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Incidence of Solid Tumors Among Pesticide Applicators Exposed to the Organophosphate Insecticide Diazinon in the Agricultural Health Study: An Updated Analysis

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Abstract

Objective: Diazinon, a common organophosphate insecticide with genotoxic properties, was previously associated with lung cancer in the Agricultural Health Study (AHS) cohort, but few other epidemiologic studies have examined diazinon-associated cancer risk. We used updated diazinon exposure and cancer incidence information to evaluate solid tumor risk in the AHS.

Methods: Male pesticide applicators in Iowa (IA) and North Carolina (NC) reported lifetime diazinon use at enrollment (1993–1997) and follow-up (1998–2005); cancer incidence was assessed through 2010(NC)/2011(IA). Among applicators with usage information sufficient to evaluate exposure-response patterns, we used Poisson regression to estimate adjusted rate ratios (RRs) and 95% confidence intervals (95% CI) for cancer sites with ≥10 exposed cases for both lifetime (LT) exposure days and intensity-weighted (IW) lifetime exposure days (accounting for factors impacting exposure).

Results: We observed elevated lung cancer risks (N=283) among applicators with the greatest number of LT (RR=1.60; 95%CI:1.11,2.31;P_{trend}=0.02) and IW days of diazinon use (RR=1.41; 95%CI:0.98,2.04;P_{trend}=0.08). Kidney cancer (N=94) risks were non-significantly elevated ($RR_{LT\ days}$=1.77; 95%CI:0.90,3.51;P_{trend}=0.09; $RR_{IW\ days}$=1.37; 95%CI:0.64,2.92; P_{trend}=0.50), as were risks for aggressive prostate cancer (N=656) .

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Conclusions: Our updated evaluation of diazinon provides additional evidence of an association with lung cancer risk. Newly identified links to kidney cancer and associations with aggressive prostate cancer require further evaluation.

Keywords

diazinon; insecticides; pesticides; organophosphate; neoplasms

INTRODUCTION

Diazinon [*O,O*-diethyl *O*-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate] is a broad-spectrum organophosphate insecticide first registered for agricultural and residential use in the mid-1950s. It has been available in several physical states and formulations, including as liquid, granules, dust, wettable powders, and impregnated materials. Residential lawn and garden use in the U.S. was phased out by 2004[1], but diazinon still ranks among the top 10 most commonly used active organophosphate insecticides [2] and is used agriculturally to control soil and foliage insects on crops and non-lactating livestock . In 2007, crop-specific restrictions were added and granular formulations of diazinon were completely banned. Additional limitations in certain parts of the U.S. aim to protect endangered species from diazinon exposure due to agricultural runoff and drift.[1]

Diazinon can be present in the ambient air as a vapor or particulate following application and end up in drinking water due to runoff from agricultural fields. Therefore, human environmental or occupational exposure is possible through ingestion, inhalation, or dermal routes.[3] Transformation of diazinon to diazoxon, a potent cholinesterase inhibitor, can occur in multiple environmental and biological media.[3] While it has not been classified for carcinogenicity by the International Agency for Research on Cancer (IARC) or the U.S. Environmental Protection Agency (EPA),[4 5] renal, liver, and pancreatic toxicity have been identified in animal models.[3]

Epidemiologic evidence of an association between diazinon and lung cancer was observed in previous analyses of pesticide applicators in the Agricultural Health Study (AHS), a large prospective cohort of applicators and their spouses,[6 7] and in a case-control study nested within a cohort of pest control workers.[8] There is some evidence for an association with other solid cancers, including soft tissue sarcoma [9] and prostate cancer.[10 11] Diazinon has also been linked to risks of leukemia and follicular lymphoma in the AHS,[7 12] and with non-Hodgkin lymphoma.[13–15] However, most of this evidence comes from case-control studies with relatively few exposed cases or limited exposure information. These findings, as well as changes in the U.S. EPA registration status of diazinon, underscore the need to assess exposure at more than one time point to adequately capture changes in usage and subsequent impacts on cancer risks. Moreover, risks for other major solid tumor sites such as bladder and kidney have not been evaluated. The current study investigated the putative associations between diazinon and solid tumors in the AHS with extended follow-up and enhanced exposure information from a follow-up survey.

METHODS

Study population

Details of the study design and cohort composition of the AHS are described elsewhere.[7 16] Initiated in 1993, the AHS is an ongoing prospective cohort of 52,394 licensed private pesticide applicators (primarily farmers) residing in Iowa (IA) and North Carolina (NC), 32,345 of their spouses, and 4,916 licensed commercial pesticide applicators in IA. We identified applicators at the time oftheir application (1993–1997) for a restricted-use pesticide license at licensing facilities, and asked them to complete an enrollment questionnaire eliciting information on use of pesticides, medical history, smoking, and demographic information. We asked all applicators to complete a more detailed "take-home" questionnaire at enrollment, where they provided lifetime use of specific pesticides, including diazinon. Approximately 44% (N=25,291) returned the take-home survey; characteristics of these applicators were not systematically different from those completing the enrollment questionnaire only [7 17]. We invited all applicators to complete a follow-up telephone survey five years later (1998–2005), where they indicated their pesticide use since enrollment. Spouses did not reported detailed pesticide usage at both time points, and were not included in this evaluation.

