7 for ovarian cancer among those exposed to triazine herbicides (Donna et al. 1986). In a central California population-based case-control study of incident cases (n=256) and random digit-dialed control subjects (n=1122) the analysis of ever versus never occupational exposure to triazines demonstrated that cases were numerically more likely to be exposed than control subjects (OR_{adjusted}=1.34 [95% CI: 0.77-2.33]) (Young et al., 2004 2005). There was no evidence of a dose-response relationship between triazines and ovarian cancer (P=0.22). In the AHS, a significant excess risk of ovarian cancer was observed among female applicators (i.e., 8 observed and only 1.9 expected) but not among female spouses of male farmers, (Alavanja et al. 2005) and it was not possible to identify an exposure responsible for this association. The total evidence is not persuasive as to the presence or absence of an association between ovarian cancer and triazine exposure but the issue is important and unresolved and more research is necessary.

DDT (1,1-dichloroethenylidene)-bis (4-chlorobenzene) and other organochlorine pesticides have received considerable attention as possible causes of breast cancer. A pooled analysis of 5 large studies in the United States, however, found no significant association between DDE levels (a metabolite of DDT) or PCBs (polychlorinated biphenyls) and breast cancer risk (Laden et al. 2001). Recently, data from the 1994-2004 National Health and Examination Survey was used to examine the association between serum concentrations of organochlorine and breast cancer, but no positive association was observed, casting doubt on the hypothesized association (Xu et al. 2010). However, the Seveso Women's Health Study observed an exposure-response relationship between breast cancer and serum TCDD levels in women in the highest dioxin exposure zone after adjusting for other major risk factors such as parity, lactation, age at first pregnancy, smoking and other factors (Pesatori et al. 2009). Although much of the recent data does not support an association between pesticides and breast cancer, some positive observations keep the issue alive but unresolved.

A significant excess risk of bladder cancer was observed among pesticide applicators in the AHS cohort who were exposed to the heterocyclic aromatic amine pesticide, imazethapyr. Rate ratios (RRs) were increased by 137% in the highest exposure group (RR=2.37 95% CI: 1.20-4.68), with a significant trend of rising risk with elevated imazethapyr exposure ($p_{\text{trend}}=0.01$). (Koutros et al. 2009). Although there is no experimental evidence linking imazethapyr to cancer in lab animals and no prior epidemiological evidence of

carcinogenicity, this newly emerging class of herbicides deserves careful post-market surveillance and biological testing.

Thyroid cancer is relatively uncommon, but it is the most common neoplasm of the endocrine system. Associations between pesticides and thyroid cancer have not been well studied. Since some pesticides have endocrine disrupting properties and at least one study has shown an association between agricultural chemicals and thyroid cancer (Sokic et al. 1994) the question of an etiological link between specific pesticides and thyroid cancer is one that needs to be more completely examined.

Malignant neoplasms of the brain account for approximately 2% of the annual cancer deaths in the United States. Meta-analyses in 1998 (Khuder et al. 1998) and in 1992 (Blair et al. 1992, Blair and Beane Freeman, 2009) found consistent positive findings that suggested there was a weak association between brain cancer and farming. The analysis in 1998 reported a relative risk equal to 1.30 [95% CI: 1.09-1.56], while the analysis in 1992 reported an elevated quantitative risk of brain cancer OR=1.05 [95% CI: 0.99-1.12]. The epidemiologic literature found only equivocal results linking specific pesticides and brain cancer (Bohnen and Kurland 1995) but some evidence suggests insecticides and fungicide exposure in women in the United States may be associated with a small increased risk for brain cancer (Cocco et al. 1999). A major limitation of the studies published to date is the lack of details regarding exposure. Analyses by job title alone often result in misclassification of exposure, resulting in an underestimation of brain cancer risk by occupation. No firm, specific pesticide link to brain cancer has been made but additional studies are warranted.

Testicular cancer is relatively uncommon in the United States with an age-adjusted incidence rate of 4.5 per 100,000 men (Amer Can Society, 2008). While studies from South Africa (Aneck-Hahn et al. 2007) and Mexico (de Jager et al. 2006) have indicated impaired semen quality associated with DDT exposure among people living in endemic malaria areas, a link with testicular cancer has not been established, nor has a link been established with any other pesticide.