Exposure assessment

At enrollment, we obtained lifetime use of diazinon for the 25,291 applicators completing the take-home survey, and updated use information during the telephone follow-up interview. We used multiple imputation to estimate pesticide exposures for applicators who did not participate in follow-up; the methodology and its validation have been reported previously.[18] Briefly, we used logistic regression and stratified sampling to impute pesticide exposure from a series of predictors, including but not limited to demographic and farm characteristics, specific medical conditions at enrollment, and characteristics of pesticide usage. For the current analysis, we imputed diazinon exposures for the period between enrollment and follow-up for the subset of applicators (28%) with missing follow-up data.

We created exposure metrics reflecting lifetime diazinon use and intensity. Lifetime exposure (LT) days were the number of application days per year multiplied by the number of years of application. Intensity-weighted lifetime exposure (IW) days further accounted for factors impacting exposure, including application method, whether or not the applicator personally mixed the pesticides, repaired pesticide application equipment, or used personal protective equipment.[19]

The decade of first use of diazinon was reported in categories at enrollment (e.g., 1960s, 1970s). We estimated this decade for the 1% of applicators missing this information by subtracting the midpoint of the categorically reported years of diazinon use at enrollment (≤1, 2–5, 6–10 11–20, or 20+ years) from the enrollment year. Although detailed information about diazinon applications was not collected at enrollment, at follow-up applicators reported the physical state (e.g., dry/granular, liquid) of the most frequently applied pesticides and type of application (e.g., crop, non-crop, animals).

Case ascertainment

We assessed cancer incidence by linkage to NC and IA state cancer registries from enrollment through December 31, 2010 for NC and December 31, 2011 for IA, and determined vital status by matching to the National Death Index. Follow-up time was censored at the date of any cancer diagnosis, date of death, migration out of state, or date of last follow-up, whichever was earlier.

This assessment added 199 incident lung cancers and 780 other solid tumors identified since the last analysis, which included cases diagnosed through 2002 and did not include bladder or kidney cancers.[7] We classified prostate cancer as aggressive by tumor characteristics as was described previously,[11] including distant stage, poorly differentiated, Gleason score ≥7, or prostate cancer as the underlying cause of death.

Statistical analysis

Among 25,291 enrolled applicators who completed the take-home questionnaire, we excluded individuals with prevalent cancer at baseline (N=622) or who were missing follow-up information (N=145). We further restricted the analysis to males (N=23,861) due to the small number of female applicators (N=663; 188 of whom reported using diazinon at follow-up). Our final analysis subset included the 22,830 male applicators with complete information for LT days (reported or imputed). Because the population exposure distribution at follow-up did not vary substantially from enrollment, we retained the exposure categories from the most recent AHS diazinon analysis [7] and evaluated cancer risks for applicators within tertiles of LT and IW days of diazinon use compared to those with no use. We evaluated risks of incident solid tumors for which there were at least ten diazinon-exposed cases. We estimated lung cancer risks by histologic subtype (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and other carcinomas). We also examined cumulative diazinon usage by the decade of first use, and computed the proportions of reported diazinon applications at follow-up by the physical state of product applied and application type.

We conducted Poisson regression to estimate rate ratios for solid tumor sites in relation to diazinon with the SAS® (version 9.2) procedure MIANALYZE, which yielded a single rate ratio (RR) for each cancer site, with a 95% confidence interval (95%CI) reflecting the average variance across separate models of five imputed exposures. We adjusted models for age at baseline (<40, 40–49, 50–59, ≥60 years), smoking history (never, tertiles of pack-years among former smokers: <3.75, 3.75–15, >15, tertiles of pack-years among current smokers: <11.5, 11.5–28.4, >28.5), education (high school or less, greater than high school), family history of cancer, and state (IA, NC), including missing covariates as categories (all covariates included in final models had ≤7% missing). There were several exceptions for covariate inclusion; we excluded alcohol or education variables and included only the categorical smoking adjustment without pack-years for kidney cancer and subtype-stratified models due to sparse data, and additionally adjusted prostate cancer models for race (white, non-white). We evaluated additional potential confounders collected at enrollment, including those linked with cancer risk in other AHS evaluations (e.g., doctor diagnosis of allergy, farm animal exposures, diesel tractor use, and solvent use in farming activities such as equipment cleaning and pesticide mixing). We assessed interactions with these binary co-

exposures via cross product terms with continuous variables of diazinon LT and IW days and Wald tests, and tested for linear trends using the median LT or IW days within categories parameterized as continuous variables.

We conducted additional analyses to explore the consistency with prior assessments of cancer risk in the AHS, timing of use, and disease latency. We conducted Spearman rank correlation analyses to identify other pesticide usage correlated with diazinon exposure, and estimated all risks further adjusted for lifetime use of pesticides previously associated with lung cancer in the AHS, including chlorpyrifos, dicamba, dieldrin, metolachlor, pendimethalin,[20] carbofuran,[21] and terbufos[22], and for the top five of other pesticides for which cumulative lifetime usage was correlated with diazinon. To address concerns regarding exposure recency, we repeated analyses after restricting to cases diagnosed in the first 10 years after enrollment and lagged exposure in 5 and 15-year intervals. To address concerns about imputed exposures, we also repeated main analyses after excluding applicators with missing follow-up information. These models could be adjusted only for age, smoking, and state. All data used were from AHS data release versions P1REL201209.00 and P2REL201209.00.

RESULTS

Of the 22,830 male applicators, 5,120 used diazinon (Table 1), two percent of whom used it for the first time after enrollment (data not shown). Non-exposed applicators were more likely to raise livestock and less likely to raise poultry, and applicators with the highest diazinon usage had nearly twice the average LT days of total pesticide exposures. Private applicators in NC were more likely to have used diazinon and had greater cumulative LT exposure than those in IA (mean=25 and 4 LT days, respectively; Supplemental Table 2). Commercial applicators had greater lifetime diazinon use overall, including more days per year of use (mean=14 days versus 6 among private applicators; data not shown).

Based on information collected in the follow-up interview, diazinon was applied predominantly in dry form, particularly among private applicators (70.3% of applications, Table 2). Private applicators applied diazinon for non-crop uses on the farm (59%), whereas commercial applicators applied it to crops (76%). Applications to animals were less frequent (1 – 3%). While relative applications to crops and animals did not vary greatly between IA and NC, the physical state of the product differed. Private applicators in IA applied dry or granular diazinon, whereas the NC private applicators reported usage more comparable to the commercial applicators in IA (33.5% and 39.7% applying dry diazinon, respectively). No clear patterns in decade of first diazinon use were evident, except that most usage began in the 1970s and 1980s (Supplemental Table 1); decade of first use was uncorrelated with age (data not shown).

A total of 2,288 incident solid tumors were diagnosed through 2010 (NC) and 2011 (IA), including 526 cases among those who used diazinon. In multivariable analyses, we observed a significant exposure-response trend for lung cancer with increasing LT days (RR >38.8 days versus non-exposed=1.60; 95%CI=1.11,2.31; P_{trend}=0.02) (Table 3). The pattern was similar for IW days (RR=1.41; 95%CI=0.98,2.04;P_{trend}=0.08). The RR increased with

cumulative LT use when we split the top tertile of LT days at the median, with RR in 38.90–108.8 LT days =1.41; 95%CI=0.88,2.27 and RR >108.8 LT days=1.80, 95%CI=1.09,2.97;P_{trend}=0.01). Corresponding risks for IW days were RR=1.39; 95%CI=0.84,2.31 and RR=1.39; 95%CI=0.86,2.24; P_{trend}=0.15, respectively. The RR of lung cancer was elevated among never smokers for both < and ≥ median LT or IW days compared to the non-exposed, but no gradients were present, and RRs were based on small numbers of exposed cases (Supplemental Table 3).

Risks for kidney cancer were also elevated in the top exposure tertiles compared to the non-exposed (RRs 1.77 and 1.37 for LT and IW days, respectively), although not statistically significantly (Table 3). When we split the top exposure tertiles at their medians, the RR continued to increase (RR in 38.90–108.8 LT days=1.58; 95%CI=0.63–3.97 and RR among those with >108.8 LT days=2.56; 95%CI=1.01,6.47;P_{trend}=0.02). Corresponding RRs for a split of the top IW tertile were RR=0.73; 95%CI=0.18,3.00 and RR=2.40; 95%CI=1.01,5.73;P_{trend}=0.05); most of the cases in the top tertile of IW exposure (6 out of 9) were above the median of the exposure level. When we restricted to only the renal cell carcinomas (~94% of cases) the association in the top tertile of diazinon exposure remained (RR=1.81; 95%CI=0.91,3.6). We saw no association for prostate cancer overall, but observed non-significantly increased risks for aggressive prostate cancer in the top tertile of LT (RR=1.16, 95%CI=0.83,1.63 P_{trend}=0.44) and IW days (RR=1.29; 95%CI=0.93,1.79;P_{trend}=0.22). Splitting the top tertile at the median did not identify further increasing risks for LT days (RR in 38.90–108.8 LT days=1.14, 95%CI=0.76, 1.73 and RR>108.8 days=1.11, 95%CI=0.65,1.90; P_{trend} =0.48). However, a suggestion of an association remained evident for IW days (RR=1.21, 95%CI=0.78, 1.87 and RR=1.29, 95%CI=0.82, 2.02; P_{trend}=0.17). The large number of prostate cancer cases allowed us to categorize exposure into quartiles, which yielded no association with LT days (RR in Q4 versus non-exposed=1.14, 95%CI=0.79, 1.64; P_{trend}=0.49) and a non-statistically significant positive association with IW days (RR in Q4 versus non-exposed=1.39, 95%CI=0.97, 2.01; P_{trend}=0.11). Risks for other cancer sites were generally null (Table 3). No differences in any of these observed associations emerged from analyses of lagged exposures (data not shown).

We found subtle differences in the association between diazinon exposure and lung cancer by histologic subtype (Table 4). There was no apparent association with squamous cell carcinoma, the most common subtype. We observed a significant exposure-response for adenocarcinoma and LT exposure days (P_{trend}=0.02) but not for IW exposure ($P_{trend=}$0.14). We observed no statistical interactions between diazinon and exposure to solvents, animals, diesel tractor use, and self-reported diagnosis of allergy for any cancer site (data not shown). Lifetime exposures to pesticides previously associated with lung cancer risk in the AHS were uncorrelated with diazinon use (ranged from ρ=0.21 to 0.50, the strongest correlation with dieldrin). We found no substantive evidence that the 5 additional most strongly correlated pesticide exposures (from among those with available usage information) were confounders in our key analyses (Supplemental Table 5). Although based on 49 lung and 14 exposed kidney cancer cases and imprecise, associations were statistically significant for LT days. When we restricted analyses to the 72% of applicators participating in follow-up, we observed similarly elevated risks for lung, kidney, and aggressive prostate cancers in the top exposure categories for both metrics. When we restricted analyses to cases diagnosed in the

first 10 years post-enrollment or to commercial applicators only, we also observed consistent patterns of association for these sites but reduced precision (data not shown).