Discussion and Conclusions

Currently, over 800 active ingredients and thousands of pesticide formulations are on the market in the United States and other countries, but only arsenical insecticides (International Agency for Research on Cancer, 1991) and TCDD (a contaminant of the phenoxy herbicide 2,4,5-T) are identified as human carcinogens by IARC (category 1)(International Agency for Research on Cancer, 1997). In IARC monograph number 53 published in 1991, "occupational exposures in spraying and application of non-arsenical insecticides" as a group are classified as "probable human carcinogens" (category 2A)" (IARC and Cancer 1991). A major challenge to epidemiology is the identification of whether specific compounds are responsible for specific human cancer risks. Such determinations are crucial for precise and effective public health action. As new scientific evidence emerges, linking specific pesticides with specific cancers, the precautionary principal would indicate a multidisciplinary reevaluation of human carcinogenicity of certain pesticides is necessary.

While new epidemiologic data will add important data on the veracity of the emerging associations, a number of conclusions can be gleaned from the existing epidemiologic evidence regarding the role of occupational pesticide exposure in the etiology of various cancers.

Chemicals in every major functional class of pesticides (i.e., insecticides, herbicide, fungicides, and fumigants) were noted to have significant associations with an array of cancer sites. Moreover, associations have been observed with specific chemicals in many chemical classes of pesticides (e.g., chlorinated, organophosphate, and carbamate insecticides and phenoxy acid and triazine herbicides). However, not every chemical in these classes has been observed to be associated with cancer in humans. This has likely diluted the apparent exposure-response associations between pesticides and cancer in many previous studies that focused on chemical class rather than specific pesticides. Focusing etiologic studies on exposures to individual pesticides and specific health endpoints is necessary to identify which specific pesticides are human carcinogens and promote cancer incidence among occupationally exposed populations. The adverse health effect of concurrent exposures to multiple pesticides is of considerable toxicological interest, but it has been even more methodologically challenging for epidemiological studies. Methodological challenges, such as small numbers of exposed cases, and crude and imprecise exposure assessments that lack specificity on specific active ingredients have hampered many previous epidemiologic studies. Additionally, inadequate ascertainment of lifestyle factors and their control in the analysis in studies that use SMRs and SIRs have distorted the etiological picture of some earlier studies masking the effect of pesticide exposure on lung, colon, rectal, pancreas, and bladder cancer.

Evidence is accumulating that suggests genetic susceptibility to the carcinogenic effects of certain pesticides may vary in a population and assessing the impact of this variation may be important to hazard identification. The use of biomarkers to identify pre-clinical disease and early biologic effects such as MGUS, MBL, telomere length analysis, and t(14:18) translocations can provide important additional compelling information to identifying which specific active ingredients contribute to the etiology of specific cancer sites. Moreover, the use of these biomarkers may be informative with regards to the mechanisms through which pesticides potentiate carcinogenesis in humans.

In conclusion, the published epidemiological literature linking specific pesticides to specific cancers has grown steadily since the IARC monograph 53, published in 1991 and IARC monograph 69, published in 1997. Important new data are now available but the information from many disciplines is scattered through the scientific literature. Informed selection of pesticides by users may mitigate cancer risk to both those occupationally and those not occupationally exposed to pesticides. Since use of pesticides world-wide results in exposure to millions of workers occupationally and to hundreds of millions of people through nonoccupational routes of exposure, identifying potential carcinogens among these chemicals should be an important public health priority. Other than arsenical insecticides and TCDD (a pesticide contaminant), which are now categorized by IARC as human carcinogens, 21 chemicals were selected from the literature emerging subsequent to the last IARC review, because they have shown significant exposure-response associations in studies

of specific cancer, while controlling for major potential confounders (Table 1). This list is not exhaustive and other candidate chemicals are likely to emerge as the literature assessing the link between specific chemicals and specific cancers expands. It is recognized that many of these observations need to be evaluated in other epidemiological studies and important data from toxicology and cancer biology need to be considered in conjunction with the epidemiologic data before a final evaluation of the epidemiologic data can be made. Nonetheless, it is now reasonable and timely to engage the scientific community and regulatory agencies in an expert review and evaluation of pesticides and their potential to induce cancer in occupational setting.