DISCUSSION

In this comprehensive analysis and largest study of diazinon and lung cancer to-date, we observed a significantly increased risk of lung cancer among male pesticide applicators reporting over 38 LT days of diazinon exposure, with significant exposure-response. This analysis included an additional 199 cases since the most recent AHS assessment of lung cancer and diazinon,[7] allowing for analyses by histologic subtype and a more robust evaluation of potential confounding and effect modification by smoking and other lung cancer risk factors. It also added 8 years of follow-up for NC participants and 9 for IA participants, and further supports a lung cancer-diazinon association. These results are consistent with the only other study to evaluate this association, a case-control study of pesticide workers, which found suggestive associations between diazinon exposure and lung cancer mortality.[8] It also suggests possible links with kidney and aggressive prostate cancers. There was no compelling evidence of diazinon-associated risk for other solid tumor sites. For a chemical still commonly used in agriculture with potential to result in environmental exposure, these findings corroborate those previously observed in epidemiologic studies as well as offer new information about associations with cancer development.

Animal studies have noted DNA methylation by diazinon, which could cause toxicity and carcinogenic action.[23] Diazinon has been linked with oxidative stress and renal dysfunction in rats,[24] liver and kidney tissue damage in mice,[25] and DNA damage in both liver and kidneys of rabbits.[26] Non-mutagenic histological changes in lung tissue [27] and in airway defense mechanisms [28] have also been noted in animal models. Dose-related genotoxic effects of diazinon have been observed in human nasal mucosal cells in vitro.[29] One proposed mechanism of altered gene expression resulting from diazinon exposure is impaired DNA excision repair activity by downregulation of the RNRM1 gene, which plays an important role in up-regulation of the PTEN tumor suppressor.[30] Excision repair protein levels have been found to be lower in lung cancer patients compared to controls,[31 32] which may indicate increased cellular mutations and transformation as a consequence of deficient excision repair processes. Oxidative stress may be another mechanism of cytotoxicity,[33] as has been demonstrated in human lymphocytes following diazinon exposure.[34]

We explored whether additional information about application as a liquid or solid could provide additional insight into the observed association with lung cancer. Usage during the follow-up period differed between NC and IA; diazinon was largely sprayed as a liquid in NC, while dry applications were more common in IA. Although both application modes can result in exposure by inhalation or ingestion, liquid applications could potentially lead to more frequent dermal exposures, which are weighted more heavily in our IW metric [19] and may be less relevant for lung cancer etiology. We also compared application patterns between states and saw no major differences as to whether diazinon was applied to crops or animals. Diazinon historically came in a variety of preparations [1] and is used on both crops

and animals, but because details for applications were not collected at enrollment, we could not assess whether these exposure patterns reflect usage during earlier time periods. Finally, we note that the AHS cohort is comprised primarily of private applicators, although the limited information we have indicates that the frequency of commercial use differs from private use on farms. We were constrained by sample sizes to further evaluate these interesting descriptive features of diazinon application in relation to cancer risk. Our observed association with kidney cancer is based on a relatively small number of exposed cases (n=21) and is the first such evaluation, to our knowledge, in a human population. However, the animal literature provides some biologic plausibility. Both renal dysfunction and damage have been reported in rats [24] and mice.[25] Long-term exposure to diazinon induced dose-dependent oxidative stress and genotoxic effects in the kidneys of rabbits.[26] The kidneys are one site of concentration of xenobiotic compounds, and may be sensitive to chemical insults.[35] Thus, although the observed kidney cancer excess may be a chance finding, the association has some biological support and should be further evaluated. We were unable to conduct stratified analyses of kidney malignancies by histologic subtype to further explore this finding, but associations in the top tertile of diazinon exposure remained when we restricted to the predominant subtype, renal cell carcinoma.

In a previous evaluation of prostate cancer and pesticides in the AHS, Koutros et al. (2013) did not find a consistent relationship between diazinon use and risk of prostate cancer overall,[11] although there was a suggestion of an increased risk of aggressive cancer in the highest category of IW days exposure (RR=1.31, 95%CI=0.87, 1.96). Our analysis differs in two important ways. First, our evaluation provides additional cases and follow-up time. Second, because our analysis is focused specifically on the diazinon exposure-response, we restricted to applicators who completed the take-home enrollment questionnaire. However, our results were similar in that we observed a non-significantly increased risk of aggressive prostate cancer among applicators in the highest categories of diazinon use. The association with IW days remained when we split the top tertile at its median and in quartile analyses, which are more directly comparable to the analyses of Koutros et al. A case-control study among Canadian farmers also found an association between diazinon use and prostate cancer (OR=1.43; 95%CI=0.99–2.07) that was stronger and statistically significant in the highest category of exposure,[10] although these tumors were not characterized as aggressive. We observed no risks for melanoma or for bladder, colon, or rectum cancers. While animal studies indicate potential liver and pancreatic carcinogenicity,[3] we had too few diazinon-exposed cases (zero and four, respectively) for meaningful analysis of these sites.

The strengths of this study include the prospective design and detailed pesticide use assessed at two time points, which allowed us to retain our original analytic subset for nearly 15 years of follow-up. We also had detailed information on smoking history. Analyses of lung cancer restricted to never-smokers indicated positive associations with diazinon, and stratified analyses showed a positive and significant trend for adenocarcinoma, a subtype less strongly linked to smoking compared to squamous and small cell carcinomas of the lung.[36] For these reasons, residual confounding by smoking is not a likely explanation for the observed associations. We were also able to adjust for other known or potential confounders and to assess effect modification by important co-exposures. We found no evidence of confounding

by use of other pesticides, including chlorpyrifos, another phosphorothioate insecticide previously associated with lung cancer in the AHS cohort.[6]

We noted some interesting patterns in application preferences and the timing of first use of diazinon, but were limited by sample sizes and lacked sufficient latency to fully explore whether trends in usage by state or time period were etiologically relevant. Notably, the majority of applicators first began using diazinon in the 1970s and 1980s, roughly 10–20 years prior to the assessment of diazinon exposure at enrollment. Therefore, in addition to the average 15 years of prospective follow-up in this analysis, considerable time since first exposure has elapsed for most applicators. Sensitivity analyses restricting to those with complete exposure data agreed with our main findings.

With additional follow-up, cases, and exposure information, results from this prospective cohort study continue to provide evidence of an association between diazinon and lung cancer risk. Furthermore, our update allowed us to evaluate several tumor sites previously unassessed in relation to diazinon exposures in the AHS. A potential association with aggressive prostate cancer and one newly identified with kidney cancer require further evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. EPA EPA. Pesticides: Reregistration: diazinon. Secondary Pesticides: Reregistration: diazinon 2012 http://www.epa.gov/pesticides/reregistration/diazinon/.
2. Grube A, Donaldson D, Kiely T, Wu L. Pesticides Industry Sales and Usage. In: Prevention OoCSaP, ed.: Environmental Protection Agency, 2011.
3. Larkin DJ, Tjeerdema RS. Fate and effects of diazinon. Reviews of environmental contamination and toxicology 2000;166:49–82 [PubMed: 10868076]
4. IARC. Overall evaluations of carcinogenicity to humans: As evaluated in IARC Monographs volumes 1–98. (Alphabetical order) In: Cancer IAfRo, ed., 2007.
5. ATSDR. ToxFAQs for Diazinon Secondary ToxFAQs for Diazinon 2008.
6. Alavanja MC, Dosemeci M, Samanic C, et al. Pesticides and lung cancer risk in the agricultural health study cohort. American journal of epidemiology 2004;160(9):876–85 doi: 10.1093/aje/kwh290[published Online First: Epub Date]|. [PubMed: 15496540]
7. Beane Freeman LE, Bonner MR, Blair A, et al. Cancer incidence among male pesticide applicators in the Agricultural Health Study cohort exposed to diazinon. American journal of epidemiology 2005;162(11):1070–9 doi: 10.1093/aje/kwi321[published Online First: Epub Date]|. [PubMed: 16236997]
8. Pesatori AC, Sontag JM, Lubin JH, Consonni D, Blair A. Cohort mortality and nested case-control study of lung cancer among structural pest control workers in Florida (United States). Cancer causes & control : CCC 1994;5(4):310–8 [PubMed: 8080942]
9. Pahwa P, Karunanayake CP, Dosman JA, Spinelli JJ, McLaughlin JR. Soft-tissue sarcoma and pesticides exposure in men: results of a Canadian case-control study. Journal of occupational and

environmental medicine / American College of Occupational and Environmental Medicine 2011;53(11):1279–86 doi: 10.1097/JOM.0b013e3182307845[published Online First: Epub Date]|.