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Abbreviations

AHS	Agricultural Health Study
CI	confidence Interval
IARC	International Agency for Research on Cancer
OP	organophosphates
OR	odds ratios
MBL	monoclonal B-cell lymphocytosis
MGUS	monoclonal gammopathy of undetermined significance RR risk ratios
SIR	standardized incidence ratio
SMR	standardized mortality ratio
TL	telomere length

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Table 1

Pesticides for which post-market surveillance data suggests human carcinogenicity

Cancer Site	Pesticide	Exposed Cases (Exposure Metric)	Relative Risk Estimate	P for trend	Reference
Prostate					
	Butylate * <i>Herbicide Thiocarbamate</i>	37 (LD)	RR=1.0(NE.Ref), 0.95(0.6-1.6), 1.7(1.0-2.8) [among study subjects with a family history of prostate cancer]	0.04	(Lynch et al. 2009)
	Clordecione <i>Insecticide Cyclodiene</i>	41 (ug/l in plasma)	OR=1.0(NE.Ref), 0.97(0.33-2.83), 3.2(1.0-10.1), 3.0(1.1-8.1) [among study subjects with a family history of prostate cancer]	<0.001	(Multigner et al. 2010)
	DDT <i>Insecticide Organochlorine</i>	114 (LD)	OR=1.0(NE.Ref), 1.24 (0.71-2.16), 1.68(1.04-2.70)	0.03	(Band et al. 2010)
	Fonofos * <i>Insecticide Phenyl ethylphosphonothioate</i>	49(LD)	RR=1.0 (NE.ref), 1.4(90.8-2.4), 1.6(0.9-2.6), 1.8(1.0-3.1)[among study subjects with a family history of prostate cancer] Significant interaction between Fonofos and 8q24	0.02	(Mahajan et al. 2006a) (Koutros et al. 2010a)
	Lindane <i>Herbicide Nitrophenyl ether</i>	71 (LD)	OR=1.0(NE.ref), 0.91(0.44-1.89), 2.02(1.15-3.55)	0.03	(Band et al. 2010)
	Simazine <i>Herbicide Triazine</i>	70(LD)	OR=1.0(NE.ref), 1.48(0.75-2.92), 1.89(1.08-3.33)	0.01	(Band et al. 2010)
Lung Cancer					
	Chlorpyrifos * <i>Insecticide Organothiophosphate</i>	73 (LD)	RR=1.0(NE.Ref), 0.8(0.4-1.5), 1.6(0.6-2.1), 1.4(0.9-2.7), 2.2(1.3-3.6)	0.002	(Lee et al. 2004a)
	Diazinon * <i>Insecticide Organothiophosphate</i>	27 (LD)	RR=1.0(NE,REF), 1.0(0.5-2.2), 0.5(0.2-1.8), 2.4(1.3-4.4)	0.005	(Beane Freeman et al. 2005)
	Dieldrin * <i>Insecticide Cyclodiene</i>	10 (LD)	OR=1.0(NE.Ref), 1.6(0.6-3.9), 2.7(1.1-7.2)	0.02	(Purdue et al. 2007)
Colo-rectal Cancer					
Colon Cancer					
	Aldicarb <i>Insecticide Oxime carbamate</i>	15 (LD)	OR=1.0 (NE.Ref), 2.7(1.1-6.6), 5.2(1.5-18.1), 4.1(1.3-12.8)	0.001	(Lee et al. 2007)
	Dicamba <i>Herbicide Benzoic acid</i>	50 (LD)	RR=1.0 (LE,Ref), 2.1 (0.9-4.6), 1.9 (0.8-4.4), 3.3(1.4-7.7)	0.02	(Samanic et al. 2006)