10. Band PR, Abanto Z, Bert J, et al. Prostate cancer risk and exposure to pesticides in British Columbia farmers. The Prostate 2011;71(2):168–83 doi: 10.1002/pros.21232[published Online First: Epub Date]|. [PubMed: 20799287]
11. Koutros S, Beane Freeman LE, Lubin JH, et al. Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study. American journal of epidemiology 2013;177(1):59–74 doi: 10.1093/aje/kws225[published Online First: Epub Date]|. [PubMed: 23171882]
12. Alavanja MC, Hofmann JN, Lynch CF, et al. Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. 2014(1932–6203 (Electronic))
13. Cantor KP, Blair A, Everett G, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer research 1992;52(9):2447–55 [PubMed: 1568215]
14. De Roos AJ, Zahm SH, Cantor KP, et al. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occupational and environmental medicine 2003;60(9):E11 [PubMed: 12937207]
15. Waddell BL, Zahm SH, Baris D, et al. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Cancer causes & control : CCC 2001;12(6):509–17 [PubMed: 11519759]
16. Alavanja MC, Sandler DP, McMaster SB, et al. The Agricultural Health Study. Environ Health Perspect 1996;104(4):362–9 [PubMed: 8732939]
17. Lee WJ, Blair A, Hoppin JA, et al. Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. Journal of the National Cancer Institute 2004;96(23):1781–9 doi: 10.1093/jnci/djh324[published Online First: Epub Date]|. [PubMed: 15572760]
18. Heltshe SL, Lubin JH, Koutros S, et al. Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study. Journal of exposure science & environmental epidemiology 2012;22(4):409–16 doi: 10.1038/jes.2012.31[published Online First: Epub Date]|. [PubMed: 22569205]
19. Coble J, Thomas KW, Hines CJ, et al. An updated algorithm for estimation of pesticide exposure intensity in the agricultural health study. International journal of environmental research and public health 2011;8(12):4608–22 doi: 10.3390/ijerph8124608[published Online First: Epub Date]|. [PubMed: 22408592]
20. Weichenthal S, Moase C, Chan P. A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort. Environmental health perspectives 2010;118(8):1117–25 doi: 10.1289/ehp.0901731[published Online First: Epub Date]|. [PubMed: 20444670]
21. Bonner MR, Lee WJ, Sandler DP, Hoppin JA, Dosemeci M, Alavanja MC. Occupational exposure to carbofuran and the incidence of cancer in the Agricultural Health Study. Environmental health perspectives 2005;113(3):285–9 [PubMed: 15743716]
22. Bonner MR, Williams BA, Rusiecki JA, et al. Occupational exposure to terbufos and the incidence of cancer in the Agricultural Health Study. Cancer causes & control : CCC 2010;21(6):871–7 doi: 10.1007/s10552-010-9514-9[published Online First: Epub Date]|. [PubMed: 20155313]
23. Zhang X, Wallace AD, Du P, et al. DNA methylation alterations in response to pesticide exposure in vitro. Environmental and molecular mutagenesis 2012;53(7):542–9 doi: 10.1002/em.21718[published Online First: Epub Date]|. [PubMed: 22847954]
24. Shah MD, Iqbal M. Diazinon-induced oxidative stress and renal dysfunction in rats. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2010;48(12):3345–53 doi: 10.1016/j.fct.2010.09.003[published Online First: Epub Date]|. [PubMed: 20828599]
25. Cakici O, Akat E. Effects of oral exposure to diazinon on mice liver and kidney tissues: biometric analyses of histopathologic changes. Analytical and quantitative cytopathology and histopathology 2013;35(1):7–16 [PubMed: 23469619]
26. Tsitsimpikou C, Tzatzarakis M, Fragkiadaki P, et al. Histopathological lesions, oxidative stress and genotoxic effects in liver and kidneys following long term exposure of rabbits to diazinon and

propoxur. Toxicology 2013;307:109–14 doi: 10.1016/j.tox.2012.11.002[published Online First: Epub Date]|. [PubMed: 23201499]

27. Rady MI. Effects of exposure to Diazinon on the lung and small intestine of Guinea pig, histological and some histochemical changes. Brazilian Archives of Biology and Technology 2009;52(2):317–26
28. Campbell H, Ravi K, Bravo E, Kappagoda CT. Effect of Diazinon PLUS on rapidly adapting receptors in the rabbit. Journal of applied physiology (Bethesda, Md. : 1985) 1996;81(6):2604–10 [PubMed: 9018512]
29. Tisch M, Schmezer P, Faulde M, Groh A, Maier H. Genotoxicity studies on permethrin, DEET and diazinon in primary human nasal mucosal cells. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2002;259(3):150–3
30. Mankame T, Hokanson R, Fudge R, Chowdhary R, Busbee D. Altered gene expression in human cells treated with the insecticide diazinon: correlation with decreased DNA excision repair capacity. Human & experimental toxicology 2006;25(2):57–65 [PubMed: 16539210]
31. Cheng L, Spitz MR, Hong WK, Wei Q. Reduced expression levels of nucleotide excision repair genes in lung cancer: a case-control analysis. Carcinogenesis 2000;21(8):1527–30 [PubMed: 10910954]
32. Paz-Elizur T, Krupsky M, Blumenstein S, Elinger D, Schechtman E, Livneh Z. DNA repair activity for oxidative damage and risk of lung cancer. Journal of the National Cancer Institute 2003;95(17): 1312–9 [PubMed: 12953085]
33. Banerjee BD, Seth V, Ahmed RS. Pesticide-induced oxidative stress: perspectives and trends. Reviews on environmental health 2001;16(1):1–40 [PubMed: 11354540]
34. Colovic M, Krstic D, Petrovic S, et al. Toxic effects of diazinon and its photodegradation products. Toxicology letters 2010;193(1):9–18 doi: 10.1016/j.toxlet.2009.11.022[published Online First: Epub Date]|. [PubMed: 19948211]
35. Lock EA, Reed CJ. Xenobiotic metabolizing enzymes of the kidney. Toxicologic pathology 1998;26(1):18–25 [PubMed: 9502382]
36. Chen F, Bina Wf Fau - Cole P, Cole P. Declining incidence rate of lung adenocarcinoma in the United States. Cancer Epidem Biomar 2007(0012–3692 (Print))

What this paper adds:

- This comprehensive evaluation of diazinon and solid tumors in a prospective cohort study included exposure information from two points in time, 337,771 person-years, and 2,288 incident cases of solid tumors.
- In the largest analysis of lung cancer risk associated with diazinon, this re-evaluation of demonstrated that lung cancer risks persist with additional exposure information, 199 cases, and 8 years of follow-up from a previous evaluation. Suggestive evidence was found for adenocarcinoma, the first time that an evaluation of histological subtypes has been conducted.
- In this first study to examine kidney cancer risk associated with diazinon exposure, there is suggestive evidence of an association which needs to be confirmed in further studies.
- Aggressive prostate cancer was also associated with diazinon exposure.

Table 1.