Cancer Site	Pesticide	Exposed Cases (Exposure Metric)	Relative Risk Estimate	P for trend	Reference
	EPTC <i>Herbicide Thiocarbamate</i>	39 (LED)	RR=1.0(NE.Ref), 0.8(0.4-1.5), 1.4(0.8-2.8), 2.1(1.3-3.5)	<0.01	(Van Bommel et al. 2008)
	Imazethapyr <i>Herbicide Imidazolinone</i>	79 (IWLD)	RR=1.0(NE.Ref), 0.9(0.6-1.4), 1.2(0.8-1.9), 1.1(0.6-2.0), 1.8(1.1-2.9)	0.02	(Koutros et al. 2009)
	Trifluralin <i>Herbicide dinitroaniline</i>	85 (IWLD)	RR=1.0(NE.Ref), 0.9(0.6-1.4), 1.1(0.7-1.8), 0.6(0.3-1.4), 1.8(1.1-3.0)	0.036	(Kang et al. 2008)
Rectal Cancer					
	Chlordane <i>Insecticide Cyclodiene</i>	9 (ILD)	RR=1.0(NE.Ref), 0.5(0.1-3.9), 2.7(1.1-6.8)	0.02	(Purdue et al. 2007)
	Chlorpyrifos <i>Insecticide organothiophosphate</i>	41 (LD)	OR=1.0(NE.Ref), 1.1(0.6-2.1), 1.1(0.6-2.3), 2.5 (1.2-5.3), 2.7(1.2-6.4)	0.008	(Lee et al. 2007)
	Pendimethalin <i>Herbicide dinitroaniline</i>	34 (LD)	RR=1.0 (LE.Ref), 1.5(0.5-4.3), 1.1(0.3-3.4), 3.5(1.2-10.8)	0.06	(Hou et al. 2006)
Pancreas Cancer					
	DDT <i>Insecticide Organochlorine</i>	6 (ever exposed)	OR=1 (NE Ref), 4.8(1.3-17.2)	0.02	Garabrant et al. 1992)
	EPTC <i>Herbicide Thiocarbamate</i>	14 (IWLD)	OR=1.0(NE ref), 1.8(0.7-4.3), 2.5(1.1-2.2)	0.01	Andreotti et al. 2009)
	Pendimethalin <i>Herbicide dinitroaniline</i>	14 (IWLD)	OR=1.0(NE ref), 1.4(0.5-3.9), 3.0 (1.3-7.2)	0.01	Andreotti et al. 2009)
Melanoma					
	Carbaryl <i>Insecticide Carbamate</i>	76 (LD)	OR=1.0(NE.ref), 1.3(0.9-2.1), 1.7(1.1-2.5)	0.013	(Dennis et al. 2010)
	Maneb/ Mancozeb <i>Fungicide Polymeric dithiocarbamate</i>	17 (LD)	OR=1.0(NE..ref), 1.3(0.9-2.1), 1.7(1.1-2.5)	0.006	(Dennis et al. 2010)
	Parathion <i>Insecticide Organothio phosphate</i>	21 (LD)	OR=1.0(NE.ref), 1.6 (0.8-3.1), 2.4(1.3-4.4)	0.003	(Dennis et al. 2010)
	Toxaphene <i>Insecticide Organochlorine</i>	8 (LD)	RR=1.0(NE.Ref), 0.7(0.2-2.3), 2.9(1.1-8.1)	0.03	(Purdue et al. 2007)
Leukemia					
	Chlordane <i>Insecticide Cyclodiene</i>	18 (LD)	RR=1.0(NE.Ref), 1.2(0.4-3.3), 2.6(1.2-6.0)	0.02	(Purdue et al. 2007)
	Diazinon <i>Insecticide Organo-</i>	11 (LD)	RR=1.0(NE.Ref), 1.1(0.3-3.7), 2.6(0.9-7.8), 3.4(1.1-10.5)	0.026	(Beane Freeman et al. 2005)

Cancer Site	Pesticide	Exposed Cases (Exposure Metric)	Relative Risk Estimate	P for trend	Reference
	<i>thiophosphate</i>				
Non-Hodgkins Lymphoma					
	Chlordane (as oxychlordane) Insecticide, cyclo-diene	329 (blood levels oxychlordane)	OR=1.0 (LE), 1.36(0.88-2.08), 1.39(0.88-2.08), 1.39(0.88-2.19), 2.68(1.69-4.24)	0.009	(Spinelli et al. 2007)
	Lindane <i>Herbicide</i> <i>Nitrophenyl ether</i>	12 (IWLD)	RR=1.0(NE.Ref), 1.6(0.6-4.1), 2.6(1.1-6.4)	0.04	(Purdue et al. 2007)
Bladder Cancer					
	Imazethapyr <i>Herbicide</i> <i>Imidazolinone</i>	41 (IWLD)	RR=1.0(NE.Ref), 1.0(0.5-1.8), 0.9(0.5-1.8), 1.3(0.6-2.9), 2.4(1.2-4.7)	0.01	(Koutros et al. 2009)

LD.=Life time Days; IWLD=Intensity-Weighted Life Days; NE Ref=No Exposure Reference group, LE. Ref=Low Exposure Reference group

* When multiple papers from the same study were reported (and consistent), only the latest paper was cited.