Selected baseline characteristics of male pesticide applicators in the Agricultural Health Study, 1993–2010/2011[a], by cumulative lifetime diazinon exposure (N=22,830).

Characteristic		Exposure category (lifetime days)					
		Non-exposed (N=17,710)		Lowest exposed (N=2,350)		Highest exposed[b] (N=2,770)	
	Person-years	N	%	N	%	N	%
Age category (years)							
<40	107,210	5398	30.5	617	26.3	648	23.4
40–49	95,079	4646	26.2	672	28.6	749	27.0
50–59	74,345	3857	21.8	547	23.3	712	25.7
≥60	61,137	3809	21.5	514	21.9	661	23.9
State of residence							
Iowa	240,882	13247	74.8	1364	58.0	1245	45.0
North Carolina	96,889	4463	25.2	986	42.0	1525	55.0
Type of applicator							
Private	304,716	16157	91.2	2154	91.7	2394	86.4
Commercial	33,055	1553	8.8	196	8.3	376	13.6
Smoking history (pack-years)							
Never	180,294	9477	53.5	1180	50.2	1188	42.9
Former	96,553	5050	28.5	749	31.9	936	33.8
Current	44,887	2290	12.9	296	12.6	463	16.7
Missing	16,037	893	5.0	125	5.3	183	6.6
Alcohol consumption							
Never in the last year	101,469	5398	30.5	774	32.9	992	35.8
Ever in the last year	221,570	11507	64.9	1476	62.8	1624	58.6
Missing	14,732	805	4.6	100	4.3	154	5.6
Education, N (%)							
High school or less	182,585	10203	57.6	1206	51.3	1389	50.1
More than high school	146,935	7054	39.8	1089	46.3	1287	46.5
Missing	8250	453	2.6	55	2.3	94	3.4
Family history of cancer							

Characteristic		Exposure category (lifetime days)					
		Non-exposed (N=17,710)		Lowest exposed (N=2,350)		Highest exposed[b] (N=2,770)	
	Person-years	N	%	N	%	N	%
Yes	136,858	7084	40.0	1054	44.9	1234	44.6
No	184,061	9682	54.7	1177	50.0	1351	48.8
Missing	16,852	944	5.3	119	5.1	185	6.7
Allergy diagnosis							
Yes	206,888	10459	59.1	1649	70.2	1727	62.4
No	90,375	5249	29.6	458	19.5	606	21.9
Missing	40,508	2002	11.3	243	10.3	437	15.8
Raise Livestock							
Yes	252,578	13279	75.0	1659	70.6	1940	70.0
No	85,193	4431	25.0	691	29.4	830	30.0
Raise Poultry							
Yes	90,484	4477	25.3	671	28.6	978	35.3
No	247,287	13233	74.7	1679	71.5	1792	64.7
Use diesel tractors							
≥Daily use in both seasons	56,801	3069	17.3	301	12.8	308	11.1
< Daily use in both seasons	243,050	12825	72.4	1812	77.1	2052	74.1
Missing	37,921	1816	10.3	237	10.1	410	14.8
Use gasoline/solvents in farm activities							
Yes	160,907	8234	46.5	1190	50.6	1392	50.3
No	143,089	7923	44.7	964	41.0	1002	36.2
Missing	33,055	1553	8.8	196	8.3	376	13.6
Mean length of follow-up, years		14.9		14.8		14.5	
Mean lifetime no. of days of all pesticide application		341.0		357.8		618.6	

[a] Follow-up was through December 31, 2010 for North Carolina applicators and through December 31, 2011 for Iowa applicators.

[b] Top 2 tertiles of lifetime number of days diazinon exposure.

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Table 2.

Diazinon applications[a] reported by male pesticide applicators at follow-up in the Agricultural Health Study, 1993–2010/2011.

	Physical State			Application Type		
Applicator type and state	**Liquid**	**Dry**	**Gas**	**Crops**	**Noncrop**	**Animals**
Commercial[b]	39.7	59.0	1.3	75.6	21.8	2.6
Private						
Overall	29.7	70.3	0	39.2	59.0	1.8
Iowa	3.4	96.6	0	40.6	58.4	1.0
NC	66.5	33.5	0	31.1	67.2	1.7

[a] Proportions among all diazinon applications reported at follow-up.

[b] All commercial applicators are in Iowa.

Table 3.

Risks for selected solid malignancies in association with cumulative lifetime diazinon exposure among male pesticide applicators in the Agricultural Health Study, 1993–2010/2011 (N=22,830).

	Lifetime # of exposure days	N	RR	95%CI	Intensity-weighted exposure days	N	RR	95%CI
Lung[a]	No exposure	199	1.00	Referent	No exposure	199	1.00	Referent
	<20	32	1.11	0.75, 1.65	<368	22	1.09	0.61, 1.53
	20.0–38.8	16	0.76	0.44, 1.30	369–1800	25	0.99	0.66, 1.52
	>38.8	36	1.60	1.11, 2.31	>1800	37	1.41	0.98, 2.04
			$P_{trend=}$	0.02			$P_{trend=}$	0.08
Bladder[a]	No exposure	132	1.00	Referent	No exposure	132	1.00	Referent
	<20	13	0.69	0.37, 1.28	<368	8	0.58	0.27, 1.24
	20.0–38.8	8	0.72	0.35, 1.48	369–1800	11	0.70	0.37, 1.32
	>38.8	11	0.93	0.49, 1.74	>1800	13	1.05	0.59, 1.90
			$P_{trend=}$	0.77			$P_{trend=}$	0.96
Kidney[b]	No exposure	73	1.00	Referent	No exposure	73	1.00	Referent
	<20	5	0.53	0.21, 1.31	<368	6	0.85	0.37, 1.96
	20.0–38.8	6	0.89	0.36, 2.22	369–1800	6	0.77	0.33, 1.78
	>38.8	10	1.77	0.90, 3.51	>1800	9	1.37	0.64, 2.92
			$P_{trend=}$	0.09			$P_{trend=}$	0.45
Prostate[c]	No exposure	995	1.00	Referent	No exposure	995	1.00	Referent
	<20	148	1.10	0.91, 1.32	<368	111	1.16	0.95, 1.43
	20.0–38.8	70	0.89	0.69, 1.17	369–1800	102	0.89	0.72, 1.12
	>38.8	79	1.01	0.79, 1.30	>1800	83	0.99	0.77, 1.28
			$P_{trend=}$	0.84			$P_{trend=}$	0.64
Aggressive prostate[c]	No exposure	505	1.00	Referent	No exposure	505	1.00	Referent
	<20	71	1.08	0.82, 1.41	<368	54	1.11	0.82, 1.50
	20.0–38.8	36	0.98	0.69, 1.39	369–1800	47	0.90	0.66, 1.23
	>38.8	44	1.16	0.83, 1.63	>1800	50	1.29	0.93, 1.79
			$P_{trend=}$	0.44			$P_{trend=}$	0.22
Colon[a]	No exposure	180	1	Referent	No exposure	180	1	Referent
	<20	16	0.84	0.50, 1.41	<368	9	0.63	0.32, 1.24

	Lifetime # of exposure days	N	RR	95%CI	Intensity-weighted exposure days	N	RR	95%CI
	20.0–38.8	14	1.03	0.57, 1.86	369–1800	19	1.21	0.75, 1.97
	>38.8	16	1.12	0.63, 1.99	>1800	18	1.03	0.56, 1.88
			$P_{trend=}$	0.67			$P_{trend=}$	0.70
Rectum[a]	No exposure	68	1.00	Referent	No exposure	68	1.00	Referent
	<20	5	0.51	0.18, 1.40	<368	5	0.67	0.24, 1.85
	20.0–38.8	5	0.88	0.32, 2.44	369–1800	2	0.18	0.02, 1.33
	>38.8	4	0.94	0.33, 2.66	>1800	7	1.62	0.71, 3.66
			$P_{trend=}$	0.94			$P_{trend=}$	0.49
Melanoma[a]	No exposure	115	1.00	Referent	No exposure	115	1.00	Referent
	<20	15	0.96	0.53, 1.71	<368	14	1.27	0.71, 2.28
	20.0–38.8	11	1.22	0.63, 2.36	369–1800	8	0.55	0.24, 1.26
	>38.8	6	0.58	0.24, 1.45	>1800	10	1.00	0.49, 2.02
			$P_{trend=}$	0.33			$P_{trend=}$	0.69

Abbreviations: RR, rate ratio.

[a]Models are adjusted for age, alcohol consumption, smoking (never, pack years among former and current smokers), education, family history of cancer, and state of residence

[b]Models are adjusted for age, smoking (never, former, current), and state of residence.

[c]Models are adjusted for age, alcohol consumption, smoking (never, pack years among former and current smokers), education, family history of cancer, state of residence, and race.

Table 4.

Lung cancer risks [a] in association with cumulative lifetime diazinon exposure days among male pesticide applicators in the Agricultural Health Study, 1993–2010/2011, by histologic subtype.

	Adenocarcinoma			Squamous cell Carcinoma			Small cell carcinoma			Other carcinomas		
Lifetime # of exposure days	**N**	**RR**	**95%CI**	**N**	**RR**	**95%CI**	**N**	**RR**	**95%CI**	**N**	**RR**	**95%CI**
No exposure	50	1.00		60	1.00		38	1.00		51	1.00	
< Median	9	1.21	0.57, 2.57	11	1.31	0.69, 2.53	4	0.71	0.25, 2.02	8	0.96	0.42, 2.19
≥ Median	14	1.37	0.75, 2.51	8	0.65	0.31, 1.38	11	1.23	0.62, 2.43	19	1.53	0.88, 2.66
			$P_{trend=}$0.02			$P_{trend=}$0.30			$P_{trend=}$0.10			$P_{trend=}$0.09
Intensity-weighted # of exposure days	**N**	**RR**	**95%CI**	**N**	**RR**	**95%CI**	**N**	**RR**	**95%CI**	**N**	**RR**	**95%CI**
No exposure	50	1.00		60	1.00		38	1.00		51	1.00	
< Median	10	1.17	0.57, 2.39	9	0.98	0.48, 1.98	4	0.63	0.22, 1.76	10	1.06	0.49, 2.29
≥ Median	13	1.43	0.76, 2.69	10	0.89	0.45, 1.76	11	1.36	0.68, 2.71	17	1.50	0.84, 2.69
			$P_{trend=}$0.14			$P_{trend=}$0.54			$P_{trend=}$0.18			$P_{trend=}$0.19

Abbreviations: RR, rate ratio.

[a]Models are adjusted for age, smoking (never, pack years among former and current smokers), family history of cancer, and state of residence.